AOGD
Good Clinical Practice
GUIDELINES

Association of Obstetricians and
Gynaecologists of Delhi
2017-18

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AOGD Guideline

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Preface

It gives us a great sense of satisfaction to present to AOGD members the much awaited ***'AOGD Good Practice Guidelines'*** put together by the AOGD Committee Chairpersons & its members. We have had several requests from AOGD members to bring out guidelines which will help them in their day -to -day practice. Wide ranging topics relevant and topical to contemporary Obstetrics & Gynaecology practice have been included. Respective AOGD Committees have worked hard to bring out these guidelines through several meetings and discussions and we hope this practical handbook becomes a ready reckoner for AOGD members.

Guidelines have been compiled on the basis of best available evidence. Evidence has largely been drawn from randomised trials but also from published guidelines of RCOG, ACOG, SOGC and other academic bodies. In addition, a number of FOGSI guidelines are also available on the FOGSI website. We have tried not to reinvent the wheel as far as possible. Relevant government of India guidelines have been provided in some articles. Guidelines cannot be a replacement for good clinical judgement and patient care has to be individualised. Any clarification regarding these guidelines may please be sought from respective committee chairpersons.

We have tried to categorise the guidelines beginning with Nutrition, Weight gain and Exercise in pregnancy, Aneuploidy screening, Critical Care Obstetrics followed by Gynecologic issues such as management of Adolescent PCOS, Genital Tuberculosis, Male Infertility, OHSS, premature ovarian insufficiency and endometriosis in young girls. An overview of common urogynecology problems such as management of Overactive bladder and Stress urinary incontinence have been amply covered. Preventive aspects of endometrial, ovarian and breast cancers are outlined followed lastly by management of adnexal masses in young girls, risk reducing salpingectomy and risk reducing salpingo-oophorectomy. We look forward to a feed back from AOGD members and hope to update it from time to time.

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Disclaimer

The guidelines have been prepared by respective AOGD subcommittees on basis of evidence and other national and international guidelines. Any clarification regarding these may be sought for respective committee chairpersons.

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Weight Gain Guidelines in Pregnancy

Sangeeta Gupta, Taru Gupta

Improvement of maternal and child health are key public health goals. Women should conceive at a weight within the range of normal BMI values. Gestational weight gain (GWG) recommendations aim to optimize outcomes for the woman and the infant, inappropriate GWG may have short and long-term consequences for the health of the mother. For example, pre-pregnancy BMI above normal values (19.8-26 kg/m^2) is associated with preeclampsia, gestational diabetes (GDM), caesarean delivery and failure to initiate and sustain breastfeeding & weight retention postpartum with associated long-term health consequences. Increased maternal BMI and GWG have also been associated with lifelong consequences for the baby, including a fourfold increased risk of large-for-gestational-age (LGA) infants and a consistent increase in BMI and blood pressure and an abnormal metabolic profile in childhood and early adult life.

Optimizing a woman's nutritional status, fitness and weight before, during and between pregnancies (including while breastfeeding) has immediate and long-term benefits for the health of both the woman and her child/children.

1. Pre-pregnancy

When a woman is planning a pregnancy, the health practitioner should discuss with the woman the most appropriate nutrition and activity choices to support pre-conceptual health. For a woman who has a BMI that falls within the obese category, the health practitioner should recommend that the woman lose weight before becoming pregnant. This is because, when compared to women with a healthy pre-pregnancy weight, obese women who become pregnant are at increased risk of miscarriage, gestational diabetes, and all the complications as mentioned above.

The health practitioner should also consider other co-morbidities, such as hypertension and diabetes, and should prescribe folic acid for any woman planning a pregnancy. Regular self-weighing has been identified as a key component in successful weight management in non-pregnant along with behavior, activity and dietary changes, and should be utilised by women who are planning pregnancy.

Women who have had bariatric surgery should be advised not to conceive in the first year post procedure during the period of dramatic weight loss.

2. During pregnancy

The 1990 IOM guidelines for weight gain during pregnancy were based on the strong association between GWG and infant size at birth. The evidence remains strong that pre-pregnancy BMI is an important determinant of many outcomes of pregnancy (Table-1).

Table 1: 1990 IOM guidelines for weight gain and rate of weight gain during pregnancy for women with singleton fetuses

Pre-pregnancy weight-for-height category	Mothers of singletons	
	Total weight gain (lb)	Rate of weight gain in the second & third trimesters (lb/wk)
Low (BMI<19.8 kg/m2)	28-40	~ 1.0 (0.5 kg/wk)
Normal (19.8-26.0 kg/m2)	25-35	1.0 (0.4 kg/wk)
High (>26.0-29.0 kg/m2)	15-25	0.66 (0.3 kg/wk)
Obese (>=29.0 kg/m2)	>=15	Not specified

2.1 Optimal weight gain during pregnancy

The recommended amount of weight that a woman gains during her pregnancy is a range that is based on her pre-pregnancy body mass index (BMI). For women with a normal weight, 11.5 - 16 kg (25-35 lbs) is the recommended weight gain during pregnancy. These ranges are applicable to all women with singleton pregnancies.

Pregnant women should be made aware of the IOM's recommendations for GWG to assist them to make informed, healthy choices. The recommendations, based on available evidence from observational studies, have been widely adopted internationally. They should be used in combination with professional judgment and a discussion with the woman regarding nutrition and physical activity (IOM and NRC 2009) (Table-2).

Table 2: 2009 IOM/NRC guidelines for weight gain and rate of weight gain during pregnancy for women with singleton foetuses and with twin fetuses

Pre-pregnancy BMI category	Mothers of singletons		Mothers of twins
	Total weight gain (lb)	Rate of weight gain in the second and third trimesters (lb/wk)	Total weight gain at term (lb)
Underweight (<18.5 kg/m2)	28-40	1.0 (1.0-1.3)	No guideline available
Normal weight(18.5-24.9 kg/m2)	25-35	1.0 (0.8-1.0)	37-54
Overweight (25.0-29.9 kg/m2)	15-25	0.6 (0.5-0.7)	31-50
Obese (>= 30.0 kg/m2)	11-20	0.5 (0.4-0.6)	25-42

Health care providers who care for pregnant women should determine a woman's BMI at the initial prenatal visit and counsel her regarding the benefits of appropriate weight gain, nutrition and exercise.

Body Mass Index (BMI) should be calculated from measured height and measured weight at booking/first visit (ideally before 10 weeks' gestation. If the woman presents after 10 weeks' gestation, the BMI can still be calculated from measured height and weight and weight gain can still be advised based on best estimate of pre-pregnancy BMI.

Women should be encouraged, where appropriate, to monitor (using the same scales each time) and record their own weight regularly (for example, monthly) during pregnancy and in the postpartum period. If it is not possible for a woman to record their own weight, they can ask to be weighed at antenatal visits.

Dieting to lose weight is not recommended during pregnancy (National Institute for Health Care Excellence 2010).

2.2 The advice below applies to women with uncomplicated singleton pregnancies

2.2.1 Overweight Women

The IOM guidelines recommend a total weight gain of 6.8–11.3 kg (15–25 lb) for overweight women (BMI of 25–29.9). For the overweight pregnant woman who is gaining less than the recommended amount but has an appropriately growing fetus, no evidence exists that encouraging increased weight gain to conform with the current IOM guidelines will improve maternal or fetal outcomes.

2.2.2 Obese Women

The IOM recommendations define obesity as a BMI of 30 or greater and do not

differentiate between Class I obesity (BMI of 30–34.9), Class II obesity (BMI of 35–39.9), and Class III obesity (BMI of 40 or greater) as differentiated by WHO. Lower GWGs, on the order of 11 kg and 9 kg, have been confirmed in large cohorts of obese women and very obese women, respectively.

Table 3: Comparison of Institute of Medicine (IOM) and World Health Organization (WHO) BMI Categories

Category	**IOM**	**WHO**
Underweight	<19.8 kg/m2	<18.5 kg/m2
Normal weight	19.8- 26 kg/m2	18.5-24.9 kg/m2
Overweight	26.1- 29 kg/m2	25-29.9 kg/m2
Obese Class I	>29 kg/m2	30-34.9 kg/m2
Obese Class II	---	35-39.9 kg/m2
Obese Class III	---	>=40 kg/m2

Given the limited data by class, the IOM recommendation for weight gain is 5–9.1 kg (11–20 lb) for all obese women. The GWG guidelines attempt to balance the risks of having LGA infants, operative delivery, small-for-gestational-age infants, and preterm births and postpartum weight retention while managing their pattern of dietary intake to avoid ketonemia; however low or no gain during pregnancy in obeese woman, particularly with glucose intolerance, can be harmful if it was associated with fetal growth restriction or ketonemia.

Total GWG in normal-term pregnancies displays considerable variability; nevertheless, some generalizations can be made regarding mean tendencies and patterns of GWG:

A consistent inverse relationship is observed between GWG and pregravid BMI category. The pattern of GWG is most commonly described as sigmoidal, with mean weight gains higher in the second than the third trimester across BMI categories, except for obese women.

Table 4: Recommended weight gain for singleton pregnancies:

Total and rate of weight gain during pregnancy, by pre-pregnancy BMI

	Total weight gain		Rates of weight gain 2nd & 3rd trimester	
Pre-pregnancy BMI	Range in kg	Range in lbs	Mean (range) in kg/wk	Mean (range) in lbs/wk
Underweight (<18.5 kg/m2)	12.5-18	28-40	0.51(0.44-0.58)	1(1-1.3)
Normal weight (18.5-24.9 kg/m2)	11.5-16	25-35	0.42(0.35-0.50)	1(0.8-1)
Overweight (25.0-29.9 kg/m2)	7-11.5	15-25	0.28(0.23-0.33)	0.6(0.5-0.7)
Obese (>= 30.0 kg/m2)	5-9	11-20	0.22(0.17-0.27)	0.5(0.4-0.6)

*Calculations assumed a 0.5-2kg (1.1-1.4 lbs) weight gain in first trimester

Table 5: Comparison of recommended maternal weight gain for singleton pregnancies

Pre-pregnancy BMI	Weight gain range in kg	
	IOM	**SOGC**
Underweight <18.5	12.5-18	12.5-18
Normal weight 18.5-24.9	11.5-16	11.5-16
Overweight 25.0-29.9	7-11.5	7-11.5
Obese >=30.0	5-9	7

2.3 Special conditions

2.3.1 Multiple pregnancy- The presence of multiple fetuses in a pregnancy has an influence on total GWG. In comparison to singleton birth the additional components of the products of a twin gestation (fetus, placenta and amniotic fluid) account for up to two additional kilograms in GWG.

For twin pregnancy, the IOM recommends a gestational weight gain of 17-25 kg (37–54 lb) for women of normal weight, 14-23 kg (31–50 lb) for overweight women, and 11-19 kg (25–42 lb) for obese women. The IOM guidelines recognize that data are insufficient to determine the amount of weight women with multifetal (triplet and higher order) gestations.

Table 6: GWG for women with multiple fetuses

Pre-pregnancy BMI	Recommended total weight gain	
	Kg	lbs
Normal weight 18.5-24.9	17-25	37-54
Overweight 25.0-29.9	14-23	31-50
Obese >=30.0	11-19	25-42

2.3.2 Bariatric surgery and pregnancy- The American College of Obstetricians and Gynecologists (ACOG) published a Committee Opinion on Obesity and Pregnancy addressing the issue of bariatric surgery and pregnancy. ACOG recommends that obese women who have undergone bariatric surgery receive the following counseling before and during pregnancy: Patients with adjustable gastric banding should be advised that they are at risk of becoming pregnant unexpectedly after weight loss following surgery. All patients are advised to delay pregnancy for 12-18 months after surgery to avoid pregnancy during the rapid weight loss phase. Women with gastric banding should be monitored by their general surgeons during pregnancy because adjustments of the band may be necessary. Patients should be evaluated for nutritional deficiencies, including iron, B12, folate, vitamin D and calcium, and supplemented with vitamins as necessary.

2.3.3 Adolescent pregnancy- Mean GWG ranges from 10.0 to 16.7 kg in normal weight adults whereas 14.6 to 18.0 kg in adolescents giving birth to term infants. Adult BMI categories are used to determine weight gain range in pregnant teenagers until more research is done to determine whether special categories are needed for them.

The recommended weight gain ranges for short women and for racial or ethnic groups are the same as those for the whole population.

To improve maternal and child health outcomes, women not only should be within a normal BMI range when they conceive but also should gain within the ranges recommended. Meeting these challenges means that women will need preconception counseling, which may include plans for weight loss.

2.3.4 During Postpartum Period- Excessive GWG and/or postpartum weight retention can lead to an increased BMI for subsequent pregnancies. An increase in a woman's pre-pregnancy weight from overweight to obese between a first and second pregnancy can result in a threefold increased risk of preeclampsia, while a reduction in pre-pregnancy weight between a first and second pregnancy from obese to normal BMI can decrease the risk of caesarean and large-for-gestational-age infants.

Discuss healthy eating, physical activity and breastfeeding as strategies for encouraging a return to pre-pregnancy weight with all postpartum women.

Opportunities for this include during antenatal visits and routine postnatal checks.

Advise women who are overweight or obese of the benefits of weight loss pre-pregnancy and between pregnancies and take action consistent with the Weight Management Guidelines for Adults.

Women who are healthy weight should be encouraged to maintain a healthy weight between pregnancies.

Conclusions and Recommendations

1. The IOM gestational weight gain guidelines provide clinicians with a basis for practice. Health care providers who care for pregnant women should determine a woman's BMI at the initial prenatal visit (an online BMI calculator is available at http://www.nhlbisupport.com/bmi).
2. It is important to discuss appropriate weight gain, diet, and exercise at the initial visit and periodically throughout the pregnancy.
3. Individualized care and clinical judgment are necessary in the management of the overweight or obese woman who is gaining (or wishes to gain) less weight than recommended but has an appropriately growing fetus. Balancing the risks of fetal growth (in the large-for-gestational-age fetus and the small-for-gestational-age fetus), obstetric complications, and maternal weight retention is essential but will remain challenging until research provides evidence to further refine the recommendations for gestational weight gain, especially among women with high degrees of obesity.
4. Offering preconceptional services, such as counseling on diet and physical activity as well as access to contraception, to all overweight or obese women to help them reach a healthy weight before conceiving. This may reduce their obstetric risk and normalize infant birth weight as well as improve their long-term health. This may also reduce their obstetric risk, reduce postpartum weight retention, improve their long-term health, normalize infant birth weight and offer an additional tool to help reduce childhood obesity.
5. Advise women who are overweight or obese of the benefits of weight loss pre-pregnancy and between pregnancies.
6. Women who are healthy weight should be encouraged to maintain a healthy weight between pregnancies.

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Exercise in Pregnancy

Chanchal Singh

"To stay inactive, is to die." [Berghella V, Editorial, AJOG, April 2017]

Introduction

We all know that exercise is good for our health, both physical and mental. Traditionally, pregnant women have been advised not only by their families but also their healthcare professionals to 'take it easy' or to rest more in pregnancy. However, there is increasing evidence that exercise in pregnancy not only benefits the mother but also improves perinatal outcomes by decreasing macrosomia.[1-6] In fact, the ACOG in its 2015 guideline on this topic has suggested that pregnancy is an ideal time to initiate lifestyle modifications even if the woman has previously been sedentary especially since she would be under medical supervision and have access to medical care at all times.[7]

1. What are the benefits and harm of exercise in pregnancy?

There is level I evidence from more than 50 randomized controlled trials (RCTs) and their metanalysis that exercise in pregnancy benefits both mother and fetus (table 1).[1-7] This benefit is seen in women with both normal BMI as well as overweight and obese women. A recent metanalysis has reported a 49% decrease in gestational diabetes (GDM), 79% decrease in gestational hypertension, 18% decrease in cesarean delivery and more importantly 9% increase in rate of vaginal delivery in women with normal BMI and an uncomplicated, singleton pregnancy who were assigned to aerobic exercise.[2] The rates of preterm birth were similar to women who were not randomized to the exercise group. Another metanalysis has reported a decrease in PTB by 38% and GDM by 39% in overweight or obese women who were randomized to exercise group in various RCTs.[3] A recent RCT reported that exercise initiated at less than 13 weeks performed for at least 30 minutes, 3 times a week till 37 weeks significantly reduced the incidence of GDM and gestational weight gain at less than 25 weeks and lowered neonate's birthweight in overweight and obese women with singleton pregnancy.[1]

Table 1: Benefits of Exercise in Pregnancy

Lower incidence of
• Gestational diabetes
• Gestational hypertensive disorders
• Preterm birth
• Caesarean delivery
• Birthweight
Higher incidence of
• Vaginal delivery

None of these studies reports any harm from exercise in pregnancy though there remains a risk of dehydration, overexertion and injury due to wrong postures or accidentally but this remains true for non-pregnant individuals as well. Thus, pregnant women are not at an increased risk of adverse outcomes when exercise is done safely and preferably under supervision. On the contrary, bedrest, which is arguably the most common non-pharmaceutical intervention advised in pregnancy is in fact harmful in pregnancy with increased risk of venous thromboembolism, bone demineralization and deconditioning.[8]

2. Which women should exercise in pregnancy?

Every pregnant woman who does not have a medical contraindication which would preclude exercise even in a non-pregnant individual, should exercise. Although ACOG has given absolute and relative contraindications to guide which women can safely exercise in pregnancy (Table 2), authors comment that none of these are substantiated by data and conditions like multiple gestation, mild vaginal bleeding, prelabour premature rupture of membranes (PPROM) have been questioned.[9] Decreased activity has been reported to be associated with increased risk of preterm birth (PTB) in women with short cervix on transvaginal ultrasound.[10] As per data from the USA, 70% of Maternal Fetal Medicine physicians recommend bed rest for preterm labour and 85% recommend bed rest in case of PPROM, with no evidence of benefit.[8] There is no comparable Indian data but as per clinical practice, our figures would be similar, if not higher. No evidence of fetal harm has been reported from moderate to intense exercise which may be associated with a 10-15 beats per minute increase in the fetal heart rate (FHR). There has been no reported increase in the incidence of fetal growth restriction or small for gestational age age.[1-7]

Table 2: Contraindications to Aerobic Exercise during Pregnancy[7]

Absolute	Relative
• Hemodynamically significant heart disease • Restrictive lung disease • Incompetent cervix or cerclage • Multiple gestation at risk of premature labour • Persistent 2nd or 3rd trimester bleeding • Placenta praevia after 26 weeks' gestation • Premature labor during current pregnancy • Ruptured membranes • Preeclampsia • Severe anemia	• Anemia • Unevaluated maternal cardiac arrhythmia • Chronic bronchitis • Poorly controlled type I Diabetes • Extreme morbid obesity • Extreme underweight (BMI<12 kg/m2) • History of extremely sedentary lifestyle • IUGR in current pregnancy • Poorly controlled hypertension • Orthopedic limitations • Poorly controlled epilepsy • Poorly controlled hyperthyroidism • Heavy smoker

3. Which exercises are safe in pregnancy?

Table 3 lists exercises which have been studies and have been found to be safe in pregnancy. Contact sports like basketball, boxing, hockey and football are unsafe in pregnancy and should be avoided. Activities which carry a high risk for fall, eg off road cycling, gymnastics, horse riding and skiing should not be done. Scuba diving and skydiving are also unsafe in pregnancy.

Table 3: Types of exercises found to be safe in Pregnancy

• Walking • Swimming • Stationary cycling • Aerobic exercises • Yoga adapted for pregnant women • Dancing • Stretching exercises • Resistance exercises including weights • For previously active women: • Running or jogging • Racquet sports • Strength training

4. How much should a pregnant woman exercise?

Most RCTs recommend that exercise can be started in the first pregnancy and that each session should last for 30-60 minutes. The minimum recommended frequency is 3 to 4 times a week and it can even be daily and should continue till delivery. ACOG recommends that women should take care of hydration before and during exercise; they should be able to carry a conversation during exercise and they should avoid lying on their backs for a prolonged period.

5. Postpartum

Women should be encouraged to resume physical activity as soon as possible following delivery. The intensity and duration of activity will be variable depending on mode of delivery and whether there are any complications. Pelvic floor exercises should be initiated immediately. It is recommended that women breastfeed before each exercise session.

Conclusion

Health professionals should actively encourage women to exercise in pregnancy as it is associated with significant decrease in maternal and perinatal adverse outcomes. Pregnancy may indeed be an ideal time to initiate lifestyle modifications in women who have been previously sedentary.

Recommendations for safe and effective exercise in pregnancy

- In the absence of obstetric and/or medical contraindications, exercise and an active lifestyle is safe and beneficial in pregnancy.
- Exercise is safe even in the first trimester; and can be started right from conception and should be continued till delivery or till the time the woman finds it tolerable.
- The woman should aim at 3-4 sessions in a week with each session lasting for 30-60 minutes. The number of sessions can even be daily if she is comfortable.
- The intensity of exercise should be such that the woman's heart rate should be less than 60-80% of age predicted maximum maternal heart rate (usually not exceeding 140 beats per minute).
- The self-reported intensity of workout should be 'moderate' (12-14 on Borg scale which is a 15-category scale from 6-20 to measure the level of perceived exertion: light exercise 6-11, 13 somewhat hard, 19 extremely hard; Borg 1982)
- Exercise in pregnancy should preferably be done under supervision, if available.
- Exercise should be resumed after delivery as soon as possible.

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Nutritional Needs during Pregnancy- An introduction

Ashok Kumar

Indian women are exposed to various challenges to their health since a long time. One of them is nutritional challenge. Approximately 51% of the Indian women of reproductive age group have anemia (Global Nutrition Report 2017).

In a cross-sectional study of 255 healthy women, aged 20–69 years, the daily dietary intake of energy, protein, fat, and calcium and the amount of physical activity were assessed.[1] Daily dietary intakes of the subjects were as follows: energy, 1563 ± 267 kcal; protein, 48.7 ± 8.7 g; fat, 31.3 ± 9.3 g; and calcium, 543.7 ± 161.3 mg. Diets were typically cereal based with a very low intake of protective foods such as milk and milk products, flesh foods, fish, fruits, and vegetables. Animal sources of protein were consumed irregularly. The daily intakes of energy, protein, and calcium of postmenopausal women were significantly lower than that of premenopausal women (1487 ± 260 kcal, 46.4 ± 9.3 g, and 496.1 ± 169.3 mg, and 1609 ± 262 kcal, 50.1 ± 8.1 g, and 572.5 ± 149.6 mg, respectively; P=0.001). There was no difference in the intake of dietary fat of pre- and postmenopausal women.[1] Mean dietary calcium intake in 251 women during pregnancy was found to be 312.84±204.63 mg/d (85.71–873.43).[2]

Indians from low-income groups subsist on diets that have inadequate calcium coupled with too few calories, proteins, and micronutrients.[3] The mean daily intakes of energy and protein were below the recommended dietary allowance (RDA) of 2225 kcal/day and 50 g/day, respectively, for these women. The calcium intake of the participants was only low as compared to the RDA of 800– 1000 mg/day, which is accepted worldwide. The RDA of daily calcium intake is 400 mg/day for Indian adults (both sexes), and the RDA for calcium has not been established for menopausal women in India.[4] The major part of this dietary calcium came from plant sources, which are known to have low bioavailability. Inhibitors of calcium absorption such as phytates and oxalates are abundant in the vegetarian diet and retard the absorption of dietary calcium. Moreover, absorption of calcium could be hampered by vitamin D deficiency as this is the major factor influencing absorption of calcium from the gut. A study by Vupputuri et al, revealed that 60% of healthy Asian Indian adults living in Delhi had 25(OH)D values < 9 ng/ml and 94.3% had serum 25(OH) concentrations suggestive of vitamin D deficiency, <20 ng/ml, which is significantly lower than the recommended vitamin D level, i.e. > 32 ng/ml.[5]

Foods rich in calcium such as milk and dry fruits are expensive and not available to this population. Therefore, age-related failing absorptive power along with poor quality of diet aggravates the situation. The intake of fat was not below the RDA of 20 g/day because of the eating habits and cooking patterns practiced in North India. [1]

It is important to eat right to get right nutrition in these special months of pregnancy. Nutritional needs of the mother increase during pregnancy. A pregnant woman requires about 350 extra calories per day, which translates to one additional meal. Either low or excessive weight gain are harmful to the pregnant women and as well as the developing fetus. Nutritional needs during pregnancy include carbohydrates, proteins, and fats. In addition, Indian pregnant women also need a daily vitamin to obtain some of the nutrients that are hard to get from foods alone, such as iron and folic acid. The various Indian food sources for a healthy pregnant woman includes milk and milk products, pulses, cereals, nuts and whole grains, fruits and vegetables, fish meat and poultry, liquids in any forms (water, fruit juices etc) & fats.

A daily supplementation with 2 grams of calcium during pregnancy significantly reduced the risk of pre-eclampsia and preterm labor in women with a baseline daily dietary calcium intake of less than 1000 mg.[2] Cochrane review also concluded that the greatest reduction in risk of pre-eclampsia after calcium supplementation was found to be for women at high risk and those with low baseline dietary calcium intake.[6]

Therefore, nutritional counseling should start before attempting to get pregnant. The body weight should be as close as possible to the recommended weight for a given height (Body Mass Index) as being overweight or underweight can affect babies' growth and development.

To summarize, a healthy diet during pregnancy should contain the right combination and balance of nutrients. Food should be rich in fiber (fiber 25 g/1000 kcal) like whole grain cereals, pulses and vegetables, to avoid constipation. Excess intake of beverages containing caffeine like coffee and tea, consumption of alcohol, tobacco chewing and smoking must be avoided. Wrong food beliefs and taboos should be discouraged. In addition, a pregnant woman should undergo periodic regular antenatal check-up for weight gain, blood pressure and anemia. Adequate intake of a nutritious diet is reflected in optimal weight gain during pregnancy (10 to 12 kg) by the expectant woman.

In view of the fact that nutrition plays an important role in pregnancy, the following sections provides a ready reference of the nutritional needs of Indian pregnant women.

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Optimum Nutritional Diet before, during & after Pregnancy

Kavita Agarwal

1. Pre-conception diet

Adequate nutrition is required during pregnancy but ideally, adopting a healthy eating plan before pregnancy is best.

1.1 What you should eat pre-conception to prepare your body for pregnancy?

1. **Folic acid:** 400-600mg daily is required to minimize the risk of birth defects. Fortified whole grains, fortified cereals, dark green leafy vegetables like collard, turnip, spinach, lettuce, cabbage, kale, and Swiss chard and citrus fruits- orange, strawberry, lemon, mango, tomato, grapefruit, kiwi, melon are great sources of folate. Other sources of folic acid are legumes, such as split peas, red and white kidney beans, black or lima beans, black-eyed peas, chick peas.
2. **Complete protein** (has all essential amino acids): improve egg quality and pregnancy rates. Diet should have 25% or more protein and 40% or less carbohydrates. Whole eggs, egg whites, white meat poultry, fish, beans, legumes, soy products. Eat whole soy products as the processed versions are not healthy and tend to be higher in sodium.
3. **Calcium:** Calcium is crucial for the developing skeleton of the fetus and it takes time to raise calcium levels in the body. Milk, cheese, yogurt, cream soups, and puddings, green vegetables, beans, dried peas, Fish (with bones), seafood, tofu, legumes, kale, broccoli are rich in calcium and should be included in preconception diet.
4. **Iron:** Iron deficiency anemia is common in women of reproductive age and increases risk of preterm delivery, low birth weight babies and many pregnancy complications. Green leafy vegetables-collard, turnip, spinach, lettuce, cabbage, whole grains- bread, cornmeal, cereal, oatmeal, lean protein- beef, seafood, poultry are rich sources of iron.
5. **Omega-3 Fatty Acids** 1,000 – 2,000 mg daily which is about 2-3 ounces of low mercury fish, 2 tablespoons of walnuts or flaxseeds or chia seeds. Flax seeds and chia seeds are great in smoothies, yogurt, on salads, or make a mix with whole grain cereal, dried fruit and flax seeds. Flaxseed oil or chia seed oil can be used in cooking or can be drizzled on salad.
6. **Fruits and Vegetables:** provide a lot of essential nutrients and antioxidants. Raspberries, blueberries, strawberries have a lot of phytonutrients.
7. **Vitamin C** help fight disease, tooth and bone development, and metabolic processes. Sources of vitamin C are orange, strawberry, lemon, mango, tomato, grapefruit, kiwi, melon, potato, peppers.
8. **Yoghurt** contains probiotics to boost immune system. Yoghurt can be eaten spoonfuls or can be used as a base for dips.
9. **Oysters** have high levels of zinc (Recommended dietary allowance is 8mg daily) which is vital for sexual growyh and maturation.

1.2 What you should avoid when you're trying to get pregnant

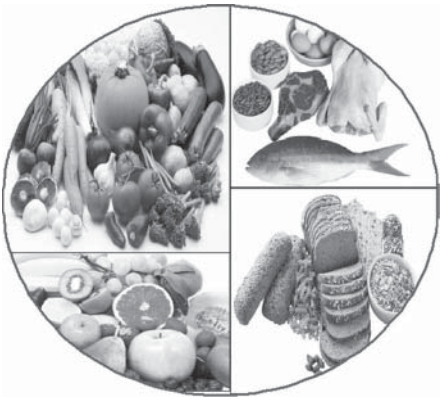
1. **High-mercury fish:** According to the American Pregnancy Association,"FDA guidelines state that no more than 12 oz of low mercury fish such as salmon should be consumed weekly. 'Highest' mercury fish should be avoided and 'high'

mercury fish should be kept to only three 6-oz servings per month."

2. **Soda and fruit juice** should be avoided as they raise blood sugar very quickly and hence can have negative impact on fertility.
3. **Eliminate trans fats**
4. **Abstain from alcohol** as it can lead to mental and physical birth defects.
5. **Non-pasteurized Milk or Cheese** may cause listeria infection which can result in miscarriage and stillbirth

2. Diet during pregnancy

A pregnant woman with normal body mass index needs to consume need to consume an **extra 300 calories** a day. If woman has twin pregnancy, she needs 600 extra calories per day. Total calorie requirement in 1st trimester is 1800 calories, 2nd trimester is 2200 calories/ day and 3rd trimester is 2400 calories/day. Diet during pregnancy is to ensure that mother and baby receives adequate nutrition. For creating a healthy diet during pregnancy, a variety of food groups, including fruits and vegetables, breads and grains, protein sources and dairy products are required.



2.1 Food Groups

2.1.1 Breads and Grains: A pregnant woman should consume minimum 6 servings of grains daily, at least 3 servings of those grains should be whole grains. Breads and grains have essential carbohydrates which are the main source of energy for pregnancy. Whole grain and enriched products provide important nutrients such as iron, B Vitamins, fiber and some protein. Fortified bread and cereal provide required amount of folic acid. **About 175g per day carbohydrate intake is recommended.** Whole grain breads, cereals, crackers, and pasta provide fiber, which is very important during pregnancy.

2.1.2 Protein: Protein is required especially in the second and third trimesters. Protein rich foods include meat, chicken, lean beef, lamb, poultry, fish and other sea food, milk, eggs, nuts and legumes- split peas, red and white kidney beans, black beans, black-eyed peas, chick peas. **About 71grams of protein per day is recommended**.

2.1.3 Fruits and Vegetables: Fruits and vegetables contain many important nutrients especially, Vitamin C, iron and Folic Acid. Pregnant women need at least **85 mg of Vitamin C and 600mcg of folic acid daily**. **A daily intake of 27 milligrams of iron is ideal during pregnancy**. Fruits such as oranges,

grapefruits and honeydew are rich in vitamin C. Include at least one citrus fruit (orange, grapefruit, tangerine) each day because citrus fruits are rich in vitamin C. Dark green (broccoli, kale, spinach), orange (carrots, sweet potatoes, pumpkin, winter squash), yellow (corn, yellow peppers), and red (tomatoes, red peppers) vegetables should be chosen.

2.1.4 Dairy Products: Milk, cheese, yogurt, cream soups, and puddings are good sources of calcium. At least **1000 mg of calcium is recommended** to support a pregnancy. Choose low fat or non-fat dairy products.

Table 1: My plate for Pregnancy

Food groups	Recommended servings	1 serving equals
Grains	6 -11servings	1 serving equals: • 1 slice of whole-grain bread, • ½ cup cooked cereal, rice, or pasta
Protein	2-3 servings	One serving equals: • 2-3 oz. cooked lean meat, poultry, or fish. • 2 eggs. • 1cup cooked beans • ¼ cup nuts.
Dairy	3 – 4 servings	One serving equals: • 1 cup milk or yogurt. • 1 ½ ounces of natural cheese such as cheddar or mozzarella
Vegetables	3-5 servings	One serving equals: • 1 cup of salad greens, • ½ cup of other cooked or raw vegetables.
Fruits	2-4 servings	One serving equals: • 1 medium apple, banana, or orange. • ½ cup chopped, cooked, or canned fruit. • 1/4 cup dried fruit such as raisins.

The new food guide, USDA's MyPlate (Table 1), was introduced in 2010, as the new guidelines for proper dietary nutrition. These guidelines, developed by the USDA in conjunction with the Department of Health and Human Services are designed to serve as the "cornerstone of Federal nutrition policy and nutrition education activities" (USDA Dietary Guidelines, 2011). Half plate includes whole grains and protein and half plate includes fruits and vegetables.

- **Orange represents the grain group** – "Make at least half your grains whole."

- **Green represents the vegetable group** – "Vary your vegetables."
- **Red represents the fruit group** – "Focus on fruits."
- **Purple represents the protein foods group** – "Go lean with protein."
- **Blue represents the dairy group** – "Get your calcium rich foods."

2.1.5 Fats

Some types of fats like omega 3 fatty acids are required in pregnancy. Fats should make up about 20–35% of total food intake. Most of the fats and oils in diet should be unsaturated fats, such as olive oil, canola, sunflower oil and peanut oil. Limit saturated fats, such as butter and fatty red meats, and avoid trans fats, which have no nutritional value.

2.1.6 **Fibre** and **water** are also essential. Drinking about eight to 12 glasses of fluid a day is recommended. A pregnant woman should eat about 25 grams of fiber daily

Fluids: water, decaffeinated drinks, juices or soups, or even foods.

Fibre: Wholegrain cereals, fruits, vegetables are good sources of fibre. Brown rice, pasta, potatoes in their jackets and wholemeal bread are good options. Pregnant woman should have at least five portions of fruit and vegetables a day.

Three small, but balanced, meals and three light snacks throughout the day ensures that mother and baby's nutritional needs are met. Try to plan meals using three or four of the food groups in each meal.

Example: Breakfast Food group

- Fruit serving: 1 medium banana
- Grain serving: 1 slice whole wheat bread (toasted).
- Meat/meat substitute serving: 1 tbsp peanut butter (on toast)
- Milk serving: 1 – 8 oz glass of 1% milk

2.2 Pregnancy meal: Trimester by Trimester

2.2.1 First trimester

Dishes should be rich in

- **Folate** for baby's developing nervous system
- **Vitamin A** for the development of baby›s organs, circulatory, respiratory and nervous systems and
- **Vitamin B6** to ease nausea

Snacks for first trimester

- Folate rich snacks are fortified breakfast cereals, salads with baby spinach leaves and beetroot, steamed asparagus with dips, oranges, or a small glass of orange juice, cantaloupe or honeydew melon
- Vitamin A rich snacks are slices of ripe mangoes, peaches and papaya added to cereal, soups with carrots, butternut squash or sweet potatoes, egg, cheese

2.2.2 Second trimester

Dishes should be rich in iron (carry oxygen, helps increase blood volume and prevent anemia), calcium (helps in development of baby teeth and bones, reduces risk of hypertension in pregnancy), vitamin D (helps in calcium absorption), magnesium (essential for bones, converts food into energy and regulate body temperature) and omega-3 fatty acids (required for baby brain and eye development).

Snacks for second trimester

- calcium rich snacks are yoghurt or milk-based drink, Dried figs and almonds
- packs of figs and apricots rich in calcium and iron
- snack of sardines fish on toast will give calcium, iron and omega -3 fatty acids
- Glass of milk, a baked potato, or a handful of sunflower or pumpkin seeds are a good source of magnesium

2.2.3 Third trimester

Dishes to provide energy boost, vitamin C, thiamine and vitamin K to heal body well after birth.

Snacks for third trimester

- A slice of whole meal toast with yeast extract and a tomato,
- A bowl of mushroom soup followed by a Satsuma
- Tomatoes in salads or blitz up strawberries, citrus fruits, and kiwi fruit into smoothies.
- B vitamins snacks are low-sugar, high-fibre, fortified breakfast cereals
- Pork is rich in thiamine (grilled sausage or slice of lean ham)
- Beans, brown rice and green vegetables are a good source of thiamine (slice of granary toast with baked beans, beans salad with beans, tomato, cucumber rich in thiamine and fibre)

3. Post Delivery Diet For Indian Mothers

- Good energy diet that should consist of whole grain, dairy products, energy rich nuts, vegetables and fresh fruits.
- A spoonful of *Ghee* or clarified butter should be taken with meals. Pure *Ghee* is high in nutritional content and helps in the recovery of the body.
- The fat consumed should always be healthy ones, like olive oil and canola oil.
- Drink lots of water.
- Any food that is believed to be 'cold' must be avoided. Apart from hot milk, even water is recommended to be served as lukewarm. It should be taken throughout the day and separately in between meals.

A good post delivery diet should be able to provide energy and fight with depression and fatigue.

3.1 Fatigue fighters: Small meals throughout the day.

- **Complex Carbohydrates and Proteins:** options include raisins with oatmeal, milk and high fibre cereals, Whole wheat toast combined with chicken salad, a sliced fruit bowl topped with almonds, pecans and walnuts with some low-fat yoghurt poured over it, whole wheat pita bread and hummus, wholesome mix of assorted dry fruits, seeds, and nuts; but make sure that you do not add those coated with chocolate or sugar.
- **Vitamin B3:** Provides energy boost. It can be obtained from poultry products, like chicken, fishes like salmon, mackerel, lean cuts of beef and pork or dried beans.
- **Vitamin E:** Antioxidant and boost energy. These include nuts, seeds, olives, almonds, asparagus and use vegetable oils as your cooking medium.

3.2 Depression Fighters: These include

Zinc: Have plenty of eggs, fish, oysters, turkey, beef, yoghurt and wheat germ to replenish the zinc reserves.

Vitamin C: Have plenty of citrus fruits, green leafy veggies, raspberries, broccoli, peas, tomatoes, spring onions and turnips.

Omega 3: Get them from sardines, tuna, salmon and herrings, and also from canola oil and walnuts.

Calcium: increase intake of cheese, yoghurt, milk, sesame seeds and sardines along with their bones.

Folic Acid: green leafy vegetables, avocados, the black-eyes peas, grapefruits and orange juices.

3.3 Example of post pregnancy day diet

Dry fruit milk shake

Breakfast: idlis (made of unpolished rice)/ Dosa (multigrain)/bread sandwich.

Fruit juice

A cup of tea in between breakfast and meal

Lunch: hot jeera or pepper rasam with rice, a salad and butter milk rice

Evening: Drinking cup of coconut water, carrot juice, melon or cucumber juice

Dinner: Smaller meal- soup, little ghee and hot rice, some green leafy vegetable curry and curd.

A glass of hot plain skimmed milk.

3.4 Essential part of Indian post pregnancy diet: can be taken in breakfast/ snack

Date Laddu: High in good fat and nutrition.

Methi Laddu: Very high in protein and nutrition content and help in lactation.

Dink or Gondh Laddu: Rich in protein, vital nutrients and helps in speeding up the recovery.

Ajwain Paratha: They aid digestion and improve lactation. *Ajwain* is also known to cleanse the uterus.

Dalia Idli: It is very high in fibre and helps deal with constipation

Harira and Panjiri: Aid lactation and replenish the mother with vital nutrients.

Aliv Kheer: It has a very high vitamin and mineral content.

Ginger Candy: It helps in digestion and is considered to improve the blood circulation and induce high energy levels.

Rava Sheera: It is high in vitamin C, essential fats and fibre.

3.5 Foods to be avoided Post Delivery

- **Candy Bars:** Such high sugar foods only enhance the depression as it only raises the hormone levels that cause that depression. Besides, candy bars contain very high levels of fat, sugar and calories and these candy bars do not have any nutrition that is so important for your body.
- **Fried Food:** They are extremely high in fat and calories. Food that is high in oil content induces fatigue and can also cause mood swings. Such food is also very high in trans-fats.
- **Chips:** They are just calories and full of fat. They have zero nutrition content and only add to your pregnancy weight.
- Stay away from alcohol, caffeine, junk, aerated drinks

These foods are harmful; induce lethargy, depressed feeling and worries regarding weight.

4. Myths and Facts

Myth: A pregnant woman should be eating for two.

Fact: It is true that nutrient needs increase, but energy requirements only increase by about 300 calories per day for the second and third trimester of pregnancy.

Myth: Gaining less weight during pregnancy will make delivery easier.

Fact: Mothers gaining less weight during pregnancy have risk of premature birth.

Myth: If woman gains the right amount of weight during pregnancy, none of it will be fat gain.

Fact: A healthy pregnancy includes fat storage which is used as energy during labor and breast feeding.

Table 2: Nutrition requirements preconception, during pregnancy and breast feeding

Nutrient	Preconception	Pregnancy	Breastfeeding
Calories	Maintain weight	+ 300 calories/day	+500 calories/day
Protein	12-20% calories	20-25% calories	
Carbohydrate	50-60% calories	40-50%	
Fat	<10% calories from saturated fat 10% from polyunsaturated fat	25-35% calories	
Folic acid	400mcg/day	600mcg/day	500mcg/day
Iron	18mg/day	27mg/day	9mg/day

Compiled using information from the following sources

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Micronutrients in Pregnancy

Ashok Kumar

Micronutrients

Micronutrients are dietary components, often referred to as vitamins and minerals, which although only required by the body in small amounts, are vital to development, disease prevention, and wellbeing. Micronutrients are not produced in the body and must be derived from diet. These substances enable the body to produce enzymes, hormones and other substances essential for proper growth and development. Though their daily requirement is small, the consequences of their absence are severe. Iodine, vitamin A and iron are most important in global public health terms; their lack represents a major threat to the health and development of populations the world over, particularly children and pregnant women in low-income countries. Micronutrients include dietary trace minerals in amounts generally less than 100 milligrams/day - as opposed to macro minerals which are required in larger quantities. The micro minerals or trace elements include at least iron, cobalt, chromium, copper, iodine, manganese, selenium, zinc and molybdenum. Micronutrients also include vitamins, which are organic compounds required as nutrients in tiny amounts by an organism[1] as well as phytochemicals.

1. Micronutrients in pregnancy

Pregnancy is associated with increased nutritional needs due to the physiologic changes of the woman and the metabolic demands of the embryo/fetus**.** Daily requirements for many micronutrients during pregnancy are higher to meet the physiologic changes and increased nutritional needs of pregnancy. Multiple micronutrient deficiencies commonly co-exist in pregnant women, especially in less developed nations.[1]

Micronutrient deficiencies result from inadequate intake of meat, fruits and vegetables. Infections can also be a cause. Multiple micronutrient supplementation in pregnant women may be a promising strategy for reducing adverse pregnancy outcomes through improved maternal nutritional and immune status. Good nutritional status prior to conception is also important for a healthy pregnancy. For instance, folic acid supplementation during the periconceptional period (about one month before and one month after conception) dramatically reduces the incidence of devastating birth defects called neural tube defects. Folic acid-iron supplementation is universally recommended during pregnancy. Deficiency of trace elements during pregnancy is closely related to mortality and morbidity in the new born .[2] Deficiencies of specific antioxidant activities associated with the micronutrients selenium, copper, zinc, and manganese can result in poor pregnancy outcomes, including fetal growth restriction, preeclampsia and the associated increased risk of diseases in adulthood, including cardiovascular disease and type 2 diabetes.[3,4,5]

Several systematic reviews of trials examining the effects of maternal multiple micronutrient supplementation have been conducted, but they have had limitations.[6]

The RDA (recommended daily allowance), which is the average daily dietary intake level of a nutrient sufficient to meet the requirements of almost all (97.5%) healthy individuals in a specific life stage and gender group, should be used in the planning of diets for individuals (Table 1).

Table 1: RDA for Micronutrients during pregnancy

RDA for Micronutrients During Pregnancy		
Micronutrient	**Age**	**RDA**
Biotin	14-50 years	30 µg/day (AI)
Folate	14-50 years	600 µg/day[a]
Niacin	14-50 years	18 mg/day[b]
Pantothenic Acid	14-50 years	6 mg/day (AI)
Riboflavin	14-50 years	1.4 mg/day
Thiamin	14-50 years	1.4 mg/day
Vitamin A	14-18 years	750 µg (2,500 IU)/day[c]
	19-50 years	770 µg (2,567 IU)/day[c]
Vitamin B_6	14-50 years	1.9 mg/day
Vitamin B_{12}	14-50 years	2.6 µg/day
Vitamin C	14-18 years	80 mg/day
	19-50 years	85 mg/day
Vitamin D	14-50 years	15 µg (600 IU)/day
Vitamin E	14-50 years	15 mg (22.5IU)/day
Vitamin K	14-18 years	75 µg/day (AI)
	19-50 years	90 µg/day (AI)
Calcium	14-18 years	1,300 mg/day
	19-50 years	1,000 mg/day
Chromium	14-18 years	29 µg/day (AI)
	19-50 years	30 µg/day (AI)
Copper	14-50 years	1 mg/day
Fluoride	14-50 years	3 mg/day (AI)
Iodine	14-50 years	220 µg/day
Iron	14-50 years	27 mg/day
Magnesium	14-18 years	400 mg/day
	19-30 years	350 mg/day
	31-50 years	360 mg/day
Manganese	14-50 years	2 mg/day (AI)
Molybdenum	14-50 years	50 µg/day
Phosphorus	14-18 years	1,250 mg/day
	19-50 years	700 mg/day
Potassium	14-50 years	4,700 mg/day (AI)
Selenium	14-50 years	60 µg/day
Sodium	14-50 years	1,500 mg/day (AI)
Zinc	14-18 years	12 mg/day
	19-50 years	11 mg/day
Choline[e]	14-50 years	450 mg/day (AI)

[a]Dietary Folate Equivalents, [b]NE, niacin equivalent: 1 mg NE = 60 mg tryptophan = 1 mg niacin [c]Retinol Activity Equivalents, [d]Alpha-tocopherol, [e]Considered an essential nutrient, although not strictly a micronutrient

AI - adequate intake

2. Important micronutrients

2.1 Vitamins

2.1.1 Biotin (Vitamin B7 or Vitamin H)

Currently, it is estimated that at least one-third of women develop marginal

biotin deficiency during pregnancy .[7]Although the level of biotin depletion is not severe enough to cause diagnostic signs or symptoms, subclinical biotin deficiency has been shown to cause birth defects in several animal species.[8] The potential risk for teratogenesis (abnormal development of the embryo or fetus) from biotin deficiency makes it prudent to ensure adequate biotin intake preconceptionally and throughout pregnancy. Supplementing biotin (at least 30 µg/day) in the form of a multivitamin that also contains at least 400 µg of folic acid can be a helpful step.

2.1.2 Folic acid

Since these birth defects occur between 21 to 27 days after conception , often before many women recognize their pregnancy, it is recommended that all women capable of becoming pregnant take supplemental folic acid. A recent systematic review of five trials, including 6,105 women, found that periconceptional folic acid supplementation, alone or with other micronutrients, was associated with a 72% lower risk of NTDs.[9] The US Preventive Services Task Force recommends a daily supplement of 400-800 µg of folic acid for all women planning or capable of pregnancy. Several countries have programs of mandatory folic acid fortification to help reduce the incidence of NTDs.

Moreover, folic acid supplementation in the form of a daily multivitamin may be more effective in reducing NTDs than when used alone. Doses of greater than 1 mg/day of folic acid are used pharmacologically to treat hyperhomocysteinemia and to prevent reoccurrence of NTDs. Women who have had a previous NTD-affected pregnancy may be advised to consume up to 4 mg/day (4,000 µg/day) of folic acid if they are planning a pregnancy. Inadequate folate status may also be linked to other birth defects, such as cleft lip, cleft palate, and limb malformations, but the support for these findings is not as clear or consistent as the support for NTDs.[9]

Impaired folate status during pregnancy may also be associated with other adverse pregnancy outcomes. Elevated blood homocysteine levels, considered an indicator of functional folate deficiency, have been associated with increased risk of preeclampsia, premature delivery, low birth weight, very low birth weight (<1,500 grams), NTDs, and stillbirth.[10] In the developing world, the incidence of megaloblastic anaemia is considerably higher- approximately 25% of women with anemia during pregnancy. It can due to deficiency of Folate or Vitamin B12.Thus, it is reasonable to maintain folic acid supplementation throughout pregnancy, even after closure of the neural tube, in order to decrease the risk of other potential problems during pregnancy.

2.1.3 Riboflavin (Vitamin B2)

The Food and Nutrition Board of the Institute of Medicine recommends that all pregnant women consume 1.4 mg of riboflavin daily. Riboflavin deficiency has been implicated in preeclamsia. Although the specific causes of preeclampsia are not known, decreased intracellular levels of flavocoenzymes could cause mitochondrial dysfunction, increase oxidative stress, and interfere with nitric oxide release and thus blood vessel dilation.

2.1.4 Vitamin A

Forms of vitamin A, known as retinoids, are involved in the regulation of gene expression, cellular proliferation and differentiation, growth and development, vision, and immunity. The retinoids, retinol and retinoic acid, are essential for embryonic and fetal development; for example, retinoic acid functions in forming

the heart, eyes, ears, and limbs.[11] Vitamin A deficiency during pregnancy has been linked to impaired immunity, increased susceptibility to infection, and increased risk of maternal morbidity and mortality.[12] Vitamin A deficiency may exacerbate iron-deficiency anemia, which is relatively common during pregnancy, because co-supplementation with vitamin A and iron seems to ameliorate anemia more effectively than either micronutrient supplement alone.

Although normal embryonic and fetal development require sufficient maternal vitamin A intake, consumption of excess preformed vitamin A during pregnancy has been demonstrated to cause birth defects. Pregnant women must avoid multivitamin or prenatal supplements that contain more than 1,500 µg (5,000 IU) of vitamin A. Moreover, pharmacological use of retinoids by pregnant women causes serious birth defects; thus, tretinate, isotretinoin and other retinoids should not be used during pregnancy or if there is a possibility of becoming pregnant.

2.1.5 Vitamin B6

The RDA for vitamin B6 during pregnancy is 1.9 mg/day. Supplementation with high-dose vitamin B6 may help mitigate nausea and vomiting in pregnancy (commonly called "morning sickness"). Results of two double-blind, placebo-controlled trials that used 25 mg of pyridoxine every eight hours for three days [13]or 10 mg of pyridoxine every eight hours for five days [14] suggest that vitamin B6 may be beneficial in alleviating morning sickness.

2.1.6 Vitamin B12

Inadequate dietary intake of vitamin B12 causes elevated homocysteine levels, which have been associated with adverse pregnancy outcomes, including preeclampsia, premature delivery, low birth weight (<2,500 grams), very low birth weight (<1,500 grams), neural tube defects (NTDs), and stillbirth.[15] Moreover, low serum levels of vitamin B12 during pregnancy have been directly linked to an increased risk for NTDs , and there is some concern that folic acid supplementation during pregnancy may mask the clinical diagnosis of vitamin B12 deficiency. For these reasons, adequate vitamin B12 intake during pregnancy (RDA=2.6 µg/day) is important. Because vitamin B12 is found only in foods of animal origin, vegans and lacto-ovo vegetarians are prone to suffer from vitamin B12 deficiency, making its supplementation even more important in countries like India.

2.1.7 Vitamin C, D, E and K

Despite of the fact that India is a vast tropical country extending from 8.4^0 N latitude to 37.6^0 N latitude where ample of sunlight is available throughout the year, nearly 42 % of the pregnant women in northern India were deficient of 25(OH)D concentrations 10 ng/ml [5]. In a study from Delhi, the prevalence of Vitamin D deficiency during pregnancy has been found to be 93.5 % (391/418) which is a matter of great concern. These women may develop severe deficiency of vitamin D, if not treated. Severe vitamin D deficiency among pregnant patients was 34.44 % (144/418). Insufficient levels of vitamin D during pregnancy were 59 %, and only 6.45 % had adequate levels of vitamin D. The mean serum 25(OH)D level in severe deficient group was 7.10 ± 1.49 ng/ml, insufficient group 18.35 ± 6.37 ng/ml, and adequate group 38.90 ± 4.22 ng/ml.[16]

Oxidative stress caused by free radicals has been implicated in many studies of the etiology of preeclampsia. Because ascorbic acid and vitamin E inhibit free radical formation, a double-blind randomized trial was conducted in 283 women

who had either a previous history of pregnancy complications or an abnormal ultrasound.[17] The supplement provided 1000 mg ascorbic acid and 400 IU vitamin E daily from week 16–22 of pregnancy, and resulted in a 76% reduction in preeclampsia and a 21% reduction in indicators of endothelial activation and placental dysfunction.

2.2 Minerals

2.2.1 Iron

The RDA is 27 mg/day for pregnant women of all ages compared to 15-18 mg for nonpregnant women. The World Health Organization estimates that the worldwide prevalence of anemia among pregnant women is 42%; iron deficiency is the primary cause of anemia during pregnancy.[18]

2.2.2 Zinc

It was estimated in 2002 by the World Health Organisation that suboptimal zinc nutrition effected nearly half the world's population.[19] During pregnancy, zinc is also used to assist the fetus to develop the brain and also to be an aid to the mother in labour. Alteration in zinc homeostasis may have devastating effects on pregnancy outcome, including prolonged labour, fetal growth restriction, embryonic or fetal death.[20] Zinc deficiency has been associated with preeclampsia since the 1980s including adolescent pregnancies.[21] It is important to note that supplemental levels of iron (38-65 mg/day of elemental iron), but not dietary levels of iron, may decrease zinc absorption.

2.2.3 Magnesium

Maternal magnesium deficiency has been associated with premature labor and has also been implicated in the pathogenesis of Sudden Infant Death Syndrome (SIDS).[22] Magnesium is believed to relieve cerebral blood vessel spasm, increasing blood flow to the brain and hence has a unique role in management of eclampsia and preeclampsia.

2.2.4 Iodine

Iodine requirements are increased by more than 45% during pregnancy. Adequate intake of iodine is needed for maternal thyroid hormone production, and thyroid hormone is needed for myelination of the central nervous system and is thus essential for normal fetal brain development.[23] Maternal iodine deficiency has been associated with increased incidence of miscarriage, stillbirth, and birth defects. Severe iodine deficiency during pregnancy can result in congenital hypothyroidism and neurocognitive deficits in the offspring.[23] A severe form of congenital hypothyroidism may lead to a condition that is sometimes referred to as cretinism and result in irreversible mental retardation.. Even mild forms of maternal iodine deficiency may have adverse effects on cognitive development in the offspring, and iodine deficiency is now accepted as the most common cause of preventable brain damage in the world.[23] Thus, adequate intake of the mineral throughout pregnancy is critical. According to public health experts, iodisation of salt may be the world's simplest and most cost-effective measure available to improve health. International Federation of Gynecology and Obstetrics (FIGO)-2015 states that that even with use of iodized salt and eating seafood 2-3 days per week, a woman's daily iodine intake would be approximately half the amount recently recommended during pregnancy and lactation.[24]

2.2.5 Chromium

Chromium is known to enhance the action of insulin; therefore, several studies

have investigated the utility of chromium supplementation for the control of blood glucose levels in type 2 diabetes. However, its use in gestational diabetes is not well studied and more RCTs are needed.

2.2.6 Others

Copper is an essential cofactor for a number of enzymes involved in metabolic reactions, angiogenesis, oxygen transport, and antioxidant protection, including catalase, superoxide dismutase (SOD) and cytochrome oxidase. Copper is essential for embryonic development.[25] Maternal dietary deficiency can result in both short-term consequences, including early embryonic death and gross structural abnormalities, and long-term consequences such as increased risk of cardiovascular disease and reduced fertilization rates.[26]

Selenium and manganese are antioxidant trace elements important for various body functions although at present sensitive biomarkers of exposure and nutritional status are not available other than some estimates from blood concentrations.

3. Indian Scenario

In India malnutrition has been called '**The Silent Emergency'**. The burden of reproductive and childhealth nutrition is greater than any other country, with 1.8 million deaths among children under 5 years and 68,000 deaths among mothers, and 52 million children who are stunted in the year 2008.[27] According to the National Family Health Survey 3carried out in 2005-06, 58% of Indian pregnant women are anaemic. Concurrent deficiencies of micronutrients are well documented among young pregnant women and young children and are a result of poor- quality diets, high fertility rates, repeated pregnancies, short interpregnancy intervals, increased physiological needs, as well as inadequate health systems with poor capacity, poverty and inequities, and sociocultural factors such as early marriage and adolescent pregnancies and some traditional dietary practices. Although iron deficiency is highly common, there is often at least one other deficiency that co-exists.[28] Pregnant women in India have coexisting deficiencies of zinc, iron, folate, and vitamin A along with a deficit in the intake of energy, protein, and fats. Deficiency of vitamin B12 is also considered to be highly prevalent in India and the metabolic signs of vitamin B12 deficiency have been reported in 75% of adult men and women from urban areas of West India.[29]

Hence, micronutrient supplementation in pregnancy is an issue which needs to be taken care of at the grassroot levels to prevent the epidemic of malnutrition in our country.

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Nutrition Guide for Special Situations: Gestational Diabetes, Multiple Pregnancy, Bariatric Surgery

Pikee Saxena

1. Gestational diabetes (GDM)

Healthy eating in gestational diabetes helps to control blood glucose level throughout pregnancy, provide adequate nutrition to the mother and the baby without developing hypoglycemia. It also helps to maintain appropriate weight gain during the pregnancy.

1.1 Weight gain and calorie intake recommendation for women with GDM

The Body Mass Index (BMI) is calculated by using pre-pregnancy weight (PPW) and height by calculating weight in kg/height in m^2 (Table-1). Calorie needs based on BMI, rate of weight gain and physical activity level are calculated. Food intake may be adjusted as the pregnancy progresses based on weight gain and blood glucose levels. The calorie requirement for GDM is 30 kcal/kg ideal body weight (pre-pregnant weight), 36 kcal/kg ideal body weight in the second trimester, and 38 kcal/kg ideal body weight in the third trimester may be used as a starting point. For the majority of women with GDM, a calorie level of 2,200–2,400 kcal is a good starting point.[1,2]

Table1: Classification of BMI in pregnant women

Pre-pregnancy weight	BMI (kg/m^2)	Total weight gain range (kg)
Normal weight	18.5 to 24.9	11.5 to 16
Under weight	Less than 18.5	12.5 to 18
Over weight	25 to 29.9	7 to 11.5
Obese (include all classes namely grade I, II, and III)	Equal/ more than 30	5 to 9

1.2 Diet assessment

The dietary reference intakes for all pregnant women, including those with GDM, recommends a minimum of 175g carbohydrate (CHO), a minimum of 71g protein (or 1.1g per kg per day protein) and 28g fiber. Dietary requirement of a diabetic pregnancy is not different from required daily allowances for a normal pregnancy.

1.2.1 Carbohydrates

Carbohydrate foods are broken down to glucose in the body and cause blood glucose levels to rise. Many foods contain carbohydrates, including grains, beans, fruit, milk and some vegetables. Therefore, it is important to balance the quantity of carbohydrate food intake throughout the day. Complex carbohydrates with lower glycaemic index are preferred. Diet should include high fiber foods and appropriate portion size to maintain and control total amount of carbohydrate.

Counting carbohydrates: Carbohydrate foods have the greatest effect on blood glucose. It is helpful to plan meals by balancing carbohydrate foods at each meal. This will help maintain blood glucose levels within the target range. Thus we can check how many carbohydrates are eaten at each meal by recording the carbohydrate grams or carbohydrate choices on a food record.

Fifteen (15) grams of carbohydrate = 1 carbohydrate choice. Therefore, 30 grams of carbohydrate= 2 choices, 45 grams of carbohydrate = 3 choices, etc.

The diet plan includes:

- Food intake throughout the day may be adequately spread out into three major meals and 2-3 snacks. There should be a gap of 2-3 hours between different meals as taking a huge amount of food at one time may raise the blood glucose to very high levels.
- 175 grams carbohydrate or 12 carbohydrate choices per day should be maintained (approximately 700 kcals from carbohydrates).
- Snacks should contain no more than one or two carbohydrate choices (15-30 grams of carbohydrate) and major meals no more than three to four carbohydrate choices (45-60 grams of carbohydrate).
- Foods high in carbohydrate such as Indian sweets, pancakes with syrup, sweets, honey, jams, sweetened cereals, doughnuts, cinnamon rolls, muffins should be avoided.
- Breakfast items that contain protein such as cottage cheese, eggs, lean meats, peanut butter, cheese, low-fat yogurt, dalia, poha, a slice of whole grain toast with peanut butter or a small corn tortilla with beans should be choosen.
- Avoid fruit juice. Drink water!
- Monitor blood glucose response to unsweetened cereals and fruit.
- The FDA has concluded the safety of six high-intensity sweeteners [saccharin, aspartame, acesulfame potassium (Ace-K), sucralose, neotame and advantame] when consumed within the acceptable daily intake by the general population, including pregnant women. Steviol glycosides and Luo Han Guo (monk fruit) extracts are also generally recognized as safe when consumed within the acceptable daily intake.

1.2.2 Fats

Saturated fats increase maternal triglycerides, which may result in macrosomia (large for gestational age) in the baby. Foods lower in saturated fat should be chosen. If weight gain is excessive, a lower-fat diet overall may help to slow down the rate of weight gain since fats have more than twice as many calories per gram as carbohydrate or protein.

Certain tips for fat intake

- All the fat from the chicken or turkey skin should be removed properly.
- Bake, roast, broil, grill or boil meats instead of frying or adding fat.
- Cook with small amounts of oil if needed**,** and vegetable oils such as canola or olive oil should be used. Try to change the oil being used and pay attention to saturated or unsaturated fatty acid content.
- Low-fat or nonfat cheese should be chosen because they contain less saturated fat.
- Low-fat or nonfat milk and yogurt should be chosen.
- Minimal amounts of ghee or butter should be used.
- Avoid adding sauces or gravies to meats, vegetables, pasta and other foods. Flavoring with herbs and spices should be taken instead.
- Chips, cakes and cookies should be replaced with whole grain pretzels or low-fat crackers.
- Food labels for processed foods that contain high amounts of fat and refined sugar should be checked.

1.2.3 Fibre

- High-fiber foods help to control blood glucose levels because they slow digestion and absorption of nutrients.
- Whole-grain foods are high in nutrients and fiber. Food labels "made with 100% wholegrain" for bread, crackers, tortillas and pasta should be used.
- Bran cereal, brown rice or bulgur should be consumed. Whole wheat or other whole grain flours in cooking and baking should be used.
- Fresh fruits are high in nutrients and fiber, but also are carbohydrates thus it is better to use them over fruit juices. Oranges, grapefruit and tangerines are high in Vitamin A and Vitamin C, important nutrients for pregnancy.
- Dark green, deep red, orange and deep yellow vegetables, such as spinach, broccoli, romaine, carrots, chilies and peppers are high in nutrients are needed for pregnancy.

1.2.4 Protein

- Bean Protein foods do not increase blood glucose levels. Three servings daily should be taken.
- Poultry and lean cuts of beef or pork (90 percent or leaner) contain less saturated fat.
- Nuts and seeds are good sources of protein that are low in saturated fat.
- Eggs (fully cooked) are a good source of protein and can easily be added to many meal plans.
- Fish is usually low in saturated fat. However, amount and type of fish must be monitored due to health risks of mercury levels found in various fish.
- Cheese, peas and other legumes are also good source of protein.

1.2.5 Water and fluids

At least 8-10 glasses of water should be consumed every day.

1.2.6 Calcium

Milk is an excellent source of calcium, and low-fat milk will provide fewer calories. Milk also contains protein and carbohydrate. Other sources of calcium include cheese, yogurt, fortified cereals and other grains, spinach, soybeans, rhubarb, and fortified orange juice.

1.2.7 Additional nutrition

Folic Acid 5mg/day should be advised 3 months before pregnancy to prevent neural tube defects and continue it during first three months.

Low-calorie sweeteners such as Sucralose (Splenda), Aspartame (Equal), Acelsulfame-potassium (Sweet One, Sunette) are considered safe for use during pregnancy(4) provided that they do not exceed the RDA.

Caffeine should not exceed >300 mg/day (two cups coffee/day).

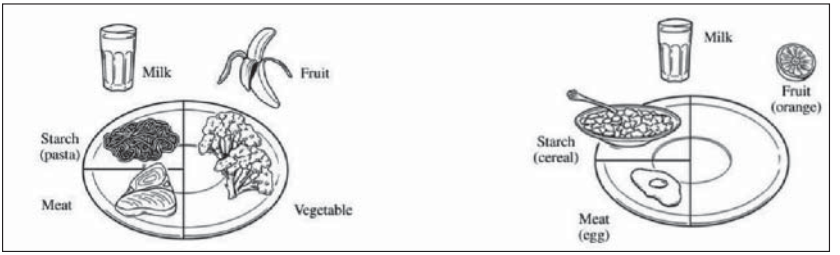
Mercury can damage the unborn baby's nervous system and is found in tilefish, swordfish, king mackerel and shark. Some fishes contain lower levels of mercury including shrimp, salmon, pollock, canned light tuna and catfish. Intake is limited to ≤ 12 ounces/week.

Women should not consume alcohol during pregnancy to prevent birth defects and avoid developmental delays caused by prenatal alcohol exposure.

1.3 Estimating portion size

The 9-inch Plate is a simple, visual method to demonstrate appropriate portions of food on a plate. Breakfast, lunch and dinner meals should have approximately 45 grams of carbohydrate (three choices) each. Meal plan should be adjusted to meet individual needs based on blood glucose response. Carbohydrate at the breakfast meal should be limited to 30 grams (two choices) by eliminating one of the choices such as cereal or fruit.

A 9-inch plate in half should be divided, and then divide one half into two quarters to illustrate what proportions of the plate should be covered by various food groups. For accurate portion sizes, food should be only ½ inch thick on the plate. Non starchy vegetables should cover half the plate for lunch and dinner. Breads, grains or starchy vegetables should cover one quarter. Protein (meat, cheese, eggs) should cover the other quarter. Fruit and milk are represented outside the plate, but must be counted in the total carbohydrates eaten at the meal. If additional food is needed, choose foods from the vegetable and protein groups.



1.4 How to recognize & manage hypoglycemia?

Any pregnant woman on insulin can develop hypoglycemia at any time. Hypoglycemia is diagnosed when blood glucose level is < 70 mg/dl. It is important to recognize symptoms of hypoglycaemia & treat immediately. Early symptoms include tremors of hands, sweating, palpitations, hunger, easy fatigability, headache, mood changes, irritability, low attentiveness, tingling sensation around the mouth/ lips or any other abnormal feeling. Severe symptoms include confusion, abnormal behaviour or both, visual disturbances, nervousness or anxiety, abnormal behaviour. Rarely patient may present with seizures and loss of consciousness

How to manage hypoglycaemia?

Three teaspoonful of glucose powder (15-20 grams) dissolved in a glass of water should be given immediately. After taking oral glucose, she must take rest & avoid any physical activity for 15 minutes. After taking glucose, she must eat one chapati with vegetable/rice/one glass of milk/idli/fruits/anything eatable which is available. If hypoglycemia continues, repeat same amount of glucose and wait.

If glucose is not available, take one of the following: Sugar - 6 TSF in a glass of water/fruit juice/honey/anything which is sweet /any food. Take rest, eat regularly and check blood glucose if possible. If pregnant woman develops >1 episode of hypoglycemia in a day, she should consult any doctor immediately.

1.5 Physical activity during GDM

Regular physical activity for 30 minutes/day, five days/week can help to reduce insulin resistance and prevent excessive weight gain. Actual heart rate should not exceed 140 beats/minute. Yoga with deep breathing exercises and exercise of the upper extremities are also recommended.

Table 4: Summary of more recent recommendations of different organizations on medical nutrition treatment of gestational diabetes mellitus

Organization	Year	Energy	CHO	GI/GL	Fiber	Fat	Protein	Number of Meals	Diet method	Diet Monitoring	Dietician
ADIPS	1998	NR but avoid a severe caloric restriction	NR [a]	NR [a]	NR [a]	NR [a]	NR [a]	NR [a]	NR [a]	NR [a]	Yes
AND	2008	DRI- for overweight and obese, a modest caloric restriction	DRI A minimum of 175 g/day <45%[b]	NR	NR	DRI	DRI	NR	NR	Food records	Yes
ADA	2007	DRI- for overweight and obese, 30% of restriction	DRI A minimum of 175 g/day	NR	NR	NR	NR	3 meals+2-4 snacks	'CHO counting'	Daily Food records	Yes
Endocrine Society	2013	NR for normal weight, under and overweight. For obese approx. 1/3 of restriction with a minimum of 1600-1800 kcal/day	35-45%[b]	NR	NR	NR	NR	3 meals+2-4 snacks	NR	NR	NR
CDA	2013	NR but no hypocaloric diets	40-50%[b]	NR	NR	Upto 40%[b]	NR	3 meals+2-4 snacks	NR	NR	Yes
DDG-DGGG	2014	Based on the following pregnancy body mass index: 35-40kcal/kg For underweight 30-40kcal/kg For normal weight 25-29 kcal/kg For overweight a maximum of 24 kcal/kg for obese or a reduction of 30-33% of daily energy requirement with a minimum of 1600-1800 kcal/day	40-50%[b] 15 to 30 g for breakfast	Avoid high GI foods	30 g/ day	30-35%[b]	20-25%[b] A minimum of 60-80g/day	3 meals+2-3 snacks	German Units to measure CHO	Dietary records	NR
NICE	2015	NR – No dieting (57)	NR	Replace high -GI foods per low -GI foods	NR	NR	NR	NR	NR	NR	Yes

Abbreviations: ADIPS- Australasian Diabetes in Pregnancy Society, AND- Academy of Nutrition and Dietetics, ADA- American Diabetes Association, CDA- Canadian Diabetes Association, DDG-DGGG- German Diabetes Association and German Association for Gynaecology and Obstetrics, NICE National Institute for Health and Care Excellence, CHO- Carbohydrates, GI-Gylcemic Index, GL- Gylcemic Load, DRI- Dietary reference intakes, NR – not reported.

[a] - not reported with conform with the principles of dietary management of diabetes in general

[b] – Percentage of total daily calories

1.6 Role of breastfeeding

Breast-feeding is highly recommended for women with GDM, as it helps in maternal weight loss and also improves fasting blood glucose levels. Breastfeeding also improves the glucose and lipid metabolism in women with GDM and also reduces the risk of type2 Diabetes mellitus. These women have lower maternal BMI, improved biochemical factors during reproductive years, lower incidence of metabolic disorders, breast cancer and ovarian cancer.

Summary of recent recommendations of different organizations on medical nutrition treatment of gestational diabetes mellitus have been given regarding number of meals, carbohydrate, protein, fat, fibre, diet method and diet monitoring. They are shown below as comparison in a Table 4.

2. Multiple Pregnancy

In multiple pregnancy mother needs to take additional nutrition because multiple growing fetuses draw nutrients from maternal resources. This leads to an accelerated depletion of maternal reserves. Weight gain is also important in multiple pregnancy because it lowers the risk of preterm labor and improves birth weight of babies at delivery. Adequate weight gain also helps to build up stores for breastfeeding.

In twin pregnancy, overall weight gain should be 35-45lb with Approximate per week weight gain of 1.5 lbs in the 2nd and 3rd trimester, 4-6 lbs should be gained during the first trimester. In triplet pregnancy, overall weight gain should be about 50lb with approximate per week weight gain of 1.5 lbs throughout pregnancy (Table-2).

Table 2: Recommendations for Total Weight Gain in Twin Pregnancies (Adapted from Institute of Medicine)

Pre-pregnancy BMI*	Recommended Total Weight Gain in Twin Pregnancies		Approximate calories intake
	Kgs	Lbs	
Underweight (<18.5)			4000 calories
Normal (18.5-24.9)	17-25	37-54	3500 calories
Overweight (25-29.9)	14-23	31-50	3250 calories
Obese (> 30)	11-19	25-42	3000 calories

Approximately 150 kcal/day above singleton pregnancy should be consumed in a twin pregnancy, or amount that is consistent with targeted weight gain progress (Table-3).

2.1 Dietary recommendations for multiple pregnancy

Table 3: BMI-Specific Dietary Recommendations for Twin Gestations[9]

BMI Group	Underweight	Normal Weight	Overweight	Obese
BMI Range	<19.8	19.8-26.0	26.1-29.0	>29.0
Calories	4000	3500	3250	3000
Protein (20% of calories)	200 g	175 g	163 g	150 g
Carbohydrate (40% of calories)	400 g	350 g	325 g	300 g
Fat(40% of calories	178 g	156 g	144 g	133 g
Exchange (servings) per day				
Dairy	10	8	8	8
Grains	12	10	8	8
Meat and meat equivalents	10	10	8	6
Eggs	2	2	2	2
Vegetables	5	4	4	4
Fruits	8	7	6	6
Fats and oils	7	6	5	5

Three major and 2-3 minor/snacks meals should be consumed every day with a gap of at least 2 hours between meals for maintaining steady glucose levels throughout the day and for improving growth of multiple fetuses.

2.1.1 Carbohydrate: During the second half of multiple pregnancy, lower maternal serum glucose and insulin concentrations, and higher plasma concentrations of *b*-hydroxybutyrate compared with maternal concentrations in singleton pregnancies, which show that there is rapid depletion of glycogen stores and resultant metabolism of fat between meals and during an overnight fast. Fasting and ketonuria both are associated with an increase in preterm labor and preterm delivery, this phenomenon is termed as "Yom Kippur effect."(10). A reduced glucose uptake from mother to fetus results in slower fetal growth, smaller birth size, and an increased risk of fetal growth restriction. Thus it has been found in studies with both twins and triplets that diet therapy with 20% of calories from protein, but a lower percentage of calories from carbohydrate (40%) for better glycemic control, and a higher percentage of calories from fat (40%), to provide additional calories with less bulk, are most effective.

2.1.2 Iron: Iron-deficiency anemia is associated with preterm delivery. Serum ferritin levels, which are lowered with iron-deficiency and elevated in the presence of infection, have also been associated to prematurity. Iron containing foods include but are not limited to jaggery, apple, lean red meats, chicken, pork, fish, beans, lentils, green leafy vegetables like spinach, raisins, apricot.

Some simple strategies that can be used to increase the body's ability to absorb non-heme iron are: consume iron containing food with vitamin C-rich foods for increasing the absorption of iron; avoid coffee and tea with meals to reduce iron absorption; soak, sprout and ferment which can improve iron absorption by lowering the amount of phytates naturally present in these foods ; use of a cast iron pan; and consume lysine-rich foods like legumes together with iron-rich meals which may increase iron absorption

Table 5: Changes in Maternal Iron Status in Twin Pregnancy[11]

	First trimester	Second trimester	Third trimester
Hemoglobin	12.8 g/dl	11.3g/dl	11.0g/dl
Hematocrit	37.3%	32.8%	32%
Ferritin	56.6g/l	34.3g/l	12.2g/l

2.1.3 Calcium, magnesium and zinc: Calcium decreases the risk of preterm. Magnesium may have a neuroprotective role, particularly for the premature infant, and also an effective therapy for preeclampsia. Maternal zinc level is related to length of gestation, infection, and risk of premature rupture of membranes.

2.1.4 Multivitamins and multiminerals: The fat-soluble vitamins, particularly vitamins A and D, are considered to be toxic during pregnancy.The pediatric and obstetric literatures include case reports of kidney malformations in children whose mothers took between 40,000 and 50,000 IU of vitamin A during pregnancy. Even at lower doses, excessive amounts of vitamin A may cause subtle damage to the developing nervous system, resulting in serious behavioral and learning disabilities in later life. The margin of safety for vitamin D is smaller than any other vitamin. Birth defects of the heart, particularly aortic stenosis, have been reported in both humans and experimental animals with doses as low as 4000 IU, which is 10 times the RDA (Recommended Dietary Allowance) during pregnancy.

2.1.5 Fatty acids: Omega-3 fatty acids, are essential for neurological and retinal development, may be particularly beneficial during pregnancy for both the mother and her developing baby. Mothers with a higher intake of omega-3 fatty acids have significantly lower rates of preterm delivery and low birth weight.

Table 6: Best practise suggestions based on currently available research on nutrition and multifetal pregnancy.[14]

Supplement	≤ 18 years	19 to 50 years
Calcium	2.5 g	2.5 g
Phosphorus	3.5 g	3.5 g
Magnesium	350 mg	350 mg[b]
Vitamin D	50 µg	50 µg
Fluoride	10 mg	10 mg
Niacin	30 mg	35 mg[c]
Vitamin B6	80 mg	100 mg
Folic acid	800 µg	1000 µg[d]
Choline	3 g	3.5 g

3. Bariatric surgery

Bariatric surgery is surgery on the stomach and/or intestines which helps a person with extreme obesity in losing weight. Bariatric surgery is an option for people who have a body mass index (BMI) above 40. Surgery is an option for people with a body mass index between 35 and 40 who have health problems like type 2 diabetes or heart disease. It is of two types- restrictive or malabsorptive surgery. Weight loss is achieved by restricting the size of the stomach with a gastric band or through removal of a portion of the stomach (sleeve gastrectomy or biliopancreatic diversion with duodenal switch) or by resecting and re-routing the small intestine to a small stomach pouch (gastric bypass surgery) which leads to malabsorption.

Bariatric surgery not only promotes weight loss, but it also shows reduces obesity-related co-morbidities.

3.1 Diet Assessment

After bariatric surgery people are recommended to eat taking small bites, dividing food intake into 4–6 meals throughout the day, chewing well in a relaxed manner, and ending meals when feeling "comfortably full" (Table-7).

Table 7: Nutritional recommendations after bariatric surgery

Topics	Recommendations
Eating habits	Frequent small meals throughout the day (4–6 meals/d, according to the post operational stage) should be planned. One should eat slowly and methodically chew food. Foods that can form phytobezoars, such as persimmons and citrus fruit pith should be avoided.
Fluid intake	Sufficient amounts of fluids to maintain adequate hydration (1.5 L/d) should be taken. It is advised to abstain from drinking 15 min before a meal and/or 30 min after the meal. Carbonated beverages should be avoided.
Prevent nutritional Deficiencies	Adequate amount of protein should be taken. A balanced diet and limit consumption of calorie-dense food and drinks (e.g., milkshakes, ice cream, cakes, and cookies) Appropriate dietary supplements should be taken.

3.2 Pregnancy after Bariatric Surgery

Pregnancy after bariatric surgery is a very complex medical challenge. Because the greatest weight loss occurs in the first 12-18 months after surgery, thus it is suggested to wait for at least 12 months prior to conception. This is based on the theory that a pregnancy occurring during a period of malnutrition could lead to adverse outcomes such as low birth weight or malformations. Fertility rates are improved after bariatric surgery because it reduces insulin resistance, decreases androgen level, reduces hirsutism and improves PCOS.

Women after bariatric surgery who become pregnant need to be followed up by a group of specialists including a nutritionist, an educated nursing staff, an obstetrician, an endocrinologist, an internal medicine specialist, and a bariatric surgeon. Most pregnancies after bariatric surgery have successful outcomes with decreased occurrences of gestational diabetes, hypertension and lower birth weight compared with controls. As women after bariatric surgery have increased incidence of nausea, vomiting and malabsorption, these women have higher risk of complications due to nutritional deficiencies (Table 8).

Table 8: Summary of some of the deficiencies and their consequences

Deficiency	Consequences	Dose
Protein	Low albumin levels in mother Fetal growth restriction Reduced liquor Fetal deaths	60g protein/day in balanced diet.
Vitamin K	Fetal cerebral bleeding	There are no recommendations about vitamin K
Vitamin A	Fetal bilateral micropthalmia and permanent retinal damage Bronchopulmonary dysplasia Increased susceptibility to respiratory and diarrhea	5000 IU/day
Vitamin B12	Maternal anemia in pregnancy Low B 12 levels in breast milk Hyperhomocysteinemia-early pregnancy loss, neurobehavioral abnormalities in the infant	3 mcg to 10 mcg in easily absorbed crystalline form or Intramuscular injections in monthly dose 1000 mcg can also be used.
Electrolytes and calcium	Electrolyte disturbances in the baby	It is recommended to increase the intake of 1000 mg of calcium to 2000 mg of calcium citrate with vitamin D (50–150 mcg). The citrate form is preferred as it does not require acidic environment for absorption
Iron	Iron deficiency anemia	40–65 mg daily in ferrous form
Folic acid	Neural tube defects Preterm delivery	Vitamins containing 5 mg of folic acid prior to and during pregnancy
Zinc	Preterm delivery, low birth weight Dermatitis in the newborn	15 mg/day
Magnesium	Fetal growth restriction, preeclampsia	200-1000mg /day
Iodine	Neonatal goitre	250mcg/day

3.3 Weight Gain

According to the Institute of Medicine of the National Academy of Sciences:

- Normal-weight women (BMI of 19.8–26): recommended weight gain is 11.5–16 kg,
- Overweight women (BMI of 26.1–29): recommended weight gain is 7 -9 kg.

3.4 Postpartum

Mothers after bariatric surgery should be encouraged to breastfeed their baby. Breastfeeding should be done for at least 6 months but may be continued for 2 years It is essential to maintain micronutrients supplementation even after delivery and during breastfeeding, to ensure appropriate vitamins and minerals requirement of the neonate and to prevent vitamin B deficiency, which may lead to severe complications including failure to thrive, megaloblastic anemia, and development delays.

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Multidisciplinary Patient Committee

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Cardio Pulmonary Resuscitation in Pregnancy- What does evidence say?

1. **Which obstetric patient needs Cardio Pulmonary Resuscitation?**
   A woman with maternal collapse, who is not responsive and is not breathing or gasping/has no palpable carotid.
2. **What is maternal collapse?**
   Maternal collapse is an acute event involving the cardiorespiratory system & /or brain, resulting in reduced/absent conscious levels & potentially death at any stage of pregnancy & upto 6 weeks postpartum[1].
3. **What should be the first step when a case of maternal collapse is encountered?**
   Shout and tap shoulders of woman from front to check for response[2].
4. **What if the woman is not responsive?**
   - Don't waste time in starting resuscitation. Even if there is nobody around start resuscitation immediately and shout for help[2,3].
   - Turn the woman on her back and quickly and open airway with head tilt and chin lift, at the same look, listen and feel for breathing[2].
   - If there are no sounds or movements of breathing or carotid pulse (do not waste precious time on looking for carotid- maximum time 10 seconds- checking for breathing and carotid pulse can be simultaneous), proceed to high quality chest compressions[2,3]. **NOTE: The focus is more on response of woman and breathing rather than pulse as a trigger to start chest compressions.**
5. **What if the woman has deep infrequent breathing sounds?**
   Agonal breaths are irregular, slow and deep breaths, frequently accompanied by a characteristic snoring sound. They originate from the brain stem, which remains functioning for some minutes even when deprived of oxygen. The presence of agonal breathing can be interpreted incorrectly as evidence of a circulation and that CPR is not needed. Agonal breathing may be present in up to 40% of victims in the first minutes after cardiac arrest and, if correctly identified as a sign of cardiac arrest, is associated with higher survival rates[2]
6. **What are high quality chest compressions?**
   - Compressions should be performed in supine position **(Class I; Level of Evidence C)**[3]
   - Rate of CPR should be 100-120/min **(Class IIa; Level of Evidence C)**[3]
   - The ratio of compressions to ventilation is 30:2 **(Class IIa; Level of Evidence C)**[3].
   - Compression should be given at the lower half of the sternum between the nipples with heel of one hand & the other hand on top with fingers interlocked **(Class IIa; Level of Evidence C)**[3]
   - Push chest hard and fast. It should be compressed at least by 5-6 cm[3].
   - Allow complete recoil of the chest wall **(Class IIa; Level of Evidence C)**[3]
   - Do not bend your elbows when doing chest compressions; doing so will deliver weak, ineffective chest compression **(Class IIa; Level of Evidence C)**[3].
   - The time interval between each compression and relaxation should be approximately the same[3]

- Minimise any interruptions to chest compression (hands-off time) **(Class IIa; Level of Evidence C)**[3]
- If available, use a prompt and/or feedback device to help ensure high quality chest compressions[4].
- Do not rely on palpating carotid or femoral pulses to assess the effectiveness of chest compressions[5].
- Resume compressions without any delay; place your hands back on the centre of the patient's chest (lower part of sternum)[3].
- Ideally the person doing compression should be changed every 2 minutes if there are enough team members so that fatigue does not compromise the quality of compression. This change should be done with minimal interruption to compressions and should be done during planned pauses in chest compression such as during rhythm assessment.

7. **Are chest compressions any different in the pregnant woman?**
   - No.
     Chest compressions are performed in the same way as in a non pregnant person **EXCEPT** that if the pregnant uterus is above the umbilicus, it should be tilted towards the left side with one hand or both hands by the assisting personnel **(Class I; Level of Evidence C)**[3]

     This is to relieve the aortocaval compression effect of the uterus so as to increase the cardiac output and make the compressions more effective (Fig 1). The 15 degree tilt of the patient which was practiced earlier is not recommended any more as it hampers effective compressions[3].

- **REMEMBER…**
  leftward displacement of uterus during CPR either with single hand or with both hands (Class I; Level of Evidence C)[3]

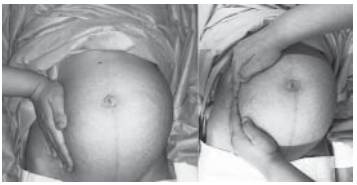

Fig 1: One handed and two handed method to achieve left uterine displacement.

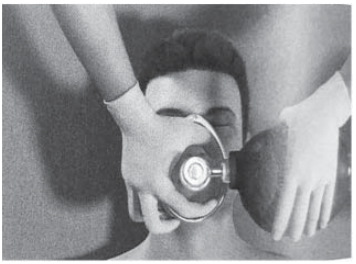

Fig 2: Technique for giving bag and mask ventilation

8. **How and when to defibrillate?**
   - The same protocol for defibrillation should be followed in pregnant patient as in non pregnant **(Class I; Level of Evidence C)**[3]
   - As soon as a defibrillator is available, the self-adhesive pads should be applied to the chest. Do not interrupt compressions during this process. The heart rhythm

will be assessed with the electrodes during a brief pause (less than 5 seconds) in compressions[2].

- If the rhythm is ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT), start defibrillation. All other team members are informed to stand clear of the patient, the fetal monitors and oxygen is placed away and shock is delivered[2,3]. The energy used is the same as for non pregnant patients.
- The patient should be defibrillated with biphasic shock energy of 120 to 200 J **(Class I; Level of Evidence B)** with subsequent escalation of energy output if the first shock is not effective and the device allows this option.
- Restart chest compressions immediately. Do not delay restarting chest compressions to check the cardiac rhythm **(Class IIa; Level of Evidence C)**[3]
- If rhythm is non shockable- asystole or pulseless electrical activity, do not defibrillate but continue CPR[2,3]
- Using a manual defibrillator it is possible to reduce the pause between stopping and restarting of chest compressions to less than 5 seconds[3].
- If staff cannot use a manual defibrillator, use an automated external defibrillator (AED). Switch it on and just follow the instructions

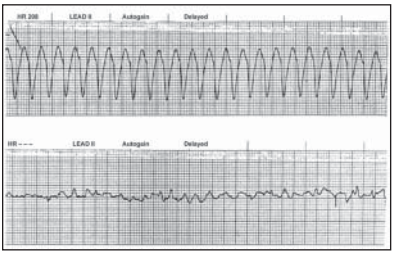

Fig 3a: Shockable rhythm

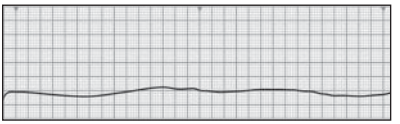

Fig 3b: non-shockable rhythm

9. **How and in what ratio should the ventilation be started?**
   - Use a bag and mask to start ventilation and supplemental oxygen should be added as soon as possible. A tight seal should be formed over the nose and with one hand such that a 'C' is formed (Figure 2).
   - The other hand should be used to inflate the bag. The inspiratory time should be around 1 second. Give enough volume to produce a visible rise of the chest wall. Avoid rapid or forceful breaths[2,3].
   - A member of the team should perform bag-mask ventilation with 100% oxygen flowing to the bag at a rate of at least 15 L/ min **(Class IIb; Level of Evidence C)**.
   - Two-handed bag-mask ventilation is preferred **(Class IIa; Level of Evidence C).**
   - The compression ventilation ratio should be no more than 30:2 **(Class IIa; Level of Evidence C)**[3]
   - Once advanced airway is in place the breaths should be given at a rate of 10/ minute and compressions at 100-120/minute[3].
   - Hypoxemia should always be considered as a cause of cardiac arrest. Oxygen reserves are lower and the metabolic demands are higher in the pregnant patient

compared with the nonpregnant patient; thus, early ventilatory support may be necessary **(Class I; Level of Evidence C)**

10. **When should the intravenous access be established and which drugs should be given?**
    - If there is no access, IV access should be established once resuscitation is underway so as to deliver the drugs.
    - Injection adrenaline 1mg IV, every 3-5 minutes **(Class IIb; Level of Evidence C).**
    - For refractory (shock-resistant) ventricular fibrillation and tachycardia, amiodarone 300 mg rapid infusion should be administered with 150-mg doses repeated as needed **(Class IIb; Level of Evidence C).**

11. **What are the causes of Cardiac arrest in a pregnant woman?**
    As soon as possible a quick evaluation to determine the cause of cardiac arrest should be done. The causes of cardiac arrest in pregnancy can be remembered by mnemonic **BEAU CHOPS**
    - **B**leeding
    - **E**mbolism:
      - Pulmonary
      - Amniotic fluid
    - **A**nesthetic Complication
    - **U**terine Atony
    - **C**ardiac disease
    - **H**ypertension:
      - Preeclampsia
      - Eclampsia
    - **O**ther:
      - Mg toxicity
      - Other differential diagnosis of standard ACLS i.e 5 Ts and 5 H
    - **P**lacenta abruptio/previa
    - **S**epsis.

➢ Immediately after resuscitation steps should be taken to identify and treat the underlying cause.

12. **What is the role of perimortem cesarean delivery (PMCD)/resuscitative hysterotomy?**
    - During cardiac arrest, if the pregnant woman (with a fundus height at or above the umbilicus) has not achieved ROSC with usual resuscitation measures with manual uterine displacement, it is advisable to prepare to evacuate the uterus while resuscitation continues (Class I; Level of Evidence C). This is called resuscitative hysterotomy or perimortem cesarean section
    - Decisions on the optimal timing of a PMCD for both the infant and mother are complex and require consideration of factors such as the cause of the arrest, maternal pathology and cardiac function, fetal gestational age, and resources (ie, may be delayed until qualified staff is available to perform this procedure). Shorter arrest-to-delivery time is associated with better outcome (Class I; Level of Evidence B).
    - PMCD should be strongly considered for every mother in whom ROSC has not been achieved after ≈4 minutes of resuscitative efforts (Class IIa; Level of Evidence C).

- If maternal viability is not possible (through either fatal injury or prolonged pulselessness), the procedure should be started immediately; the team does not have to wait to begin the PMCD (Class I; Level of Evidence C).
- When PMCD is performed, the following are recommended:
  a. The woman should not be transported to an operating room for PMCD during the management of an in-hospital maternal cardiac arrest **(Class IIa; Level of Evidence B)**.
  b. The team should not wait for surgical equipment to begin the procedure; only a scalpel is required **(Class IIa; Level of Evidence C)**.
  c. The team should not spend time on lengthy antiseptic procedures. Either a very abbreviated antiseptic pour should be performed, or the step should be eliminated entirely **(Class IIa; Level of Evidence C)**.
  d. Continuous manual LUD should be performed throughout the PMCD until the fetus is delivered **(Class IIa; Level of Evidence C).** Care should be taken to avoid injury to the rescuer performing the manual LUD during PMCD.

- The time frame can be extended to 6-14 minutes with good results as reported recently[6].
- A study by Rose et al reinforced the concept that arrangements for delivery should be made at the same time with initiation of maternal resuscitative efforts if the uterus is palpable at or above the umbilicus. The authors also added that if maternal condition is not rapidly reversible, hysterotomy with delivery should be performed regardless of fetal viability or elapsed time since arrest[7]. It has also been suggested that the 4-5 minute rule is not essential to perform PMCD. In fact it can be done earlier with good outcome.
- The resuscitation is more effective after PMCD as the aorto-caval compression is relieved, the maternal oxygen requirement reduces and lung mechanics improve[8,9].
- PMCD should not be delayed by moving the woman – it should be performed where resuscitation is taking place and there is no need to administer anaesthesia.
- A PMCD section tray should be available on the resuscitation trolley in all areas where maternal collapse may occur, including the accident and emergency department.
- The principle of successful PMCD is rapid incision, rapid delivery and rapid closure. It is best obtained with large vertical abdominal incisions, Classical LSCS and closure with large running sutures in a single layer[8,9].
- PMCD is relatively bloodless, since there is no circulation and cardiac output. Chest compressions and ventilation should be continued. If mother is resuscitated then she can be shifted to OT for proper closure of uterus & abdomen; and subsequently to ICU.
- Best survival rate for infants >28 weeks occurs when delivery of infant occurs in <5 minutes after the mother's heart stops beating.

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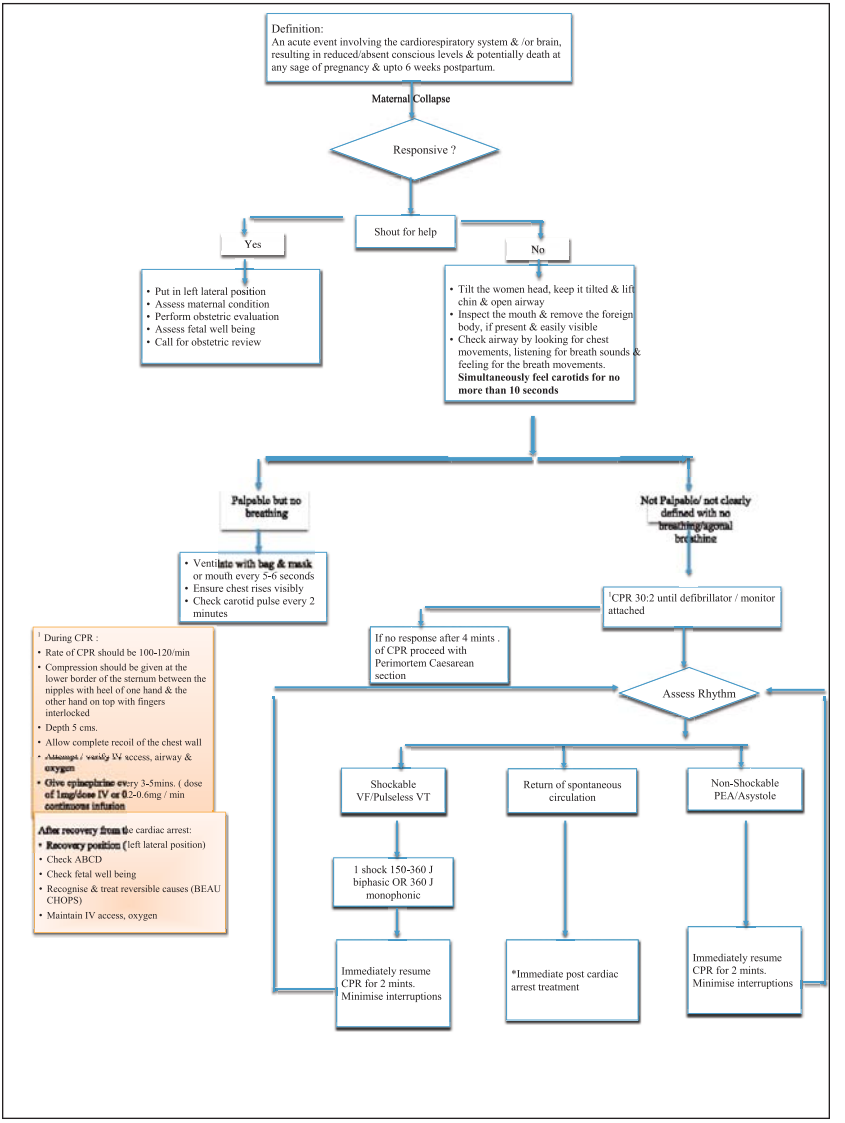

Fig 1: Algorithm for management of Maternal Collapse

Shock in Pregnancy

1. **When should we suspect shock?**
   Any women with anxiety, restlessness and altered mentation in the presence of hemodynamic instability should be evaluated for shock.

   ***Abnormal mental status*:** begins with agitation, progresses to confusion or delirium, and ends in obtundation or coma. It is due to poor perfusion or metabolic encephalopathy.

2. **What are early features of shock?**
   Shock index ≥ 0.9, (Shock index is Heart rate/Systolic blood pressure)[1]

3. **What are definitive features of shock?**
   ***Hypotension*:** Earliest feature is narrowing of the pulse pressure (<25 mmHg). Hypotension may be absolute (SBP <90 mmHg and/or MAP <65 mmHg), relative (drop in SBP of >40 mmHg), orthostatic (fall in SBP of >20 mmHg or DBP of >10 mmHg with standing), or profound (vasopressor-dependent).

   ***Tachycardia*:** can be isolated or occur in association with weak peripheral pulses and hypotension, may be absent if woman is taking beta blockers

4. **What are the supportive features of shock?**
   - ***Tachypnea**:* Although respiratory rate may be high among pregnant women, it is a useful tool to identify patients at risk of clinical deterioration.
   - ***Cool, clammy or cyanotic skin*:** Prolonged capillary refill (>2 seconds) and cool, clammy skin, or cyanotic, mottled appearance. However, warm, hyperaemic skin may be present in early stages of distributive shock and in terminal shock (due to failure of compensatory vasoconstriction).
   - ***Oliguria*:** can be prerenal due to shunting of renal blood flow to other vital organs, and intravascular volume depletion or renal due to direct injury to the kidney
   - ***Metabolic acidosis*:** presence of a high anion gap metabolic acidosis should always raise the clinical suspicion for the presence of shock. However, in the absence of shock, metabolic acidosis may be present due to other causes of acute kidney injury.
   - ***Hyperlactatemia*:** signifies tissue hypoxia, an elevated serum lactate level has been associated with development of shock and adverse outcomes.

5. **What are causes of shock in pregnancy?**
   Causes of shock are enumerated in Fig 1.

   The shock may be caused by more than one factor as in following situations:

   Incomplete abortion leads to haemorrhagic and endotoxic shock, secondary to infection.

   Ectopic pregnancy and rupture uterus lead to haemorrhagic and neurogenic shock.

6. **How will you proceed if a woman presents in shock?**
   - Call for help and turn the woman on her left side or elevate the right hip to prevent supine hypotension
   - Ensure that patient can breathe- open, protect and maintain airway

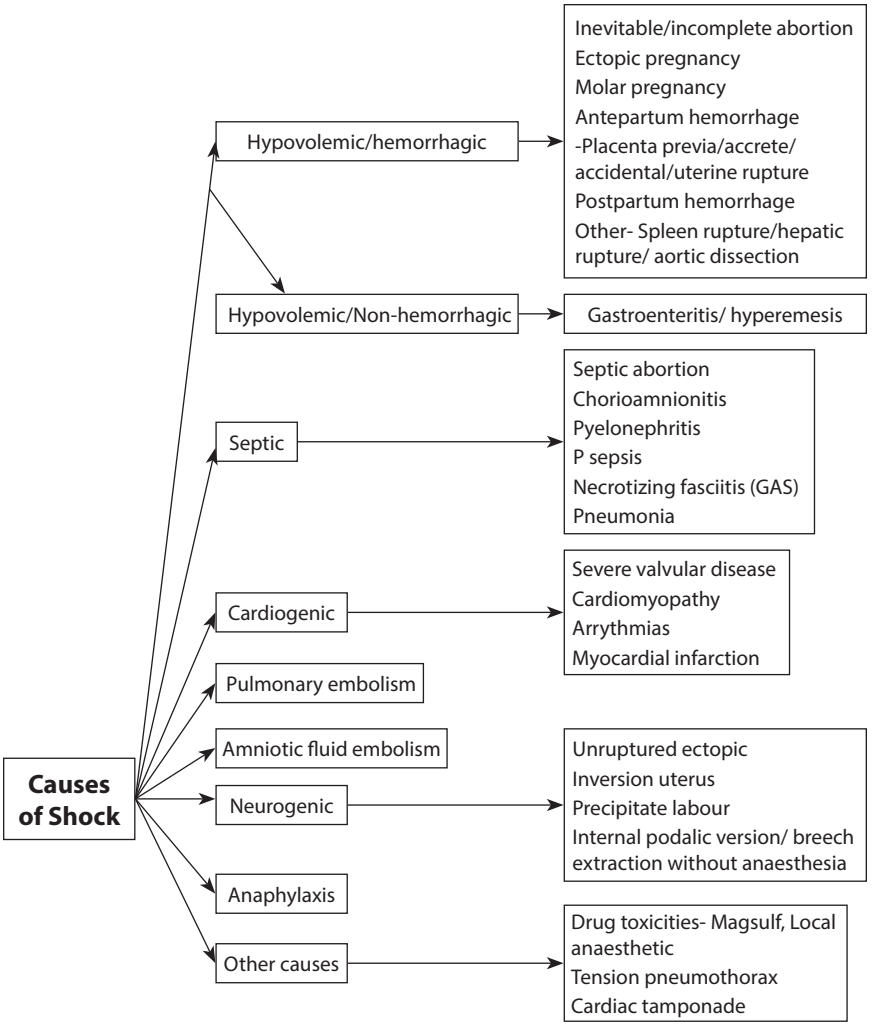

Fig 1: Causes of Shock

- Give oxygen at 6-8 l/min
- Intubate early if necessary
- Observe the respiratory rate, depth and difficulty; auscultate chest
- In absence of breathing refer to CPR guidelines
- Insert two large-bore intravenous cannula (16 or 18G)
- Collect blood and send for Group/Type and crossmatch, Complete blood count, Urea, creatinine & electrolytes , Liver function tests, Coagulation screen and Acid-base analysis & serum lactate
- Administer 1-2 L of warm crystalloid solution (e.g. Ringer's lactate/saline) as a volume expander initially. Initial one litre in 15 minutes.[2]
- Assess for cause of shock and start the targeted treatment.
- Modify fluid resuscitation according to the cause

- Vasopressor if target mean arterial pressure of 65 mmHg is not achieved- norepinephrine- 8 to 12 mcg/minute (0.1 to 0.15 mcg/kg/minute), maximum dose is 35 to 100 mcg/minute (0.5 to 0.75 mcg/kg/minute; up to 3.3 mcg/kg/minute is rarely indicated.
- If refractory to I/V and vasopressor therapy consider inotropic therapy with dobutamine
- Communicate with the relative
- Monitor every 15 minutes, the heart rate, blood pressure, and peripheral perfusion every 15 minutes until the woman's condition stabilises; continuous monitoring preferable . Initiate pulse oximetry, if available
- An indwelling catheter should be inserted to monitor urine output.
- Debriefing of the patient before discharge

7. **How will you differentiate between various types of shock?**

Table 1: Clinical picture of shock

Parameters	Cardiogenic shock	Hypovolemic shock	Septic shock
History	Chest pain, Dysponea, confusion, H/o heart disease	Haemorrhagic- H/o bleeding- revealed, pain abdomen- concealed Nonhaemorrhagic- vomitings/diarrhoea	Fever or rigors Diarrhoea or vomiting Rash Abdominal /pelvic pain Offensive vaginal discharge Productive cough Urinary symptoms
Identified site of infection	-	-	++
Extremities	Cold	Cold	Warm initially; cold in the late stage
Pulse pressure	↓	↓	↑
Diastolic pressure	↓	↓	↓↓↓
Dehydration	-	+	+
Cyanosis	+/-	-	-
Jaundice	-	-	+
Capillary refill	Slow	Slow	rapid
JVP	↑	↓	↓
Respiratory crepts	+++	-	-
S3,S4 Gallop rhythm	+++	-	-
Abdomen examination	Non tender, in pregnancy- uterus corresponds to gestation age, after delivery- well involuted	Tenderness+ in ectopic pregnancy, abruption, rupture uterus Uterus not correspond to gestation age- abortion, ectopic, molar After delivery- atonic	Abdomen tenderness ++, uterus subinvoluted, wound infection, renal angle tenderness
Chest Xray	Large heart, Pulm edema	Diminished cardiac size	Normal unless pneumonia

8. **How will you manage a case of hypovolemic shock?**
   - Along with initial stabilization of patient (refer to Q6), rapid volume repletion is

indicated in patients with hypovolemic shock. At least one to two liters of isotonic crystalloid are initially given as rapidly as possible in an attempt to restore tissue perfusion. Early correction of the volume deficit is essential in hypovolemic shock to prevent the decline in tissue perfusion from becoming irreversible. Fluid repletion continues at the initial rapid rate as long as the systemic blood pressure remains low.

- For patients with non-hemorrhagic hypovolemic shock: give initial fluid replacement with an isotonic crystalloid (RL or NS) solution rather than a hyperoncotic starch solution (eg, hydroxyethyl starch [Hetastarch]) (**Grade 1A**) or an albumin-containing solution (**Grade 2B**). In case of hemorrhagic hypovolemia or hemorrhagic shock, red blood cell and other blood components should also be transfused as soon as available.
- Clinical parameters and dynamic variables to guide fluid resuscitation: Clinical signs, including MAP > 65 mm Hg, urine output > 30 ml/hour, improving mental status, and peripheral perfusion, are guides to successful resuscitation. A central venous catheter may be required in patients who fail to respond promptly to initial fluid resuscitation. Dynamic parameters to assess fluid responsiveness are more informative to guide fluid therapy. Clinical bedside test which can be used is passive leg raising test, inferior vena cava collapsibility on inspiration can be used to guide fluid resuscitation. Another dynamic variable to guide fluid resuscitation is respiratory variation in the arterial pressure tracing which can be used to estimate the adequacy of fluid resuscitation.
- Control the ongoing hemorrhage: attention should be paid to arrest hemorrhage, in case of ectopic pregnancy the patient will require immediate surgery. Urgent surgical evacuation of the products is needed in women with shock due to incomplete or inevitable abortion. In case of atonic PPH uterotonics and tranexamic acid are given as per PPH management protocol and surgical management for atonic PPH refractory to medical management and in cases of traumatic bleeding.
- Important- Assessment of blood loss and coordination with blood bank and OT team
- Broad spectrum antibiotics must be started in all these cases as they are prone to sepsis

9. **What is the role of Bicarbonate therapy in Hypovolemic shock?**
   - Patients with marked hypoperfusion due to hypovolemia may develop lactic acidosis. The role of intravenous bicarbonate in this situation is uncertain.
   - Bicarbonate therapy is recommended in severe acidemia (pH < 7.1 and serum bicarbonate ≤6 meq/L). If pH is ≤7.1 and the serum bicarbonate level is >6 meq/L, then PCO2 is > 20 mmHg, which indicates inadequate ventilation. Inadequately ventilated patients with severe acidemia should be started on mechanical ventilation as sodium bicarbonate in these women worsens the respiratory acidosis.
   - Dose of sodium bicarbonate is 1 to 2 meq/kg as intravenous bolus. Serum electrolytes and blood pH should be measured after 30 to 60 minutes, and if pH is still <7.1, dose of sodium bicarbonate is repeated.

10. **What are diagnostic criteria for septic shock?**
    - Women with sepsis who despite adequate fluid resuscitation, require vasopressors to maintain a MAP ≥65 mmHg and have a lactate >2 mmol/L (>18 mg/dL)[3]

- Septic shock is associated with a greater risk of mortality than sepsis alone (≥40% vs ≥10%)

11. **What is the role of fluid resuscitation in septic shock?**
    - Fluid resuscitation is the initial step in the management of septic shock. Intravenous fluids are recommended as first-line therapy (**Grade 1B).** Rapid infusions of intravenous fluids (Ringer lactate/normal saline) 30 mL/kg or fluid boluses with 500ml NS or RL are repeated until blood pressure and tissue perfusion are acceptable, pulmonary edema ensues, or there is no further response
    - Use a crystalloid solution rather than albumin-containing solution (**Grade 2B**)
    - Hyperoncotic starch solution NOT administered (**Grade 1A**)
    - ***Goals of initial fluid resuscitation-*** MAP ≥65 mmHg, Urine output ≥0.5 mL/kg/hour, CVP 8 to 12 mmHg, Central venous (superior vena cava) oxyhemoglobin saturation ($ScvO_2$) ≥70%, mixed venous oxyhemoglobin saturation (SvO_2) ≥65 percent, lactate clearance [(initial lactate - lactate >2 hours later)/initial lactate] x 100. Lactate levels monitored 6 hrly.

12. **How will you manage a woman with septic shock?**
    - Along with initial stabilization of patient (refer to Q 6) and the fluid resuscitation mentioned above, antimicrobial therapy is administered, preferably after taking cultures of- Blood, urine, high vaginal, wound discharge & sputum. Take at least 2 blood samples, rest according to focus of infection, sample from I/V catheters if in place from more than 48 hours in addition to blood sample. If cultures are not taken within one hour, broad spectrum antibiotics are administered.
    - It is justified to give combination antimicrobial therapy in septic shock
    - As the source of infection is mostly unknown, broad spectrum combination antibiotics are indicated.
        - ***Give one for MRSA***- I/V Vancomycin or linezolid, or Deptomycin
        - ***If Pseudomonas is unlikely-*** add one of the following:
            - Cephalosporin, 3rd generation (eg, ceftriaxone or cefotaxime) or 4th generation (cefepime), or
            - Beta-lactamase inhibitor (eg, piperacillin-tazobactam, ticarcillin clavulanate), or
            - Carbapenem (eg, imipenem or meropenem)
        - ***If Pseudomonas is a possible pathogen-*** Combine vancomycin with two of the following
            - Antipseudomonal cephalosporin (eg, ceftazidime, cefepime), or
            - Antipseudomonal carbapenem (eg, imipenem, meropenem), or
            - Antipseudomonal beta-lactamase inhibitor (eg, piperacillin tazobactam, ticarcillin-clavulanate), or
            - Fluoroquinolone with good anti-pseudomonal activity (eg, ciprofloxacin), or
            - Aminoglycoside (eg, gentamicin, amikacin), or
            - Monobactam (eg, aztreonam)

Treatment Guidelines for Antimicrobial Use in Infectious Diseases for obstetric infections[4]

- For sepsis in Pregnancy/after pregnancy- Piperacillin-Tazobactam 4.5 g IV 6 hourly

or Cefoperazone+Sulbactam 3 g IV 12 hourly and MRSA cover with Vancomycin/ Teicoplanin may be required if suspected or colonized

- For septic abortion/Endomyometritis/Septic Pelvic Vein Phlebitis- Empirical therapy with Ampicillin 500 mg 6 hourly + Metronidazole 500 mg IV 8 hourly. In case of previous partial treatment with antibiotics, send blood cultures and start Piperacillin-Tazobactam or Cefoperazone-sulbactam till the sensitivity report is available. Alternative regimen- Ceftriaxone 2g IV OD
- For complicated Pyelonephritis with sepsis- Empirical therapy with Piperacillin-Tazobactam 4.5 gm IV 6 hourly or Amikacin 1 g OD IV or Cefoperazone-Sulbactam 3gm IV 12 hourly. Alternative regimen- Imipenem 1g IV 8 hourly or Meropenem 1gm IV 8 hourly. De-escalate to Ertapenem 1 gm IV OD, if Imipenem/meropenem is initiated. Monitor renal function if aminoglycoside is used.
- For necrotizing fasciitis- Empirical therapy with Piperacillin-Tazobactam 4.5 gm IV 6 hourly or Cefoperazone-Sulbactam 3 gm IV 12 hourly + Clindamycin 600-900 mg IV 8 hourly. Alternative regimen- Imipenem 1g IV 8 hourly or Meropenem 1gm IV 8 hourly + Clindamycin 600-900 mg IV TDS/linezolid 600 mg IV BD/daptomycin 6mg/kg/day. Alternative regimen- Ceftriaxone 2g IV OD.
- For secondary peritonitis, Intra-abdominal abscess/ GI perforation- Empirical therapy with Piperacillin-Tazobactam 4.5 gm IV 8 hourly or Cefoperazone-Sulbactam 3 gm IV 12 hourly, In sick patients-fluconazole iv 800 mg loading dose day 1, followed by 400 mg OD. Alternate regimen- Imipenem 1g IV 8 hourly or Meropenem 1gm IV 8 hourly or Doripenem 500 mg 8 hourly or Ertapenem 1 gm IV OD. Source control is important to reduce bacterial load, if excellent source control is achieved antimicrobials for 5-7 days; other wise 2-3 weeks.
- For mastitis with abscess- Drainage with antibiotic cover for MRSA, Clindamycin 300 QID or Vancomycin 15 mg/kg IV 12 hourly (maximum 1gm 12 hourly) Or Teicoplanin 12 mg/kg IV 12 hourly x 3 doses followed by 6 mg once daily IV
- Routine administration of antifungal therapy is not warranted in non-neutropenic patients

Deescalate antimicrobial therapy as soon as cultures are available or after clinical response to therapy or after drainage of septic focus

13. **What is the role of steroids in sepsis?**
    If fluid resuscitation and vasopressors are not able to restore haemodynamics give Corticosteroids **-** hydrocortisone 200 mg I/V per day

14. **What are the other supportive measures to improve the outcome of patients in sepsis and septic shock?**
    The supportive measures which have been seen to reduce the morbidity and mortality of sepsis patients and are recommended in all critically ill patients are:
    - **Glucose control-**with insulin, target blood glucose levels between 140 and 180 mg/dl
    - **Bicarbonate therapy**- not recommended for achieving haemodynamic stability in hypoperfusion induced lactic academia with pH ≥7.15.
    - **Venous thromboembolism-** Combination pharmacological and mechanical VTE prophylaxis if no contraindications to pharmacological VTE, LMWH preferred over UFH.
    - **Prophylaxis for stress ulcers**- for prevention of GI bleeding, in all women with septic shock- either proton pump inhibitors or H2 receptor antagonists

- **Renal replacement therapy**- should be used early in women with septic shock and acute renal injury
- **Nutrition-** Early parental nutrition is not recommended, rather early enteral feeding should be started if not contraindicated, I/V glucose till enteral feeding is contraindicated

15. **How will you manage anaphylactic shock?**

Along with other resuscitative measures, give IV epinephrine 0.1-0.2 mg i.e. 1-2 ml of 1:1000 in 10 ml 0.9% NaCl [0.1mg/ml], repeat every 1-2 minutes until patient responds.

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AOGD Good Clinical Practice Recommendations on Aneuploidy Screening in Pregnancy

Drafted by AOGD Fetal Medicine Sub-Committee (2017-2019)

These practice recommendations have been drafted after reviewing the currently updated guidelines from American College of Obstetricians and Gynecologists, Society of Obstetricians and Gynecologists of Canada and the Royal College of Obstetricians and Gynecologists. In addition, various large trials and meta-analyses relevant to the PICO (Population Intervention Control and Outcome) questions being studied were reviewed. The guidelines from these standard organizations have been modified to suit the socio-cultural, economical and medico-legal milieu of our country.

The intended users of these guidelines are the general practitioners who should understand the options of screening available in their commonly encountered scenarios. An emphasis has been laid on the decision points and thresholds for referral to a geneticist/fetal medicine specialist to avoid delay in definitive diagnosis. This document presents a general guide to management and must be integrated into practice keeping in mind the logistics and resources available.

1. **Why should aneuploidy screening be offered?**

   Magnitude of problem

   Chromosomal abnormalities affect approximately 0.4% of births (1/250) according to the population-based registries. These include live births, fetal deaths, and pregnancy terminations of which Trisomy 21 accounts for more than 50% of cases, Trisomy 18 for 15%, and Trisomy 13 for 5%[1]. Because of its profound social and economic impact on the family, there is a great emphasis on early detection of these anomalies during pregnancy giving a choice to the parents about termination of pregnancy. The availability of high definition ultrasound and serum markers for the screening of aneuploidies has revolutionized the concept of prenatal care with respect to aneuploidy screening.

   Prenatal screening versus Diagnosis

   The screening tests are done to assess whether a pregnant woman is at increased risk of having a fetus affected by aneuploidy. In contrast, prenatal diagnosis is intended to determine, with as much certainty as possible, whether a specific condition is present in the fetus. Usually a diagnostic test follows if the screening test puts women at high risk of aneuploidy.

2. **Who should be offered screening?**

   All pregnant women should be offered screening for aneuploidies after an informed counselling.

   It was earlier believed that only elderly women should be screened for aneuploidies as the risk for having an affected fetus is higher in them. However, it has been seen that the majority of affected fetuses are born to low risk women and hence universal screening should be the norm.

   However, certain categories of women are considered high risk for aneuploidies e.g;

- Maternal age at delivery 35 years or more
- Fetal ultrasonographic findings indicating an increased risk of aneuploidy

- Personal or family history of prior pregnancy with a trisomy
- Parental Balanced Robertsonian Translocation with increased risk of T21 or T13

In these women screening tests with higher sensitivity (e.g cfDNA) or even some form of diagnostic testing can be offered.

3. **What are the general principles of screening for aneuploidies?**
   - All pregnant women, regardless of age, should be offered the option of prenatal screening test for the most common clinically significant fetal aneuploidies.
   - Informed non-directive counselling is a must before advising the screening test. It includes information about the condition being tested, sensitivity and specificity os screening tests and the need for invasive testing if she is screen positive and the possibility of false negative or a false positive report. Each patient has the right to accept or decline screening test.
   - The options for aneuploidy screening are available in both first and second trimester. These are the combined screening test in the first trimester and quadruple test or triple test in the second trimester. Integrated and sequential screening protocols combine the first and second trimester results to give a composite risk. Cell-free DNA testing can be done in all trimesters. Ultrasound can also be used as a screening test in both trimesters.
   - In the context of the laws prevalent in our country, the tests should be offered in conjunction with appropriate pre-test and post-test counselling about the feasibility of termination of affected pregnancy only up to 20 weeks in case the couple so wishes.
   - At a minimum, any prenatal screen offered should have a detection rate of 75% with no more than a 5% false-positive rate[2]. Therefore, offering maternal age, triple test or only nuchal translucency as standalone tests should be avoided.
   - Prenatal aneuploidy screening using age and NT measurement in the first trimester is appropriate for screening in multiple gestations.
   - Cost and logistics should be considered while deciding the best modality for screening. Considering the resource differences in various settings, a single screening protocol may not be applicable for all.
   - Biochemical tests should be done in accredited labs and the Ultrasounds should be done by sonologists certified to do 11-13+6 weeks scan
   - For all screening tests, correct dating is important.
   - Appropriate post-test counselling must be available. Those with positive screening test are at an increased risk of evaluated aneuploidies and should be offered secondary screening by cff DNA or diagnostic test.
   - Those with a negative screening test should be counseled about their lower adjusted risk and may be discharged from the routine screening protocol. All women should undergo a scan at 18-20 weeks gestation for the detection of structural anomaly.

4. **How to screen for aneuploidies in the first trimester?**
   - A **combined screening** by Ultrasound markers (Nuchal translucency) and serum biochemistry (PAPP-A and free B-hCG) should preferably be offered if the patient presents in the first trimester. This has a detection rate or 80-85% with a false positive rate of 5%.[2,3]
   - **Mandatory background information** for serum biochemistry should include – ethnicity, maternal age (preferably date of birth), weight, method of conception, diabetes, smoking, number of fetuses and chorionicity.

4.1 **Serum markers**

Beta-HCG: hCG is a glycoprotein of 244 amino acids produced by the developing embryo and later by the placenta. Beta-HCG levels are, on average, twice as high in pregnancies affected with fetal Down syndrome than in euploid pregnancies. Beta-hCG can be assayed in its free or total form. Free and Total beta-hCG are effective serum markers at 9 to 13+6 weeks and 11 to 13+6 weeks respectively and the performance improves as gestational age advances within this interval.

PAPP-A: PAPP-A is a complex, high molecular weight glycoprotein. Its levels, on average, are lower in pregnancies affected with fetal Down syndrome. In contrast to beta-hCG, PAPP-A performance as a screening marker decreases with increasing gestational age between 9 and 13 weeks.

Timing

The blood tests and ultrasound examination for the combined test are most commonly performed at about the same time between 11 and 13+6 weeks of gestation.

Changes

Table 1: Changes in Serum Analytes in First Trimester in aneuploidies

	β-hCG (MoMs)	PAPP-A (MoMs)
Trisomy 21	↑ 2.2	↓ 0.5
Trisomy 18	↓ 0.3	↓ 0.2
Trisomy 13	↓ 0.5	↓ 0.3
Turners	↔	↓ 0.5
Triploidy (diandric)	↑ 8.0	↓ 0.8
Triploidy (digynic)	↓ 0.2	↓ 0.1

4.2 **The 11 -13+6 weeks scan**

Scan done at 11-13^{+6} weeks is an important screening tool for detecting common chromosomal abnormalities (Trisomy 21,18 and 13) in pregnancy. The scan is done between 11 weeks to 13^{+6} weeks when the Crown rump length (CRL) is between 45 – 84 mm.

Following criteria should be checked during the 11-13+6 weeks scan:

1. Nuchal translucency (NT) thickness (minimum)
2. Nasal bone

4.2.1:**Criteria for measuring NT (see Figure -1)**

Table 2: Criteria for measuring NT

CRL	45-84 mm
Mid-sagittal plane of the fetus	Echogenic nasal bone Rectangular palate is seen anteriorly Diencephalon in the center Nuchal membrane posteriorly
Magnification of the image	Fetal head and thorax should occupy the whole screen
Fetus is in neutral position	Fetal neck should neither be flexed nor extended with amniotic fluid seen clearly between the fetal chin and thorax
Calipers (use '+' and not 'x' or '*')	Inner border of the horizontal line of the caliper (**+**) to be placed ON the line that defines NT - from inside to the line outside (on-on);
Trained and certified operators	

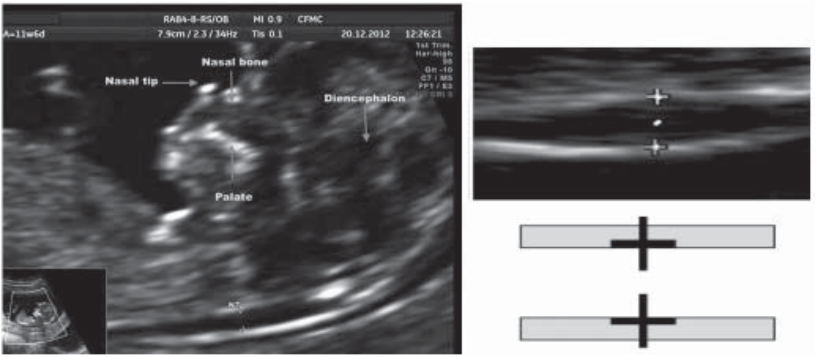


Fig 1: Criteria for measuring NT

4.2.2 Criteria for measuring Nasal Bone (NB)

Absent or hypoplastic nasal bone is seen in 55% of Trisomy 21 cases[4].

Prerequisites for assessment of nasal bone are:

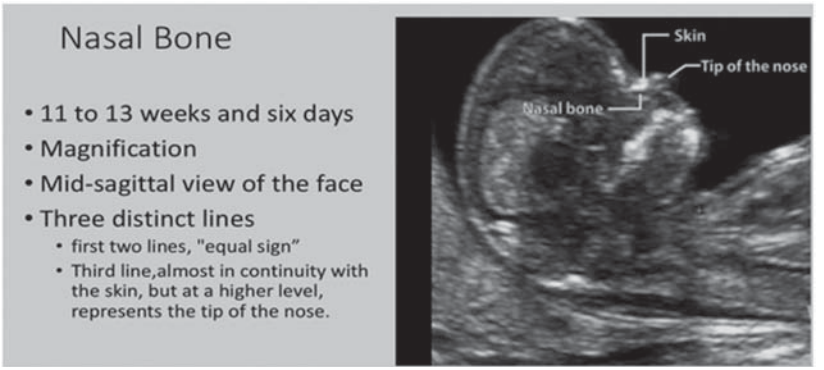


Fig 2: Criteria for measuring Nasal Bone

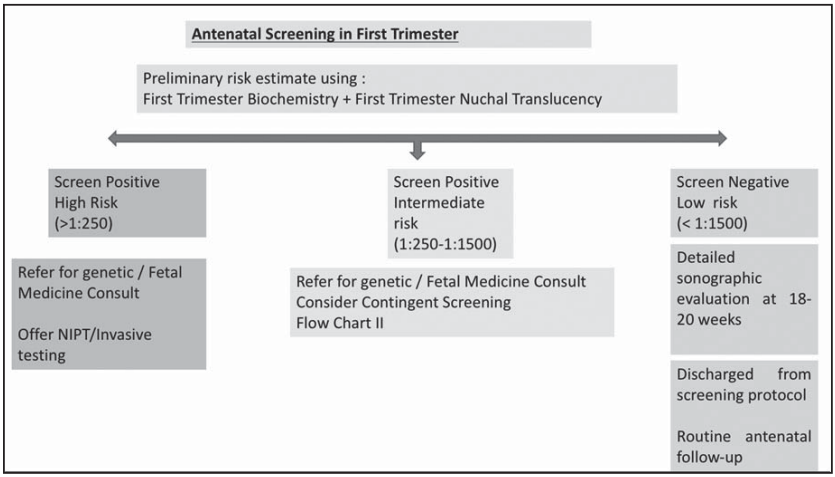
Nasal bone is marked as present only when bottom line (representing the bone) is more echogenic than the upper line (which represents the skin), marked as absent if echogenicity is less or equal.

Other markers for aneuploidy on first trimester ultrasound are tricuspid regurgitation and absent or reversed 'a' waves in ductus venosus. Targeted scanning for these increases the detection rate of the first trimester screening while decreasing the false positivity. However, the integration of risk ratios requires specialized software and is possible only at fetal medicine centers. ***The techniques of measurement and relevance to aneuploidy screening have been mentioned separately in Annexure 1.***

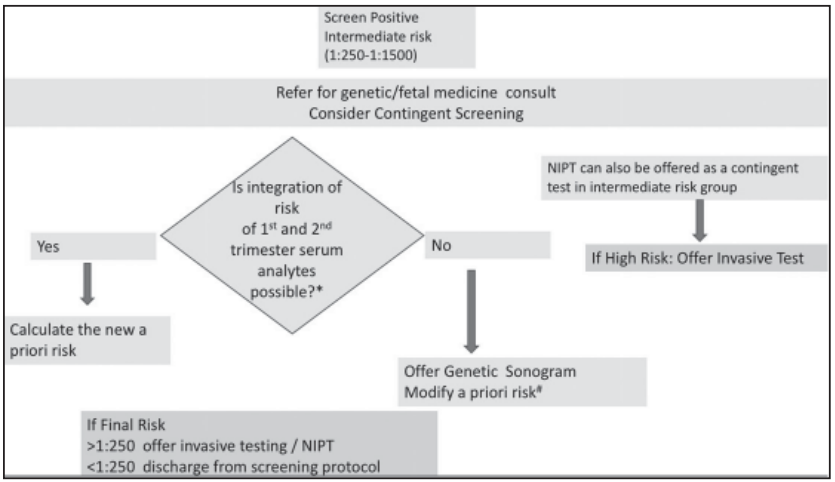
5. **What is the desirable screening protocol for women who present in first trimester?**

   Women considered at high risk for aneuploidy can be offered NIPT/invasive testing/ combined screening after appropriate counseling (Flow chart I & II).

Flow Chart I: Desirable Screening Protocol in the first Trimester



Flow Chart II: Contingent Screening in Intermediate Risk Group



**Combination of first and second trimester biochemical markers needs specialised accredited software and hence, integration is possible only if biochemical markers are analysed both in first and second trimester on the same platform.*

 # See flow chart IV

6. **How to screen for aneuploidies in the second trimester?**
   - For pregnant women presenting for first time in second trimester a quadruple test should be offered. Triple test is suboptimal as it has lower detection rate. Both the tests need correct dating and screen for open neural tube defects.
   - Women with a low risk on first trimester combined screening test result should be counseled about their lower adjusted risk and should be discharged from the routine screening protocol. They should however undergo a detailed ultrasound at 18-20 weeks, to detect anatomic abnormalities.

6.1 Serum Analytes

Alpha fetoprotein (AFP): AFP is a glycoprotein of 591 amino acids produced by the

yolk sac and the fetal liver.

Unconjugated oestriol(uE3): Estriol in maternal circulation undergoes conjugation with glucuronides or sulphate but about 10% remains as the unconjugated form. It is made in the placenta from the 16-hydroxydehydroepiandrosterone produced by the fetal liver.

Inhibin-A (Inh A): Inhibin-A is a dimeric molecule produced by the corpus luteum and the placenta during pregnancy.

Triple test: It measures serum hCG, Alpha Fetoprotein and unconjugated estriol.

These three biochemical markers and maternal age are used to calculate risk of aneuploidy.The test provides sensitivity of 69% at a 5% positive rate, for detection of Down syndrome[5].

Quadruple test: Involves an additional analyte dimeric inhibin A. The detection rate for Down Syndrome is 75 - 80% with a 5% positive result rate[6].

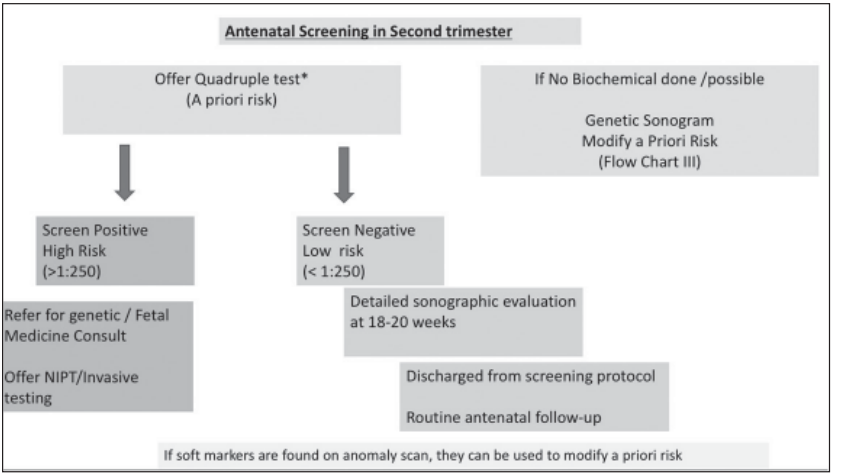
Timing

Second trimester screening can be performed between 15-22 weeks, though best time is 16-18 weeks' gestation.

Accurate dating is important for proper interpretation.

6.1 **How should a woman who presents for the first time in the second trimester be screened? (Flow chart III)**

Flow Chart III: Screening for women presenting in second trimester



**In situations where quadruple test is not feasible or possible a triple test may be offered with appropriate pre and post test counselling and should be interpreted in conjunction with a genetic sonogram preferably by a fetal medicine expert*

7. **How to combine first and second trimester screening?**
   - Combination of first and second trimester biochemical markers needs specialised software and hence, integration is possible only if biochemical markers are analysed both in first and second trimester on the same platform.
   - Integrated and stepwise sequential test protocols improve the detection rates and reduce the false positive rates **(Annexure II)**.
   - Contingent screening using cut-off for high risk as 1:250 will only improve the detection rates but will not reduce the false positive rate.

- Doing Quadruple test without integration after low risk first trimester screen, may actually increase false positive rate and hence, should be avoided.
- Genetic sonogram in second trimester can be used to modify first trimester/ second trimester screening risk without need for any specialized software.

8. **What is the role of ultrasound in second trimester aneuploidy screening?**
   - All women should be offered a detailed ultrasound at 18-20 weeks, to detect structural abnormalities. "Soft markers" can also be detected at same time and they can be used to modify a priori risk.
   - Scan for soft markers should be done by certified sonologists.

   Timing of Scan: Mid trimester scan/ Anomaly scan should be routinely offered to all pregnant women at 18 – 20 weeks of gestation. If views are suboptimal, repeat scan may be advised at 22 – 24 weeks

   Standards/ Audit: It is desirable that person performing the scan performs it to a certain standard. FMF certification helps ensure the standards, and should be strived for all those who are performing Anomaly scans.

   Dating: Dating if not already performed by early pregnancy or first trimester scan, then should be done by HC at this time. In case of cranial malformation, Femur length should be used for dating. Reference chart used should be mentioned clearly in the report.

   Soft Markers: Soft markers increase the probability of aneuploidies when present, though in absence of aneuploidies these are considered normal variants and do not affect quality of life of baby.

   Pre-test counselling is important for parents to understand that normal scan does not guarantee a healthy baby though it is reassuring.
   - Second trimester ultrasound is the least effective method of screening for Down syndrome, with a detection rate of 50-60%, and should not be used in isolation.
   - Various soft markers have different associations with Down syndrome, hence the risk with each marker should be considered individually, as shown in the Table below.
   - Detection of a soft marker warrants looking for other soft markers and detailed evaluation of fetal anatomy and offering biochemical screen if not done already to calculate a composite risk.

   Meta-analysis by Maria Agathekolous[7] provides excel sheet which can be used for calculation of risk for aneuploidies with presence or absence of multiple soft markers like

   1. Absent /hypoplastic Nasal Bone – less than 5th centile for gestational age, or <3.8mm at 18 – 20 weeks will be considered short for Indian population[8]
   2. Ventriculomegaly – lateral ventricle more than 10mm at any gestational age.
   3. Increased Nuchal Fold – more than 6 mm at 18 – 24 weeks
   4. Mild Hydronpehrosis – AP diameter of renal pelvis more than/= 4 mm, either unilateral or bilateral
   5. Intracardiac Echogenic Focus – equal to or brighter than bone in vicinity-may be
   6. Single or multiple, in left or right ventricle.
   7. Echogenic Bowel – brightness equal to or more than bone in vicinity
   8. Short Femur – less than 5th centile for gestational age
   9. Short Humerus – less than 5th centile for gestational age

10. Aberrant Right Subclavian Artery – right subclavian artery originating from descending aorta and going behind the trachea.
11. There are other soft markers like clinodactyly, sandal gap, short ear, wide iliac angle and so on which are poorly defined and are difficult to include in risk calculation.

Table 3 gives the likelihood ratios of important soft markers and can be used to modify a priori risk:

Table 3: Likelihood ratios of soft markers for Trisomy 21[7]:

Marker	LR+	LR-	LR isolated*
Echogenic intracardiac focus	5.83	0.8	0.95
Ventriculomegaly	27.52	0.94	3.81
Increased NFT	23.3	0.8	3.79
Echogenic Bowel	11.44	0.9	1.65
Mild Hydronephrosis	7.63	0.92	1.08
Short Humerus	4.81	0.74	0.78
Short Femur	3.72	0.8	0.61
ARSA	21.48	0.71	3.94
Absent/hypoplastic NB	23.27	0.46	6.58

**Derived by multiplying the positive LR for the given marker by the negative LR of each of all other markers, except for short humerus. ICEF, intracardiac echogenic focus, NFT, nuchal fold thickness, ARSA, aberrant right subclavian artery; NB, nasal bone*

If a woman has had pervious screening in first trimester or Quadruple test, a priori risk will be the adjusted risk from previous screening. In case of no previous screening, a priori risk will be age based risk at term. New risk will be calculated by multiplying by positive LR of the markers present and negative LR of markers absent (As short humerus and short femur are highly correlated, both cannot be used together, and only one of the two should be used for calculation of risk). E.g, a woman who had a risk of 1: 2500 from previous screening, has mild hydronephrosis and intracardiac echogenic focus, and all other markers absent, then her new risk will be (1/2500) *7.63 (LR+ of mild hydronephrosis)*5.83 (LR+ of ICEF)*0.94*0.8*0.9*0.74*0.71*0.46 (LR – of all other markers not found) = 1/343

If the estimated risk is more than 1:250 at term, invasive procedure should be offered.

If no soft markers is present the apriori risk is reduced to half (X 0.5)

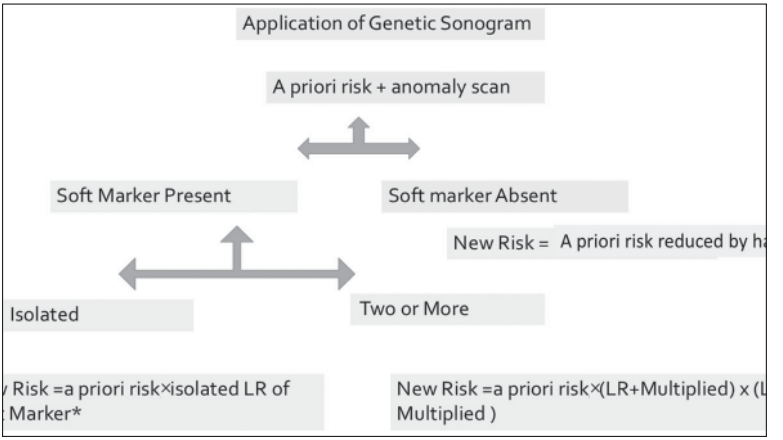
Important pointers to correct interpretation of soft markers:

- Some soft markers like increased Nuchal Fold Thickness, ventriculomegaly, Absent Right Subclavian Artery, echogenic bowel and absent nasal bone with high likelihood ratio may warrant an invasive test despite low risk on screening, hence should be referred for counseling to a Geneticist or a Fetal medicine specialist.
- No additional evaluation is required if earlier screen is negative and single soft markers like echogenic intracardiac cardiac focus, choroid plexus cyst are present.
- For women with no previous screening – isolated markers with high positive LR like absent NB, ARSA, ventriculomegaly, increased NFT should be offered invasive testing. If these markers are absent but out of the rest two or more markers are present, invasive test should be offered.
- There is a role for modifying a priori risk in those who have not had any screening or after second trimester screen to reduce invasive procedures (Flow Chart III)

Post scan counselling is again important to make sure that parents understand the

results of the genetic sonogram. **The patients should preferably be referred to a Geneticist/ fetal medicine specialist for risk calculation and counseling (Flow chart IV).**

Flow Chart IV: Algorithm for use of genetic sonogram for modifying a priori risk



**Excel sheet for calculation of LR in presence of multiple marker is available freely and can be downloaded using this link: http://onlinelibrary.wiley.com/store/10.1002/uog.12364/asset/supinfo uog12364-sup-0002-AppendixS1.xls?v=1&s=2c3d7d64b93d99dd665c355ac0ff687eda3bc708*

9. **What is the current role of Cell Free Fetal DNA or Non Invasive prenatal screening (NIPS) in screening for fetal aneuploidies?**
   - Conventional screening methods remain the most appropriate choice for first-line screening for most women in the general obstetric population.
   - Certain subgroups of women may be offered NIPS which include:
     - Maternal age 35 years or older at delivery,
     - Sonographic findings indicating an increased risk of aneuploidy
     - History of a prior pregnancy with a trisomy,
     - Positive Combined screening tests/ Quadruple test
     - Parental balanced Robertsonian translocation involving chromosome 13,18 or 21
   - Contingent NIPS can be implemented in routine clinical practice after pretest counselling.
   - Cell-free DNA screening has not been validated for women with multiple gestations.
   - The cell-free DNA test will screen for 5 common aneuploidies involving chromosomes 13, 18, 21 and sex chromosomes.
   - Routine cell-free DNA screening for microdeletion syndromes should not be performed.
   - Most appropriate time to offer NIPT in India is after 11-13 $^{+6}$ scan, however test can be done from 9 weeks and any time until delivery.
   - An ultrasound for viability, number of fetuses and fetal structural malformations should always be done before sending NIPS. If a fetal structural anomaly or increased NT/NFT is identified on ultrasound examination, diagnostic testing should be offered rather than cell-free DNA screening.
   - Minimum fetal fraction for a reliable result is 4%.
   - Management decisions, including termination of the pregnancy, should not be

based on the results of the cell-free DNA screening alone.

- Women whose results are not reported, indeterminate, or uninterpretable (a "no call" test result) from cell-free DNA screening should receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing because of an increased risk of aneuploidy.
- Women with positive NIPS should be offered amniocentesis rather than CVS

10. **How should aneuploidy screening be done in multifetal gestation?**
    - Maternal age combined with nuchal translucency may be offered as an acceptable method for aneuploidy screening in twin pregnancies with a DR of 75% with a FPR of 5%.
    - First trimester serum screening may be offered for twin pregnancies with slight improvement in performance of screening when combined with age and nuchal translucency
    - Chorionicity has definite implications on screening and hence should be reported necessarily. Risk in a dichorionic twins is per fetus while in monochorionic twins the risk is calculated per pregnancy.
    - In monochorionic twins a discrepant NT can be an early sign of twin-twin transfusion syndrome .
    - For second trimester serum screening in twins, the opinion of a geneticist/fetal medicine expert should be sought as the tests have a low detection rates (50%) with high false positivity(10%)[9]. They should be considered only if first trimester screening was not performed and interpreted with caution in conjunction with a genetic sonogram to keep the invasive testing to a minimum

12. **How to approach a case with increased nuchal translucency?**
    - Increased nuchal translucency is an indication for invasive testing to look for chromosomal abnormalities. NIPS should not be offered. If karyotype is normal, further genetic counseling and ultrasonography for fetal structural abnormalities and detailed echocardiography for cardiac abnormalities is also required. Maternal screening for viral infections should be performed (including TORCH, parvo, varicella).

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ANNEXURES

Annexure I: Additional Markers for aneuploidy on First Trimester Ultrasound

1.1 **Measuring Ductus Venosus flow**

The ductus venosus is a fetal venous structure which connects the hepatic portion of the umbilical vein and the inferior vena cava. Normally there should be forward flow in DV throughout the cardiac cycle. However in a small number of normal fetuses as well as many aneuploid fetuses the a-wave is seen reversed. Abnormal DV PI has been reported in 59-93% of aneuploid fetuses[10].

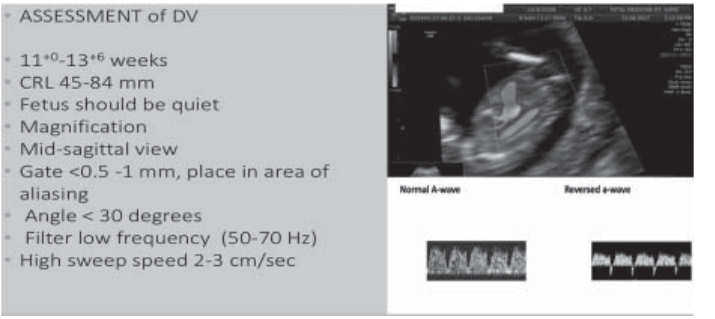


Fig 3: Criteria for measuring Ductus Venosus

1.2 **Measuring Tricuspid Regurgitation**

Congenital cardiac defects are common findings in aneuploidfetuses. In the first trimester Tricuspid Valve can be used for evaluation using pulsed DopplerAround 55% of fetuses with trisomy 21 have tricuspid regurgitation as compared to 1% of chromosomally normal fetuses between 11 to 13+6 weeks' gestation[11].

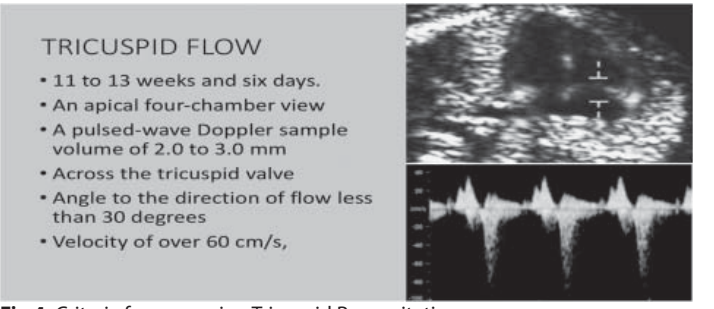
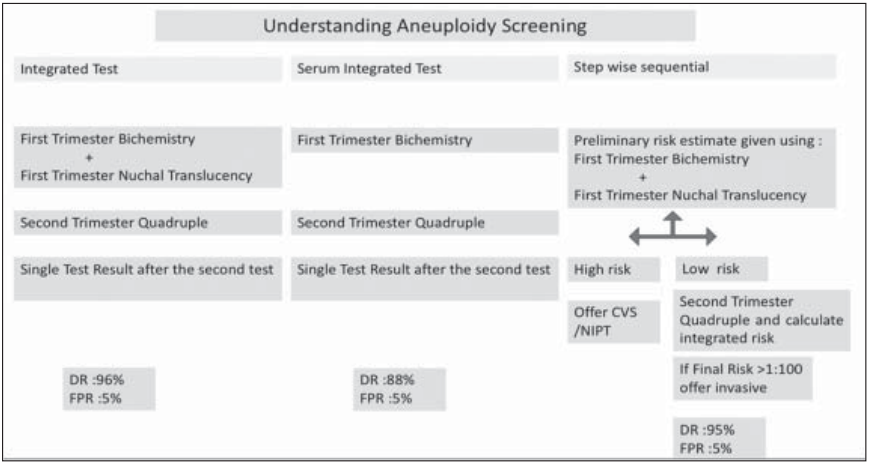


Fig 4: Criteria for measuring Tricuspid Regurgitation

Annexure II: Understanding Combined First and second trimester Aneuploidy Screening protocols(Integrated and step-wise sequential)

These protocols have high detection rates with low false positive rates but are not routinely advised due to feasibility issues. These require tests to be done in both trimesters and results integrated in a software and the final result being given in the second trimester even in low risk groups (Flow chart 5). Integration is possible and advisable in a contingent manner as has already been discussed above (Flow chart 2).

Flow Chart 5: Understanding Combined First and second trimester Aneuploidy Screening protocols (Integrated and step-wise sequential)[12,13]



Annexure III: Alterations of serum analytes with maternal demographics

	PAPP-A	bHCG	AFP	uE3	Inhibin A
Diabetes			Decreased (20%)	Decreased (5-10%)	
IVF	Decreased (10-20%)	Increased		Decreased	Increased
Smoking	Decreased	Decreased	Increased	Decreased	Increased
Increasing maternal weight	Decreased	Decreased	Decreased	Decreased	Decreased

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Management Guidelines of PCOS in Adolescents

Methodology

These guidelines GCPR are in accordance to the American Association of Clinical Endocrinologists (AACE) protocol for standardized production of clinical practice guidelines. Recommendations are based on clinical importance (graded as A: strongly recommended, B: suggested, and C: unresolved) coupled by four intuitive levels of evidence (1 = 'at least one randomized controlled trial (RCT) or meta-analysis of RCTs', 2 = 'at least one non-randomized or non-controlled, prospective epidemiological study', 3 = 'cross sectional or observational or surveillance or pilot study' and 4 = 'existing guideline or consensus expert opinion on extensive patient experience or review').[1]

1. **Recommendations on risk factors for assessment of PCOS**

   The clinical practice guidelines from Endocrine society, USA,[2] PCOS Australian alliance, Australia,[3]The Royal College of Obstetricians and Gynecologists (RCOG), UK,[4] and Society of Obstetricians and Gynecologists of Canada (SOGC), Canada[5] do not recommend a system of risk classification in general population. But in Indian clinical practice a preliminary risk assessment in general population is likely to help in further referrals to higher medical centres for appropriate diagnosis and management.

   It is recommended that Indian women showing at least one biochemical characteristic along with one clinical symptom should be considered for further evaluation for likelihood of PCOS (Grade A, Evidence level (EL) 3).

1.1 **Biochemical characteristics**: high BMI for overweight/ obesity >23 kg/m2 for adults and > 97.5th percentile for age in adolescents), insulin resistance (aconthosis nigricans as clinical marker of insulin resistance), family history of diabetes or PCOS, obesity and inadequate lifestyle, any marker of lipid metabolic dysregulation (elevated serum total cholesterol, triglyceride and LDL-C levels),

1.2 **Clinical symptoms**: pubertal deviations (early or late), disturbances in periodicity/ timing of menstrual cycle, presence of PCO and clinical signs of hyperandrogenism such as early acne or hirsutism, persistent severe acne, frequent relapse in acne, acne in facial 'V' area, persistent acne and hirsutism for more than two years

- In women suspected to have PCOS, screen and appropriately document all clinical and biochemical risk factors in the case history (Grade A, EL 4).
- Patients who currently show either a clinical symptom or fit into a biochemical characteristic may be referred for further diagnosis when feasible or should be regularly monitored for appearance of other presentations of PCOS (Grade A, EL 4)
- Individual patients with two or more clinical risk factors be subjectively assessed by the gynecologist and referred to an appropriate healthcare provider for further diagnosis of PCOS (Grade B, EL 4).

2. **Diagnosis**

   In adolescents, presence of oligomenorrhea or amenorrhea beyond two years of menarche should be considered an early clinical sign of PCOS[6,7], followed by Rotterdam criteria (of adults) for diagnosis of PCOS (Grade B, EL 4).

   The high serum androgen and leutinizing hormone (LH) levels, occurring naturally during anovulatory cycles of adolescence, might not be sufficient to diagnose PCOS in them.[8]

- Minimal diagnosis of PCOS in adolescents should include 5 tests (Grade A, EL 4):
- Serum total testosterone (cut off 60 ng/dL)
- OGTT (at zero and two hours after 75 g glucose load)
- Serum 17– hydroxy progesterone (assessed at 8 am)
- Serum TSH
- Serum prolactin levels
- For the diagnosis of PCOS in adolescents, serum LH, follicle stimulating hormone(FSH) and cortisol should be assessed as indicated (Grade B, EL 4).

Table 1: Diagnostic Tests for Exclusion of PCOS

Test	Disorder	Abnormal values
Serum thyroid stimulating hormone	Thyroid disease	Hypothyroidism: If TSH > upper limit (0.5 mU/L) Hyperthyroidism: If TSH < lower limit (< 0.1 mIU/L)
Serum prolactin	Prolactin excess	> Upper limit of normal (2 - 29 ng/mL)
Serum 17-hydroxy progesterone*	Non-classical congenital adrenal hyperplasia	Early follicular phase of normal cycle: 200 - 400 ng/dL

PCOS: Polycystic ovary syndrome, TSH: Thyroid stimulating hormone, *To be done before 8 a.m.

3. Management of Patients with PCOS[9]

3.1 *Non-pharmacological interventions for management of obesity and body weight in patients with PCOS*

3.1.1 Exercise

Physical activity, at least 150 minutes of per week, improves metabolic status and incidence of diabetes in high risk group of general population.[10,11]

In Indian adolescents with PCOS, compared to controlled (C) treatment with physical exercise, holistic yoga (Y) was found to significantly reduce the T levels (Y=-6.01, C=+2.61, p = 0.014), mFG score for hirsutism (Y=-1.14, C=+0.06, p = 0.002), and improved menstrual frequency (Y=0.89, C=0.49, p = 0.049). [70] Another RCT on adolescents with PCOS from India found significantly improved fasting insulin and glucose levels, HOMAIR, and lipid values, independent of their anthropometric changes, with yoga practice compared to conventional physical exercise.[12]

Clinical practice guidelines from Endocrine society and RCOG suggest exercise therapy in the management of weight and obesity in PCOS.

The clinical practice guidelines from Endocrine society, RCOG and PCOS Australia alliance, suggest using low calorie diet as first-line therapy for the management of obesity in PCOS.

Recommendations on non-pharmacological management of PCOS-

Physical activity

- In adults and adolescents with PCOS, daily strict physical activity sessions for at least 30min/day or 150min/ week are recommended (Grade A, EL 4).[10,11]

3.1.2 Dietary

- For the management of obesity in adults (BMI > 23 kg/ m2) and adolescents

(BMI > 97.5th percentile for age) with PCOS, it is recommended to follow lifestyle modifications in combination with healthy, balanced diet consisting of regular, calorie-restricted meals (Grade B, EL 4).

- Routinely screen for BMI and waist circumference as an index for increasing adiposity and development of hyperandrogenism (Grade A, EL 3).
- Follow calorie restricted diet (low carbohydrate and fat, high protein) in consultation with dietician and lifestyle modification as first-line therapy for at least 6 months, then add metformin as second-line therapy (Grade B, EL 4).

3.2.2 *Pharmacological Interventions for Management of Patients with PCOS*

3.2.1 Management of Menstrual irregularity

- In adolescents with PCOS, use low dose COCs (with or without anti-androgenic progestins drospirenone and desogestrel) for the management of MI (Grade A, EL 4).
- Between 12-16 years of age, low-dose COCs only to be used, for short period (up to 7 days)
- After 16 years, low-dose COCs to be used
- Menstrual regularity: 4 cycles/year in adolescents of 12-16 years
- In adults and adolescents with PCOS with menstrual irregularity and hirsutism, low-dose COCs are suggested (Grade A, EL 2).
- It is essential to regularly monitor the risk and provide three months of pause after one year of COC regimen to minimise risk of VTE.[13]

3.2.2 Management of acne

Use topical medication along with pharmacological interventions based on the clinical presentation of acne as early as possible, in consultation with dermatologist (Grade A, EL 4).

Selection of anti-acne agents should be carefully done according to clinical presentation and individual patient needs.

Topical applications-

Benzoyl peroxide, topical retinoids, and topical antibiotics to be used as first-line treatment for acne management in consultation with dermatologist.

Hormone therapy-

Due to the limited evidence on long-term use of COCs for hyperandrogenic features in adolescents, use of COCs in adolescents should be based on the clinical presentation of acne, in consultation with a dermatologist. Improvement in acne was observed with the use of oral contraceptives with anti-androgen activity.

Cyproterone acetate has been shown to be more beneficial than other progestins in Indian conditions.

3.2.3 Recommendations for management of Hyperandrogenism in PCOS

Hirsutism

Following options can be used alone or in combination to suit individual patient needs and clinical requirements for the management of hirsutism:

- In adult women with PCOS who do not intend to conceive, it is recommended to use low-does COCs with anti-androgen progestin (cyproterone acetate, drospirenone, or desogestrel) for the management of hirsutism (Grade A, EL 1). Cyproterone acetate has been shown to be more beneficial than other

progestins in Indian conditions.

- Use of direct hair removal methods are recommended along with COCs as fist-line therapy (Grade A, EL 1).
- If there is no improvement with COCs or COCs are not tolerated, it is recommended to use spironolactone or finasteride (Grade A, EL 2); spironolactone or finasteride are suggested but recommended to stop 6 months before planned pregnancy.
- In women with PCOS, if menstrual irregularity and hirsutism are diagnosed, low-dose COCs with anti-androgenic activity (CPA, drospirenone, desogestrel) are suggested (Grade A, EL 2)The ideal time to stop hormonal therapy for hyperandrogenism cannot be established with existing evidence (Grade A, EL 4).
- Risk of thromboembolism with use of COCs can be managed by identifying susceptible patients and/or pausing treatment for 3 months after one year of treatment (Grade A, EL 4).
- In adolescents/children with hyperandrogenism, obesity and signs of insulin resistance, lifestyle modification is first-line therapy; metformin is second-line therapy with a wait period of 2 years post-menarche in children (Grade A, EL 4).
- In adolescents with hyperandrogenism, if glucose intolerance is not established by OGTT, metformin should not be started (Grade B, EL 4).
- Due to insufficient evidence, alternative (acupuncture) and complementary therapeutic options (e.g. myoinositol, omega-3 fatty acids) are not recommended for the management of hyperandrogenism (Grade B, EL 4).

3.2.4 Alopecia

COCs and androgen blockers are recommended as first line therapy (Grade B, EL 3).

No effective treatment for alopecia is known (level B).

3.3 Evaluation and management of associated morbid conditions

3.3.1 *Psychosocial management*

Depression

In adults and adolescents with PCOS, it is recommended to routinely screen for depression and anxiety with appropriate psychological instruments (Grade B, EL 3).

Psychological counseling by an appropriate professional is suggested, based on severity of disease (Grade B, EL 4).

3.3.2 *Type 2 diabetes mellitus*

It is recommended to screen adult and adolescent women with PCOS periodically for impaired glucose tolerance and T2DM using a 75 gm oral glucose tolerance test; an HbA1c test should be used only when an OGTT is not feasible (Grade A, EL 2).

- In impaired glucose tolerance or T2DM, it is recommended to use metformin alone, or in combination with oral contraceptives (Grade A,EL 1).
- Early referral to specialist diabetological care is recommended for timely management of diabetes and its complications (Grade A, EL 4).

3.3.3 *Recommendations for obstructive sleep apnea*

In adult and adolescent women with PCOS, it is suggested to routinely screen for OSA and insomnolence, if symptoms are suggestive of OSA, investigate using

polysomnography and refer to appropriate institution for further therapy (Grade B, EL 4).

3.3.4 *Recommendations for Non -Alcoholic Fatty Liver Disease (NAFLD) and Non -Alcoholic Steatohepatitis (NASH) in PCOS*

- In adult and adolescent women with PCOS, provide sufficient awareness on symptoms and complications of NAFLD and NASH and carry out appropriate screening in those diagnosed with insulin resistance and/or metabolic syndrome (Grade B, EL 4).
- In patients with PCOS and NASH, treatment with vitamin E is preferred and metformin is not suggested for reduction of metabolic syndrome with specialist inputs from a multidisciplinary team (Grade B, EL 1).

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Good Clinical Practice Guidelines for Diagnosis and Management Genital Tuberculosis in Females

Nalini Mahajan, Ritu Jain, Neena Malhotra, Nymphaea Valecha, Shivani Sabharwal, Shilpa Sharma

Aim

The aim of these good clinical practice guidelines is to encourage a uniform, evidence-based practice for suspecting, diagnosing and managing female Genital Tuberculosis.

Standardised case definitions for TB

World Health Organization criteria are:

1. ***Active disease***: a) Bacteriologically confirmed TB b) Presumptively treated TB
2. ***Latent infection*:** The presence of immune responses to MTB antigens (IGRA or TST positive) without clinical evidence of active TB

Summary of Recommendation

A. Definition

1. Genital Tuberculosis is a result of infection by Mycobacterium Tuberculosis (MTB). It is always secondary to primary contained infection in the lung.
2. The disease exists in Clinical (symptomatic with actively replicating bacteria) or Sub-clinical state (asymptomatic with presence of dormant MTB).
3. Disease progression in an individual depends on their immune competence.
4. MTB attacks the fallopian tubes in 90% cases followed by the endometrium leading to gross damage in the absence of specific symptoms
5. Clinical /Active GTB refers to bacteriologically confirmed disease- HPE, Culture, AFB detected on staining.
6. Latent TB is a term often used in GTB. LTB is diagnosed by a positive TST or IGRA in an asymptomatic individual as per CDC recommendations and is ***not a tissue diagnosis.***
7. ***Since asymptomatic GTB is a tissue diagnosis, it is recommended that the term 'Subclinical GTB (SGTB') should replace LGTB***.
8. SGTB is an important cause of infertility in India.

B. Evaluation

- Confirmatory specific tests for diagnosis of active GTB are culture of endometrial/ target tissue, HPE, AFB staining.
- Diagnosis of sub-clinical GTB is difficult because of the pauci-bacillary status and lack of specific symptoms.
- ***Diagnosis of sub-clinical GTB should be based on a combination of tests rather than one single test - NAAT, Koch's culture, AFB staining and Endoscopy.***
- NAAT (DNA PCR) pick up cases with low bacterial load. Both dead and living MTB are estimated.
- The traditional non-automated DNA PCR tests have a false positive rate of 20%.
- The test remains positive for a long time so ***should not be used in previously treated patients to check disease clearance or make a diagnosis of recurrence.***

- Gene Xpert is a fully automated DNA PCR test. It has a ***high negative predictive value***. Identifies Rifampicin resistance. Recommended to reduce false positives.
- ***IGRA's could contribute supplementary information*** as part of the diagnostic work-up. (ECDC guidance document). ***IGRA identifies host reaction to primary exposure.***
- IGRA's have a ***99.8% negative predictive value*** for progression. High NPV for progression of IGRAs indicates that ***at the time of testing and in the context of an overall risk assessment, progression to active TB in healthy immunocompetent individuals with negative IGRAs is very unlikely in the next 2 years*** based on follow up of patients. Therefore, IGRAs may be used in this context. (ECDC Guidance document).
- ***Endoscopic evaluation*** – signs of tubercular infection can be visualized on endoscopy. Definitive signs include caseation. Other evidence eg hydrosalpinx, pelvic or IU adhesions ***can be suggestive but not diagnostic*** as other pelvic infections can mimic the picture. ***Hence NAAT and Culture are required to clinch the diagnosis. IGRA may help in confirming primary exposure.***

There is an urgent need for accurate tests to diagnose SGTB and treat persons with high risk of reactivation and avoid unnecessary treatment

C. Management

- A decision on management of SGTB based on a combination of tests is more prudent.
- For active TB i.e culture positive, HPE diagnosis or AFB stain positive, ATT should be advised for 6 months (Index TB Guidelines). ***Culture should be repeated after 3 months of treatment***. Drug sensitivity initially (if possible) or in the event of a repeat culture positive should be carried out.
- In patients of **Unexplained Infertility** having an EB positive for DNA PCR but negative Koch's culture and IGRA, treatment should be withheld, as it may be a false positive. A repeat IGRA may be done after 3 months to look for conversion. A repeat endometrial sample can be obtained by endometrial curettage under GA for gene X.
- If the patient becomes pregnant IGRA may be repeated at 8-12 weeks of pregnancy as activation of MTB may occur during pregnancy when immunity is altered.
- In patients of UI if both IGRA and EB for NAAT is positive full course of ATT should be offered. Neither of the tests should be repeated, as they remain positive even after treatment. ***Repeat treatment on the basis of a positive EB for NAAT is not advised.***
- In patients with **TF, Asherman's or frozen pelvis** ATT may be offered even when tissue diagnosis is negative. Previous surgical intervention or non- MTB infection may also lead to adhesions and IGRA may be helpful in identifying primary exposure. Decision on advising ATT in such a situation rests with the treating physician. ***ATT does not reverse the damage that has occurred. ATT in these cases may not improve the outcome of fertility treatment.***
- ATT can lead to liver toxicity. ***Baseline LFT needs to be done***. Monitoring of LFT every 4-6weeks is important if patient is symptomatic or in patients > 35 years old, daily alcohol consumption, abnormal baseline LFTs or a history of hepatic disease. Patient should be apprised to look out for other side effects eg joint pains, visual symptoms, s/o peripheral neuropathy. (Guidelines for management of adverse effects of ATT)

- **NTM/MOTT cannot be treated with ATT**. They require identification of species and specific sensitivity tests. There is paucity of literature on extra-pulmonary effects of MOTT. NTM are often resistant to treatment. The macrolides clarithromycin and azithromycin have become the cornerstones of therapy for MAC, Ofloxacin and Ciprofloxacin also seem to be effective.

Background

Tuberculosis (TB) is caused by the bacterial pathogen Mycobacterium tuberculosis (MTB). It is one of the oldest and hardiest diseases known to mankind. The earliest mention of the disease is in Ayurveda by Charak 3000BC and in Egyptian mummies. World Health Organization Global Tuberculosis Report (2013) states that there were 8.6 million incident tuberculosis (TB) cases globally and India contributed 26% to this global scenario. Epidemiological data indicates that 15-20% of all TB cases are extra-pulmonary TB (EPTB) this figure increases to 50% in HIV infected individuals ((Sharma S et al 2014). Approximately 10% of infected individuals develop active tuberculosis at a later stage of their life, 5% in the first 2 years after infection and 0.1% per year thereafter**.** ***Risk of progression is highest within the first 2 years of exposure. Impaired immunity such as HIV infection increases the risk to 10% per year and ~50% per lifetime***. The remaining infected individuals have asymptomatic or latent tuberculosis (LTB) and do not spread infection to others.

Tuberculosis can affect any organ in the body through haematogenous or lymphatic spread from its primary site of infection - the lung. In females, genital TB infection (FGTB) first strikes the fallopian tubes (90 %), followed by the endometrium (50 %-60%) and ovaries (10-30 %), cervical involvement is seen in 5–15% patients (Schafer), vaginal and vulval disease is rare about 1%. Symptomatology is varied with the commonest presentation being infertility and menstrual irregularity. One percent of all gynaecological admissions in India and 17.4% in infertility clinics are for GTB (Arora et al 2014). The prevalence of FGTB amongst infertile women in India has been reported to be 18 – 19% (Das et al 2008)

Table 1: Symptoms related to genital tuberculosis

Systemic	Infertility	Menstrual	others
Weight loss Fatigue Low grade fever	Primary Secondary	Amenorrhea Menorrhagia Metrorrhagia Oligomenorrhea	Abdominal swelling Post-coital bleeding Vaginal discharge Pelvic pain Dyspareunia

Host Response to MTB

MTB triggers a complex immune response within the body to fight and control the infection by creating a pool of long-lasting memory T-cells specifically directed against the MTB antigens. Immune response develops 4–6 weeks after primary infection. Macrophages are the body's first line of defence, having the ability to ingest and kill the bacterium. MTB bacilli can however persist within the macrophages because of immune escape mechanism (Russel et al 2010). The classic tubercular granuloma is formed as a result of tissue reaction at the site of infection. It contains macrophages surrounded by T & B lymphocytes & fibroblasts. The outcome of infection- primary active infection or development of adequate immunity, is determined by the balance between host immunity and bacillary multiplication. Reactivation & development of post-primary TB can occur many years after latency (Gideon and Flynn 2011).

Latent Tuberculosis Infection (LTBI)

Latency is a clinical term suggesting exposure to infection in the absence of any clinical symptoms. Centre for disease control & prevention (CDC 2010) states that 'latent TB designates a condition in which an individual is infected with MTB but does not currently have active disease. Persons with LTBI are asymptomatic, have a negative chest radiograph & are not infectious. Diagnosis is based on a positive Tuberculin skin test (TST), a delayed hypersensitivity reaction to the purified protein derivative of MTB or Interferron gamma release assay (IGRA), a T-cell response to MTB-specific antigens'. MTB remains viable in people with latent infections and reduced immunity can lead to reactivation. Latent infection has been described as a dynamic process of bacterial persistence & immunologic control. It has been suggested that TB infection should be viewed as a continuous spectrum extending from **sterilizing immunity**, to **subclinical active disease, to fulminant active disease** (Lin & Flynn 2010**)**. This dynamic equilibrium between host and parasite appear to be genetically controlled (Kondratieva et al 2014).

Dormancy: ***Dormancy is a stable non-replicative state*** of the bacterium where bacteria have reduced metabolic activity, including transcription and translation. *It can occur during antibiotic therapy if the bacterium develops a resistant cell wall* preventing penetration of the drug. Dormant bacteria can be resuscitated into a metabolically active growing population by exogenous factors.

Reactivation of MTBI and GTB- Risk factors

1. Immuno-compromise is the most important cause of reactivation. Reactivation or susceptibility to infection is seen in immuno-compromised HIV individuals and in patients administered biological agents (TNF alpha antagonists) for treatment of arthritis.
2. Surgical manipulation- reactivation has been observed after laparoscopy, hysteroscopy, hysterosalpingography and pelvic surgery (Ballon et al 2010).
3. High steroid levels and an increased vascularity during ovarian stimulation are thought to be the triggering factors in the infertile population going through in-vitro fertilization.
4. Use of steroids and immune therapies – common in infertile patients with recurrent implantation failure and recurrent pregnancy loss.

For resource-limited countries and other middle-income countries where burden of disease is high WHO recommendation for treatment of LTBI is limited to people living with HIV and children below 5 years of age who are household or close contacts of people with TB.

(Guidelines on the management of LTB1 2015). Given the adaptive ability of the mycobacterium indiscriminate use of ATT has an immense potential to promote drug resistance. In India levels of multidrug-resistance are lower than 2.2% (1.9–2.6) among new cases and as high 15% among retreatment cases (Tuberculosis control in the South East-Asia Region 2015).

Diagnosis of female Genital TB (FGTB)

FGTB is almost always secondary to a tubercular lesion in another part of the body. Diagnoses poses a unique challenge because of an asymptomatic presentation, non-specific signs and symptoms, pauci-bacillary status and poor sensitivity of available tests.

Tests for TB

Both specific and non-specific tests are available.

Specific Tests available for diagnosis of tuberculosis are:

- AFB staining
- Culture methods
- Histopathology
- Immunological test
- Molecular tests -Nucleic Acid Amplification Tests (NAAT).

Non-Specific Tests

- Imaging methods.
- Endoscopy

Specific Tests

AFB staining

Ziehl-Neelsen (ZN) staining for acid fast bacilli (AFB) requires 10^4 -10^6 bacilli/ml of tissue or fluid specimens to give a positive result. AFB is not species specific. It is limited by its poor sensitivity and poor predictive value. The detection rate is 10%. (Wang et al 2002)

Histopathology

Histopathology is easy, quick and cheap, identifying the characteristic features of M. tuberculosis. A caseous granuloma with giant epithelioid cells is suggestive of TB. Ideal time for endometrial sampling is the late secretory phase of the menstrual cycle which is favourable to identify the classic giant cells and tubercles. For better pick-up multiple site biopsy is advisable as the infecting organisms are scarce in genital TB (Norbis et al 2014, Thangappa et al 2011). It is important to rule out pregnancy before taking a pre-menstrual biopsy. Correlating diagnostic criteria and HPE results by bivariate analysis, the sensitivity of HPE was 10.7 per cent and the specificity was 100 per cent (Santosh K et al 2013).

Limitations

1. Similar lesions may be found in other conditions like leprosy, rheumatoid arthritis, systemic lupus erythematous, pneumoconiosis and sarcoidosis, fungal infections and syphilis.
2. In the fallopian tube in early disease there may be non-caseating granulomas while in the ovary, vagina and vulva caseation is rare. TB of the cervix may mimic cervical malignancy.
3. Endometrial shedding leads to inadequate granuloma formation.
4. Bacteriologically mute lesions may be present.

Tissue Culture

Culture remains the gold standard for laboratory confirmation of MTB and is also required for isolating bacteria for drug-susceptibility testing and genotyping. 10-100 bacilli/ml of sample are required and it takes 2-6 weeks for the growth of Mycobacterium in culture. Traditionally Lowenstein-Jensen culture has been used, addition of the BACTEC MGIT™ (Mycobacteria Growth Indicator Tube) system has shortened the time to diagnosis to 2weeks though the culture dish is still observed for 6weeks before a negative result is reported. BACTEC MGIT is a rapid liquid culture method that utilizes fluorescence technology. It senses oxygen reduction in the culture media, which is then centrifuged and stained with ZN stain to identify MTB. Positive cultures are reported usually

within 10 – 12 days. The advantages of liquid culture are its sensitivity, identification of *Mycobacterium* species and ability to perform phenotypic drug susceptibility tests (DSTs) and genotyping for further molecular epidemiology studies. Goel et al 2013, showed that the positivity in LJ medium and BACTEC for premenstrual samples were 1.83 and 8.8 per cent, respectively. The radiometric culture BACTEC has a sensitivity of 80- 90% whereas the LJ medium has a sensitivity of only 30- 35% for endometrial sample (Shrivastav et al 2014). This high sensitivity is particularly useful in cases of genital TB as traditional methods show poor recovery of AFB. In addition to pauci-bacillary status bacteriostatic substances can inhibit growth of MTB leading to a low rate of positivity in culture.

Immunological Tests

There are currently two diagnostic methods that support the diagnosis of LTBI: the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs). Both tests are immunological methods that detect an immune response to antigens and consequently do not allow a direct measure of persistent infection (ECDC).

Tuberculin Skin Test (*TST)*

The TST is performed by injecting 0.1 ml of tuberculin purified protein derivative (PPD) into the inner surface of the forearm intra-dermally and read after 48-72 hrs. A positive Mantoux test >10mm is taken as an important criterion to suspect MTB. Tuberculin skin test specificity is low and variable in BCG-vaccinated populations (Pai et ai 2008).

Limitations

1. It can be *false positive* in infection with non- tuberculosis mycobacteria, previous BCG vaccination and false negative in cutaneous anergy, overwheming TB infection, recent tuberculosis and in immune-compromised state.
2. Mantoux testing is not recommended for diagnosis in case with previous TB disease and where past Mantoux reactions ≥ 15 mm.
3. It *cannot differentiate* between LTBI or active disease. (CDC fact sheet)

IGRA's

IGRAs detect the presence of cellular immune responses towards MTB - specific antigens. They measure Interferon-gamma (IFN-γ) release in response to the RD1-encoded (genomic region of difference) immunodominant antigens ESAT-6 (early secretory antigenic target-6), CFP-10 (culture filtrate protein 10) and the TB7.7 antigens. IGRA's cannot distinguish between active TB and LTBI but results are not confounded by BCG vaccination and exposure to NTM (Lange et al). Antigens used in IGRA are absent in most of NTM (with the exception of M. flavescens, M. marinum, M. kansasii and M. szulgai), as well as from BCG strains (Harboe et al 1996, Mahairas et al 1996, Anderson et al 2000).

Two commercial IGRAs are available, the QuantiFERON-TB Gold In-Tube assay (QFT-GIT) (Cellestis Ltd., Australia) and the T-SPOT-TB (Oxford Immunotec, UK). Indeterminate results reflect technical factors (e.g. inappropriate storage of blood) or an individual with impaired immune response and a repeat test is recommended in this situation to differentiate between the two. IGRAs are ideal for serial testing and can be repeated any number of times without sensitization and boosting (Pai et al 2007).

The ECDC guidance document suggests ***that IGRA's should not replace the standard diagnostic methods for diagnosing active TB****. In certain clinical situations (e.g. patients with extrapulmonary TB, patients who test negative for acid-fast bacilli in sputum and/*

or negative for M. tuberculosis on culture, TB diagnosis in children, or in the differential diagnosis of infection with NTM) ***IGRAs could contribute supplementary information as part of the diagnostic work-up***. A negative IGRA does not rule out active TB.

Sensitivity, Specificity, Negative and Positive predictive values: Specificity is 99.4% (CI 97.9-99.9) and is unaffected by BCG vaccination. Anergy due to advanced disease, malnutrition, and HIV-associated immune suppression may lower the sensitivity of IGRAs.

According to the ECDC guidance document the positive predictive value (PPV) for progression of IGRAs may be used as part of the overall risk assessment to identify individuals for preventive treatment (e.g. immunocompromised persons, children, close contacts, and recently-exposed individuals). Similarly, the high NPV for progression of IGRAs indicates that ***at the time of testing and in the context of an overall risk assessment, progression to active TB in healthy immunocompetent individuals with negative IGRAs is very unlikely in the next 2 years*** based on follow up of patients. Therefore, IGRAs may be used in this context. Studies included in the meta-analysis also included subjects who were at high risk of developing TB disease, such as close contacts of active TB patients. The NPV for progression was 99.8%.

Nucleic acid amplification tests (NAAT)

NAA tests are used to amplify DNA (Deoxyribose nucleic acid) and RNA segments with high specificity to rapidly identify the microorganisms in a specimen. Turnaround time is 48-72 hours. False positives may occur due to contamination of specimens with M. tuberculosis DNA product from the PCR laboratory. One of the major disadvantages of PCR is the inability to detect a difference between viable and nonviable organisms. ***Therefore, the test can remain positive for long periods in patients who are taking anti-TB medications or who have completed TB treatment. It should therefore not be used for detection of LGTB1in patients treated for pulmonary or extra-pulmonary Koch's previously***. False negative results may occur because of the inefficient extraction of the DNA due to low mycobacterial numbers, or the presence of PCR inhibitors. The presence of PCR inhibitors has been reported in sputum, pus samples and tissue biopsies (Zakham et al 2012). Shrivastav et al 2014 in his study found that PCR negative samples were positive by culture methods and concluded that DNA PCR done alone is not reliable for TB diagnosis and suggested that it should be combined with culture. ***Even for pulmonary TB where bacterial numbers are high and sample collection is easy it is suggested that NAATs should be interpreted within the context of the patient's signs and symptoms, and should always be performed in conjunction with AFB smear and culture.***

Types of NAAT

1. **DNA-PCR**
   a. Ampiclor: amplifies a portion of the 16S rRNA gene that contains a sequence that hybridizes with an oligonucleotide probe specific for M. tuberculosis complex bacteria
   b. MTD-2: should not be used for patients who have taken TB medications in the last twelve months or who have taken TB medications for more than 7 days.
   c. In-house DNA PCR tests – eg. Mycoreal. Many laboratories have developed in-house DNA PCR tests.

      Gene-Xpert: The Xpert MTB/RIF (Xpert) assay (Cepheid Inc., Sunnyvale, CA, USA) is a cartridge-based, semi-automated, rapid molecular assay, which permits rapid TB diagnosis through detection of the DNA of MTB and simultaneous

identification of a majority of the mutations that confer rifampicin resistance (which is highly predictive of multi-drug resistant TB [MDR-TB]). The entire process is carried out in a closed automated system except for addition of the specimen into the cartridge thus reducing contamination. ***WHO now recommends gene Xpert over conventional tests for diagnosis of TB in extrapulmonary tuberculosis as it has pooled specificity of >98.7%, Senstivity - 58.2%, Positive predictive value- 66.7% and Negative predictive value 97.7% for extrapulmonary specimens.*** Xpert MTB/RIF assay appeared to be more reliable method for the diagnosis of TB for AFB smear-positive samples, but less sensitive (47.2%) for smear-negative samples especially in extrapulmonary samples (Ozkutuk et al 2014) It can increase the detection of MTB in EPTB by 2-3 times as compared to conventional techniques. Xpert could detect 12.5% and 15% more positive cases as compared to L.J culture and ZN microscopy respectively indicating a higher sensitivity (Iram et al 2015).

Limitation

1. Affected by humidity and heat.
2. Detects non-viable bacteria.

2. Single tube nested reverse transcription polymerase chain reaction (STN RT-PCR)

Detects only the live organism in the clinical specimen as well as Phenotypic drug susceptibility testing. The major drawback is that it needs to be transported in ice to the laboratory within 2 hours to prevent degradation of RNA since the average half-life of bacterial mRNA is three minutes (Therese et al 2012).

Of the NAATs only the line probe assay and Xpert MTB/RIF have been endorsed by the Word Health Organization for use in low- to middle-income countries. The line probe assay simultaneously detects MTB and common rifampicin and isoniazid resistance mutations, but has a sensitivity of 58–80 % and still necessitates laboratory PCR facilities beyond the reach of many resource-limited settings. The Xpert MTB/RI is automated and rapid. Xpert MTB/RIF has a lower sensitivity in smear-negative sputum samples (68 %), and its ***sensitivity in extra-pulmonary TB samples is highly variable*** (median 77.3 %, range 25.0–96.6 %), leaving a significant proportion of TB disease reliant on sub-optimal accuracy from diagnostic tests.

Role of whole genome sequencing

This may overcome the shortcomings of the NAAT's.

Whole genome sequencing (WGS) of clinical MTB isolates has been used to retrospectively track MTB transmission events and discriminate between re-infection and relapse cases (Haas et al 2016). WGS may identify the organism 1–3 days after a liquid culture flags positive.

Studies comparing diagnostic tests for FGTB

Conventional methods of diagnosis namely, HPE, AFB smear and culture have low sensitivity. There is a significant difference in sensitivities of different tests 33.79% for ZN smear examination, 48.9% for LJ culture, 55.8% for BACTEC culture,74.4% for PCR test (Shrivastav et al 2014). Studies comparing various testing modalities are given below.

Studies Evaluating IGRSs

Diagnostic value of IGRAs has rarely been evaluated in FGTB only two studies (Lui et al 2016 & Mahajan et al 2016) are available.

a. **Lui et al 2016** evaluated the diagnostic value of T- SPOT.TB for diagnosing FGTB in an area with high TB burden. Their study enrolled ***66 patients***, 32 were diagnosed with confirmed FGTB, 33 with non-TB including ovarian tumor, pelvic inflammatory diseases, endometriosis, endometrial polyp, abscess of fallopian tube, cyst of fallopian tube, and endometrial carcinoma. T SPOT.TB results were evaluated against patients' final diagnosis of FGTB which was made based on clinical manifestations, radiology, microbiological and histopathological evaluation, and response to anti-TB treatment.

   The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, and negative likelihood ratio of T-SPOT.TB for diagnosis of FGTB were **94%**, 70%, 75%, **92**%, 3.09, and 0.09, respectively. T-SPOT. TB appeared to be a valuable and rapid diagnostic method for FGTB in TB endemic settings **with high sensitivity and NPV**.

b. **Mahajan et al 2016** – sought to evaluate if IGRA could be used in GTB diagnosis in combination with NAAT and culture to improve diagnostic accuracy and also to develop an algorithm for treatment of GTB. EB for DNA PCR and Koch's culture was correlated with IGRA in **180** treatment naïve infertile Indian women. Taking Koch's culture as the gold standard for diagnosis the sensitivity of Q gold was 100% and specificity was 61.2%, PPV was 9.46%, NPV was 100% and agreement between tests was 62.7%. Koch's culture correlation with DNA PCR showed sensitivity and specificity of 0% and 71.6% respectively, the positive predictive value (PPV) was 0% and negative predictive value (NPV) was 94.6%, the agreement between tests was 68%**. *They concluded that the high negative predictive value of IGRA could be valuable in ruling out GTB. However, for a confirmatory diagnosis, a combination of tests should be carried out. Importantly EB for DNA PCR was negative in 7 cases with positive cultures re-emphasizing the need for doing both culture and NAAT.***

Studies evaluating NAAT

a. **Shrivastav et al 2014:** Compared the modalities of PCR technique, AFB culture and staining. They concluded that conventional methods of diagnosis like microscopy and culture were less sensitive when compared with PCR. An important limitation was that **PCR negative samples were found to be positive by culture methods**. They concluded that Deoxyribose nucleic acid PCR is not reliable for TB due to false positive or negative result and suggested that **both culture and PCR as important diagnostic methods for detection of GTB.**

b. **Radhika AG et al 2016**: compared diagnostic accuracy of standard diagnostic tests in three subsets of gynaecological conditions (infertility, menstrual abnormalities and pelvic inflammatory disease). Total of **90 patients** recruited in three groups of 30 each underwent endometrial sampling. The biopsied tissue was sent for histopathological examination, AFB smear examination, culture in Lowenstein-Jensen (L-J) and BACTEC 460 TB culture media and nested PCR testing. BACTEC had a sensitivity of 40% with a specificity of 90% while PCR showed a sensitivity and specificity of 62.5% and 54%, respectively, as compared to conventional methods (L-J culture or histopathology). ***Addition of PCR to BACTEC improved sensitivity from 40% to 52%.*** They concluded that combination of BACTEC and PCR improved detection as compared to conventional tests with an advantage of early results.

Studies evaluating Gene Xpert in GTB

a. **Denkinger et al 2014**: systemic review and meta-analysis 18 studies involving **4461 samples**. Xpert pooled specificity was consistently >98.7% against CRS (composite reference standard), across different sample types. Based on this systematic review,

the ***World Health Organization now recommends Xpert over conventional tests for diagnosis of TB in lymph nodes and other tissues, and as the preferred initial test for diagnosis of TB meningitis***. CRS being - smear/ culture/ histopathology/ cytology/biochemical analysis/ response to treatment at 6 months/ADA levels/ radiological findings - **any two positive**.

b. Singh et al 2016: Prospective cohort study on treatment naïve TB patients. **761** extra-pulmonary samples unfortunately study had no endometrial samples. Comparison of GeneXpert results to CRS demonstrated sensitivity of 100% and 90.68%, specificity of 100% and 99.62% for pulmonary and extra-pulmonary sample.

c. **Gürsoy et al 2016: 1019** extra-pulmonary/2160 total samples. Xpert was evaluated against culture and AFS. Sensitivity of Xpert MTB/RIF test for extra-pulmonary samples was found to be at moderate level; sensitivity of the test was found to be decreased especially in AFS negative samples with less bacilli load. ***Specificity of Xpert MTB/RIF test to the agent in all samples was found to be extremely high.***

d. **Sharma SK et al 2014** sought to evaluate the performance of GeneXPERT in extrapulmonary TB. In a study of 1376 samples they had **95 endometrial** samples. All adult subjects with clinical suspicion of EPTB were enrolled and were either treatment naıve or were on anti-TB treatment for <2 weeks. The samples were subjected to Ziehl Neelsen staining, Xpert MTB/RIF assay and culture on both BACTEC and Lowenstein–Jensen media. The **overall sensitivity and specificity of Xpert MTB/RIF assay with culture were 71% and 95%, respectively**. The sensitivity increased from 50% to 91% with increasing conventional diagnostic parameters (of the CRS) taken as positive, which clearly suggests that if the result by Xpert MTB/RIF test is positive for a sample, the case is more likely to be a true case of TB. For **endometrial samples the specificity was 100%, sensitivity 33 %PPV 100% and NPV 96% Addition of CRS improved sensitivity to 50%**.

Non - Specific Investigations for GTB

Imaging

Chest Radiograph

Old healed or active infection is usually present in 10-50% genital tuberculosis; hence chest radiograph is important for treatment and for contact tracing and prevention.

Abdominal Radiography

There are no characteristic radiographic features that are pathognomonic for genital tract TB but certain findings raise suspicion of its presence.

An ***X Ray of abdomen*** may show calcified pelvic and abdominal lymph nodes, a characteristic and recognized sequela of healed genital tract TB.

Hysterosalpingography

HSG may reveal certain abnormalities that are suggestive of pelvic TB, though procedure is not done to diagnose tuberculosis. Hysterosalpingography is contraindicated in the presence of recent acute pelvic infection or tuberculosis, for fear of exacerbation following the procedure.

Ultrasound

High-resolution abdominal and transvaginal ultrasonography may demonstrate features suggestive of MTB infection.

CT scan & MRI

CT/MRI may show adnexal mixed (solid & cystic) mass with multi-locular caseous necrotic enhancement, high density ascites, thickened and enhanced peritoneum.

Lymphadenopathy with low density in the centre may be seen in upto 40% of patients. MRI is useful in TO masses.

Findings suggestive of GTB on imaging are listed in Table 2.

Table 2: Radiological and Ultrasound findings in GTB

Investigation	Findings
X-ray- HSG	Fallopian tubes first to be affected in TB may appear as • Beaded - ragged outlines with multiple strictures. • Rigid with small terminal sacculations of the ampullary end. • Occluded-at corneal or distal end. Distal occlusion has the appearance of a sperm head or tobacco pouch. • Gross hydrosalpinx may be seen. Uterus and endometrium • Uterine cavity may appear shrivelled, deformed with ragged margins. • There may be filling defects, • Intrauterine adhesions • Lymphatic extravasation of the dye. • Uterine cavity may give maltese cross appearance in case of severe damage. • Fistulous tracts between the genital tract and other pelvic organs may be identified.
X-ray abdomen	calcified pelvic and abdominal lymph nodes.
Ultrasound	Variable: ranging from normal findings to Thin endometrium Heterogeneous appearance of endometrium Endometrial fluid Endometrial calcifications Endometrial bands Subendometrial calcifications Intrauterine synechie: Disruption in the continuity of the endometrium or as irregularities in the endometrium surrounded by cystic spaces Tuboovarian mass Hydrosalphinx-cog wheel sign Inhomogeneous enlarged ovaries Follicles with echogenic rims Adnexa appears fixed Free and loculated peritoneal fluid On Doppler:Impaired endometrial midcycle vascularity On Sonohysterography :Intrauterine adhesions appear as linear echogenic bridges in the fluid filled endometrial cavity Poor distensibility of the cavity
CT Scan MRI	Adnexal mass mixed (solid & cystic) with multilocular caseous necrotic enhancement, High density ascites, Thickened and enhanced peritoneum, Lymphadenopathy TO Masses Lymphadenopathy Intestinal thickenning

Endoscopy

Endoscopy remains the gold standard for evaluation of pelvic infection. Laparoscopy and Hysteroscopy serve as an aid to diagnosis with the added advantage of allowing intervention at the same sitting. Laparoscopy aids in visual inspection of the ovaries, fallopian tubes, peritoneal cavity and biopsy of the tuberculous lesions. Hysteroscopy allows identification and treatment of intra-cavity lesions.

Laparoscopy

Presents a variable picture depending on the degree of damage caused by MTB. Unfortunately, these features are not restricted to GTB and may also result from gonococcal/pyogenic bacilli infection. Table 3 lists the various findings on endoscopy.

Sharma et al 2008 reported findings in acute and chronic stage GTB. In subacute stage, there appeared to be congestion, edema and adhesions in pelvic organs with multiple fluid-filled pockets. Miliary tubercles, white yellow and opaque plaques were also seen over the fallopian tubes and uterus. In the chronic stages varies nodular salpingitis, patchy salpingitis, unilateral or bilateral hydrosalpinx with retortshaped tubes and pyosalpinx or caseosalpinx were found. In a follow up of these patients after ATT the authors reported that ATT did not improve advanced fibrotic lesions (eg, pelvic and perihepatic adhesions, bilateral blocked tubes)(Sharma JBet al 2016)

ArpithaVJ et al 2016: carried out a prospective observational study in which infertile women who had clinical and HSG findings suggestive of GTB underwent endometrial TB-PCR and hystero-laparoscopy. On laparoscopy 60% of cases showed positive correlation with endometrial TB- PCR and tubal involvement was seen in majority of cases.

Table 3: Endoscopic Findings in FGTB

Procedure	Findings
Laparoscopy	Normal Subacute stage, Congestion, edema and adhesions in pelvic organs with multiple fluid-filled pockets. Chronic stage Adhesions – Pelvic, Peri-tubal, Bowel / Omental adhesions, Supra-hepatic adhesions. Fallopian tube- Hydrosalpinx, Pyosalpinx, Haematosalpinx, Caseo-salpinx. Cornual block, Beading, Rigid tubes, Fimbrial phimosis, TO mass. Peritoneal – Straw coloured fluid in Pouch of Douglas Tubercles on the peritoneal surface Miliary tubercles, white yellow and opaque plaques over the fallopian tubes and uterus. Uterus showing intravasation of dye. Oophoritis Caseous deposits Frozen pelvis
Hysteroscopy	Normal appearance Bald endometrium Spotted endometrium Endometrial caseation Endometrial calcification Endometrial tubercles Irregular appearance of uterine cavity Intrauterine adhesions Distorted ostia Periosteal fibrosis Caseous material coming out of the ostia Poor distensibility of uterine cavity Irregular appearance of endocervical canal Cervical stenosis/adhesions

S. Rajaram et al 2016: conducted a prospective study on 50 patients with chronic pelvic pain to estimate the prevalence of GTB and correlate laparoscopic findings with microbiological and histological diagnosis of TB. Prevalence of GTB was 36% and the concordance of results between laparoscopy and specific diagnostic tests, showed a substantial agreement (kappa value = .716) for PCR. Another important observation was that four women with laparoscopic features suggestive of TB did not have positive TB-PCR. In addition, ***PCR failed to detect two cases that were positive by culture and histology.***

Baxi et al 2011: in a correlation between endoscopic findings and EB DNA PCR in 174 patients found that the sensitivity and specificity of endoscopic evaluation was 85.71 and 22.8% respectively. The presence of periovarian adhesions, cornual block, tubal beading, tubercles, intrauterine adhesions, and ostial fibrosis had very strong association with positive TB PCR.

Hysteroscopy

Major physical changes to the endometrium take a long time to appear because of repeated shedding. Hysteroscopy may reveal a pale looking endometrium, caseation or various degrees of adhesions. In advanced cases, uterine cavity may be shrunken with poor distensibility. Table 3 details the findings. The overall incidence of positive TB PCR with hysteroscopic finding was reported to be between 32.18 % (Baxi et al) and 39 % (Subrat et al).

Management

Management of GTB in general gynaecological patients

This does not pose too much of a problem as the patients are symptomatic and have suggestive clinical features. The larger problem is ensuring appropriate investigation of women for GTB if signs and symptoms are vague eg AUB, prolonged vaginal discharge, unexplained infertility etc.

Management of GTB in Infertile women

It is important as delay in treatment may lead to irreversible damage and sterility. ***In order to avoid development of MDR-TB empirical treatment or treatment on basis of sole PCR positive should be avoided***. Kriplani et al 2017 conducted a prospective randomized study on 100 women with primary or secondary infertility. Women with positive endometrial DNA-PCR, patent tubes on laparoscopy, and all other tests being negative for genital TB were randomized into two groups. Group 1 received ATT for 6 months while Group 2 were not given ATT. The pregnancy rate in both groups did not show any difference (p=0.422). Their study did not validate ATT for positive DNA-PCR. They also provided evidence that repeating PCR at 6 months and at 12 months has no role and ATT should not be repeatedly given to the patient on the basis of repeat DNA-PCR alone. An ICMR study (to be published) has arrived at a similar conclusion regarding treatment of GTB on basis of EB PCR from MTB.

In endemic areas in the context of Genital Koch's all cases should be treated with a **full course of ATT for 6months**. Treatment for 6 or 9 months has a similar rate of relapse (WHO guidelines). Side-effects of ATT include dermatological, gastro-intestinal, neurological effects and arthralgia. Adverse effects such as hepatitis, dyspepsia, exanthema and arthralgia were responsible for termination of therapy in up to 23% of patients during the intensive phase (WHO update). ***Baseline LFT needs to be done***. Monitoring of LFT every 4-6weeks is important if patient is symptomatic or in patients > 35 years old, daily alcohol consumption, abnormal baseline LFTs or a history of hepatic

disease. Patient should be apprised to look out for other side effects eg joint pains, visual symptoms, s/o peripheral neuropathy. In case of severe reactions drugs should be withheld till symptoms improve. (Guidelines for management of adverse effects of ATT)

Table 4: Adverse Effects of ATT

System	Most common adverse effect	Management
Dermatologic Adverse Effects	Cutaneous "flushing" reactions Hypersensitivity reactions	Mild rash: Symptomatic management / antihistaminics Severe-Stop all drugs, identify causative drug by restarting each drug at a lower dose every 4 days
Gastrointestinal Adverse Effects	Nausea/vomiting Diarrhea Hepatotoxicity	Symptomatic management Symptomatic Hepatotoxicity: *Asymptomatic*- SGOT, SGPT <3-5*- continue ATT & monitor SGOT, SGPT>3-5* withhold INH till transaminases return to normal Elevated bilirubin with normal transaminases: continue ATT. Levels usually return to normal ***Symptomatic Patient*** Rpt LFT LFT normal- continue ATT, monitor closely LFT abnormal - stop ATT till symptoms resolve and LFT transaminases decrease to < 2x normal
Miscellaneous Adverse Effects	Arthalgias (joint pain) Influenza syndrome Neurotoxicity (nervous system) Optic neuritis (vision)	NSAID's Symptomatic Pyridoxine 50 mg once a day Discontinue drug

1. **Active GTB**: HP diagnosis, MTB Growth on culture
   Management: Full course of ATT for 6mths. Wherever possible drug sensitivity should be carried out. Repeat culture after completing 3mths of treatment (2mths active phase and 1 month of maintenance).

2. **Sub-clinical GTB**

   Patients with Unexplained Infertility

   a. ***Normal Endoscopy, EB Koch's culture negative, EB NAAT positive***
   This could be a false positive. Treatment not advised in the absence of any other signs or symptoms. If index of suspicion is high a repeat EB for DNA PCR using gene Xpert can be done. A supplementary ***Negative IGRA*** **is helpful.**

   b. ***Endoscopy normal, IGRA positive. EB NAAT positive, Koch's culture negative***. Treatment may be offered to the patient since this could be an early paucibacilliary stage of the infection or even a dormant phase which could get reactivated during infertility treatment.

   Management: A full course of treatment for 6months is recommended.

   c. **Only IGRA is positive:**
   This indicates exposure to MTBI it does not indicate GTB in the absence of tissue diagnosis. In endemic countries ***EPTB guidelines do not recommend treatment*** of LTBI in high burden areas. If the physician elects to treat on clinical suspicion, then a full course of ATT is advisable in endemic areas rather than a single /dual agent to avoid risk of MDR-TB.

3. **Patients with Tubal &/or Uterine factor infertility**

Healed/ contained GTB: Pelvic adhesions on laparoscopy &/or Intra-uterine adhesions with negative Tissue culture, NAAT, AFB stain can be classified as healed TBI. The healing process involves fibrosis, the Mycobacterium being sealed within.

Management: Management decision in these cases is difficult as these adhesions can be a result of bacterial infection or a previous surgical trauma. In India since the possibility of Koch's is high, a full course of ATT should be considered especially if there is no previous history of pelvic infection, vaginitis or surgical interference. Isolation of MTB from tissue samples may be difficult. The fibrotic lesion may house viable bacteria which could get reactivated during phases of lowered body immunity. IGRA may be of help in confirming exposure to infection.

FGTB can lead to serious damage to the reproductive organs leading to increased morbidity, infertility and subsequent sterility. Diagnosis is difficult and delayed given the low bacillary load and inaccessibility of the fallopian tube, the first structure to be affected, for tissue diagnosis. Since infertility is labelled as a symptom the term ***Subclinical GTB*** instead of LGTB should be used. ***LTBI diagnosis is based solely on a positive IGRA or TST without symptoms and signs (x-ray) of disease, limiting the ability to detect subclinical disease***.

Studies suggest that the diagnosis of EPTB especially GTB should be based on a combination of tests. Drugs used for ATT have serious side-effects especially drug induced hepato-toxicity and should preferably be started after adequate confirmatory tests. Indiscriminate use of ATT can also lead to drug resistance with serious consequences. Counselling and a full discussion with patients before giving ATT are of paramount importance, given the increasingly litigative nature of society. **There is an urgent need for accurate tests to diagnose SGTB and treat persons with high risk of reactivation and avoid unnecessary treatment.**

NTM /MOTT

Mycobacteria other than *M. tuberculosis* complex and *M. leprosy* are known as Non-Tuberculous Mycobacteria (NTM) and are known by various acronyms. The incidence of NTM infections is increasing worldwide. International Union against Tuberculosis and Lung Diseases (IUATLD) found that the most frequently isolated species in India, China and Korea was *M. avium* complex (MAC). Standardized or accepted criteria to define NTM respiratory disease are lacking. Most infections are acquired either from the water (treated or untreated) or soil. MAC and *M. fortuitum* are frequently isolated from the drinking water distribution systems and swimming pools in both developing and developed countries. They are known to cause a TH1 response. The macrolides clarithromycin and azithromycin have become the cornerstones of therapy for MAC. Ofloxacin and Ciprofloxacin are also effective (Hoon et al 2017).

'Strength of Recommendation' and 'Level of Evidence' for Evaluation and Management FGTB

Evaluation

- Confirmatory specific tests for diagnosis of active GTB are culture of endometrial / target tissue, HPE, AFB staining. **Level 1. Grade A**
- Diagnosis of sub-clinical GTB should be based on a combination of tests rather than one single test - NAAT, Koch's culture, AFB staining and Endoscopy**. Level I1-1 Grade A**
- DNA PCR test remains positive for a long time so should not be used in previously treated patients to check disease clearance or make a diagnosis of recurrence. **Level 1. Grade A**

- Gene Xpert is a fully automated DNA PCR test. It has a high negative predictive value. Identifies rifampicin resistance. Recommended to reduce false posistives. **Level II-I, Grade B**
- ***IGRA's could contribute supplementary information*** as part of the diagnostic work-up. (ECDC guidance document). **Level 1I-2, Grade B.**
- Endoscopic evaluation – signs of tubercular infection can be visualized on endoscopy. Provides supportive evidence. Specific tests required to confirm diagnosis. **Level II-2, Grade A**

Management

- A decision on management of SGTB based on a combination of tests is more prudent. **Level II-3, Grade B**
- For active TB i.e culture positive, HPE diagnosis or AFB stain positive, ATT should be advised for 6 months (Index TB Guidelines). **Level 1, Grade A**
- Culture should be repeated after 3 months of treatment. Drug sensitivity initially (if possible) or in the event of a repeat culture positive should be carried out. (Level III, Grade C)
- In patients of **Unexplained Infertility** having an EB positive for DNA PCR (traditional) but negative Koch's culture treatment should be withheld, as it may be a false positive. **Level 1, Grade A**
- In patients of UI if both IGRA and EB for NAAT is positive full course of ATT should be offered. (Level III, Grade C)
- Repeat treatment on the basis of a positive EB for NAAT is not advised. (Level 1, Grade A)
- In patients with **TF, Asherman's or frozen pelvis** ATT may be offered even when tissue diagnosis is negative. Decision rests with the treating physician. ATT does not reverse the damage that has occurred. ATT in these cases may not improve the outcome of fertility treatment. **(Level II-2, Grade B)**
- ATT can lead to liver toxicity. Baseline LFT needs to be done. Monitoring of LFT every 4-6weeks is important if patient is symptomatic or in patients > 35 years old, daily

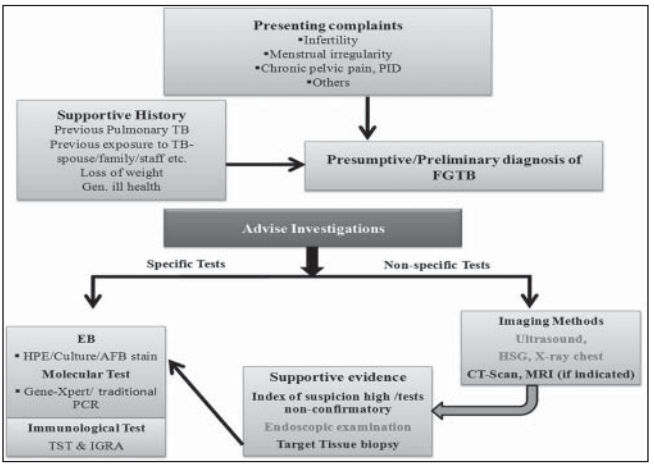

Fig 1: Diagnostic algorithm for female genital tuberculosis (FGTB). PID (pelvic inflammatory disease); EB (endometrial biopsy); HPE (histopathology examinations); AFB (acid-fast bacilli); PCR (polymerase chain reaction); TST (tuberculin skin test); IGRA (interferon gamma release assay); HSG (hysterosalpingography); CT (computed tomography); MRI (Magnetic resonance imaging).

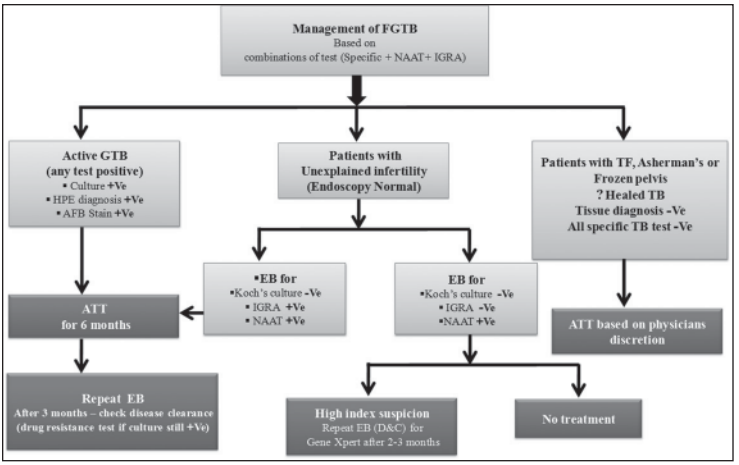

Fig 2: Management algorithm for female genital tuberculosis (FGTB). EB (endometrial biopsy); HPE (histopathology examinations); AFB (acid-fast bacilli); IGRA (interferon gamma release assay); NAAT (nucleic acid amplification test); ATT (antitubercular treatment); D&C (dilatation and curretage).

alcohol consumption, abnormal baseline LFTs or a history of hepatic disease. Patient should be apprised to look out for other side effects eg. joint pains, visual symptoms, s/o peripheral neuropathy. (Guidelines for management of adverse effects of ATT) **Level III, Grade A**

- **NTM/MOTT cannot be treated with ATT**. They require identification of species and specific sensitivity tests. Treatment with macrolides clarithromycin and azithromycin ofloxacin and ciprofloxacin also seem to be effective. **Level III, Grade B.**

The level of the evidence was evaluated using the following grading system
Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed con- trolled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in un- controlled trials might also be regarded as this type of evidence.

Level III: Descriptive studies, case series, case reports, letters, non-systematic reviews, opinions based on clinical experience, and reports of expert committees.

The strength of the recommendation was evaluated as follows:

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

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Infertility Committee

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Management of Infertile Male

K D Nayar, Rhythm Ahuja

Objective: *Male factor is responsible solely for about one third cases of infertility and contributes to another one third. It is important that both male and female partner is evaluated simultaneously. The purpose of this document is to provide clinicians with principles and strategies for the evaluation of couples with male infertility problems, also manage them or refer them timely to expert as needed.*

1. Evaluation of Infertile Male

1.1 Indications for Evaluation

- All couples who fail to achieve a successful pregnancy after 12 months of regular unprotected intercourse.
- Couples need earlier evaluation and treatment, if indicated by medical history and physical findings.
- After 6 months for couples in which the female partner is >35 years old
- Men concerned about future fertility should be evaluated.

1.2 Initial Evaluation

Reproductive history and one semen analysis is minimum for male evaluation.

1.2.1 Reproductive History:

Clinical male infertility history outline

1. Infertility history: Age of partners, time attempting to conceive, Contraceptive methods/duration Previous pregnancy (actual partner/other partner), Previous treatments Treatments/evaluation of female partner
2. Sexual history: Potency, libido, lubricant use, Ejaculation, timed intercourse, frequency of masturbation
3. Childhood and development: Cryptorchidism, hernia, testicular trauma Testicular torsion, infection (e.g., mumps), Sexual development, puberty onset
4. Personal history: Systemic diseases (diabetes, cirrhosis, hypertension) Sexually transmitted diseases, tuberculosis, viral infections
5. Previous surgeries: Orchidopexy, herniorraphy, orchiectomy (testicular cancer, torsion). Retroperitoneal and pelvic surgery Other inguinal, scrotal and perineal surgery, Bariatric surgery, bladder neck surgery,transurethral resection of the prostate.
6. Gonadotoxin exposure: Pesticides, alcohol, cocaine, marijuana abuse, Medication (chemotherapy agents, cimetidine, sulfasalazine, nitrofurantoin,,allopurinol, colchicine, thiazide, b- and a-blockers, calcium blockers, finasteride), Organic solvents, heavy metals, Anabolic steroids, tobacco use, High temperatures, electromagnetic energy, Radiation (therapeutic, nuclear power plant workers), etc.
7. Family history: Cystic fibrosis, endocrine diseases Infertility in the family
8. Current health status Respiratory infection, anosmia, Galactorrhea, visual disturbances, Obesity

1.2.2 Semen Analysis

It is the most crucial test in evaluation of Male.

Instructions for semen sample collection[1]

- The sample should be collected after a minimum of 2 days and a maximum of 7 days of sexual abstinence
- The sample should be obtained by masturbation and ejaculated into a clean, wide-mouthed container made of glass or plastic, from a batch that has been confirmed to be non-toxic for spermatozoa.
- The specimen container should be kept at ambient temperature, between20 °C and 37 °C, to avoid large changes in temperature that may affect the spermatozoa after they are ejaculated into it. It must be labelled with the man's name and identification number, and the date and time of collection.
- The specimen container is placed on the bench or in an incubator (37 °C) while the semen liquefies.
- Note in the report if the sample is incomplete, especially if the first, sperm-rich fraction may be missing. If the sample is incomplete, a second sample should be collected, again after an abstinence period of 2–7 days.

Reference for Semen Analysis:

The semen analysis provides information on semen volume as well as sperm concentration, motility, and morphology. Reference values as published by the World Health Organization (WHO) 2010 are used (Table 1). The diagnosis of azoospermia can be established only after the specimen is centrifuged (preferably at 3,000g) for 15 minutes and the pellet is examined. The current WHO criteria for evaluating sperm morphology are similar to the "strict criteria" described by Kruger (Tygerberg)

1.3 Need of Physical Examination

Table 1: WHO Reference Values for Semen Analysis

Parameter	Lower reference limit (range)
Semen volume (mL)	1.5 (1.4-1.7)
Total sperm number (106/ejaculate)	39 (33-46)
Sperm concentration (106/mL)	15 (12-16)
Total motility (PR + NP)	40 (38-42)
Progressive motility (PR, %)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms, %)	4 (3.0-4.0)
Other consensus threshold values	
pH	> 7.2
Peroxidase-positive leukocytes (106/mL)	< 1.0
Optional investigations	
MAR test (motile spermatozoa with bound particles, %)	*< 50*
Immunobead test (motile spermatozoa with bound beads, %)	*< 50*
Seminal zinc (µmol/ejaculate)	*≥ 2.4*
Seminal fructose (µmol/ejaculate)	*≥ 13*
Seminal neutral glucosidase (mU/ejaculate)	*≤ 20*

CIs = confidence intervals; MAR = mixed antiglobulin reaction NP = non-progressive; PR = progressive.

When the initial screening evaluation reveals an abnormal male reproductive history or demonstrates abnormal semen parameters, a thorough evaluation by a urologist or other specialist in male reproduction is indicated.

Besides a general physical examination ***local examination*** under following headings to be done-

- Examination of the penis, noting the location of the urethral meatus
- Palpation and measurement of the testes

- The presence and consistency of both vasa and epididymides
- The presence or absence of a varicocele
- Secondary sex characteristics, including body habitus, hair distribution, and breast development; and
- Digital rectal examination where indicated.

The diagnosis of congenital bilateral absence of the vasa deferentia (CBAVD) is established by physical examination; scrotal exploration is unnecessary.

Based on the combined results of history, examination semen analysis obtained, additional tests and procedures may be recommended, including serial semen analyses, endocrine evaluation, post-ejaculatory urinalysis, ultrasonography, specialized tests on semen and sperm, and genetic screening.

1.4 Role of Other Investigations[2]

1.4.1 Endocrine Evaluation

- An endocrine evaluation is indicated for men having:
- abnormal semen parameters, particularly when the sperm concentration is <10 million/mL impaired sexual function
- other clinical findings that suggest a specific endocrinopathy.

The minimum initial hormonal evaluation should include measurement of serum FSH and total testosterone (T) concentrations.

When the total T level is low (<300 ng/mL), more extensive evaluation is indicated and should include a second early morning measurement of total T and measurements of serum free testosterone (T), LH, and prolactin (PRL).

The relationships among serum T, Leutinizing hormone (LH), follicle-stimulating hormone (FSH), and PRL concentrations help to provide an understanding of the source of abnormal total T levels. Measurement of the thyroid-stimulating hormone (TSH) concentration also should be obtained in men who require a more thorough endocrine evaluation.

1.4.2 Post-ejaculatory Urinalysis

Table 2: Basal Hormone Levels in Various Clinical Situations

Clinical condition	FSH	LH	T	PRL
Normal spermatogenesis	Normal	Normal	Normal	Normal
Hypogonadotropic hypogonadism	Low	Low	Low	Normal
Abnormal spermatogenesis[a]	High/normal	Normal	Normal	Normal
Complete testicular failure/hypergonadotropic hypogonadism	High	High	Normal/low	Normal
PRL-secreting pituitary tumor	Normal/low	Normal/low	Low	High

[a] Many men with abnormal spermatogenesis have a normal serum FSH, but a marked elevation of serum FSH is clearly indicative of an abnormality in spermatogenesis.

Indication: in men having an ejaculate volume <1.0 mL, except in those diagnosed with hypogonadism or CBAVD. Also rule out improper or incomplete collection or a very short abstinence interval (<1 day).

Procedure: Centrifuge the urine specimen for 10 minutes at 300g, followed by microscopic examination of the pellet at 400X. In men with azoospermia or aspermia, the presence of any sperm in the post-ejaculatory urinalysis suggests retrograde ejaculation. In men with low ejaculate volume and oligozoospermia, "significant numbers" of sperm must be observed to support the diagnosis of retrograde ejaculation; there is no consensus of expert opinion on the minimum number required.

1.4.3 Ultrasonography

Transrectal ultrasonography

It reveals pathology of seminal vesicle, ejaculatory duct, prostate. Transrectal ultrasonography (TRUS) is indicated for oligospermic men having low volume ejaculates, palpable vasa, and normal testicular size with normal serum T.

Scrotal ultrasonography

Scrotal ultrasonography can be used for identifying occult varicoceles that are not palpable, for better defining vague or ambiguous physical examination findings or abnormalities (including apparent masses) and can be performed in men having testes located in the upper scrotum, a small scrotal sac, or other anatomy that hinders physical examination, men with cryptorchidism or a previous testicular neoplasm, but not as a routine screening procedure.

1.5 Specialized Clinical Tests on Semen and Sperm

1.5.1 Quantification of Leukocytes in Semen

Men with true pyospermia (>1 million leukocytes/mL) should be specifically evaluated with culture to exclude genital tract infection or inflammation.

1.5.2 Sperm Viability Tests

***Aim*:** To determine whether nonmotile sperms are viable by identifying which sperm have intact cell membranes.

***Procedure*:** Sperm viability can be assessed by mixing fresh semen with a supravital dye, such as eosin Y or trypan blue, or by the use of the hypoosmotic swelling (HOS) test. In dye tests, viable sperm actively exclude the dye and remain colorless whereas nonviable sperm readily take up the stain. Unfortunately, sperm judged to be viable by means of dye tests can not be used for IVF. In the HOS test, viable nonmotile sperm, which swell when incubated in a hypoosmotic solution, can be used successfully for ICSI. Viable nonmotile sperm can also be identified by means of incubation in pentoxifylline. Viable sperm will develop motility after exposure to pentoxifylline.

1.5.3 DNA fragmentation

The term "DNA fragmentation" refers to denatured or damaged sperm DNA that can not be repaired. A number of clinical tests have been developed to measure sperm DNA fragmentation rates. Direct methods, such as the single-cell gel electrophoresis assay (Comet) and terminal deoxynucleo- tide transferase–mediated dUTP nick-end labeling (TUNEL) assays, specifically analyze the number of breaks in the DNA. Indirect tests, such as the sperm chromatin structure assay (SCSA), define abnormal chromatin structure as an increased susceptibility of sperm DNA to acid-induced dena- turation in situ. Threshold values used to define an abnormal test are 25%–27% for the SCSA and 36% for TUNEL assays

Factors causing DNA damage: advanced paternal age, inadequate dietary intake, drug abuse, environmental pesticide exposure, tobacco use, varicocele, medical diseases, hyperthermia, air pollution, genital inflammation and infectious diseases. DNA damage could occur as a result of protamine sulfate deficiency (with aberrant chromatin remodeling), ROS, abortive apoptosis, and alterations in topoisomerase II activity. DNA damage can also occur due to oxidative stress caused by the generation of ROS from contaminating leukocytes, defective sperm and antioxidant depletion. DNA damage is rare in fertile men whereas abnormal levels of DNA damage are observed in approximately 5% of infertile men with normal semen analysis and in 25% of infertile patients with

abnormal semen analysis. Damaged DNA may cause errors in DNA replication, transcription, and translation during embryogenesis. Sperm DNA damage is associated with spontaneous recurrent miscarriage. However the clinical utility of assessing sperm DNA integrity is debatable.

Existing data do not support a consistent relationship between abnormal DNA integrity and reproductive outcomes.

At present, the results of sperm DNA integrity testing alone do not predict pregnancy rates achieved through natural conception or with IUI, IVF, or ICSI. However, further research may lead to validation of the clinical utility of these tests.

Recommendation[2]

There is insufficient evidence to recommend the routine use of sperm DNA integrity tests in the evaluation and treatment of the infertile couple (Level C).

1.6 Less Commonly Used Specialized Tests

Routine use of ICSI during IVF for male-factor infertility couples has obviated the need of sperm penetration assays. A number of biochemical tests of sperm function have been studied, including measurements of sperm creatine kinase and reactive oxygen species (ROS). ROS appear to be generated by both seminal leukocytes and sperm cells and can interfere with sperm function by per- oxidation of sperm lipid membranes and creation of toxic fatty acid peroxides. Other tests and procedures have been used to select sperm for ICSI and may identify gametes with better quality, including hyaluronic acid binding, membrane maturity testing, apoptotic evaluation, and magnified sperm examination. However, these tests have a very limited role in the evaluation of male infertility because they have limited clinical utility and typically do not affect treatment.

1.7 Tests for Antisperm Antibodies

Antisperm antibodies (ASA) are a rare cause of male subfertility that do not require routine testing and are typically managed with the use of ICSI.

1.8 Genetic Screening

Men with non obstructive azoospermia or severe oligozoospermia (<5 million/mL) are at increased risk for having a genetic abnormality compared to fertile men (Table 3).

1.8.1 ***Cystic fibrosis gene mutations***

There is a strong association between CBAVD and mutations of the CFTR gene, which is located on chromosome 7. Genetic evaluation should also be considered for those having either abnormality - congenital bilateral obstruction of the epididymis or unilateral vasa agenesis.

- Almost all men with clinical cystic fibrosis exhibit CBAVD.
- Additionally, as many as 80% of men with CBAVD have documented mutations of the CFTR gene.
- Failure to detect a CFTR abnormality in men with CBAVD does not exclude the presence of a mutation that cannot be identified with currently available methods. Therefore, most men with CBAVD should be assumed to have a CFTR gene mutation unless they have renal anomalies.
- To determine the risk of conceiving a child affected with cystic fibrosis, it is important to test the female partner of an affected man. Even if the female partner is negative according to currently available testing, the couple remains at some risk because some of the less common mutations may be missed unless the entire gene is sequenced.

1.8.2 *Karyotypic chromosomal abnormalities*

Prevalence is 10%–15% in azoospermic men, 5% in men with severe oligozoospermia (<5 million/mL), and <1% in men with normal sperm concentrations.

Who to test: Men with nonobstructive azoospermia or severe oligozoospermia Such couples are at increased risk for miscarriages and for having children with chromosomal and congenital defects.

Sex chromosomal aneuploidy (Klinefelter syndrome; 47,XXY) accounts for about two thirds of all chromosomal abnormalities observed in infertile men. Rare azoospermic men may be found to have the 46,XX disorder of sexual development resulting from translocation of sex-determining region Y (SRY) to one of their X chromosomes.

1.8.3 *Y-chromosome microdeletions*

Found in 7% of infertile men with severely impaired spermatogenesis, compared with 2% of normal men, 16% in men with azoospermia or severe oligozoospermia

Testing by: Polymerase chain reaction techniques to analyze sequence- tagged sites that have been mapped along the entire length of the Y chromosome. Most deletions causing azoospermia or oligozoospermia occur in regions of the long arm of the Y chromosome (Yq11) known as the azoospermia factor (AZF) regions, designated as AZFa (proximal), AZFb (central) and AZFc (distal). The DAZ (deleted in azoospermia) gene, which encodes a transcription factor usually present in men with normal fertility, is located in the AZFc region.

Who to test: Y-Chromosome analysis should be offered to men who have nonobstructive azoospermia or severe oligozoospermia before performing ICSI with their sperm.

Many men with a microdeletion in the AZFc region of the Y chromosome have severe oligozoospermia. Others with AZFc region deletions are azoospermic but may still produce sufficient numbers of sperm to allow testicular sperm extraction. Sperm production in such men appears to be stable over time, and the results of ICSI are not affected adversely by the AZFc deletion. In contrast, deletions involving the entire AZFb or AZFa region appear to predict a very poor prognosis for sperm retrieval.

Sons of individuals with Y-chromosome microdeletions will inherit the abnormality and, therefore, may also be infertile.

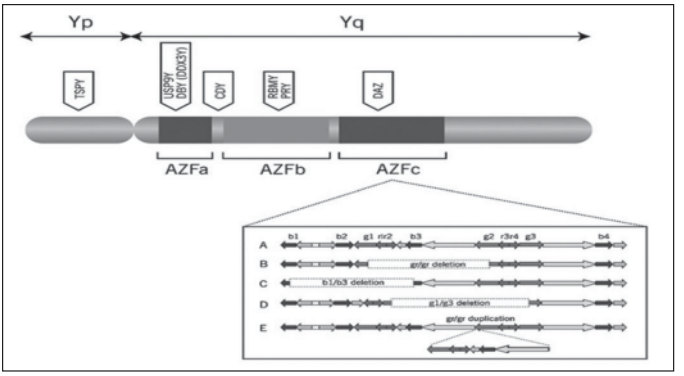

Fig 1: Y Chromosome Microdeletions

1.8.4 *Chromosome aneuploidy*

Sperm DNA aneuploidy can be assessed by fluorescent in situ hybridization technology. One study has reported that up to 6% of men presenting with infertility and a normal karyotype had an increased frequency of meiotic alterations detect- able in their sperm. Men with the highest risk of sperm aneuploidy are those with karyotypic abnormalities, severely abnormal sperm morphology, and nonobstructive azoospermia. Patients with recurrent pregnancy loss and recurrent IVF failure also may benefit from sperm aneuploidy testing. Currently, limitations to the routine use of this technology include cost, inability to screen the actual sperm used in ICSI, and difficulty of assigning a meaningful risk assessment to couples based on the test.

Recommendations[3]

Table 3: Genetic Testing/ Counselling in Male Infertility

Recommendations for Genetic testing/ Counseling	Grade of Recommendation
From a diagnostic view point, standard karyotype analysis should be offered to all men with damaged spermatogenesis (spermatozoa < 10 million/mL) who are seeking fertility treatment by IVF.	**B**
Genetic counselling is mandatory in couples with a genetic abnormality found in clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	**A**
All men with Klinefelter's syndrome need long-term endocrine follow-up and usually require androgen replacement therapy.	**A**
Testing for microdeletions is not necessary in men with OA (with normal FSH) when ICSI is used because spermatogenesis should be normal.	**A**
Men with severely damaged spermatogenesis (spermatozoa < 5 million/mL) should be advised to undergo Yq microdeletion testing for both diagnostic and prognostic purposes. Yq microdeletion also has important implications for genetic counselling.	**A**
If complete AZFa or AZFb microdeletions are detected, micro-TESE should not be performed because it is extremely unlikely that any sperm will be found.	**A**
If a man with Yq microdeletion and his partner wish to proceed with ICSI, they should be advised that microdeletions will be passed to sons, but not to daughters.	**A**
When a man has structural abnormalities of the vas deferens (unilateral or bilateral absence), he and his partner should be tested for CF gene mutations.	**A**

2. Management

2.1 *Primary Testicular failure*

Primary testicular failure (PTF) or hypergonadotropic hypogonadism refers to conditions where testes fail to produce sperm despite adequate hormonal support.

Table 4: Causes of Primary Testicular Insufficiency

Factors	Causes
Congenital	Anorchia
	Testicular dysgenesis/cryptorchidism
	Genetic abnormalities (karyotype, Y-chromosome deletions)
Acquired	Trauma
	Testicular torsion
	Post-inflammatory forms, particularly mumps orchitis
	Exogenous factors (medications, cytotoxic or anabolic drugs, irradiation, heat)
	Systemic diseases (liver cirrhosis, renal failure)
	Testicular tumour
	Varicocele
	Surgery that may compromise vascularisation of the testes and lead to testicular atrophy
Idiopathic	Unknown aetiology
	Unknown pathogenesis

2.1.1 *Diagnosis*

Semen analysis: In NOA, semen analysis shows normal ejaculate volume and azoospermia after centrifugation. A recommended method is semen centrifugation at 3000 g for 15 min and a thorough microscopic examination by phase contrast optics at ×200 magnification of the pellet.

Hormonal determinations: In men with testicular deficiency, hypergonadotrophic hypogonadism is usually present, with high levels of follicle-stimulating hormone (FSH) and luteinising hormone (LH), and sometimes low levels of testosterone.

Testicular biopsy: Testicular sperm extraction (TESE) is the technique of choice. Spermatogenesis may be focal, which means that in about 50% of men with NOA, spermatozoa can be found and used for ICSI. Most authors therefore recommend taking several testicular samples. There is a good correlation between the histology found upon diagnostic biopsy and the likelihood of finding mature sperm cells during testicular sperm retrieval and ICSI

2.1.2 Treatment for Infertility: Sperm retrieval techniques

Recommendations:[3]

Table 5: Sperm retreival techniques recommendations

Recommendation	Grade
Men who are candidates for sperm retrieval must receive appropriate genetic counselling.	**A**
Testicular biopsy is the best procedure to define the histological diagnosis and retrieve sperm in the same procedure. Spermatozoa have to be cryopreserved for use in ICSI.	**A**
For patients with NOA who have spermatozoa in their testicular biopsy, ICSI with fresh or cryopreserved spermatozoa is the only therapeutic option.	**A**
Men with NOA can be offered TESE with cryopreservation of the spermatozoa to be used for ICSI.	**A**
To increase the chances of positive sperm retrieval in men with NOA, TESE (microsurgical or multiple) should be used.	**A**

2.2 *Secondary (hypogonadotrophic) hypogonadism*

Secondary (hypogonadotrophic) hypogonadism is caused by insufficient gonadotropin-releasing hormone (GnRH) and/or gonadotropin (FSH, LH) secretion.

Table 6: Various causes of Hypogonadotrophic Hypogonadism

Congenital
Idiopathic hypogonadotrophic hypogonadism
Normosmic
Hiposmic/anosmic (Kallmann syndrome)
Acquired (tumours in the following regions)
Diencephalon (craniopharyngioma or meningioma)
Hypothalamus or pituitary
Empty sella syndrome
Granulomatous illnesses
Fractures of the skull base
Ischaemic or haemorrhagic lesions in hypothalamic area
Hyperprolactinaemia
Drugs/anabolic steroids, radiotherapy

2.2.1 Diagnostic work-up-

Endocrinology

Serum Testosterone, FSH, LH, Prolactin

2.2.2 *Pituitary Imaging*

In cases of acquired hypogonadotropic hypogonadism (low testosterone with low-normal FSH and LH levels) not clearly attributable to a specific cause, pituitary imaging studies with MRI or computed tomography may be needed to evaluate for structural lesions in the hypothalamic pituitary region.

2.2.3 Management

- Male patients with onset of hypogonadotropic hypogonadism before completion of pubertal development may have testes generally smaller than 5 mL. These patients usually require therapy with both hCG and human menopausal gonadotropin (or FSH) to induce spermatogenesis.
- Men with partial gonadotropin deficiency or who have previously (peripubertally) been stimulated with hCG may initiate and maintain production of sperm with hCG therapy only.
- Men with postpubertal acquired hypo- gonadotropic hypogonadism and who have previously had normal production of sperm can also generally initiate and maintain spermatogenesis with hCG treatment only.
- Therapy with hCG is generally begun at 1,000 to 2,000 IU intramuscularly two to three times a week. It may take 2 to 3 months to achieve normal levels of testosterone and spermatogenesis.
- Because of the high cost of human menopausal gonadotropin (or FSH) preparations, hCG should be the initial therapy of choice for at least 6 to 12 months.
- If spermatogenesis has not been initiated by the end of 6 to 12 months of therapy with hCG or LH, administration of an FSH-containing preparation is initiated in a dosage of 75 IU intramuscularly three times a week along with the hCG injections. After 3-6 months, if sperm are not present or are present in very low numbers (<100,000/mL), the human menopausal gonadotropin (or FSH) dosage can be increased to 150 IU intramuscularly three times a week for another 6 months. [4]
- GnRH Therapy: In patients with an otherwise intact pituitary gland and hypogonadotropic hypogonadism, synthetic GnRH can be given in a pulsatile fashion subcutaneously through a pump every 2 hours. GnRH therapy is monitored by measuring LH, FSH, and testosterone levels every 2 weeks until levels are in the normal range, at which point monitoring can be adjusted to every 2 months.

Recommendations [3]

Table 7: Recommendations for Secondary Hypogonadism

Recommendation	Grade
Effective drug therapy is available to achieve fertility in men with hypogonadotrophic hypogonadism.	**A**
Testosterone replacement is strictly contraindicated for the treatment of male infertility (low levels of FSH and LH).	**A**

2.3 Obstructive azoospermia (OA)

Obstructive azoospermia (OA) is the absence of spermatozoa and spermatogenetic cells in semen and post-ejaculate urine due to obstruction. OA is less common than NOA and occurs in 15-20% of men with azoospermia. Men with OA present with normal FSH, normal size testes, and epididymal enlargement. Sometimes, the vas deferens is absent.

Diagnostic evaluation

2.3.1 Clinical examination

Clinical examination should follow suggestions for the diagnostic evaluation of infertile men. The following findings indicate OA:

- At least one testis with a volume > 15 mL, although a smaller volume may be found in some patients with OA and concomitant partial testicular failure.
- Enlarged and hardened epididymis.
- Nodules in the epididymis or vas deferens.
- Absence or partial atresia of the vas.

2.3.2 Semen analysis

At least two examinations must be carried out at an interval of 2-3 months, according to the WHO. When semen volume is low, a search must be made for spermatozoa in urine after ejaculation. Absence of spermatozoa and immature germ cells in semen smears suggest complete seminal duct obstruction.

2.3.3 Hormone levels

Serum FSH levels may be normal, but do not exclude a testicular cause of azoospermia. FSH level is normal in 40% of men with primary spermatogenic failure.

2.3.4 Ultrasonography

In addition to physical examination, a scrotal ultrasound may be helpful in finding signs of obstruction (e.g., dilatation of rete testis, enlarged epididymis with cystic lesions, or absent vas deferens) and may demonstrate signs of testicular dysgenesis (e.g., non-homogeneous testicular architecture and microcalcifications) and associated ITGCN. For patients with a low seminal volume and in whom distal obstruction is suspected, transrectal ultrasound (TRUS) is essential. Invasive diagnosis, including testicular biopsy, scrotal exploration, and distal seminal duct evaluation, are indicated in patients with OA in whom an acquired obstruction of the seminal ducts is suspected. Explorative and recanalisation surgery should be carried out simultaneously.

2.3.5 Testicular biopsy

In selected cases, testicular biopsy may be indicated to exclude spermatogenic failure. Testicular biopsy should be combined with extraction of testicular spermatozoa (i.e., TESE) for cryopreservation.

2.3.6 Recommendations: [3]

Table 8: Recommendations for Obstructive Azoospermia

Recommendation	Grade
In azoospermia caused by epididymal obstruction, standard procedures include vasovasostomy and tubulovastomy	**B**
Sperm retrieval techniques, such as MESA, TESE, and PESA, can be used additionally. These methods should be used only when cryostorage of the material obtained is available.	**B**
In azoospermia caused by epididymal obstruction, scrotal exploration with microsurgical epididymal sperm aspiration and cryopreservation of spermatozoa should be performed. Microsurgical reconstruction should be performed, if applicable. Results of reconstructive microsurgery depend on the cause and location of the obstruction, and the surgeon's expertise.	**B**

2.4 *Varicocele* [5]

- Abnormal dialation, elongation & tortuosity of pampiniform venous plexus in spermatic cord

- Incidence 15% of normal population and 40% of infertile men, Secondary > primary
- Left more than Right, isolated right varicocele is rare
- Most common reversible cause of non obstructive azoospermia
- Only clinically palpable varicocele have clear association with infertility.

Varicocele is a common abnormality which may be associated with the following andrological conditions:

- Failure of ipsilateral testicular growth and development.
- Symptoms of pain and discomfort.
- Male subfertility.
- Hypogonadism.

2.4.1 Classification

The following classification of varicocele is useful in clinical practice:

Subclinical: Not palpable or visible at rest or during Valsava manoeuvre, but can be shown by special tests (Doppler ultrasound studies).

Grade 1: Palpable during Valsava manoeuvre, but not otherwise.

Grade 2: Palpable at rest, but not visible.

Grade 3: Visible and palpable at rest.

2.4.2 Management

Table 9: Treatment Options for Varicocele

Treatment	Recurrence/ persistence %	Complication rates
Antegrade sclerotherapy	9	Complication rate 0.3-2.2%: testicular atrophy, scrotal haematoma, epididymitis, left-flank erythema
Retrograde sclerotherapy	9.8	Adverse reaction to contrast medium, flank pain, persistent thrombophlebitis, vascular perforation
Retrograde embolisation	3.8-10	Pain due to thrombophlebitis, bleeding haematoma, infection, venous perforation, hydrocele, radiological complication (e.g., reaction to contrast media), misplacement or migration of coils, retroperitoneal haemorrhage, fibrosis, ureteric obstruction
Open operation		
Scrotal operation	-	Testicular atrophy, arterial damage with risk of devascularisation and testicular gangrene, scrotal haematoma, postoperative hydrocele
Inguinal approach	13.3	Possibility of missing out a branch of testicular vein
High ligation	29	5-10% incidence of hydrocele (< 1%)
Microsurgical inguinal or subinguinal	0.8-4	Postoperative hydrocele arterial injury, scrotal haematoma
Laparoscopy	3-7	Injury to testicular artery and lymph vessels; intestinal, vascular and nerve damage; pulmonary embolism; peritonitis; bleeding; postoperative pain in right shoulder (due to diaphragmatic stretching during pneumoperitoneum); pneumoscrotum: wound infection

2.4.3 Recommendations

Who to treat?

- In couple contemplating pregnancy:
  - Palpable varicocele
  - Couple has known infertility
  - Female partner has normal fertility or potentially treatable cause of infertility, and time to conception is not a concern
  - Male partner has abnormal semen parameters
- Adult male with palpable varicocele, abnormal semen parameters, desire for future fertility or pain related to varicocele
- Adolescents/young adults: reduced ipsilateral testicular size, Abnormal semen parameters

(Grade A)

2.5 *Male Accessory Gland Infection*

Infections of the male urogenital tract are potentially curable causes of male infertility. The WHO considers urethritis, prostatitis, orchitis and epididymitis to be male accessory gland infections (MAGIs). However, specific data are not available to confirm that these diseases have a negative influence on sperm quality and male fertility in general.

2.5.1 Diagnostic evaluation

Ejaculate analysis

Ejaculate analysis clarifies whether the prostate is involved as part of a generalised MAGI and provides information about sperm quality. In addition, leukocyte analysis allows differentiation between inflammatory and non-inflammatory chronic pelvic pain syndrome (CPPS)

Microbiological findings

After exclusion of urethritis and bladder infection, $>10^6$ peroxidase-positive white blood cells (WBCs) per millilitre of ejaculate indicate an inflammatory process. In this case, a culture should be performed for common urinary tract pathogens. A concentration of $>10^3$ cfu/mL urinary tract pathogens in the ejaculate is indicative of significant bacteriospermia. The ideal diagnostic test for Chlamydia trachomatis in semen has not yet been established. In contrast to serological findings in women, antibody tests for C. trachomatis in seminal plasma are not indicative if no type-specific methods are used.

Sperm quality

The deleterious effects of chronic prostatitis on sperm density, motility and morphology is debatable.

Reactive oxygen species

Reactive oxygen species might be increased in chronic urogenital infections associated with increased leukocyte numbers. However, their biological significance in prostatitis remains unclear.

2.5.2 Conclusions and recommendations for male accessory gland infections (Table 10)[3]

Table 10: Recommendations for Male Accessory Gland Infections

Recommendation	Grade
Urethritis and prostatitis are not clearly associated with male infertility.	3
Antibiotic treatment often only eradicates microorganisms; it has no positive effect on inflammatory alterations, and cannot reverse functional deficits and anatomical dysfunction.	2a
Although antibiotic treatment for MAGI might provide improvement in sperm quality, it does not necessarily enhance the probability of conception.	2a
Patients with epididymitis that is known or suspected to be caused by N. gonorrhoeae or C. trachomatis must be instructed to refer their sexual partners for evaluation and treatment.	B

2.6 Idiopathic male Infertility & Unexplained Male Infertility

Male infertility of unknown origin is a condition in which fertility impairment occurs spontaneously or due to an obscure or unknown cause. It includes two categories, unexplained male infertility and idiopathic male infertility. The dividing line between them is semen analysis, which is normal in the unexplained category and abnormal in idiopathic infertility. After ruling out female infertility factors, erectile problems and coital factors, modern andrology may help to analyze the unexplained male fertility problem on the basis of cellular and subcellular mechanisms. Furthermore, this analysis may lead to the selection of proper treatment options fitting the needs of patients with unexplained infertility.

2.6.1 Idiopathic Male Infertility

Recommendation

Medical treatment of male infertility is recommended only for cases of hypogonadotrophic hypogonadism.	A

Clomiphen citrate and tamoxifen have been widely used in idiopathic OAT but there is no proven evidence for their benefit. A recent meta-analysis reported some improvement in sperm quality and spontaneous pregnancy rate. Androgens, hCG/HMG, bromocriptine, alpha-blockers, systemic corticosteroids and magnesium supplementation are not effective in the treatment of OAT syndrome. Follicle-stimulating hormone might be beneficial in a selection of patients. A Cochrane analysis showed that men taking oral antioxidants had an associated significant increase in live birth rate in IVF patients (2011) when compared with men taking the control treatment.

2.6.2 Unexplained Male Infertility[6]

For men with unexplained infertility and normal semen analyses the following possibilities should be considered: (i) presence of a female factor, (ii) inappropriate coital habits, (iii) erectile dysfunction, (iv) the presence of antisperm antibodies (ASAs) (autoimmune infertility), and (v) sperm dysfunction

Work-up plan for unexplained male infertility: ROS, reactive oxygen species; ICSI intracytoplasmic sperm injection; and ART[7] The management of male infertility and role of aromatase inhibitor is summarized in Fig 2 & 3.

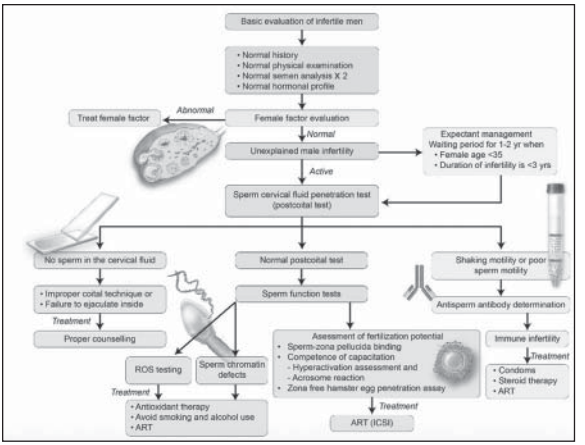

Fig 2: Management of Male Infertility

Role of Aromatase Inhibitor:

Obesity is associated with high aromatase activity and oligozoospermia. Normally Total Testosterone (ng/dl) / Estradiol levels (pg/ml) is more than 10. However in obese oligospermic men this ratio when less than 10 indicates use of Aromatase Inhibitors (Letrozole 2.5 mg daily) with weight reduction.

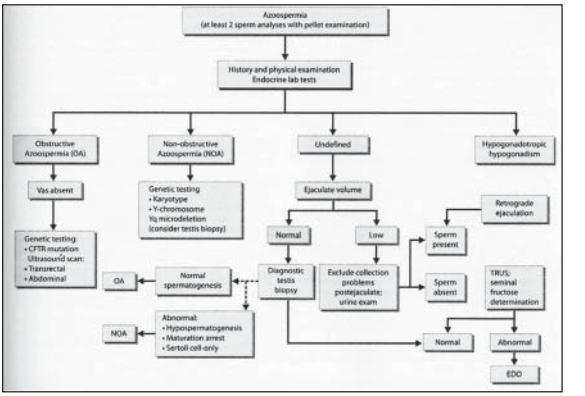

Fig 3: Algorithm for Male Patient with Azoospermia

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Guidelines for the Management of OHSS

K D Nayar, Aanchal Agarwal

Ovarian Hyperstimulation syndrome (OHSS) is an iatrogenic complication of assisted reproductive technology. The syndrome is characterized by cystic enlargement of the ovaries and a fluid shift from intravascular compartment to third space due to increased capillary permeability and ovarian neoangiogenesis.

1. **Objective:** The purpose of these guidelines is to enable the clinician diagnose and effectively treat ovarian hyperstimulation syndrome. Since OHSS is associated with significant physical and psychological morbidity and has been associated with maternal death early recognition and prompt treatment is required.

2. **Pathophysiology:** Exposure of ovaries to human chorionic gonadotropin (hCG) or Luteinising hormone (LH) following controlled ovarian stimulation by Follicle stimulating hormone (FSH) leads to production of proinflammatory mediators. Most important of these is vascular endothelial growth factor (VEGF).[1,2,3] Release of VEGF in large amounts increases vascular permeability, which, in turn, leads to loss of fluid into the third space This manifests as ascites, pleural effusion and rarely pericardial effusion. Leakage of fluid further leads to hypovolemia and hypo- osmolality (due to reduced sodium).[4]

   It has been postulated that there is a ' resetting' of osmotic threshold of vasopressin and thirst in these patients around a new lower level which enables them to still concentrate and dilute their urine. This phenomenon is also responsible for the paradoxical combination of hypovolemia and hypo-osmolality characteristically seen in this condition.[5,6]

3. **Risk factors**

3.1 What are the risk factors for occurrence of OHSS ?
(Evidence Level 2+)

Primary risk factors[7]

- Young age
- Lean body
- PCOS
- Previous history of OHSS
- Elevated repose to gonadotropin

Secondary risk factors[8]

These are ovarian response parameters that have an ability to predict the development of OHSS.

- Absolute value of E2/ rate of increase of E2
- Number of follicles and their size
- Number of oocytes collected

Although there is no consensus but largely > 20 follicles in IVF and > 6 in IUI should alert the physician. Similarly, E2 levels >3000 pg/ml in IVF and >1700in IUI are alarming.

These factors taken together are predictive of OHSS.

4. **Incidence**

4.1 What is the incidence of OHSS ?
(Evidence Level 3)

Incidence of moderate OHSS is 3-6% and severe is 0.1-3.1 %of all cycles.[9]

5. Diagnosis

5.1 How is the condition diagnosed ?
(Evidence Level 3)

Diagnosis of OHSS is made on basis of clinical symptoms and signs. Though the symptoms are not specific, typically there is a history of ovarian stimulation followed by trigger.

5.1.1 ***Detailed history in the initial assessment should include:***

H/o Ovarian stimulation?

How many follicles on USG?

Terminal E2 (Estradiol)value?

Medication used for trigger?

Was embryo transfer done?

How many embryos were transferred?

H/o polycystic ovarian syndrome

Time of onset of symptoms with regards to trigger

One or more of following symptoms may be present- patient should be enquired in detail about the same.

1. Abdominal bloating
2. Abdominal discomfort / Pain of varying severity
3. Nausea + Vomiting
4. Breathlessness
5. Reduced urine output
6. Leg swelling/Vulval swelling

5.1. 2 ***Examination of a woman with suspected OHSS***

General: Record Pulse rate, blood pressure, respiratory rate, body weight, hydration, edema.

Abdomen: Measure abdominal girth, assess for ascitic fluid and presence of any palpable mass.

Chest & CVS: Record Respiratory rate, look for Pleural effusion / pericardial effusion/ pulmonary edema.

5.1.3 ***Investigations***

A) Mandatory

Table 1: Mandatory Investigations in OHSS

Investigation	Changes expected in OHSS
1) Haematocrit (HCT) -	Hemoconcentration
2) Total Leucocyte count (TLC)	Elevated
3) Coagulation Profile	Elevated fibrinogen and reduced antithrombin.
4) Liver function tests	(Elevated enzymes ,reduced serum proteins and reduced serum albumin

5) Blood urea and creatinine	(May be raised due to hemoconcentration or compromised kidney function).
6) Electrolytes	(Hyponatraemia and Hyperkalaemia).
7) Serum Osmolality	(Hypo – Osmolality).
8) Coagulation Profile	Elevated fibrinogen and reduced antithrombin).
9) Beta HCG	To determine outcome of treatment cycle.
10) Ultrasound (TAS)	Ovarian size and ascitic volume fluid, USG chest for pleural effusion/ pericardia effusion/ovarian torsion.

B) Not mandatory, may be needed

Table 2: Investigations

1. ECG/chest X Ray /Echocardiogram.
2. Arterial blood gases.
3. CTPA - Computerised Tomography Pulmonary Angiogram
4. VQ Scan- Ventilation perfusion scan.

5.2. What are the Differential Diagnosis?

(Evidence Level 3)

Similar presentation is seen in following conditions:

Pelvic infection

Pelvic abscess

Appendicitis

Ovarian Torsion

Ovarian Cyst rupture

Ectopic Pregnancy

Bowel Perforation[10]

6. Assessment of severity

6.1. The management of a patient with OHSS depends on severity of problem. How do you assess severity ?

(Evidence Level 4)

Table 3: Assessment of Severity (RCOG Classification)[11]

Category	Features
Mild OHSS	Abdominal bloating mild abdominal pain Ovarian size usually < 8 cm.
Moderate OHSS	Moderate abdominal pain Nausea ± Vomiting Ultrasound evidence of ascites ovarian size usually 8-12 cm.
Severe OHSS	Clinical ascites (±hydrothorax) Oliguria(<300ml/dayor< 30ml/hour) Haematocrit >0.45 Hyponatremia(sodium<135mmol/l)Hypo-Osmolality(<282mOsm/kg) Hyperkalaemia(Potassium>mmol/l)Hypoproteinaemia (Serum albumin <35g/l) Ovarian size usually >12cm.
Critical OHSS	Tense ascites/large hydrothorax Haematocrit>0.55 White cell count > 25ooo/ml Oliguria/anuria Thromboembolism Acute respiratory distress syndrome (ARDS)

7. Prevention

7.1 What measures should be taken for prevention of OHSS ?

All possible measures should be taken to prevent occurrence of OHSS. Since this is an iatrogenic problem and infertility treatment being an elective one, the treatment process should be as safe as possible.

Primary Prevention

Level 1: Identification of patient 'at risk'

Level 2: Optimal ovarian stimulation

Level 3: Close monitoring

Level 4: Control on rapidly rising estradiol levels and rapidly developing multiple follicles

Level 5: Prevention of pregnancy occurrence.

Level 6: Prophylactic medical treatment like Intravenous colloids (Albumin) Crystalloids, dopamine agonist or GnRH antagonists.

Secondary Prevention - Consists of early diagnosis and treatment once the signs and symptoms are established.

The following precautions may be taken for prevention.

7.1.1 Identifying the patient characteristics which put them at high risk of developing OHSS like young age, lean body type, PCOS, exaggerated response to ovarian stimulation or history of OHSS in a previous cycle.

7.1.2 Reducing exposure to gonadotropins

a. ***Implementation of low dose protocols*** to reduce the dose and aiming at development of few follicles rather than multiple follicles. Ideal number of follicles should be 8-10 in IVF and 2-3 in IUI. Antagonist protocols in ART cycles in women with PCOS has been shown to have a beneficial effect in reducing OHSS rate.[12]

b. ***Coasting***: When high risk patients have rapidly rising high serum estradiol levels (>3000 pg/ml) and large number of follicles (>12 per ovary) during stimulation , gonadotropin administration can be decreased or stopped while continuing GnRH agonist /antagonist administration .This allows larger follicles to continue to grow, while intermediary and small follicles undergo atresia.[13] Coasting up to 3 days reduces risk of OHSS without affecting pregnancy rate. However,with holding for four or more days is associated with lower implantation rate due to an effect on endometrial receptivity.[14]As per latest Cochrane review, this seems to be a promising intervention and should be researched further for this purpose.[12]

c. ***Modification of ovulation triggering agent****:* Replacement of hCG by LH (endogenous or exogenous) may reduce the risk since LH is short acting (half life-20 minutes) whereas hCG is long acting (half life-24-36 hours). Using GnRH agonist in an antagonist cycle is a very good option. As per Cochrane overview, GnRH agonist trigger in donor oocyte or freeze all program has definitely shown to reduce the rate of OHSS.

d. ***Metformin treatment before and during an ART cycle***[12]

e. ***Avoidance of hCG for luteal phase support***.

7.1.3 Continuation of antagonist after ovum pick up in an agonist cycle.

7.1.4 Freeze all: withholding embryo transfer and freezing all the embryos for use in a subsequent cycle abolish the risk of a late OHSS. Maximum number of follicles should be aspirated in a hyper stimulated ovary since it removes the glanulosa cells which are a potential source of vasoactive cytokines.

7.1.5 Cycle cancellation: withholding trigger and not performing IUI in a hyper stimulated patient.

7.1.6 Administration of macromolecules:

a. ***Hydroxy ethyl starch solution (HESS)*** administration on the day of ovum pick up (and again on a subsequent day if needed) helps in preventing leakage of fluid in third space. Due to its high molecular weight, it helps in retaining fluid in intravascular compartment.[15]

b. Albumin can be used for the same purpose. It helps by increasing the plasma oncotic pressure and binding mediators of ovarian origin. However, there are potential side effects like viral transmission, nausea, vomiting, febrile and allergic reactions. It is more expensive also. However, as per the latest Cochrane overview, there is insufficient evidence to support the use of Albumin.[12]

7.1.7 Administration of Dopamine agonist: Cabergoline/Bromocriptine inhibits partially the VEGF receptor 2 phosphorylation levels and associated vascular permeability. It may be started from the day of ovum pick up for 8 days.

All women undergoing ovarian stimulation for ART should be informed in detail about the signs and symptoms of OHSS. They should also be provided with a 24 hour telephone number. These women should be asked to report to the emergency unit if any of the signs and symptoms of severe OHSS develop. Any women developing signs and symptoms of OHSS should be assessed by the concerned physician for severity.

8. Treatment

8.1 Which patients with OHSS are suitable for an out patient treatment ?

Women with mild to moderate OHSS may be managed on outpatient basis. These women should be advised in detail regarding fluid intake. At least one litre of fluid should be taken per day. However, they should be encouraged to drink to thirst rather than a set amount.[6] They should also be advised to maintain a fluid input – output chart. Urine output of less than 1000 ml per 24 hours or a positive fluid balance of greater than 1000ml over 24 hours needs urgent review.

For pain relief, paracetamol and oral opiates including codeine should be advised NSAIDS should be avoided for fear of renal function compromise.[16]

Majority of mild – moderate cases are self limiting. Symptoms subside by 7-10 days in most patients. In case of pregnancy, symptoms may worsen due to onset of late OHSS.

8.2 How should women with mild to moderate OHSS being managed on outpatient basis be monitored?

(Evidence Level 4)

These women should be explained in detail about their condition and should be provided with details regarding where to report in case of emergency.

In addition, these women should be checked every 2-3 days.

They should be advised to report immediately in any of following stimulation which

indicate worsening of condition: [17,18]

1. Inadequate oral intake.
2. Worsening of abdominal pain.
3. Increasing abdominal distension.
4. Excessive vomiting.
5. Shortness of breath.
6. Feeling of dizziness or palpitations.
7. Reducing (<1000ml/24hrs) or absent urine output.
8. Positive fluid balance> 1000ml over 24 hrs.
9. Weight gain.

8.3 When should women with OHSS be admitted ?

(Evidence Level 3)

Hospitalization should be considered in following situations:

1. Inadequate pain control.
2. Inadequate fluid intake due to nausea / vomiting.
3. Signs and symptoms of worsening of condition(as mentioned above).
4. Tachycardia or hypotension
5. Inability to come for regular follow up.
6. Severe / Critical OHSS.

8.4 Where should these women be admitted ?

(Evidence Level 4)

Women with severe /critical OHSS should be admitted in an ICU setup with multidisciplinary assistance. A clinician experienced in ART procedures and in management of OHSS should be overall in charge of her case.

8.5 What are the components of inpatient management ?

1. Assessment and monitoring.
2. Symptom relief.
3. Fluid management.
4. Management of complications.

8.6 How should women hospitalized with OHSS be monitored ?

(Evidence Level 3)

These women should be kept under constant supervision in ICU setting.

Body weight, Abdominal Girth (AG), fluid intake and output should be measured once daily. Blood parameters like Hematocrit, Total Leucocyte count, Liver function tests, Kidney function tests and electrolytes should be done at least once daily. Other tests like ECG, Electrocardiography, chest X-Ray, Arterial blood gases may be required depending on clinical features. Weight gain, increasing abdominal girth, oliguria/anuria, positive fluid balance , increasing hematocrit are signs of deterioration.

Conversely, reduction in body weight / abdominal girth, diuresis and normalization of hematocrit indicate recovery.[17,18]

8.7 How should the symptoms of OHSS be relieved ?

(Evidence Level 3)

Analgesics like paracetamol and opiates should be given for abdominal pain.

NSAIDS should be avoided for fear of nephrotoxicity. Antiemetics that are safe in pregnancy should be given for nausea and vomiting. If pain becomes severe,complications like ovarian torsion /rupture, ectopic pregnancy and pelvic infection should be ruled out.

8.8 How is fluid management done ?

(Evidence Level 3)

Oral fluid in take guided by thirst is the most physiological approach to correcting intravascular dehydration. Vigorous intravenous fluid administration might increase third space collection in a setting of increased vascular permeability. Therefore, oral route should be used wherever possible. In acute dehydration / excessive nausea, intravenous fluids may be needed Colloids like hydroxy ethyl starch (HES 6%) and albumin 25% have an advantage over crystalloids in this setting. Due to their high molecular weight,they help to retain fluid in intravascular compartment for longer periods.

Human albumin solution (25%) may be used in doses of 50-100g, infused over 4 hours and repeated 4-12 hourly.[17]

Persistent hemoconcentration or low urine output despite adequate volume replacement by colloids is an indication to seek multidisciplinary assistance. In these cases, invasive haemodynamic monitoring through a central line and continuous urine output measurement may help in fluid management more accurately.

In case of persistent oliguria, fluid challenge should be given with 1 litre saline over one hour followed by D5 normal saline at the rate of 150ml / hour. Alternatively, diuresis may be accomplished using sequential administration of 50ml of 25% albumin followed by furosemide 10mg given intravenously. This combination can be repeated 3 to 4 times per 24 hours as necessary.[19] Serum sodium, potassium and creatinine must be monitored closely when employing albumin or furosemide diuresis. Diuretics should be avoided as far as possible. They cause loss of fluid from an already shrunken intravascular compartment. However, they may be used in persistent oliguria despite fluid replacement. Paracentesis should be done in cases which fail to respond to fluid therapy.

9. Complications

9.1 What complications could arise in OHSS ?

(Evidence Level 3)

Severe /critical OHSS may develop following complications:

1. Ascites/Pleural effusion / pericardial effusion.
2. Thrombosis.
3. Acute Renal failure.
4. Acute Respiratory Distress Syndrome (ARDS).

9.2 How should ascites and effusion be managed ?

(Evidence Level 4)

Paracentesis should be considered in the following situations:

1. Tense ascites causing severe pain or discomfort.
2. No oral intake due to tense ascites.
3. Persistent oliguria not responding to volume replacement. This could be due to high abdominal pressure causing reduced renal perfusion.
4. Pleural /Pericardial effusion.

Paracentesis can be done abdominally or vaginally. It should always be done under ultrasound guidance to avoid injury to hyper stimulated, hyper vascular ovaries. Removal of large volumes should be accompanied by intravenous colloid (Albumin) replacement since protein is lost with the ascitic fluid. Removal of fluid from peritoneal cavity helps in reducing pleural / pericardial effusion as well. Once intra peritoneal fluid reduces, there is seepage of pleural and pericardial fluid through the diaphragm into the abdominal cavity .Separate pleural / pericardial tapping is not needed.

9.3 When is thromboprophylaxis indicated ?
(Evidence Level 3)

Indications of Thromboprophylaxis include:

1. Women admitted with severe / critical OHSS.
2. Moderate OHSS with predisposing risk factors like reduced mobility, obesity or a pre existing thrombophilia.
3. Unusual neurological symptoms in women with OHSS even if the symptoms appear weeks after apparent improvement.

Hemo concentration and vascular endothelial dysfunction are the main reasons for thrombosis in women with OHSS. It mainly affects arterial system of upper body sites. This might have unusual presentation like dizziness, loss of vision and neck pain. Thrombosis may be managed with LMWH and anti embolism stockings. It is always wise to collaborate with hematologist for managing this problem. Similarly, Acute respiratory distress syndrome and acute renal failure should be managed in collaboration with the respective specialists.

10. Is surgical management indicated ?
Hyperstimulated ovaries are highly vascular and liable to damage on handling. Therefore, surgery is only indicated if there is a coincident adnexal torsion, ovarian rupture or ectopic pregnancy and should be performed by an experienced surgeon.

11. Are there any risks associated with pregnancy and OHSS ?
Pregnancies complicated by OHSS may be at an increased risk of pre-eclampsia and preterm delivery.

Conclusion

The key pathophysiological feature of OHSS is a fluid shift with extravascular fluid accumulation combined with intravascular volume depletion and hemoconcentration. Knowledge of risk factors, clinical presentation, and classification of severity are essential for correct diagnosis and effective treatment. Mild form is common occurring in upto one third of women being stimulated for IVF. Mild to moderate form can usually be managed on out patient basis if frequent monitoring and assessment is possible. Hospitalisation may occasionally be necessary if severity increases. Continued research will further our understanding of this condition and may advance our ability to predict and prevent this serious problem. The aim is to attain " **OHSS free clinics ".** It works on segmentation concept. Segment A consists of optimization of the ovarian stimulation in a GnRH antagonist cycle with agonist trigger. Segment B consists of cryopreservation of oocyte or embryo vitrification. Segment C includes embryo replacement in a non-stimulated endometrium in a subsequent cycle. This can help in erasing OHSS completely.

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Classification of evidence levels

1++	High-quality meta-analyses,systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses,systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses,systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case– control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding,bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding,bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Clinical Practice Guidelines: Premature ovarian insufficiency

Kanad D Nayar, Shikha Jain

Objectives

Premature ovarian insufficiency is a pathological condition of declining ovarian function. The clinical spectrum comprises of menstrual irregularity, decreased fecundity, and vasomotor symptoms on one hand while increased morbidity due to osteoporosis and cardiovascular disease on the other. Despite having common problems, POI is different from natural menopause, therefore the clinical approach is distinct. The following guidelines are an attempt to define, diagnose and direct appropriate management strategy to the subset of women with POI. We have reviewed current literature but the studies done in women with POI are limited. The majority of the recommendations made here are based on European Society of Human Reproduction and Embryology (ESHRE) Guidelines for the 'Management of women with premature ovarian insufficiency', 2015.

1. **Definition**

   "Premature ovarian insufficiency (POI) is the clinical condition described as loss of ovarian activity before the age of 40 years." [1]

   or

   "POI is a condition characterized by hyper gonadotropic hypogonadism in women younger than age 40 years. It includes women with premature menopause." [2]

   The age limit of 40 is approximately two standard deviations (SD) below the average age at natural menopause (50 ± 4 years). POI is characterized by premature depletion of ovarian follicular pool and lack of ovarian steroidogenesis resulting in raised gonadotropin and low estradiol levels. The typical manifestation of estrogen deficiency is amenorrhea/ oligomenorrhea and infertility along with vasomotor and psychological dysfunction. It can manifest as primary amenorrhea (if the onset is before menarche) or secondary amenorrhea (if the onset is after menarche). The first report in literature about primary ovarian insufficiency comes from the paper by Albright et al in 1942.[3]

2. **Common Synonyms[1]**
   - Premature ovarian insufficiency
   - Premature ovarian failure
   - Premature menopause
   - Hyper gonadotropic hypogonadism
   - Ovarian dysgenesis/ Gonadal dysgenesis

   POI needs to be differentiated from the natural menopause as the causes, symptomatology and clinical approach is different for them.

   Also there is a lot of confusion regarding the status of ovarian reserve, hence POI are often mistaken for certain subgroups in ART, like diminished ovarian reserve (DOR) which indicates a reduced number and/or reduced quality of oocytes, such that the ability to reproduce is decreased. [2]

3. **Prevalence**

   The global prevalence of POI is approximately 1%[1], however it varies according to ethnicity, geographical areas and lifestyle factors. Wu et al reported prevalence of 2.8 % in Chinese women.[4]

4. Causes (Table-1)

Table 1: Causes of Premature Ovarian Insufficiency

Category	Causes
Genetic defects	Chromosomal defects mostly involving X chromosome Fragile X syndrome Galactosemia Autosomal gene mutations
Autoimmune	Addison's disease Autoimmune polyendocrine syndrome (APS) type 2 Thyroiditis Type I Diabetes mellitus Coeliac disease Systemic lupus erythematosus
Infections	Mumps, Human immunodeficiency virus, Herpes zoster, Cytomegalovirus, Tuberculosis, Malaria, Varicella and Shigella
Iatrogenic	Chemotherapy, radiation, and surgery
Environmental	Smoking, alcohol, nutritional, and exposure to endocrine disruptors
Unexplained/ Idiopathic	No cause found in 75-90% cases

5. Clinical presentation

The clinical manifestations of POI are mostly due to estrogen deficiency. They can be divided into general and reproductive health related. Symptoms may be transient or intermittent, and may be variable in severity, reflecting the fluctuations in ovarian activity (Table 2). Young women with POI experience lesser symptoms.

Table 2: Symptoms of POI

General symptoms	Reproductive health
Hot flushes	Oligomenorrhoea
Sleep disturbance	Amenorrhea
Mood changes	Infertility
Poor concentration	Low libido
Altered urinary frequency	Dyspareunia
Lack of energy	Vaginal dryness

In women < 40 years with oligo/amenorrhea with estrogen deficiency symptoms, POI should be excluded. Patients may also present with symptoms specific to underlying cause, like characteristic features of Turner syndrome.

Diagnosis and Investigations

The diagnosis of POI is based on the presence of menstrual disturbance and biochemical confirmation. **ESHRE guidelines recommends the following diagnostic criteria[1]:**

- Presence of oligo/amenorrhea for at least 4 months, and
- Elevated serum FSH level > 25 IU/l on two occasions > 4 weeks apart

Pelvic ultrasonography may reveal smaller ovaries (volume < 3 cc) with poor antral follicle count. At present there is no role of anti mullerian hormone (AMH), laparoscopy and ovarian biopsy in making the diagnosis of POI. After establishing the diagnosis,

equally important is to find out the cause. **The recommendations of ESHRE guidelines for investigating the cause for POI are as follows[1]:**

6.1 Genetic tests

- Chromosomal analysis is recommended in all cases of non-iatrogenic POI.
- Gonadectomy is advised in women with Y chromosome due to risk of gonadal tumors.
- Fragile-X syndrome (FMR 1 gene pre-mutation) testing is indicated in POI. The implications of the fragile-X pre-mutation should be discussed beforehand. The relatives of women with fragile X pre-mutation should be offered genetic counselling and carrier testing.
- Autosomal genetic testing should not be done in all women with POI, unless there is evidence suggesting a specific mutation.

6.2 Immunological tests

- Screening for anti-adrenal antibodies (21-hydroxyalase or adrenocortical antibodies) should be considered in women with POI of unknown cause or if an immune disorder is suspected.
- Screening for thyroid antibodies (anti thyroid peroxidase) should be performed in women with POI of unknown cause or if an immune disorder is suspected. In patients with a positive TPO-Ab test, thyroid stimulating hormone (TSH) should be measured every year.

6.3 Miscellaneous

- There is insufficient evidence to recommend routine screening for diabetes in POI.
- Infection screening is not recommended in women with POI.
- The possibility of POI being a consequence of a medical or surgical intervention should be discussed with women as part of the consenting process before the treatment.

7. Management options for women with POI

7.1 Lifestyle measures

- Adequate counselling about the cause and sequelae of POI should be made.
- The women who are prone to POI should be advised to stop smoking.
- Alcohol intake should be moderate.
- Regular exercise and healthy diet regimen should be followed.

7.2 Reproductive health

Depending upon the age of onset, POI can affect the reproductive and sexual health of the women in multiple ways. Hence the clinical management can be categorized as per the need of women.

7.2.1 ***Induction of puberty***

- Puberty should be induced or progressed with 17β-estradiol, starting with low dose (1/10-1/8 of adult dose) at the age of 12 years when there has been no spontaneous start to puberty and the dose is gradually increased over next 2 to 3 years.
- Oral (ethinylestradiol or natural micronized) or transdermal application (preferable) results in more physiological levels of estrogen in blood.
- In cases of late diagnosis of pubertal failure and for those girls in whom growth is not a consideration, estrogens may be started at higher doses and escalated more rapidly.

- Oral contraceptive pill is contraindicated for puberty induction.
- For regular withdrawal bleeding and normal breast and uterine development progestogen should be added at least 2 years after starting estrogen or when breakthrough bleeding occurs.
- Consultation with endocrinologist should be sought for attainment of height and physical growth.

7.2.2 ***Sexual health***

- Systemic estrogen replacement, with additional local treatment if necessary for dyspareunia, should be ensured in women with POI and sexual dysfunction.
- Women having concerns of low sexual desire despite adequate estrogen replacement, may benefit from short-term use of testosterone patches of 300 µg daily.
- Non-medical approaches like psychosexual therapy should be discussed.

7.2.3 ***Fertility***

- The chances of spontaneous conception in women with POI are very low (5 to 10 %)
- There are no known treatments which reliably increase ovarian activity, ovulation rate, and the possibility of natural conception.
- There is no role of ovulation induction drugs or exogenous gonadotropins.
- In vitro fertilization (IVF) with oocyte donation is the treatment of choice in women with POI desiring pregnancy.
- Oocyte donation from sisters carries a higher risk of cycle cancellation.
- There is loss of the ovarian follicle pool, thus fertility preservation interventions (oocyte, embryo or ovarian tissue cryopreservation) would appear futile in established cases of POI.
- Fertility preservation may also be considered for women at risk of POI. These might include survivors of childhood and adolescent cancer, and sisters of women with POI.

7.2.4 ***Pregnancy***

- Spontaneous pregnancies after idiopathic POI or after most forms of chemotherapy do not show any higher obstetric or neonatal risk than the general population.
- Abdomino-pelvic radiotherapy is reported to be associated with poor uterine function with increased risks of late miscarriage, prematurity, low birth weight, stillbirth, neonatal hemorrhage and postpartum hemorrhage [5]
- Oocyte donation pregnancies are obstetrically high risk. There is high prevalence of miscarriage (40%), pregnancy-induced hypertension (22%), prematurity (13%), low birth weight and small for gestational age babies (18% and 15%, respectively), caesarean section (61%), and postpartum hemorrhage (15%) in these pregnancies.
- Antenatal aneuploidy screening should be based on the age of the oocyte donor.
- Pregnancies in women with Turner Syndrome are at high risk and may have a maternal mortality as high as 3.5%. Pre-conception screening, especially for cardiac risk factors, may help reduce maternal risks in pregnancy as well as to screen those in whom pregnancy is contraindicated.

- A cardiologist should be involved in care of pregnant women who have received anthracyclines and/or cardiac irradiation or women with Turner Syndrome.
- Pre pregnancy screening of POI women should include assessment of blood pressure, renal function, thyroid and adrenal function, karyotype and echocardiography.
- 75mg aspirin daily from 12 weeks of pregnancy until delivery should be given in these pregnancies, especially when it is the first pregnancy or in a woman with Turner Syndrome.[6,1]

7.2.5 *Contraception*[7]

- As the ovarian function is intermittent and unpredictable, there are chances of spontaneous conception although very low (5- 10 %).
- Oral contraceptive pills are the first choice for contraception as it simultaneously protects against the adverse effects of hypoestrogenemia.
- Non hormonal methods (barrier or intrauterine devices) may necessitate use of HRT.

7.3 Non Reproductive/ General health

7.3.1 Quality of life

Women with POI report lower levels of psychological wellbeing compared to women in the general population. They suffer from depression, anxiety, stress, vasomotor symptoms like hot flushes, night sweats, mood swings and sleep disturbances which negatively affect their quality of life. Lifestyle modification, behavioral therapy, psychological counselling, HRT and non-hormonal pharmacological therapy should be offered.

7.3.2 Cardiovascular

Women with POI are at increased risk for impaired endothelial function, early onset of coronary heart disease and increased cardiovascular mortality. Women with Turner Syndrome have a higher prevalence of aortic coarctation and bicuspid aortic valve, thus at higher risk for infective endocarditis, aortic valve disease, aortic dilatation and rupture. All women with POI should be assessed for cardiovascular risk factors. At least blood pressure, weight and smoking status should be monitored annually with other risk factors like lipids, fasting glucose and HbA1c need to be assessed if indicated. HRT in POI has beneficial effects on plasma lipids, blood pressure, insulin resistance, and endothelial function. In the absence conclusive data, treatment should be individualized according to choice and risk factors.

7.3.2 Bone health

Women with POI have reduced bone mineral density, and this has been associated with the presence, degree, and duration of estrogen deficiency. POI is associated with increased risk of fracture. Non pharmacological measures include balanced diet, weight-bearing exercise, maintaining a healthy body weight, cessation of smoking and moderation of alcohol intake. The recommended dietary intake for calcium is 1000 mg/day, and for vitamin D 800 IU/day. HRT is recommended to maintain bone health and prevent osteoporosis which will further reduce the risk of fracture. The combined oral contraceptive pill can be used but effects on bone mineral density are less favorable. The use of bisphosphonates is not recommended in young women.

7.3.4 Genitourinary

POI women may experience vaginal dryness, irritation, urinary frequency, and incontinence. Vaginal lubricants, moisturizers and HRT (both systemic and topical) can be used to treat genito-urinary symptoms. Vaginal lubricants may be used where systemic treatment is contra-indicated, or if genitourinary symptoms persists despite adequate dose of HRT.

7.3.5 Neurological

In genetic cases of POI as Turner syndrome, Fragile X syndrome, Trisomy X there are reports of cognitive impairment, mental retardation and learning difficulties respectively. Higher risk of dementia, cognitive dysfunction and Parkinsonism is seen in women with iatrogenic POI under the age of 50 years. HRT in addition to lifestyle measures is helpful to prevent cognitive decline or improve cognitive function in women with POI until the age of natural menopause.

7.3.6 Life expectancy

POI is associated with increased risk of premature death mainly from cardiovascular disease. They should be counselled to reduce risk factors by not smoking, taking regular exercise, and maintaining a healthy weight.

7.4 Hormone replacement therapy (HRT)

7.4.1 Indications

- HRT is mainly indicated for the treatment of estrogen deficiency symptoms in women with POI.
- POI women not desiring pregnancy need contraception.
- The occurrence of vasomotor symptoms is a major indication to use HRT in women with POI.
- Early initiation of HRT is strongly recommended in POI to prevent against cardiovascular disease.
- Estrogen replacement is recommended to maintain bone health and prevent osteoporosis. It may reduce the risk of fracture.
- HRT might reduce the risk of cognitive impairment.
- Both systemic & local estrogens are effective in treatment of genito-urinary symptoms.
- HRT may be of indirect benefit to improve quality of life and life expectancy.

7.4.2 Risks

- No increase in the risk of breast cancer with HRT in POI before the age of natural menopause.
- Cyclical combined estrogen & progestogen therapy should be prescribed in order to protect the endometrium in POI women with an intact uterus.

7.4.3 Options for HRT: Types of preparation, regimens and route of administration, doses and duration

- The goal of HRT in POI is physiological sex steroid levels with optimal patient compliance and minimal risks.
- 17 β Estradiol is preferred over ethinyl estradiol and conjugated equine estrogen.
- Natural micronized progesterone is equally effective to synthetic progestogens.
- Although guidelines recommends transdermal route for estrogen and vaginal/

intrauterine route for progestogen, patient preference should be considered.

- The bioequivalent doses for HRT in POI are: [8]

Estrogen

17 β Estradiol-1-2 mg (oral) & 100 mcg (transdermal)

Conjugated equine estrogen 0.625-1.25 mg

Progestogen

Continuous (daily): 2.5-5 mg medroxyprogesterone acetate or 100 mg micronized progesterone

Sequential (12 days/ month): 10 mg medroxyprogesterone acetate or 200 mg micronized progesterone

Combined oral contraceptive pills

The advantage of compliance to be weighed against the risk of venous thromboembolism due to higher dose of estrogen and progesterone in OCP in comparison to HRT.

Androgens

Indication to use androgens in women with POI are diminished sexual function, neurological complaints and decreased bone density. The women should be counselled about the risks associated with use of androgen therapy like masculinizing effects, endometrial hypertrophy and breast cancer. Testosterone may be administered trans dermally, orally or through an implant. If androgen therapy is commenced, treatment effect should be evaluated after 3-6 months and should not be continued beyond 2 years.

However there is no consensus on optimal dose of HRT. It depends upon the indication to use, preparation and route of administration.

HRT should be continued at least until the age of natural menopause, i.e. around 50 years of age.

7.4.4 Monitoring

- Currently, there is no evidence regarding the optimum HRT monitoring strategy.
- Estrogen dosage should be titrated to achieve symptom control and adequate bone density.
- Serum estradiol is not helpful in clinical practice.
- POI women should be reviewed annually to follow up on compliance, satisfaction and adverse effects.
- No routine monitoring tests are required but may be prompted by specific symptoms or concerns, like mammography or bone DEXA (dual energy X ray absorptiometry).

Conclusion

Premature ovarian insufficiency is the clinical condition with significant psychological, physical and reproductive health implications. The healthcare providers should take extreme care in making the diagnosis of POI along with discussing various health issues associated with it. Although further research is required in few areas, psychological support, lifestyle measures and hormone replacement therapy remains the mainstay of management. Special care need to be taken in adolescents and young women where fertility and pregnancy are the major treatment goals.

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Managing Endometriosis in Young Women Desiring Future Fertility

Pikee Saxena, Madhavi Gupta, Seema Singhal, Swati Sinha, Renu Misra

Preamble

With earlier menarche, late childbearing and changes in lifestyle, we are seeing endometriosis at a much younger age. The clinician is expected in such situations to provide symptomatic relief in patients presenting with pain. In asymptomatic patients, with incidental diagnosis of ovarian endometriomas on ultrasound, patients need to be counselled on how to minimize the risk of disease progression and preserve future fertility.

This guideline specifically focusses on young women (< 30 years) presenting with a diagnosis of endometriotic cysts (endometriomas), with or without pain, who do not desire immediate pregnancy (unmarried or recently married) but keen to preserve future fertility.

Disclaimer

The guideline has been compiled on the basis of best available evidence. Yet it can only provide general guidance, and cannot supersede clinical judgement or the need to individualize treatment plan.

Introduction

Endometriosis is a chronic, relapsing, inflammatory disorder in which the endometrium and the stromal tissue is present outside the uterine cavity. It is a chronic disease that requires life-long management to improve quality of life, preserving functional anatomy and fertility, and avoiding repeated surgical procedures.

The issues that the clinician faces in these women are:

- What is the best way to provide symptomatic relief without comprising future fertility.
- What is the best strategy for incidentally detected endometriomas – expectant, medical or surgical, to optimise future fertility.
- Is it advisable to offer postoperative medical treatment?
- How should young women with suspected endometriosis managed?

1. Management of incidentally diagnosed endometrioma

The true prevalence of asymptomatic endometriosis is not known but between 3 and 45% of women undergoing laparoscopic sterilization have been diagnosed with endometriosis.[1,2] Asymptomatic endometriosis is defined as the incidental finding of peritoneal, ovarian or deep endometriosis without pelvic pain and/or infertility.[3] The ovaries are affected in 20-50% women with endometriosis.[4] However, what percentage of these are asymptomatic has not been documented.

It is not uncommon in the present day to find an endometrioma on ultrasound in a young woman, whether this has an impact on future fertility is not clear.

1.1 Does the presence of an endometrioma affect the ovarian function?

Since there are no studies comparing the outcome of expectant versus surgical/ medical management in women with asymptomatic endometriomas, we have looked at surrogate markers like rate of spontaneous ovulation and response to controlled ovarian hyperstimulation (COH) in ART cycles.

Effect on spontaneous ovulation. In a study of 244 women with a mean age of 34.3 years with unilateral endometriomas (55% with left endometrioma and 45% with right endometrioma) were monitored for ovulation during 1199 cycle. The mean diameter of endometriomas was 5.3 cm ± 1.7 cm. Ovulation occurred at similar rates from the normal ovary and the endometriotic ovary (49.7 percent versus 50.3 percent). The observation was confirmed in women with cysts ≥ 4 cm and ≥ 6 cm.[5] (Evidence level 2+)

Effect on ovarian response to COH. In a retrospective analysis in women with unilateral endometriomas ≥ 5cm undergoing IVF, the total number of oocytes retrieved from affected ovaries were significantly lower.[6] However, surgical removal of endometriomas prior to IVF did not improve the outcome.[7] (Evidence level 2++)

Although spontaneous ovulation is not affected by endometriomas, number of mature oocytes retrieved from ovaries with endometriomas in IVF are lower than normal ovaries, and does not improve after excision of the cyst. (B)

1.2 **Is there a role of medical treatment?**

A multicentric trial in Japan showed that drospirenone/ethinyl estradiol given for six cycles resulted in significant reduction in the size of endometrioma.[8] (Evidence level 2++) Another study in which 8 women with 14 endometriomas were given daily 5 mg of Letrozole plus 5 mg of norethindrone acetate as add-back for three months showed a decrease in mean diameter and volume of endometriomas by 50% and 75% respectively.[9] However there are no studies conducted in patients with asymptomatic endometriomas. (Evidence level 2+)

Medical treatment has been shown to reduce the size of endometriotic cysts, but there is no clear recommendation whether asymptomatic women should be treated due to potential side effects and uncertain benefit of prolonged drug therapy. (C)

1.3 **Expectant or surgical management?**

There is no evidence based consensus on whether asymptomatic endometriomas should be treated surgically or managed expectantly, or what should be the cut off beyond which surgical intervention is desirable.

In a study, asymptomatic women with ovarian cysts < 6 cm were followed up prospectively. No significant change in the size of endometriotic cysts was observed over a mean follow up of 42 months.[10] (Evidence level 2+)

There are also proponents of treating endometriomas surgically in young women irrespective of size to prevent further damage to the ovary due to the disease itself and the possibility of less invasive surgical procedure on smaller cysts.

If surgery is decided, ovarian cystectomy should be preferred as the risk of recurrence is lower.[11] (Evidence level 1)

There are however concerns of reduced ovarian reserve after excision of the cysts, and the risk of recurrence. A meta-analysis on cystectomy for endometriomas reported a significant reduction in anti-Müllerian hormone levels in women after cystectomy compared to before surgery.[12] (Evidence level 2++)

Ovarian cystectomy for bilateral endometriomas may result in a greater reduction in AMH levels than unilateral ovarian cystectomy.[13,14] Recurrence after surgery has been reported in 25% cases.[15] The pros and cons of surgery should be discussed with the patient keeping in view the age of patient, size of the cyst, unilateral or bilateral, and plans for pregnancy.

If expectant management is pursued, ultrasound may be repeated every 6 months for 1-2 years, then annually. Two consecutive scans demonstrating increase in cyst size, change in complexity of the cyst, or development of symptoms should prompt surgical intervention.

Asymptomatic cysts < 6 cm can be followed up with serial ultrasounds (C)

If surgery is decided, cystectomy should be preferred to cyst drainage and ablation. (A)

There is a significant reduction in AMH after cystectomy for endometriomas (B)

Surgery cannot be endorsed as a standard of care in asymptomatic women with endometriotic cysts. (GPP)

2. Endometriomas associated with pain

There is a lack of data from randomized trials regarding the optimal management of endometriomas with respect to pain relief, recurrence, and fertility.

2.1 Is medical treatment effective in pain relief?

Medical treatment is variably effective in providing pain relief in women with endometriosis.

NSAIDs are generally tried for pain relief although there is no good evidence that they are effective in endometriosis-related pain relief. Women should be counselled about the side effects of NSAIDs. Hormonal therapy should be given if NSAIDs are ineffective or provide partial pain relief.

Hormonal therapy. Combined oral contraceptive pills and progestins may be used as first line hormonal treatment for pain relief.[16] (Evidence level 1). Combined hormonal contraceptives in the form of oral pills, vaginal ring or transdermal patches may be used for symptomatic relief.

OCPs were shown to significantly reduce dysmenorrhoea and non-menstrual pain in a randomized double blind placebo controlled trial.[17] (Evidence level 1++). Continuous combined pills may be more effective than cyclic administration, especially in relief of dysmenorrhoea.[18] (Evidence level 2). A break for seven days can be given if breakthrough bleeding occurs, and pills restarted after seven days.

Progestogens can also be used as first line therapy as an alternative to combined estrogen-progestogen preparations, the choice depending on side effects and any contraindications to combined pills.[16] Commonly used progestogens and their doses are given in the Table-1.

Second line drugs are GnRH analogues and LNG-IUS. Danazol should not be used in young women because of severe androgenic side effects. There is no clear evidence to show that one form of hormonal therapy is superior to others. Newer drugs which have been shown to be effective are aromatase inhibitors, cabergoline, and selective progesterone receptor modulators (SPRM) including ullipristal and mifepristone.

Table1: Progestogens used for treatment of endometriosis

Progestin	Dose
Norethisterone	5-20 mg/day
Dienogest	2 mg/day
Dydrogesterone	10–30 milligrams a day
Medroxyprogesterone acetate	30 - 60 mg/day
Depot medroxyprogesterone acetate	150 mg IM injection every 2–3 months
Levonorgestrel intrauterine system	Releases 20 µg/day up to 5 years

Combined hormonal pills and progestogens are effective and may be used as first line treatment for pain relief (A)

Continuous OCP may be more effective than cyclic for dysmenorrhoea (C)

2.2 What is the place of surgery for pain relief?

In young women, classical medical therapies should be tried first, and surgery should be considered only if medical treatment fails to provide pain relief, unless fertility is desired in near future. Cystectomy or cyst excision provides greater pain relief as compared to drainage and ablation.[11] Laparoscopic uterosacral nerve ablation (LUNA) should not be performed as an additional procedure to reduce endometriosis-associated pain.[19]

Cystectomy provides better pain relief than drainage and ablation of cyst (A)

3. Postoperative hormonal therapy

Endometriosis is known to be a recurrent disease. The objectives of postoperative hormonal therapy are to prolong pain relief after surgery and prevent recurrence of symptoms and disease

3.1 **Can postoperative hormonal therapy reduce the risk of recurrence?**

Evidence:

In a study, of 277 patients who underwent excision of endometrioma, 102 patients took cyclic oral contraceptive pills (OCP). Endometrioma recurrence rate was 6% compared to 49% in those who did not take any postoperative hormones during a median follow up of 28 months.[20] (Evidence level 2). Another study randomized 239 women after laparoscopic cystectomy for endometrioma into three groups, continuous OCP, cyclic OCP, or no therapy. The recurrence rates in the three groups were 8.2%, 14.7%, and 29% respectively, the difference between the two OCP groups was not statistically significant.[21] (Evidence level 1+)

Recent systematic reviews and metaanalysis have concluded that postoperative use of continuous OCP was associated with a reduction in the recurrence rate of dysmenorrhea, delay in the presentation of dysmenorrhea, reduction in nonspecific pelvic pain, and reduction in the recurrence rate for endometrioma.[22,23] (Evidence level 1, 2++)

A multicentre randomized trial evaluating the efficacy of dienogest with estradiol valerate versus GnRH analogues in preventing recurrence after laparoscopic surgery found both therapies equally effective.[24] (Evidence level 1). A Cochrane review which included three randomized trials showed a significant reduction in the recurrence of dysmenorrhoea in women who were randomized to receive LNG-IUS after undergoing surgery for endometriosis.[25] (Evidence level 1+)

Postoperative hormonal therapy in the form of OCP, dienogest with estradiol valerate, gonadotropin releasing hormone analogues, or LNG-IUS have all been shown to be effective in secondary prevention of symptoms and recurrence of endometrioma. (A)

Combined oral contraceptives, cyclic or continuous, should be given for at least 18-24 months, or LNG-IUS which can be inserted at the time of surgery, if pregnancy is not desired. (C)

Continuous OCP may be more beneficial than cyclic OCP following conservative surgery for endometriosis. (C)

4. Suspected endometriosis: Diagnosis and Management

Endometriosis may be suspected on the basis of symptoms and /or examination. Laparoscopic examination or histopathology are not mandatory to start treatment.

4.1 When should the diagnosis of endometriosis be considered?

Pelvic pain, dysmenorrhoea, dyspareunia, abdominal pain, intermenstrual pain, infertility.[26] (Evidence level 2). Non-gynaecological symptoms like dyschezia, dysuria, haematuria and rectal bleeding, painful bowel movement, shoulder pain.[19]

4.2 What findings on clinical examination support the diagnosis?

Vaginal examination or rectal examination in women not sexually active - induration and/or nodules of the rectovaginal wall, adnexal mass. Normal clinical examination does not rule out endometriosis.

4.3 Which imaging modality is useful in a case of suspected endometriosis?

No imaging modality can detect overall pelvic endometriosis with accuracy. Transvaginal ultrasound is the best imaging modality to diagnose endometriotic cysts. Additionally transvaginal ultrasound may be used to map rectosigmoid endometriosis.[27] (Evidence level 1)

Transabdominal ultrasound may be done in women who are not sexually active.

4.4 Should biomarkers be used for diagnosis?

Biomarkers including CA 125 have poor predictive value and therefore not recommended for diagnosis.[28] (Evidence level 1)

4.5 How should young women with suspected endometriosis be managed?

Hormonal therapy can be given empirically without definitive diagnosis by laparoscopy, particularly in adolescents and young adults. For details of hormonal therapy, see section B.

Laparoscopy is the gold standard for diagnosis. If response to medical treatment is inadequate, laparoscopy is warranted to confirm diagnosis. If endometriosis is diagnosed on laparoscopy, endometrial implants should be treated by ablation or excision. Cystectomy should be the preferred to drainage and coagulation for surgically treating endometriomas.[11]

A diagnosis of endometriosis should be considered with symptoms like pelvic pain, dysmenorrhoea, dyspareunia, abdominal pain, intermenstrual pain, infertility (B)

TV ultrasound is the best imaging modality to diagnose endometriotic cysts (A)

Biomarkers including CA 125 are not reliable for diagnosis of endometriosis (A)

Hormonal therapy should be used as first line, laparoscopy offered if there is inadequate pain relief (GPP)

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Classification of evidence levels	**Grades of recommendations**
1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias	**A** At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or
1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias	A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias	**B** A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or
2++ High-quality systematic reviews of case–control or cohort studies or high- quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal	Extrapolated evidence from studies rated as 1++ or 1+
2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal	**C** A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or
2- Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	Extrapolated evidence from studies rated as 2++
3- Non-analytical studies, e.g. case reports, case series	**D** Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
4- Expert opinion	**Good practice point** Recommended best practice based on the clinical experience of the guideline development group

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Laparoscopy in Management of Endometriosis

Endometriosis, one of the most common diseases encountered by gynaecologists, is defined as the presence of endometrial glands and stromal tissue outside the uterus. This ectopic endometrial tissue induces chronic, estrogen dependent inflammatory response[1]. The most common sites affected are the ovaries, uterine ligaments, recto and vesico-vaginal septum, pelvic peritoneum, cervix, labia, and vagina.

1. **Prevalence**
   Endometriosis is one of the most common conditions encountered in gynaecological practiceand its incidence is on rise. Major studies have reported that 25-50% of infertile women have endometriosis and 30-50% of women with endometriosis are infertile.[2] The true prevalence of endometriosis is difficult to quantify as very wide ranges have been reported in literature. Endometriosis is found in 45% - 82% of women with chronic pelvic pain and in 2.1%-78% of infertile women. It affects 6 to 10 percent of women of reproductive age, and it is present in approximately 38 percent of women with infertility and in up to 87 percent of women with chronic pelvic pain[2]. An Indian study found the frequency of endometriosis in women with infertility to be 48.38%.[3]

2. **Laparoscopic Findings**
   Laparoscopy and directed biopsy forms the gold standard for diagnosis of endometriosis. In the absence of signs and symptoms of ovarian endometrioma, invasive disease or infertility, laparoscopy is not mandatory before commencing medical therapy. Again, laparoscopy should be considered when symptoms are severe and/or persistent despite medical treatment.[4]
   1. **Typical lesions:** Powder burn or gun shot--black, dark-brown, or bluish puckered lesions, nodules or small cysts containing old haemorrhage surrounded by a variable extent of fibrosis.
   2. **Atypical lesions:** Red implants (petechial, vesicular, polypoid, haemorrhagic, red flame-like) and serous or clear vesicles.
   3. **Endometrioma**: These arise from the ovary, contain thick chocolate colored fluid. There is often surrounding fibrosis with involvement of fallopian tubes or bowel.
   4. **Deep infiltrative disease**: The endometriotic nodules extend >5 mm beneath the peritoneum and may involve the uterosacral ligaments, vagina, bowel, bladder, or ureters. Depth of invasion is proportional to severity of symptoms[5].

3. **Ultrasonography**
   When suspected TVS is modality of choice to diagnose or exclude ovarian enometrioma. Ground glass echogenicity and one to four compartments and no papillary structures with detectable blood flow are some of characteristics of endometromas[6]. Transvaginal ultrasonography with bowel preparation and transrectal ultrasonography can detect deep infiltrating lesions affecting the bowel, bladder, and rectovaginal pouch[7]. If there is suspicion of deep infiltrative disease the involvement of abdominal organs like bladder, ureter, or bowel should be evaluated by additional imaging studies like MRI. However, diagnosis, staging & management often includes laparoscopic management.

4. **Staging of endometriosis**
   American Society for Reproductive Medicine (ASRM) has classified endometriosis

into different stages depending on location, extent, and depth of endometriosis implants; presence and severity of adhesions; and presence and size of ovarian endometriomas (Figure 1). Minimal and mild endometriosis is characterised by few superficial implants and mild adhesions. Moderate and severe endometriosis is characterised by deep implants, presence of endometriomas and dense adhesions.

Fig 1: American society of reproductive medicine classification for endometriosis

5. Management

Endometriosis should be viewed as chronic, progressive disorder characterised by presence of pain and associated with infertility. It requires individualised management plan with goal of minimising repeated surgical procedures and taking in account of women preferences, age, presenting symptomatology and presence of infertility. The current modalities are medical management, surgical management or combination of both.

5.1 *Surgical management*

Surgery for endometriosis associated pain is indicated when medical management fails, patient declines, severe side effects of medical therapy, or suspicion of invasive disease Peritoneal endometriosis can be eliminated by division of adhesions and excision or ablation of endometrial implants with either electosurgery or laser. Laparoscopy is preferred surgical route for surgical management in view of magnified view, short hospital stay, and quick return to routine activities. Excision of implants could be

seen as better option as it will retrieve samples for histology. Surgical treatment of endometriosis associated pain has been compared with diagnostic laparocopy and medical management in a Cochrane trial and it is shown to be more effective in relieving pain at 6 and 12 months[8]. In presence of advance disease involving other abdominal organs patient should be managed with multidisciplinary approach.

Recommendations[9,10]

- Laparoscopy should be performed to diagnose endometriosis, although evidence is lacking that a positive laparoscopy *without histology* proves the presence of disease. (GPP)
- A positive laparoscopy should be confirmed by histology, since positive histology confirms the diagnosis of endometriosis, even though negative histology does not exclude it. (GPP)
- Histology should be obtained in women undergoing surgery for ovarian endometrioma and/or deep infiltrating disease, to exclude rare instances of malignancy. (GPP)
- When endometriosis is identified at laparoscopy, clinicians are recommended to surgically treat endometriosis, as this is effective for reducing endometriosis-associated pain i.e. 'see and treat'. (Grade A)

5.1.1 Surgical Management of Endometriomas

Endometriomas are formed by invagination of the cortex containing blood from bleeding of endometrial implants, which are located superficially on the ovarian surface. The presence of endometrioma implies severe disease and it is important to consider the patient's reproductive desire and her fertility potential. Surgical options include excision of the cyst wall or drainage and coagulation of the cyst bed. Cystectomy is superior in terms of recurrence of pain and recurrence of endometrioma when compared to drainage and coagulation[10].

5.1.2 Ovarian Cystectomy

The procedure begins with freeing the cyst by adhesiolysis and mobilising ovary. Then the cortex of the endometrioma is held by grasper and incision is made along anti mesenteric border away fromhilum of ovary. Then by creating plane between capsule of ovary and cyst, cystectomy is done. Should the spillage of contents of cyst occurs, irrigation and drainage of peritoneal cavity is done to prevent chemical peritonitis. The cyst is then decompressed by suction drainage and cyst wall from inside is inspected. By using traction and counter traction technique cyst wall is removed and bed of remaining ovary is inspected for bleeders. Recurrence rate of 23.6 % has been reported[11].

Recommendation

- Cystectomy instead of drainage and coagulation should be performed, as cystectomy reduces endometriosis-associated pain. (Grade A)
- Cystectomy should be performed rather than CO2 laser vaporization in women with ovarian endometrioma, because of a lower recurrence rate of the endometrioma. (Grade B)

5.1.3 Endometriosis and infertility

Endometriosis is found in upto 38% of patients of infertility. In case of minimal to mild endometriosis operative laparoscopy with removal of implants either by excision or by ablation improves fertility than diagnostic laparoscopy[12,13]. The woman should be counselled regarding the possibility of reduced ovarian function after surgery and the loss of the ovary[10].

Recommendations[10]

- In infertile women with AFS/ASRM stage I/II endometriosis, operative laparoscopy i.e. excision or ablation of the endometriosis lesions should be performed including adhesiolysis, rather than performing diagnostic laparoscopy only, to increase ongoing pregnancy rates (Grade A)
- In infertile women with AFS/ASRM stage I/II endometriosis, CO2 laser vaporization of endometriosis, instead of monopolar electrocoagulation, should be considered since laser vaporization is associated with higher cumulative spontaneous pregnancy rates (Grade C)
- In infertile women with ovarian endometrioma undergoing surgery, excision of the endometrioma capsule, instead of drainage and electrocoagulation of the endometrioma wall, should be performed to increase spontaneous pregnancy rates (Grade A)
- Women with endometrioma should be counseled regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery. (GPP)
- In infertile women with AFS/ASRM stage III/IV endometriosis, operative laparoscopy, instead of expectant management, should be performed to increase spontaneous pregnancy rates (Grade B)

5.1.4 Deep Endometriosis

Deep endometriosis extends beneath the peritoneum and may affect the uterosacral ligaments, pelvic side walls, rectovaginal septum, vagina, bowel, bladder or ureter. Excision of these nodules is usually performed when surgical treatment is chosen. Colorectal involvement is not rare with deep endometriosis, and the treatment approaches for this condition include superficial shaving, discoid resection and segmental resection of the bowel to remove the deep endometriosis nodules. Surgery improves pain and quality of life in women with deep endometriosis. However, surgery in women with deep endometriosis is associated with substantial intraoperative and postoperative complication rates.

Recommendations[10]

- Surgical removal of deep endometriosis should be performed, as it reduces endometriosis-associated pain and improves quality of life (Grade B)
- Women with suspected or diagnosed deep endometriosis should be reffered to a centre of expertise that offers all available treatments in a multidisciplinary context. (GPP)

5.1.5 Adhesion prevention after endometriosis surgery

There are a number of barrier, fluid and pharmacological agents that have been tried for adhesion prevention during gynaecological surgery. These include oxidised regenerated cellulose (Interceed®), polytetrafluoroethylene surgical membrane (Gore-Tex®), fibrin sheet, sodium hyaluronate and carboxymethylcellulose combination (Seprafilm®), polyethylene oxide and carboxymethylcellulose gel (Oxiplex/AP®), steroids, dextran, icodextrin 4% (Adept®), hyaluronic acid products and polyethylene glycol hydrogel (SprayGel®). Most of these agents have not been studied specifically for endometriosis; only a few studies reported outcome data separately for women with endometriosis.[10]

Recommendations[10]

- Oxidised regenerated cellulose can be used during operative laparoscopy for endometriosis, as it prevents adhesion formation (Grade B)
- Icodextrin use is not reasonable after operative laparoscopy for endometriosis to prevent adhesion formation, as no benefit has been shown (Grade B)
- Other anti- adhesion agents (polytetrafluoroethylene surgical membrane, hyaluronic acid products) have been studied and proven to be effective for adhesion prevention in the context of pelvic surgery, although not specifically in women with endometriosis. (GPP)

Conclusion

In case of minimal to mild endometriosis operative laparoscopy with removal of implants either by excision or by ablation improves fertility than diagnostic laparoscopy. The woman should be counselled regarding the possibility of reduced ovarian function after surgery and the loss of the ovary. Surgery for advance disease follows principal to restore pelvic anatomy with operative laparoscopy may enhance fertility.

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Evidence-based Guidelines for Safe Laparoscopic Entry

Purpose and scope

The majority of laparoscopic surgeries are without problems but serious complications occur in about one in 1000 cases, and a significant proportion occur at the time of laparoscopic abdominal wall entry.[1] Laparoscopic injuries frequently occur during the blind insertion of needles, trocars and cannulae through the abdominal wall and, hence, the period of greatest risk is from the start of the procedure until visualization within the peritoneal cavity has been established. This guideline aims to highlight strategies to reduce complications while abdominal entry in laparoscopy.

1. Background

Although complications associated with laparoscopic surgery fortunately are rare, a significant proportion of these occur at the time of laparoscopic abdominal wall entry. Meta-analyses and large multicenter studies have provided pooled risks of vascular and bowel injury at the time of laparoscopic entry as 0.2 per 1,000 and 0.4 per 1,000, respectively.[2,3] Such complications may lead to serious morbidity and mortality, and if injuries like bowel injury, are not detected at the time of original surgery, the complications are compounded.

Two laparoscopic entry methods are used principally in gynecology and general surgery:

- Closed entry laparoscopy with creation of a pneumo- peritoneum at the umbilicus or Palmer's point
- Open (Hasson) laparoscopy

Other techniques, used less frequently and with limited supporting evidence are **direct entry, optical access trocars, and radially expanding trocars**.

According to current evidence, based mainly on observational studies, no one laparoscopic entry method has demonstrated clear superiority over another. This has led to wide variation among clinicians as to which entry method should be recommended. It has been suggested that open entry is superior to closed entry techniques because vascular injury is less likely to occur, although this view-point has been challenged.

Methodology

The guideline is adapted from a review comprising of literature search of various guidelines (e.g. Royal College of Obstetricians and Gynaecologists [RCOG], Society of Obstetricians and Gynaecologists of Canada [SOGC] and specialist international laparoscopy organization (e.g., American Association of Gynecologic Laparoscopists [AAGL], Society of American Gastrointestinal Endoscopic Surgeons (SAGES), Royal Australian & New Zealand College of Obstetricians & Gynaecologists (RANZCOG).[4,5,6,7&8] The literature was critically appraised according to established evidence-based criteria.

2. Guidelines[4]

- Patient should be lying flat with an empty bladder; palpation should be used for the abdominal aorta, any masses; and the Veress needle should be checked for spring action and gas patency. (*Level of evidence and grade of recommendation 4, GPP)*
- Incision: 10-mm vertical intraumbilical incision starting deep inside the umbilicus pit and extending caudally. (*Level of evidence and grade of recommendation 4, GPP*)

- Insertion of the Veress needle: At the deep umbilical pit, 90° to the skin, with stabilizing or elevating the umbilical sheath/fascia or anterior abdominal wall, and in a controlled manner with insertion of less than 2 cm of the Veress needle tip. Before insertion, checking patency & spring action of Veress needle should be performed. *Level of evidence and grade of recommendation2+, C (indirect evidence from knowledge of abdominal anatomy)*
- No movement of the Veress needle after insertion to avoid converting a possible needle point injury into a large complex tear. (*Level of evidence and grade of recommendation 4, GPP)*
- Safety abdominal pressure check of Veress placement: most reliably achieved by using a Veress IAP of less than 10 mmHg. If pressure >10 mm Hg, there is possibility of incomplete entry or localized adhesion. Lifting abdominal wall and changing direction of needle might help in creating pneumoperitoneum, if tip of needle is getting obstructed by omentum or other intra-peritoneal structures. *(Level of evidence and grade of recommendation 2+, C)*
- Safety abdominal pressure check for primary trocar: the IAP should be 15-25 mmHg to achieve the maximum safe distance between the anterior abdominal wall and the underlying abdominal contents. *(Level of evidence and grade of recommendation 2+, C)*
- Vertical primary trocar insertion: inserted in a controlled two-handed screwing manner at an angle (45 to 90 degree) to abdominal wall depending upon the abdominal fat content, with only the tip of the trocar inserted through the abdominal wall. Once yellow coloured omentum or bowel is seen, it confirms intraperitoneal entry. *(Level of evidence and grade of recommendation 2+, C)*
- Consider alternative entry (e.g., Palmer's point or open Hasson technique or Lee-Huang Point) for patients with risk factors such as previous abdominal surgery, obesity, extremely thin physique, or known abdominal adhesions. *(Level of evidence and grade of recommendation 2++, B)*
- Injury check: an initial 360° laparoscopic check for intra-peritoneal organ injury is performed. *(Level of evidence and grade of recommendation 4, GPP)*
- Secondary trocar(s) should be inserted under direct vision in a controlled two-handed manner at 90° to the skin, avoiding inferior epigastric vessels. *(Level of evidence and grade of recommendation 2+, C (Indirect evidence from knowledge of abdominal anatomy)*

3. Counseling and consent

Women must be informed of the risks and potential complications associated with laparoscopy. This should include discussion of the risks of the entry technique used: specifically, injury to the bowel, urinary tract and major blood vessels, and later complications associated with the entry ports: specifically, hernia formation.

Surgeons must be aware of the increased risks in women who are obese or significantly underweight and in those with previous midline abdominal incisions, peritonitis or inflammatory bowel disease. These factors should be included in patient counselling where appropriate. (*Grade of Recommendation-C*)

4. Safe surgical techniques and training

1. Surgeons intending to perform laparoscopic surgery should have appropriate training, supervision and experience.
2. Surgeons undertaking laparoscopic surgery should be familiar with the equipment, instrumentation and energy sources they intend to use.
3. Surgeons undertaking laparoscopic surgery should ensure that nursing staff

and surgical assistants are appropriately trained for the roles they will undertake during the procedure.

5. Laparoscopic entry techniques

5.1 Veress needle (closed) laparoscopic entry technique

In most circumstances the primary incision for laparoscopy should be vertical from the base of the umbilicus (not in the skin below the umbilicus). Care should be taken not to incise so deeply as to enter the peritoneal cavity.

The Veress needle should be sharp, with a good and tested spring action. A disposable needle is recommended, as it will fulfil these criteria.

The operating table should be horizontal (not in the Trendelenburg tilt) at the start of the procedure. The abdomen should be palpated to check for any masses and for the position of the aorta before insertion of the Veress needle.

The lower abdominal wall should be stabilised in such a way that the Veress needle can be inserted at right angles to the skin and should be pushed in just sufficiently to penetrate the fascia and the peritoneum. Two audible clicks are usually heard as these layers are penetrated.

Excessive lateral movement of the needle should be avoided, as this may convert a small needle-point injury in the wall of the bowel or vessel into a more complex tear. The needle should be patent and check before insertion. Syring filled with saline may be used to check entry.

5.1.1 *What intra-abdominal pressure should be achieved to safely insert the primary trocar?*

An intra-abdominal pressure of 15–25 mmHg should be used for gas insufflation before inserting the primary trocar.

The distension pressure should be reduced to 12–15 mmHg once the insertion of the trocars is complete. This gives adequate distension for operative laparoscopy and allows the anaesthetist to ventilate the patient safely and effectively.

5.1.2 *Where should the primary trocar be inserted?*

The primary trocar should be inserted in a controlled manner at 90 degrees to the skin, through the incision at the thinnest part of the abdominal wall, in the base of the umbilicus. Insertion should be stopped immediately the trocar is inside the abdominal cavity.

Once the laparoscope has been introduced through the primary cannula, it should be rotated through 360 degrees to check visually for any adherent bowel. If this is present, it should be closely inspected for any evidence of haemorrhage, damage or retroperitoneal haematoma.

If there is concern that the bowel may be adherent under the umbilicus, the primary trocar site should be visualised from a secondary port site, preferably with a 5-mm laparoscope.

On completion of the procedure, the laparoscope should be used to check that there has not been a through-and-through injury of bowel adherent under the umbilicus by visual control during removal.

5.2 Alternative laparoscopic techniques

5.2.1 *Hasson (open) entry technique*

When the Hasson open laparoscopic entry is employed, confirmation that the

peritoneum has been opened should be made by visualising bowel or omentum before inserting the blunt tipped cannula. (Evidence level IIb)

The Hasson technique of open laparoscopic entry is an alternative to closed laparoscopy that avoids the use of sharp instruments after the initial skin incision. It allows the insertion of a blunt-ended trocar under direct vision.

Once the fascial edges are incised, they should be held by a lateral stay suture on either side of the incision. Once the peritoneum is opened, the fascial sutures are then pulled firmly into the suture holders on the cannula to produce an airtight seal with the cone of the cannula. Gas is insufflated directly through the cannula to produce the pneumoperitoneum.The blunt trocar is withdrawn only after the abdomen is partially distended.At the end of the procedure, the fascial defect should be closed using the stay sutures (and possibly additional sutures) to minimise the risk of herniation.

5.2.2 *Direct trocar insertion*

Direct trocar insertion is an acceptable alternative trocar insertion method. This technique was developed to overcome the difficulty associated with grasping the abdominal wall already distended by the pneumoperitoneum. In experienced hands it is the most rapid method of entry and can be safely used if the cases are carefully selected. Nowadays, it is not widely used within gynaecological practice.

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Appendix. Scottish Intercollegiate Guidelines Network (SIGN) grading system

Levels of evidence

1++ High-quality metaanalyses, systematic reviews of RCTs or RCTs with a very low risk of bias

1+ Well-conducted metaanalyses, systematic reviews of RCTs or RCTs with a low risk of bias

1– Metaanalyses, systematic reviews of RCTs or RCTs with a high risk of bias

2++ High-quality systematic reviews of case-control or cohort studies; High-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal

2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal

2– Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal

- **3** Nonanalytic studies (e.g., case reports, case series)
- **4** Expert opinion

Grades of recommendation

- **A** At least one metaanalysis, systematic review, or RCT rated as 1++ and directly applicable to the target population, or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
- **B** A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
- **C** A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
- **D** Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

GPP Good practice points: recommended best practice based on the clinical experience of the guideline development group

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Management of Overactive Bladder

The International Continence Society (ICS) defines Overactive Bladder (OAB) as the presence of "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology."[1] Therefore, OAB symptoms consist of four components: urgency, frequency, nocturia and urgency incontinence. OAB that occurs with incontinence is known as 'OAB wet'. OAB that occurs without incontinence is known as 'OAB dry'.[2]

Urgency is defined by the ICS as the "complaint of a sudden, compelling desire to pass urine which is difficult to defer."[1] It is considered the hallmark symptom of OAB.

Urinary frequency can be highly variable based upon hours of sleep, fluid intake, comorbid medical conditions and other factors. Traditionally, up to seven micturition episodes during waking hours has been considered normal.[3]

Nocturia is the complaint of interruption of sleep one or more times because of the need to void.[1] Like daytime frequency, nocturia can often be due to factors unrelated to OAB (e.g., excessive night time urine production, sleep apnea).

Urgency urinary incontinence (UUI) *or OAB wet* is defined as the involuntary leakage of urine, associated with a sudden compelling desire to void.

When women are evaluated for OAB, counselling about treatment should begin with conservative options. The evaluation in women with symptoms of OAB includes the following steps:

1. **History**
   The purpose of history taking is to determine the type of urinary incontinence (UI) that is bothersome to the patient (eg. stress, urge, mixed) [EL = 4][2], precipitating events, frequency of occurrence, severity, pad use, and effect of symptoms on activities of daily living.(Table 1)[4]

Table 1: Differentiation from other incontinence

Symptoms	OAB wet/ UUI	Stress Urinary Incontinence (SUI)	Mixed Symptoms
Urgency (strong, sudden desire to void)	Yes	No	Yes
Frequency with urgency (> 8 times/24 h)	Yes	No	Yes
Leaking during physical activity (eg, coughing, sneezing, lifting)	No	Yes	Yes
Amount of urinary leakage with each episode of incontinence	Large (if present)	Small	Variable
Ability to reach the toilet in time following an urge to void	Often no	Yes	Variable
Waking to pass urine at night	Usually	Seldom	Maybe

Also, negative responses to queries regarding symptoms of leakage on effort or physical exertion, incomplete emptying, incontinence associated with chronic urinary retention (previously referred to as overflow incontinence), functional impairment, continuous leakage, incomplete emptying and a lack of continuous leakage in women with recent pelvic surgery or radiation exposure rules out other types of incontinence.

Differentiation from other conditions

Nocturnal polyuria is the production of greater than 20 to 33% of total 24 hour urine output during the period of sleep, which is age-dependent with 20% for younger individuals and 33% for elderly individuals[5]. The nocturnal voids are frequently normal or large volume as opposed to the small volume voids commonly observed in nocturia associated with OAB. Sleep disturbances, vascular and/or cardiac disease and other medical conditions are often associated with nocturnal polyuria.

In *polydipsia*, urinary frequency occurs with normal or large volume voids and the intake is volume matched. Similarly, diabetes insipidus also is associated with frequent, large volume voids and should be distinguished from OAB.

The clinical presentation of *interstitial cystitis/ bladder pain syndrome* shares the symptoms of urinary frequency and urgency, with or without urgency incontinence; however, bladder and/or pelvic pain, including dyspareunia, is a crucial component of its presentation in contradistinction to OAB.

Also in the menopausal female patient, *atrophic vaginitis* can be a contributing factor to incontinence symptoms. There is some evidence for symptom improvement with the use of vaginal (but not systemic) estrogen.[6]

Thorough medical and neurologic histories should be obtained. Certain conditions, such as diabetes and neurologic disorders, can cause UI. In addition, a complete list of the patient's medications (including nonprescription medications) should be obtained[3]. Agents that can affect lower urinary tract function include diuretics, caffeine, alcohol, narcotic analgesics, anticholinergic drugs, antihistamines, psychotropic drugs, alpha-adrenergic blockers, alpha-adrenergic agonists, and calcium-channel blockers.

2. Physical Examination

This should include an abdominal examination, a rectal/ genitourinary examination, an assessment of lower extremities for edema, assessment of cognitive impairment. The primary purpose is to exclude confounding or contributing factors to the incontinence or its management.

3. Investigations

3.1 Urinalysis Urinary tract infections should be identified using urinalysis and treated before initiating further investigation or therapeutic intervention for UI. At the clinician's discretion, further evaluation can be done.

The clinician should engage in a diagnostic process to document symptoms and signs that characterize OAB and exclude other disorders that could be the cause of the patient's symptoms; the minimum requirements for this process are a careful history, physical exam and urinalysis. At the clinician's discretion, a urine culture and/or post-void residual assessment may be performed and information from bladder diaries and/or symptom questionnaires may be obtained. (Clinical Principle)[7]

3.2 Urine culture is considered if urinalysis seems unreliable. Only one-third of positive tests are associated with bacteriologically proven UTIs. [EL = DS II][2]

3.3 Postvoid Residual (PVR) Assessment Anti-muscarinics should be used with caution in patients with PVR 250–300 ml.[9] The sensitivity and specificity of ultrasound (using a bladder scanner) in the detection of post-void residual urine volume, in comparison with catheterisation, is within clinically acceptable limits. [EL = DS II] The former is less invasive with fewer adverse effects. [EL = 4] The sensitivity of bimanual examination to detect small post-void residual volumes is poor. [EL = DS Ib][2]

3.4 Bladder diaries is useful for patient education, to document baseline symptom [EL=4]and treatment efficacy. Encourage women to complete a minimum of 3 days of the diary covering variations in their usual activities, such as both working and leisure days.[2]

3.5 Symptom Questionnaires are useful in the quantification of bladder symptoms. Examples of Validated Urinary Incontinence Questionnaires with good test-retest reliability [EL=3][2] are

- Urogenital Distress Inventory (UDI)
- Incontinence Impact Questionnaire (IIQ)
- Questionnaire for Urinary Incontinence Diagnosis (QUID)
- Incontinence-Quality of Life Questionnaire (I-QoL)
- Incontinence Severity Index (ISI)
- International Consultation on Incontinence Questionnaire (ICIQ)

3.6 Urodynamics, cystoscopy and **ultrasound** should only be used for complicated or refractory patients. [EL=3][2] (Clinical Principle)[7]

4. Treatment

Prior to initiating treatment, the patients should be given education regarding normal and abnormal bladder function so that they can understand and actively participate in treatment plan.

The Patient should be counselled that acceptable symptom control may require trials of multiple therapeutic options before full response. Optimization of other comorbidities (i.e., diabetes, Constipation, Chronic Heart Failure) can also be effective (Gr B/C)[15].

The clinician must weigh the risks against the benefits of each therapy and individualise the treatment e.g. in elderly patients with cognitive deficit or severely reduced mobility due to dementia, severe arthritis, severe obesity, hemiparesis/plegia, and lower extremity amputations; incontinence due to OAB cannot be corrected pharmacologically, while associated adverse effects might cause more harm.

4.1 First-Line Treatments: Behavioural Therapies

Behavioural therapies for minimum 6 weeks have the advantages that they can be combined with all other therapeutic techniques and virtually have no adverse effects.[EL=4, Gr B][2,15]

There are two fundamental approaches to behavioural treatment for OAB.

1. Modification of bladder function by changing voiding habits
   - self-monitoring (bladder diary)
   - bladder training by scheduled voiding, delayed voiding and double voiding [EL=1B, Gr B]
   - urge control techniques (distraction, self-assertions)[EL+3B. Gr B]
   - fluid management[8] [EL 1B, Gr B][15], caffeine reduction [EL=3][2], dietary changes (avoiding bladder irritants) [EL 2+, Gr C]
   - weight loss[10] and other life style changes [EL=3/1B, Gr B][2,15]
2. Focus on the bladder outlet to improve strength and control
   - techniques for urge suppression
   - pelvic floor muscle training and exercise (including pelvic floor relaxation)

[EL=1B. Gr B][11, 15]

- active use of pelvic floor muscles for urethral occlusion and urge suppression (urge strategies),
- normal voiding techniques including position on toilet seats
- biofeedback, electrical stimulation.

4.2 Second-Line Treatments [Gr A]:

4.2.1 Anti-Muscarinics have an antagonistic action on muscarinic receptors throughout the body, but improve OAB symptoms by blocking the M2 and M3 receptors in the bladder and urothelium, and therefore affect both involuntary detrusor contraction and increased sensory afferent signalling.

Clinicians should offer following oral anti-muscarinics (currently available in India) with recommended doses (IR= Immediate release; ER= Extended release):

- Darifenacin 7.5/ 15 mg OD
- Oxybutynin IR: 2.5/ 5 mg BID, TID, QID; ER: 5/10 mg OD
- Solifenacin 5/ 10 mg OD
- Tolterodine IR: 1/ 2 mg BID, ER: 2/4 mg OD
- Trospium ER: 60 mg OD

(listed in alphabetical order; no hierarchy is implied)

There is no compelling evidence for differential efficacy across medications as per conclusions of several published systematic reviews.[12]

Before starting drug, the clinician should always discuss with women the likelihood of success and associated common adverse effects, the frequency and route of administration, and that some adverse effects such as dry mouth and constipation may indicate that treatment is starting to have an effect, and that they may not see the full benefits until they have been taking the treatment for 4 weeks.[13]

ER formulations should preferentially be prescribed over IR formulations because of lower rates of dry mouth. Standard (Gr B)

If a patient experiences inadequate symptom control and/or unacceptable adverse drug events with one anti- muscarinic medication, then a dose modification or a different anti-muscarinic medication may be tried. (Clinical Principle)

Anti-muscarinics should not be used in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist and should be used with extreme caution in patients with impaired gastric emptying or a history of urinary retention. (Clinical Principle)

Clinicians should manage constipation and dry mouth before abandoning effective anti-muscarinic therapy. Management may include bowel management, fluid management, dose modification or alternative anti- muscarinics. (Clinical Principle)

Clinicians must use caution in prescribing anti-muscarinics in patients who are using other medications with anti- cholinergic properties. (Expert Opinion)

Clinicians should use caution in prescribing anti-muscarinics in the frail OAB patient. Clinical Principle Patients who are refractory to behavioural and medical therapy should be evaluated by an appropriate specialist if they desire additional therapy. (Expert Opinion)[14]

4.2.2 Beta-3 adrenoceptor agonist (Gr A) activates beta-3 adrenoceptors, allowing bladder relaxation, improving bladder filling and storage of urine. A starting dose of 25 mg, and increasing to 50 mg is recommended. The lowest dose is also recommended for renal and hepatic impairment.

If the initial selected drug is not tolerated or does not provide adequate symptom relief, patients should be offered an alternative medication, preferably with a different mechanism of action (Expert opinion). The adverse event profile and possible contraindications should be considered when prescribing the drug of choice as second-line treatment (Expert opinion). Immediate release formulations of AMs should be avoided if other formulations are available (Gr A). Patients who remain incontinent after the initial treatment with an AM could be offered combination treatment with solifenacin and mirabegron (Gr C).[15]

4.2.3 Desmopressin (oral dose ranging from 100 to 400 micro grams and an intranasal dose 20 micro grams) may be considered specifically to reduce nocturia in women with UI or OAB who find it a troublesome symptom[EL=1+], but use particular caution in women with cystic fibrosis and avoid in those over 65 years with cardiovascular disease or hypertension.

Pretreatment and early posttreatment (72 hours) serum sodium monitoring is recommended. Where there are new symptoms or a change in medication, further measurement of serum sodium is recommended. [EL = 4][2]

Special considerations in frail older people
Age-related changes in pharmacokinetics affect AM drugs for UI and these factors should be incorporated into treatment planning (Gr B). Drugs may be effective at lower doses in frailer compared with healthier older per- sons (Gr C). Polypharmacy increases the chance of adverse reactions to drug therapy, which are more common in the frail elderly (Gr A). Furthermore, drug-drug and drug-disease interactions are common in frail older persons (Gr A/B). AMs for treatment of OAB remain as potentially inappropriate medications for frail older people (Gr B/C).[15]

4.3 Third-line treatment:

4.3.1 OnabotulinumtoxinA (100 U) may be offered as long-term therapy to carefully selected patients with symptoms of frequency, urgency, and urgency incontinence who have had an inadequate response to or are intolerant of OAB pharmacotherapy (Gr A/B)[7,15]. Patients considering onabotulinumtoxinA must be carefully counselled regarding the need for close follow up, the possible need for catheterization (indwelling or CIC), and likelihood of repeat injections to maintain symptom improvement.

4.3.2 Peripheral tibial nerve stimulation (PTNS) does require a system capable of providing frequent clinic appointments, typically lasting 30 minutes to one hour in length, and patients must be compliant and able to continue frequent follow up. Therefore, attention must be paid to the patient's level of motivation and travel resources (Gr C)[7].

Do not offer percutaneous posterior tibial nerve stimulation for OAB unless: there has been a multidisciplinary team (MDT) review, and conservative management including OAB drug treatment has not worked adequately, and the woman does not want botulinum toxin A or percutaneous sacral nerve stimulation. [EL=3][13]

4.3.3 Sacral Neuromodulation (SNM) is considered as more invasive and higher-

risk than other third-line treatment, but a suitable option for patients with OAB symptoms refractory to preferred treatment options (Gr C/B).[7,15]

4.4 Additional treatments

Absorbent products, hand held urinals and toileting aids should not be considered as a treatment for UI [EL=4]. Use them only as:

- a coping strategy pending definitive treatment
- an adjunct to ongoing therapy
- long-term management of UI only after all treatment options have been explored.[2]

Indwelling catheterization, augmentation cystoplasty or other urinary diversions are rare long-term management strategies for OAB and should only be considered after all other medical and surgical options have been exhausted and only after careful consideration of the likely benefits and risks. (Expert Opinion) [2] (Gr D)[14]

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Note: *Abbreviations used Gr: Grade, EL: Evidence level*

Management of Stress Urinary Incontinence

Stress urinary incontinence (SUI) is a condition of involuntary loss of urine on effort, physical exertion, sneezing, or coughing that is often bothersome to the patient and frequently affects quality of life.

When women are evaluated for SUI, counselling about treatment should begin with conservative options. The evaluation in women with symptoms of SUI includes the following steps:

1. History

The history should include questions about the type of incontinence (eg. stress, urge, mixed), precipitating events, frequency of occurrence, severity, pad use, and effect of symptoms on activities of daily living.

After the urologic history, thorough medical and neurologic histories should be obtained. In addition, a complete list of the patient's medications (including non-prescription medications) should be obtained to determine whether individual drugs may be influencing the function of the bladder or urethra. Surgical, gynecologic, and obstetric histories also should be elicited.

2. Physical Examination

The primary purpose of the physical examination is to exclude confounding or contributing factors to the incontinence or its management. A urethral diverticulum (an out-pouching of the urethral lumen) can produce incontinence or postvoid dribbling. Occasionally, vaginal discharge can be confused with urinary incontinence. Extraurethral incontinence, caused by a fistula or ectopic ureter, is rare but can be seen on examination.

Pelvic organ prolapse (POP) beyond the hymen can produce a relative obstruction of the urethra that can impair bladder emptying. Therefore, it is recommended that all pelvic support compartments (anterior, posterior, and apical) be assessed[1,2]. Pelvic organ prolapse can mask or reduce the severity of SUI symptoms; this is referred to as occult, potential, masked, or hidden SUI. When POP is reduced with a nonobstructing pessary or large cotton swabs, SUI may become apparent or worsen[3].

2.1 Pelvic floor assessment

It is integral to continence and is done by means of digital vaginal examination. Two fingers are kept posteriorly in the vagina at 2-4cm from the hymenal ring and patient is asked to contract the muscles as used to "hold their urine" or "to avoid passing gas". Her ability to contract pelvic muscles of each side with their strength and duration of contraction is judged and graded.

NICE states poor Inter- and intra-observer reliability of grading systems [EL = 3], however recommends routine digital assessment of pelvic floor muscle contraction before the use of supervised pelvic floor muscle training for the treatment of UI (4).

2.2 Demonstration of Stress Incontinence

Cough Stress Test

Stress urinary incontinence should be objectively demonstrated before any anti-incontinence surgery is performed[5-7]. Visualization of fluid loss from the urethra

simultaneous with a cough is diagnostic of SUI. Delayed fluid loss is considered a negative cough stress test result and suggests cough-induce detrusor overactivity. The cough stress test can be performed with the patient in the supine position during the physical examination. However, if urine leakage is not observed, the cough stress test needs to be repeated with the patient standing and with a full bladder (or a minimum bladder volume of 300 mL) to maximize test sensitivity[6].

2.3 Assessment of Urethral Mobility

Anti-incontinence surgery is more successful in women with *urethral mobility*, defined as a 30 degree or greater displacement from the horizontal when the patient is in a supine lithotomy position and straining. Lack of urethral mobility is associated with a 1.9-fold increase in the failure rate of midurethral sling treatment of SUI[8].

The traditional tests like **Q-tip**[9]**, POP-Q, Bonney, Marshall** and **Fluid-Bridge tests** are not recommended by NICE for assessment of women with UI[4], however other methods of evaluating urethral mobility include measurement of point Aa of the POP Quantification system, visualization, palpation, and ultrasonography[10-12].

3. Investigations

3.1 Urinalysis

Urinary tract infections should be identified using urinalysis and treated before initiating further investigation or therapeutic intervention for UI.

3.2 Postvoid Residual Urine Volume

The presence of an elevated postvoid residual urine volume can indicate a bladder-emptying abnormality or incontinence associated with chronic urinary retention (previously referred to as overflow incontinence). An elevated postvoid residual urine volume in the absence of POP is uncommon and should trigger an evaluation of the bladder-emptying mechanism, usually with a pressure-flow urodynamic study.

Additional Evaluations

Determination of the need for additional diagnostic testing before surgery should be based on clinical judgment after completion of the basic UI evaluation outlined in this document. Clinical judgment should guide the physician decision to perform preoperative testing or to refer the patient to a specialist with appropriate training and experience in female pelvic medicine and reconstructive surgery.

Physicians should perform additional evaluations in patients being considered for surgical intervention who have the following conditions: (Expert Opinion)[13]

- Inability to make definitive diagnosis based on symptoms and initial evaluation
- Inability to demonstrate SUI
- Known or suspected neurogenic lower urinary tract dysfunction
- Abnormal urinalysis, such as unexplained hematuria or pyuria
- Urgency-predominant mixed urinary incontinence
- Elevated post-void residual per clinician judgment
- High grade pelvic organ prolapse (POP-Q stage 3 or higher) if SUI not demonstrated with pelvic organ prolapse reduction
- Evidence of significant voiding dysfunction

Physicians may perform additional evaluations in patients with the following conditions: (Expert Opinion)[13]

- Concomitant overactive bladder symptoms

- Failure of prior anti-incontinence surgery
- Prior pelvic prolapse surgery

3.3 Cystoscopy and Multichannel Urodynamic Testing

These are not necessary before planning primary anti-incontinence surgery in women with uncomplicated SUI, as indicated by observed urinary leakage from the urethra by provocative stress measures, a normal urinalysis result (without urinary tract infection), no POP beyond the hymen, and a normal postvoid residual urine volume.

3.4 Other nonspecific optional tests

Voiding diaries

Voiding diaries are a semi-objective method of quantifying symptoms, such as daytime and night-time frequency of SUI episodes and provoking factors. They also quantify urodynamic variables, such as amount of leakage. This can be used to support diagnoses as well as to monitor treatment response.

EUA recommends voiding diaries of 3-7 days duration to evaluate co-existing storage and voiding dysfunction in clinical practice and in research [GR A][14]. NICE also recommends use of bladder diaries for a minimum of 3 days, covering variations in their usual activities, such as both working and leisure days[4].

The pad test

The simplest method of measuring urine loss, by weighing a perineal pad before and after use, was described by Caldwell in 1974[15]. The pad test is a diagnostic tool that assesses the degree of incontinence in patients in a semiobjective manner.

The short-term (1-hr) pad test is often used in office practice because of its convenient nature. Patient is asked to drink a fixed amount of fluid (500 ml of sodium-free liquid) within 15 min. Specific standardized physical activities are performed in 1-hr time, including walking, climbing stairs, standing, coughing vigorously, running on the spot, bending to pick up objects, and hand washing with running water. After 1 h, any increment in pad weight of more than 1 g is considered incontinence.

The long-term pad test requires patients to wear pads for 24 or 48 h during regular everyday activities. Patients are instructed to record the frequency and amount of fluid intake as well as their episodes of micturition and incontinence. The pad is weighed at the end of the test. Pads are collected in resealed plastic bags. Incontinence is diagnosed if pad weight is more than 8 g/24 h on the long-term pad test[16].

The drawback is that this test cannot differentiate between causes of UI. Also there are chances of false positive results due to perspiration and vaginal discharge and false negative results due to drying out. Patient adherence to home pad testing protocols is poor and there could be a problem of weighing scale accuracy.

Pad tests are not recommended by NICE in the routine assessment of women with UI[4]. While EUA recommends it for quantification of UI and to measure objective treatment outcome [GR C], but also states that Home-based pad tests longer than 24 hours provide no additional benefit and a weight gain > 1.3 g in a 24-hour home-based test can be used as a diagnostic threshold for UI[14].

4. Treatment

4.1 Pelvic floor muscle training (PFMT)

This technique is only effective if the patient tightens the PFM correctly; it should

result in a closing and lifting sensation without tensing the leg, buttock, or abdominal muscles. To facilitate teaching, the patient can be asked to imagine the passing of gas without tensing any of the previously mentioned muscles. This helps the patient isolate the proper PFM. The PFMT regimen ideally should consist of repeating the contraction for 10 seconds, 15 times in a row with equal breaks of 10 seconds a total of time times a day, totalling 45 PFM contractions in a day.

The PFMT should be incorporated into the activities of daily life to promote compliance and adherence. It should be done in different positions, such as sitting, standing, and lying down. Continuous training is needed to maintain the gained strength of PFMs.[17]

NICE recommendations are to offer a trial of supervised pelvic floor muscle training of at least 3 months' duration as first-line treatment to women (EL 3)[4]

4.2 Vaginal cones

There is no evidence of a difference in effectiveness between cones and PFMT. Compared with PFMT, cones are associated with more adherence problems. [EL = 1+]

Vaginal cones are not suitable for all women. Cones are inappropriate for use in some circumstances, such as when there is a moderate to severe prolapse, too narrow or too capacious a vagina causing difficulty with insertion or misplacement of the cone, untreated atrophic vaginitis, vaginal infection, or during menstruation or pregnancy. [EL = 4]

4.3 Biofeedback

Evidence does not indicate additional benefit from biofeedback with PFMT in comparison with PFMT alone in treating UI. [EL = 1+]

Biofeedback with PFMT is more costly than PFMT alone and therefore is not cost effective given a lack of additional benefit.

4.4 Magnetic therapy

There are limited data on the use of magnetic therapy for UI, and its role in the treatment of women with UI is unclear. [EL = 3]

4.5 Electrical stimulation

There is no evidence of additional benefit of electrical stimulation in combination with PFMT compared with PFMT alone. [EL = 1–]

*While there is no evidence of effectiveness for either biofeedback or electrical stimulation, one should consider that the information and support generated by biofeedback may assist motivation for some women, and that electrical stimulation may be of value for those who are unable to initiate a pelvic floor muscle contraction***.** [EL 4][4]

4.6 Drug therapy

Duloxetine

It should not be used as a first-line treatment for women with predominant stress UI and may be offered as second-line therapy only if women prefer pharmacological to surgical treatment or are not suitable for surgical treatment.

If duloxetine is prescribed, counsel women about its adverse effects. Adverse effects, particularly nausea, and discontinuation rates are very common (more than 10%). There is a lack of long-term safety data.[4]

4.7 Surgery

If conservative management for SUI has failed, offer (GR A):

- Synthetic mid-urethral tape, **or**

- Open colposuspension, **or**
- Autologous rectus fascial sling.

Burch colposuspension and autologous rectus fascial sling should continue to be recommended because synthetic tapes are unacceptable for some women. Women should be advised of the risks and prognosis for different procedures so that an informed decision can be made.[4]

Refer women to an alternative surgeon if their chosen procedure is not available from the consulting surgeon.[13]

Laparoscopic colposuspension is not recommended for routine surgical treatment of SUI (GR A).[4] However, it might be considered in women who need a concomitant laparoscopic surgery and, in these cases, experienced laparoscopic surgeons should perform it (GR D).[18]

When offering a **synthetic mid-urethral tape (MUS) procedure**, surgeons should:

- use procedures and devices for which there is current high-quality evidence of efficacy and safety
- only use a device that they have been trained to use
- use a device manufactured from type 1 macroporous polypropylene tape
- consider using a tape coloured for high visibility, for ease of insertion and revision.

If women are offered a procedure involving the *transobturator approach*, make them aware of the lack of long-term outcome data.[4]

Warn women who are being offered transobturator insertion of MUS about the higher risk of pain and dyspareunia in the longer term. (GR A)[14]

Warn women who are being offered a *retropubic insertion* of MUS about the relatively higher risk of peri-operative complications compared to transobturator insertion. (GR A)[14]

Use 'top-down' retropubic tape approach only as part of a clinical trial.[4]

Warn women who are being offered a *single-incision sling* that long-term efficacy remains uncertain. (GR A)[14] The evidence on the safety of single-incision short sling mesh insertion for SUI in women shows infrequent but serious complications. These include lasting pain, discomfort and failure of the procedure. The mesh implant is intended to be permanent but, if removal is needed because of complications, the anchoring system can make the device very difficult or impossible to remove. The evidence on efficacy in the long term is inadequate in quality and quantity.[4]

Do a cystourethroscopy as part of the insertion of a MUS. (GR C)[14]

Warn women undergoing **autologous fascial sling** (AFS) that there is a high risk of voiding difficulty than MUS and the need to perform clean intermittent self-catheterisation; ensure they are willing and able to do so. (GR C)[14]

AFS is an effective treatment for SUI that has longevity and may be more effective than other biological and synthetic slings (grade A). The porcine dermal graft appears to lose tensile strength over time and is associated with a decreased cure rate compared to AFS and MUS.[18]

Physicians should not offer stem cell therapy for stress incontinent patients outside of investigative protocols. (Expert Opinion)[13]

Special Cases

In patients with SUI and a fixed, immobile urethra (often referred to as 'intrinsic sphincter deficiency') who wish to undergo treatment, physicians should offer pubovaginal slings/ Bladder neck Slings (gr A), retropubic MUS, urethral bulking agents, or artificial urinary sphincter (Gr B). (Expert Opinion)[18]

Physicians should not place a mesh sling if the urethra is inadvertently injured at the time of planned MUS procedure. (Clinical Principle)

Physicians should not utilize a synthetic MUS in patients undergoing concomitant urethral diverticulectomy, repair of urethrovaginal fistula, or urethral mesh excision and SUI surgery. (Clinical Principle)

Physicians should strongly consider avoiding the use of mesh in patients undergoing SUI surgery who are at risk for poor wound healing (e.g., following radiation therapy, presence of significant scarring, poor tissue quality). (Expert Opinion)

In patients undergoing concomitant surgery for pelvic prolapse repair and SUI, physicians may perform any of the incontinence procedures (e.g., MUS, pubovaginal sling, Burch colposuspension). (Conditional Recommendation; Evidence Level: Grade C)

Physicians may offer patients with SUI and concomitant neurologic disease affecting lower urinary tract function (neurogenic bladder) surgical treatment of SUI after appropriate evaluation and counselling have been performed. (Expert Opinion)

Physicians may offer synthetic MUS, in addition to other sling types, to the following patient populations after appropriate evaluation and counselling have been performed: (Expert Opinion)[13]

- Patients planning to bear children
- Diabetes
- Obesity
- Geriatric

Offer a **follow-up** appointment (including vaginal examination to exclude erosion) within 6 months to all women who have had continence surgery.

Training should include competence in cystourethroscopy. An annual workload of at least 20 cases of each primary procedure for stress UI is recommended. Surgeons undertaking fewer than 5 cases of any procedure annually should do so only with the support of their clinical governance committee; otherwise referral pathways should be in place within clinical networks.[4]

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Note: *Abbreviations used Gr: Grade, EL: Evidence level*

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Prevention of Endometrial Cancer

1. Risk factors for endometrial cancer

1. Age- the older women have higher chances of suffering from endometrial cancer.

Two types of endometrial cancers are known:[1]

a. Type I (80% of cases) estrogen dependant, and it appears that more a woman is exposed to estrogens in her lifetime more are her chances of getting endometrial cancer e.g.
   i. Early menarche
   ii. Late menopause
   iii. Nulliparity
   iv. No breastfeeding
   v. No use of oral contraceptive pills.

b. Type II (20% of cases) not estrogen dependent and tends to present with more aggressive disease.

2. Obesity

   21-50 lb overweight- Relative risk: 3

   >50 lb overweight- Relative risk: 10

3. Diabetes
4. Hypertension
5. Tamoxifen Use – a drug used in Breast cancer.
6. Family history of endometrial cancer – the greatest risk is in the first degree relatives, Lynch Syndrome (HNPCC), genetic mutation.
7. Patients with history of breast cancer are at high risk of endometrial cancer, maybe, because the risk factors of breast cancer and endometrial cancers overlap.[2]

2. Prevention of Endometrial Cancer

Most endometrial carcinomas are sporadic, but about 10% of cases have a hereditary basis[3]. The various ways to prevent endometrial cancer are as follows:

1. OCPs - Oral contraceptive pills or depo-provera can reduce the risk of developing both endometrial and ovarian cancer.
2. Combined hormone replacement therapy also appears to decrease the risk of endometrial cancer. But, both OC Pills and combined hormone replacement have several side effects so they cannot be taken for long periods.
3. Exercise also helps to reduce the risk of developing endometrial cancer.
4. Diet high in animal fats increases the risk of endometrial cancer,
5. Diet rich in fruits and vegetables may have preventive effect.
6. Diets high in naturally occurring phytoestrogens (e.g.in soy products) and fatty fishes may decrease the risk of endometrial cancer, but further studies need to be done before these nutritional recommendations can be made regarding preventing endometrial cancer.
7. Carriers of Lynch Syndrome need to have more rigorous screening done for endometrial cancer. They can be offered prophylactic hysterectomy. This should only be done when a woman has finished having children, and it can eliminate the possibility that a woman will contract endometrial cancer.

a. Increased incidence of endometrial cancer associated with Lynch II Syndrome, inherited in an autosomal dominant fashion, highly penetrant disorder with 80%-85% chance of endometrial cancer.[4,5]

b. HNPCC or Lynch Syndrome is caused by an inherited mutation in one of the following mismatch repair genes: hMSH2, hMLH1, PMS1, PMS2 or hMSH6.[6]

c. The lifetime risk of endometrial cancer in women with Lynch Syndrome is 32% to 60% and the lifetime risk of ovarian cancer is 10% to 12%.[7]

3. Screening tests for endometrial cancers

Patients diagnosed with early endometrial cancers definitely responds better to treatment than patients with more advanced cancers, so it is beneficial to detect endometrial cancers as early as possible.

3.1 Recommendations

Currently, there are no screening recommendations for endometrial cancer for the general population (women without high risk factors e.g. hereditary cancer syndromes etc.).

- Since endometrial cancers presents with postmenopausal bleeding, patients usually reports early and should be thoroughly investigated.
- Besides, pre-menopausal women, those who have risk factors for endometrial cancer, and are on tamoxifen or estrogen replacement therapy, or who have abnormal uterine bleeding, intermenstrual bleeding or irregular bleeding per vaginum should also be carefully evaluated.
- Women with a strong family history and many risk factors or who have a proven hereditary cancer syndrome need rigorous screening for endometrial cancer.
- **Currently, the American Cancer Society recommends that women**, who have Lynch Syndrome (HNPCC) or, who have a family member with Lynch Syndrome, or, who have a strong family history of colon cancer (even with negative genetic testing), should get annual endometrial biopsies starting at 30 to 35 years of age.[8]

Key points

- Maintaining a healthy weight is the most important way to prevent endometrial cancer.
- Being physically active for at least 30 minutes every day protects against this disease.
- The cancer preventive diet includes: taking 2/3 or more of the diet of vegetables, whole grains, legumes and other plant foods, and 1/3 or less of animal foods.

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Ovarian Cancer Prevention

Till date, ovarian cancer screening strategies have not been proven to be effective in detecting early stage disease. Ovarian cancer does not have a clear cut pre-invasive condition. So it merits considerable study for new prevention strategies because of the high mortality associated with ovarian cancer.

1. Factors That Increase the Risk for Ovarian Cancer[1]

1.1 Age- Ovarian cancer risk increases with age.

1.2 Family history of ovarian, breast, or colorectal cancer- a woman is at high risk if

- A first-degree relative has ovarian cancer at any age, risk increases with the number of affected first-degree relatives.
- A first-degree relative (or two 2nd -degree relatives) with early onset breast cancer before age 50
- A family member with history of both breast and ovarian cancer
- A history of male breast cancer
- A family history of hereditary nonpolyposis colorectal cancer (HNPCC)
- Ashkenazi (Eastern European) Jewish ancestry

1.3 Genetic mutations

1.3.1 BRCA1 and BRCA2 genes

- Women who have documented BRCA1 or BRCA2 mutations have a significantly increased lifetime risk of ovarian and breast cancer.
- In BRCA1carriers the lifetime risk of Ovarian Cancer is 28-66%, whereas in BRCA2 carriers the risk of ovarian cancer by the age 50years is <1%, but by age 70 it is 27%[2,3]

1.3.2 HNPCC

There is about 12% lifetime risk of developing ovarian cancer.

The probability of a 50 year old Non-Jewish Woman Carrying a BRCA1 Mutation to have ovarian cancer in her life time is

- No affected relatives - 8% risk of ovarian cancer
- One relative with breast cancer – 10% risk of ovarian cancer
- One relative with ovarian cancer – 20% risk of ovarian cancer
- One relative with breast and ovarian cancer 40% risk of ovarian cancer

Probability of a 50 year Jewish Woman Carrying a BRCA1 Mutation to have Ovarian Cancer

- No affected relatives - 30% risk of ovarian cancer
- One relative with breast cancer – 40% risk of ovarian cancer
- One relative with ovarian cancer – 55% risk of ovarian cancer
- One relative with breast and ovarian cancer 78% risk of ovarian cancer

1.4 Obesity increases the risk for ovarian cancer.

1.5 Hormone replacement therapy use- More than 5 years of hormone replacement therapy (HRT) may increase the risk of developing and dying from ovarian cancer, especially if estrogen-only HRT has been taken.

1.6 Menstrual and reproductive history- Fewer menstrual periods and ovulations appear to be associated with reduced risk for ovarian cancer. Women are at increased risk for ovarian cancer if they began menstruating at an early age (before age 12), have not had children, had their first child after age 30, or experienced late menopause.

2. Risk Factors with Less Conclusive Evidence

- There is an association between a high intake in animal fats and a greater risk of cancer,
- Use of the fertility drug e.g. clomiphene
- The environmental factors includes: radiation exposure, talcum powder, and asbestos

3. Factors That Reduce the Risk for Ovarian Cancer

3.1 **Oral contraceptive use: 30-**40% risk reduction of ovarian cancer. The greatest reduction occurs with 4-6 yrs of use. The longer use, more the protection. The protection can last 20 or more years after last use. This is relevant for both low risk and high risk women

3.2 **Pregnancy and childbirth-** Single pregnancy causes 20-40% risk reduction and each additional pregnancy causes 10-15% additional decrease in relative risk of ovarian cancer

3.3 **Tubal ligation and hysterectomy**- causes 50-70% risk reduction and the benefit is observed in both Low and High risk population.

3.4 **Tea** consumption is associated with reduced risk of ovarian cancer. **Vitamin A** causes risk reduction.

3.5 **Drugs: Aspirin**- causes 25% risk reduction especially in women taking it weekly for > 6 months. **Aceto-aminophen**- 40-60% reduced risk of ovarian cancer. Approximately 1.3% of women in the general population will develop ovarian cancer in their lifetime.[4]

The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) trial randomised 202,000 women to observation alone, multimodal screening (MMS), with an algorithm based on serial values of CA125 and follow on transvaginal ultrasound scanning (TVS) for abnormal results, or serial TVS alone. The results showed no reduction in mortality in the primary analysis, but a possible reduction in mortality after exclusion of prevalent cases after 7 years of follow-up.[5]

The UK Familial Ovarian Cancer Screening Study (UKFOCCS) study evaluated a strategy of annual ultrasound and CA125 measurement in 3,653 women considered at >10% risk of development of ovarian cancer and who declined risk-reducing salpingo-oophorectomy (RRSO). The positive and negative predictive values of incident screening were 25.5% (95% CI, 14.3 to 40.0) and 99.9% (95% CI, 99.8 to 100), respectively.

4. Screening Tests

Early stage ovarian tumors are rarely found clinically due to the deep anatomical location of the ovary. The tumors detected by pelvic examination are usually at an advanced stage and associated with poor prognosis.

4.1 Ovarian Cancer Symptom Index (OCSI)- The symptoms of abdominal pain, bloating, increased abdominal size, difficulty in eating, early satiety, occurring more than 12 times a month with symptoms present for less than one year should give suspicion of the possibility of an ovarian cancer.

Other symptoms may include: postmenopausal bleeding; unexplained weight loss; fatigue or changes in bowel habit.[6]

4.2 Diagnostic methods - Current guidance

Sequential testing with CA125 and ultrasound in women presenting to primary care with symptoms suggestive of ovarian cancer is recommended. This is especially so in women over the age of 50. Urgent referral to secondary care is indicated, if both tests are abnormal, or if women present to primary care with a pelvic or abdominal mass.[6]

Screening tests recommendations

- There is currently no role for organized screening programmes in women considered at low risk of development of ovarian cancer (Grade A). The role of ovarian cancer screening in women at high risk of ovarian cancer has yet to be established (Grade B)
- Pap smear occasionally may reveal malignant cells but its sensitivity is only 10%.
- Tests that may be useful include:
  - Tumor markers CA 125, USG/ Doppler, Proteomics
  - **CA 125- Glycoprotein antigen** – is elevated in 50% of women with early stage and in 80% with advanced disease. HE4 and CA 125 combined showed 93.8% cases of epithelial ovarian cancer as high risk. In US this assay is approved for monitoring women with ovarian cancer & disease recurrence or progression but not for screening.

    Prospectively acquired evidence from the United Kingdom Collaborative Trial of Ovarian Cancer Screening Cancer (UKCTOCS) - with 46,237 women triaged using MMS in whom serial CA-125 measurements were interpreted via the risk of ovarian cancer algorithm (ROCA®) - has shown that screening by using ROCA® doubles the number of screen-detected EOC compared with a fixed cut off of 35 IU/ml.
  - HE4 (human epididymis protein 4) has shown promising diagnostic and prognostic value in triaging younger women, with HE4 not raised in cases of pelvic inflammatory disease and endometriosis despite CA125 elevation being observed.[7-9]
  - **Four marker panels (CA-125, HE4, CEA and VCAM-1) can diagnose e**arly stage disease with86% sensitivity.

TVS has been found to be more accurate with sensitivity of 100% specificity of 98.7% and PPV is 6.8%, but only drawback is lack of specificity as a small decrease in specificity provides a large decrease in the PPV.

5. Preventive Strategies for High-Risk Women

5.1 Genetic Counseling and Screening - The U.S. Preventive Services Task Force (USPSTF) recommend *BRCA1and BRCA2 Genes* testing for women at high risk for ovarian cancer.

5.2 CA-125- is not approved for screening in the general population

5.3 Ultrasound- It is not helpful for identifying early-stage ovarian cancer. It does not provide enough specific information to determine which abnormal masses are malignant or benign.

5.4 Risk of malignancy index (RMI I)

The RMI is a product of the ultrasound scan score (U), the menopausal status (M) and the serum CA125 level (IU/ml). RMI = U x M x CA125. If RMI >= 250 then must be referred to a specialist gynae-oncologist

5.5 HE4- Human epididymis protein 4 (HE4) is a biomarker overexpressed by both serous and endometrioid ovarian cancers and is expressed by 32%of ovarian cancers lacking CA125 expression.

5.6 Removal of ovaries (Risk Reducing Salphingo-oophrectomy)-

- Risk-reducing salpingo-oophorectomy (RRSO) prevents development of epithelial ovarian cancer and reduces mortality in women at high risk for epithelial ovarian cancer (Grade B Recommendation).
- Prospective multicentre cohort studies have demonstrated that risk-reducing salpingo-oophorectomy (RRSO) is associated with a lower risk of EOC, first diagnosis of breast cancer, all-cause mortality, breast cancer–specific mortality, and ovarian cancer–specific mortality in BRCA1- and BRCA2-mutation carriers, although there is still a residual risk for peritoneal cancer.[10, 11] On-going studies are evaluating the role of opportunistic salpingectomy in the prevention of ovarian cancer in low risk women.[12]

6. Secondary Care

These examinations are advised prior to deciding treatment of ovarian tumor.

- CA125 and pelvic ultrasound scan (+/- TVS as indicated) should be considered the initial investigations for post-menopausal women presenting with signs or symptoms of ovarian cancer (Grade B). Women with an RMI of ≥250 should have further investigations and be referred to the specialist gynaecological centre MDT (Grade B).
- Where CA125 is elevated, a preoperative CA125/CEA ratio < 25, especially in combination with an elevated CA19-9, may indicate peritoneal carcinomatosis from a gastrointestinal tumour and bi-directional gastrointestinal endoscopy should be considered prior to upfront primary debulking surgery.[Grade B]
- In patients with presumed ovarian cancer, radiological staging will provide further information about the extent of disease and potential distant metastases or secondary cancers. (Grade C)
- There are simple ultrasound rules derived from the IOTA group (Table-1). The use of specific ultrasound morphological findings without CA-125 has been shown to have high sensitivity, specificity and likelihood ratios. Using these rules the reported sensitivity was 95%, specificity 91%, positive likelihood ratio of 10.37 and negative likelihood ratio of 0.06.

Table 1: Ultrasound features of ovarian masses

B-rules	M-rules
Unilocular cysts	Irregular solid tumour
Presence of solid components where the largest solid component <7 mm	Ascites
Presence of acoustic shadowing	At least four papillary structures
Smooth multilocular tumour with a largest diameter <100 mm	Irregular multilocular solid tumour with largest diameter ≥100 mm
No blood flow	Very strong blood flow

CT prediction of suboptimal cytoreduction is not sufficiently reliable and in the absence of favourable data from larger, prospective trials should not be used alone to decide management. (Grade B)

MRI should not be routinely used for assessing women with suspected ovarian cancer outside of clinical trials, but can be useful where the results of the USS are not helpful in confirming a diagnosis, especially in young women with a solitary pelvic mass who want a fertility sparing approach. (Grade B)

PET CT is not recommended for routine preoperative staging in the NHS outside a clinical trial. (Grade C)

Key points (Table-2)

Table 2: Summary

What Puts Women at Risk
1. Family history of ovarian and breast cancers
2. Infertility
3. Endometriosis
4. Talc use
5. Hormone replacement therapy
Does Anything Prevent Ovarian Cancer?
1. Oral contraceptives
2. Pregnancies
3. Breast feeding (long duration)
4. Tubal ligation
5. Oophorectomy and hysterectomy
6. Vitamin A
7. NSAIDS
What can we Change?
BRCA Mutation Carriers
1. Oophorectomy after family size completed
2. Oral contraceptive use
3. Tubal ligation and hysterectomy

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Breast Cancer Screening

Sunita Malik, Swati Gupta

Breast cancer is the most common female cancer in the world with an estimated 1.67 million new cancer cases diagnosed in 2012 and among Indian women also with age adjusted rate as high as 25.8 per 100,000 women and mortality of 12.7 per 100,000 women[1]. While the age adjusted incidence rates of breast cancer in India is lower than the western countries, because of the large population, the burden of breast cancer is high and many may be unreported. With an annual incidence of approximately 144,000 new cases of breast cancers in India, it has now become the most common female cancer in urban India, even more than cervical cancer. Breast cancer in India varies from as low as 5 per 100,000 female population per year in rural areas to 30 per 100,000 female population per year in urban areas[2]. At present, India is viewing increase in breast cancer cases reported in younger age groups and even more troubling situation is that, 70% of cancers are reported in the advanced stage. So, there is urgent need for spreading more awareness, among the masses related to breast cancer.

India, being a resource constraint country and also existing multiple social, cultural and environmental barriers for women to access the healthcare facilities there is need to develop policies and recommendations for breast cancer screening tailored according to local needs. The international guidelines promoting more stringent ways may not be applicable for Indian masses due to logistic issues. Moreover, due to paucity of RCTs available there is lack of consensus even among the international bodies regarding several issues like, age at starting the screening, modalities used for screening and age at stopping the screening.

Screening essentially means looking for disease in apparently healthy population. In order, to make screening more effective, some methods like following could be done: screening from broader age group, using more than one modality for screening and increasing the frequency for screening. Out of all of them, increasing the frequency of screening is essentially associated with the drawbacks of increased false positive rates.

So, for making screening programmes to be more successful in India, increasing awareness among the masses is most important. More strategies should be developed to facilitate opportunistic screening like combining breast and cervical cancer screening programs in India. Low cost modalities like ultrasonography and breast self examination can be used on a larger scale so as to include more women.

Government of India issued operational guidelines for screening for non-communicable diseases in 2016 (Table-1). According to it, screening for cancer like breast, cervix and oral should be done every five years. Target population includes women of age more than 30 years. It also involves, training the ASHA workers in clinical breast examination and timely referral to higher centres in case of detection of any abnormality.

Breast self awareness

- a new lump or lumpiness, especially if it's only in one breast
- change in the size or shape of the breast
- change to the nipple, such as crusting, ulcer, redness or inversion of a nipple
- discharge that occurs without squeezing
- change in the skin of the breast such as redness or dimpling
- an unusual pain that doesn't go away

ICMR, in 2016, gave consensus guidelines for breast cancer in India[2]. According to

it, widely used guidelines in India are based on the National Comprehensive Cancer Network (NCCN)[3,4], St. Gallen International Expert Consensus[5] and the European Society of Medical Oncology (ESMO)[6,7] and the National Institute for Health and Care Excellence (NICE) of the U.K. NCCN guidelines are also followed by NGOs like the PINK initiative for screening in India. These are based on evidence from clinical trials from a patient population which in general has better tolerance to systemic chemotherapy and greater access of high quality care required for optimal management of acute and late complications of treatment.

NCCN Guidelines:[3,4]

1. **Normal risk woman, 20 to 40 years of age**
   For a woman who does not have an increased risk for breast cancer and who is between 20 to 40 years of age, the screening (early detection) guidelines are as follows:
   - Clinical Breast Examination: This must be done every 1 to 3 years. Every year may sound impractical, but a visit to a doctor just once every three years should not be a problem.
   - Breast Awareness (Table 1)

2. **Normal risk woman, more than 40 years of age:** For a woman who does not have an increased risk for breast cancer and who is more than 40 years of age, the early screening protocol is as follows:
   - Annual Clinical Breast Examination: A yearly examination by qualified and trained medical personnel is a must.
   - *Annual* Mammography from 40 to 50 years of age: yearly mammography is recommended. After 50 years of age, mammography may be done every *2 years*.
   - Breast Awareness

Table 3: Risk factors for breast cancer

• Positive Family History: One or more family member (blood relation) has a history of breast or ovarian cancer (eg, prostate and pancreatic cancer)
• Known deleterious gene mutations(most commonly BRCA1/2)
• Prior breast biopsy with specific pathology(atypical hyperplasia, lobular carcinoma in situ)
• Early menarche
• Late menopause
• Nulliparity
• Prolonged interval between menarche and first pregnancy
• Menopausal hormonal therapy
• Not breast feeding
• Increasing age
• Alcohol consumption
• Smoking
• Higher body mass index
• Dense breast on mammography
• Prior exposure to high dose chest irradiation in younger women(10-30years)

3. **Women with increased risk of breast cancer (Table 3):**

   For a woman who has an increased risk for breast cancer, the screening (early detection) guidelines are as follows:
   - Annual clinical Breast Examination
   - Breast Awareness

- Annual Mammogram: For women, who have received radiation therapy to the chest, a mammogram should be done *annually after 25 years of age*. *For those with a family history of breast or ovarian cancer, annual mammogram should start by 35 years of age*. For women belonging to proven breast and ovarian cancer families (genetically) or those who have multiple first or second degree relatives with breast or ovarian cancers (and some other related cancers, explained below), an annual mammogram must start much early, by around 25 years of age.
- MRI of the breast: In the above high risk categories, an annual MRI of the breast is also recommended as an adjunct to mammogram

Screening should continue as long as the woman is in good health and is expected to live 10 more years or longer. It is the need of the hour to spread awareness among the masses regarding the breast cancer and develop more stringent policies acknowledging local conditions and resources.

Table1: Government of India operational guidelines for screening for non-communicable diseases, 2016

Type of cancer	Age of beneficiary	Method of screening	Frequency of screening	If positive
Oral	30 -65 years	Oral Visual Examination (OVE)	Once in 5years	Referred to Surgeon/Dentist/ENT specialist/Medical officer at CHC/ DH for confirmation* and biopsy.
Breast	30-65 years	Clinical Breast Examination (CBE)	Once in 5years	Referred to Surgeon at CHC/DH for confirmation using a Breast ultra sound probe followed by biopsy
Cervical	30-65 years	Visual Inspection with Acetic acid (VIA)	Once in 5years	Referred to the PHC/CHC/DH for further evaluation and management of pre-cancerous conditions where gynecologist/trained Lady Medical Officer is available

*The biopsy specimen either to be sent to the nearest Medical college or using the mechanism under the referral system.

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Guidelines for Management of Adnexal Mass in Young Girls

Shruthi Bhatia

Adnexal masses are commonly encountered by gynecologists and often present diagnostic and management dilemmas, especially when present in young girls. Most of these masses are detected incidentally on physical examination or on imaging. Less commonly, a mass may present with symptoms of acute or intermittent pain. The purpose of this document is to provide guidelines for evaluation and management of adnexal masses in young girls.

The Medline database and the Cochrane library were used to conduct a literature search to locate relevant articles. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Guidelines published by the American College of Obstetricians and Gynecologists and by Royal College of Obstetricians and Gynaecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force-

I: *Evidence obtained from at least one properly designed randomized controlled trial.*

II-1: *Evidence obtained from well-designed controlled trials without randomization.*

II-2: *Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.*

II-3: *Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.*

III: *Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.*

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories-

Level A: *Recommendations are based on good and consistent scientific evidence.*

Level B: *Recommendations are based on limited or inconsistent scientific evidence.*

Level C: *Recommendations are based primarily on consensus and expert opinion.*

Introduction

Adnexal masses represent a spectrum of conditions, including gynecologic and non-gynecologic pathologies. They may be benign or malignant. It is estimated that 9% to 11% of all adnexal masses are malignant.[1]Presenting symptoms may vary and may include acute abdominal pain, pressure symptoms, and less commonly precocious puberty or vaginal bleeding. The initial evaluation of an adnexal mass requires a thorough history and physical examination, followed by appropriate laboratory and radiographic studies.

Adnexal masses in young girls are uncommon, but not rare. They encompass a wide variety of lesions of ovaries and fallopian tubes, including ovarian cysts and tumors (benign or malignant), fallopian tube cysts and abscesses, para-tubal cysts, and endometriomas. Adnexal masses may also be due to non-gynecologic conditions like appendicular abscess, bladder diverticulum,or ectopic pelvic kidney(Table 1).[2]

Table 1: Differential diagnosis of Adnexal masses

Gynaecologic	Non-gynaecologic
Benign Ovarian	Benign
Corpus luteum cyst	Appendiceal abscess
Follicular cyst	Appendicitis
Mature teratoma	Bladder diverticulum
Ovarian torsion	Diverticular abscess
Polycystic ovaries	Pelvic kidney
Serous and mucinous cystadenoma	Peritoneal cyst
Theca-lutein cyst	Urethral diverticulum
Malignant Ovarian	Malignant
Borderline tumors	Gastrointestinal carcinoma
Epithelial carcinoma	Retroperitoneal sarcoma
Ovarian germ cell tumor	Metastases
Ovarian sarcoma	
Sex-cord or stromal tumors	
Non-ovarian	
Ectopic pregnancy	
Endometrioma	
Hydrosalpinx	
Leiomyoma	
Tubo-ovarian abscess	
Mullerian anomalies	

1. Signs and symptoms

Accurate and detailed history, along with comprehensive physical examination is necessary to reach a diagnosis. The clinical presentation of young girls with adnexal mass will vary depending on the specific etiology. Majority will present with pelvic or abdominal pain, often due to torsion of the mass, hemorrhage in the lesion or functional rudimentary horn. Mild chronic abdominal pain may be present due to mass effect. There could be associated nausea, vomiting or fever. Functional cysts of the ovary and neoplasms that produce hormones can cause precocious puberty, which may be the presentation in a pre-menarchal adolescent (Table 2).[3]

1.1 History

- Duration and nature of pain, association with menstrual cycle, and its severity.
- History of fever, chills, vomiting, and vaginal discharge.
- History of any chronic illness like tuberculosis.
- History of any congenital disorder.
- Menstrual history.
- Sexual history, including details of contraceptive practices, history of sexually transmitted diseases, and possible abuse.
- Family history.

1.2 General examination

- General assessment, including peripheral lymph nodes like cervical, supra-clavicular, axillary, and inguinal.
- Chest auscultation to look for associated lung/ pleural lesions.
- Detailed abdominal examination to assess for ascites, pelvic mass, tenderness, and hepatosplenomegaly.

- In pre-pubertal girls, look for signs of precocious puberty like breast development, axillary and pubic hair.
- In non-sexually active girls, abdominal palpation along with rectal examination can assist in diagnosis. In sexually active girls, vaginal bimanual examination is helpful.
- If more detail physical examination is warranted, then examination under anesthesia should be considered.

Table 2: Signs and symptoms of different adnexal masses

Condition	Suggestive symptoms	Possible physical examination finding
Ectopic pregnancy	Lower abdominal (usually unilateral and severe) pain, amenorrhea	Adnexal tender mass, hypotension, tachycardia
Endometrioma	Abnormal uterine bleeding, worsening pain with menses	Adnexal mass or tenderness, tenderness over uterosacral ligaments
Mullerian anomalies	Dysmenorrhoea, cryptomenorrhoea	Adenexal mass with or without haematometra
Functional ovarian cyst	Unilateral pelvic pain or heaviness, pain during middle of cycle	Adnexal mass or tenderness
Leiomyoma	Dysmenorrhea, menorrhagia	Abdominal mass, uterine enlargement
Ovarian cancer	Pelvic or abdominal pain, abdominal fullness and pressure, bloating, indigestion, urinary frequency	Abdominal or adnexal mass, ascites, lymphadenopathy, pleural effusion
Ovarian torsion	Sudden onset of unilateral and severe lower abdominal or pelvic pain, associated with nausea or vomitting	Abdominal or adnexal tenderness
Tubo-ovarian abscess	Fever, lower abdominal or pelvic pain, nausea, vaginal discharge	Abdominal or adnexal tenderness, fever, vaginal discharge
Polycystic ovary syndrome	Oligomenorrhea, amenorrhea, or menorrhagia, associated with obesity and hirsutism	Unilateral or bilateral adnexal fullness or enlarged ovaries

2. Investigations

2.1 Imaging

Recommendations

- A pelvic ultrasound is the single most effective way of evaluating an adnexal mass (LevelA, Evidence level I).
- Color Doppler, computed tomographic (CT) scan, or magnetic resonance imaging (MRI) may be used if required (Level B, Evidence level II-1).

The preferred initial imaging modality is ultrasound of pelvis. Ultrasound is safe, inexpensive, and widely available. No alternative imaging modality has demonstrated sufficient superiority over ultrasound to justify its routine use. Repeating ultrasound assessment in the post-menstrual phase may be helpful in cases of doubt. It is important to note that no single ultrasound finding differentiates between benign and malignant ovarian masses.

Ultrasound findings that raise concern regarding malignancy include cyst size greater than 10 cm, papillary or solid components, irregular margins, presence of ascites, and increased vascularity. Ultrasound characteristics of benign masses

include thin walled cysts, absence of solid components and septations, and absence of internal blood flow on color Doppler.[4] This sonographic 'pattern recognition' along with color Doppler flow assessment can accurately diagnose most adnexal masses.[5]

There are simple ultrasound rules given by the **International Ovarian Tumor Analysis (IOTA)** group. The use of these specific ultrasound morphological findings, has been shown to have high sensitivity, specificity and likelihood ratios. The masses have been classified as benign (B-rules) or malignant (M-rules) (Table 3).[6]

Table 3: IOTA group ultrasound 'rules' to classify masses as benign (B-rules) or malignant (M-rules)

B-rules	M-rules
Unilocular cysts	Irregular solid tumor
Presence of solid components where the largest solid component < 7 mm	Ascites
Presence of acoustic shadowing	At least four papillary structures
Smooth multilocular tumor with largest diameter < 100 mm	Irregular multilocular solid tumor with largest diameter ≥100 mm
No blood flow	Very strong blood flow

There is no clear consensus regarding the need for further imaging beyond ultrasound in the presence of apparently benign disease. However, contrast enhanced CT scan, MRI, or PET- CT may be used in evaluation of complex lesions. MRI is often helpful in differentiating the origin of pelvic masses that are not clearly seen in ultrasound, especially leiomyomas.[7] CT scan is best used to evaluate the abdomen for metastasis when cancer is suspected. CT scan can detect ascites, omental metastases, peritoneal implants, pelvic and para-aortic lymphadenopathy, and possibly an alternate primary cancer site, including pancreas or colon.[8]

2.2 Blood investigations

Recommendations

- Serum CA-125 assay need not be done in girls when ultrasound diagnosis of simple ovarian cyst has been made (Level B, Evidence level II-1).
- Lactate dehydrogenase (LDH), alpha-fetoprotein (AFP), and beta subunit of human chorionic gonadotropin (β-HCG) should be measured in all young girls with complex ovarian mass, because of possibility of germ cell tumors (Level B, Evidence level II-2).
- Pregnancy test should be done in post-menarchal girls to rule out ectopic pregnancy, whenever there is a suspicion (Level C, Evidence level III).
- Other tests like complete blood counts, urine analysis, and fecal occult blood testing may be done, depending on history and examination (Level C, Evidence level III).

Ovarian masses < 10 cm in size, primarily cystic, and with negative tumor markers are generally considered benign.[9,10] An estimation of the malignancy risk of an ovarian mass is essential to guide further management. Various algorithms and scoring methods have been formulated, including **Risk of Malignancy Index (RMI), Risk of Ovarian Malignancy Algorithm (ROMA), and multivariate index assay**. However, all these tests have been validated in post- menopausal women and not in young females. Hence, in young females, a good ultrasound and clinical assessment along with tumor markers wherever indicated, will guide the management.

3. Treatment

Recommendations

- Conservative treatment with serial ultrasounds is recommended for simple asymptomatic ovarian cysts 2-5 cm in size (Level B, Evidence level II-1).
- Simple cysts more than 5 cm in size but less than 10 cm, and which are asymptomatic can be followed for upto 3 months (Level B, Evidence level II-3).
- Aspiration of ovarian cysts is less effective and is associated with high rate of recurrence (Level B, Evidence level II-1).
- All symptomatic cysts, or asymptomatic cysts that persist for more than 3 months, should be electively excised (Level B, Evidence level II-1).
- Mixed cystic and solid and completely solid masses require surgical intervention (Level A, Evidence level II-1).
- Intraoperative frozen section should be used, if available (Level C, Evidence level III).
- Whenever possible, laparoscopic techniques or minimal invasive procedures should be used (Level B, Evidence level II-1).
- Gynecologic oncologist should be involved whenever indicated (Level B, Evidence level II-1).
- Efforts should be made for ovarian tissue preservation and fertility preservation (Level A, Evidence level II-1).
- Adjuvant chemotherapy is recommended based on stage of cancer (Level A, Evidence level I).

3.1 Surgical therapy

Adnexal masses which require surgical intervention are-

1. Ovarian cysts that persist or increase in size are unlikely to be functional and may warrant surgical management. Mature cystic teratomas (dermoid cysts) have been shown to grow over time, increasing the risk of pain andtorsion. Most workers recommend surgery for larger cystic teratomas > 5-6cm in diameter.[11]
2. Adnexal masses that are symptomatic, should be operated. Most common symptom is pain or discomfort in lower abdomen, usually associated with larger size. Unilateral, severe pain is usually due to torsion of an adnexal mass.
3. Masses with suspected malignancy require surgery. Large size of tumor,elevated tumor markers, ascites, mixed solid-cystic/ predominantly solid mass, or evidence of abdominal or distant metastases, are indicative of malignancy.[9] These cases should be operated by gynecologic oncologist.[12]

The goal of surgery for benign lesions is preservation of ovarian tissue, wherever possible, while relieving the symptoms. Cystectomy is preferred, so as to preserve normal ovarian tissue. If required, unilateral oophorectomy or salpingo-oophorectomy may be done.

Ovary can be preserved even in a case of torsion. The common ovarian lesions associated with adnexal torsion include benign teratomas, tubal-cysts, follicular or corpus luteal cysts, and serous or mucinous cystadenomas.[13]Adnexal torsion should be managed by reduction of the torsion with concomitant ovarian cystectomy, for identified ovarian pathology. In most cases, the residual ovary will regain perfusion and remain viable. Despite evidence of necrosis or ischemia at the time of surgery, ovarian function is preserved in almost 90% of cases. Ovarian fixation remains controversial, but maybe considered in cases of recurrent torsion.[14]

Given advancements in minimally invasive surgical techniques, laparoscopic management of presumed benign adnexal masses is appropriate and desirable. Several retrospective studies have shown low complication rates in laparoscopic management of adnexal masses. In these studies, conversion of laparoscopy to laparotomy was very low. The most common reason of conversion was suspected malignancy on laparoscopy.[15,16]

Spillage of cyst contents should be avoided where possible as preoperative and intra-operative assessment cannot absolutely preclude malignancy. Consideration should be given to the use of a tissue bag, during laparoscopy,to avoid peritoneal spill of cystic contents.[17]In the presence of large masses with solid components (for example large dermoid cysts), laparotomy may be appropriate. In cases where malignancy is suspected, minimal invasive procedure should be undertaken only by an expert team, which can both adequately stage and debulk the disease using this technique.

Whenever possible, intraoperative frozen section should be used. It has high accuracy and sensitivity, especially in malignancies. However, tumor size > 10 cm and borderline histology limit its accuracy.[18,19]

Majority of the ovarian cancers in young females are malignant germ cell tumors which are usually diagnosed in early stage. Moreover, effective multi-agent chemotherapy is associated with high cure rates. Hence, the intent of surgery in all stages is fertility preservation.

The Children's Oncology Group recommends removal of the tumor without spilling its contents, sparing of the fallopian tube if not adherent, harvesting ascites for cytology, examination and palpation of the omentum with biopsy or removal of suspicious areas, and examination and palpation of the iliac and aorto-caval nodes with removal of enlarged nodes.[20]Several recent studies have also confirmed the safety of fertility preserving conservative surgical approaches in young females with malignancy.[21,22]

Table 4: Serum tumor markers elevated in ovarian neoplasm

Tumor marker	Associated neoplasm
AFP	Immature teratoma
	Sertoli-Leydig cell tumors
	Yolk sac tumors
	Embryonal carcinoma
β-HCG	Dysgerminoma
	Embryonal carcinoma
LDH	Dysgerminoma
	Immature teratoma
CA-125	Epithelial tumors
CA-19-9	Epithelial tumors
CEA	Epithelial tumors
Testosterone	Sertoli-Leydig cell tumors
Estradiol	Juvenile granulosa cell tumors

3.2 Adjuvant chemotherapy

Of all the ovarian malignancies in young girls, approximately 85% are germ cell tumors, 8% are epithelial cell carcinoma, and 5% are sex cord stromal tumors.[23]

With the use of postoperative chemotherapy, 90% to 95% of malignant germ cell

tumors are curable.[24]Adjuvant chemotherapy is recommended for all patients except those with stage IA, and IB dysgerminoma, stage IA, grade I immature teratoma,stage IA embryonal tumors, or stage IA yolk sac tumors. The regimen of bleomycin, etoposide, and cisplatin (BEP) has most favourable therapeutic index. For epithelial cell carcinomas, carboplatin and paclitaxel are the preferred drugs.[25]

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Risk Reducing Bilateral Salpingo-Oophorectomy (RRBSO) Guidelines

Swasti

Background

BRCA mutations are associated with an increased risk of breast and ovarian cancer. Women with BRCA1 mutations have a 67% average cumulative risk for breast cancer by age 80 years and 45% for ovarian cancer[1-4]. In BRCA2 carriers, the average cumulative risks are 66% and 12%, respectively[1-4]. Risk-reducing bilateral salpingo-oophorectomy (RRBSO) in BRCA carriers offers 80% ovarian cancer risk reduction and 50% breast cancer risk reduction[5].

More recent evidence suggests that BRCA1 carriers may not significantly benefit with RRBSO in terms of breast cancer-risk reduction[6,7]. Cancer risk estimates for BRCA carriers are age-dependent and tend to be higher in younger age populations[7].

Current guidelines recommend RRBSO for BRCA carriers before age 40 years or after completion of child-bearing[8-11].

Prophylactic bilateral salpingo-oophorectomy (PBSO) is also known as risk-reducing salpingo-oophorectomy (RRSO). Both these terms will be used interchangeably in this guideline.

1. How to identify women who need and should be offered RRBSO?

NCCN has updated the guidelines in October 2017 and defined the indications for genetic risk assessment and counselling (all are Category 2A recommendations)[12].

1.1 Genetic Risk Assessment and Counselling

Women who are concerned about or are suspected to have a higher propensity for developing breast and or ovarian cancer, an initial risk assessment should be undertaken to determine whether a formal risk assessment is needed or not.

Patient's needs and concerns, detailed family history, detailed personal medical and surgical history and a focussed clinical examination is of utmost importance following which the need for formal risk assessment is established. Before offering genetic testing, it is recommended that a pre-test counselling session by genetic counsellor, medical geneticist, oncologist and all those involved in patient care must be performed.

Pre-test counselling includes the following

1. Collection of patients detailed family history which must include first-, second- and third-degree relatives from both sides
2. Evaluation of patients cancer risk
3. A differential diagnosis is thereafter made and the patient is educated on inheritance patterns, penetrance, variable expressivity and the possibility of genetic heterogeneity
4. Patient has to be counselled regarding positive outcomes, negative or uncertain test results and an informed consent needs to be obtained

1.2 BRCA 1 or 2 Testing Criteria

Testing of an individual without cancer diagnosis should be considered only when an appropriate affected family member is unavailable for testing. Meeting one

or more of the following criteria[12] warrants further personalized risk assessment, genetic counselling and often genetic testing and management.

- Individual from a family with a known deleterious BRCA1/BRCA2 gene mutation
- Personal history of breast cancer – one or more of the following
- Diagnosed ≤45 years
- Diagnosed ≤50 y with:

  An additional breast cancer primary

  ≥1 close blood relative with breast cancer at any age

  ≥1 close relative with pancreatic cancer

  ≥1 relative with prostate cancer (Gleason score ≥7 or metastatic)

  An unknown or limited family history
- Diagnosed ≤60 y with:

  Triple negative breast cancer
- Diagnosed at any age with:

  ≥2 close blood relatives with breast, pancreatic or prostate cancer (Gleason score ≥7 or metastatic) at any age

  ≥1 close blood relative with breast cancer diagnosed ≤50 y

  ≥1 close blood relative with ovarian carcinoma

  A close male blood relative with breast cancer

  For an individual of ethnicity associated with other mutation frequency (eg. Ashkenazi Jewish) no additional family history may be required
- Personal history of ovarian carcinoma
- Personal history of male breast cancer
- Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic or prostate cancer (Gleason score ≥7 or metastatic) at any age
- Personal history of metastatic prostate cancer (radiographic evidence of biopsy-proven disease)
- Personal history of pancreatic cancer at any age with ≥1 close blood relative with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic or prostate cancer (Gleason score ≥7 or metastatic) at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- BRCA 1/2 pathogenic mutation detected by tumor profiling on any tumor type in the absence of germline mutation analysis
- Family history only (significant limitations of interpreting test results of an unaffected individual should be discussed:

  First- or second-degree blood relative meeting any of the above criteria

  Third-degree blood relative who has breast cancer and/or ovarian carcinoma who has ≥2 close blood relatives with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian carcinoma

Post-test counselling includes discussion of the following aspects:

1. Results of genetic testing along with their impact and significance and management options

2. Interpretation of results in context of personal and family history of cancer
3. Informing and testing at-risk family members
4. Regarding the available disease specific support groups and research studies

2. Alternatives to RRBSO

Identification of women benefiting from RRBSO is simply not enough. All the women with BRCA1/2 mutation recommended to undergo RRBSO may not opt for it. Younger women wishing to preserve their fertility for completion of their family may seek alternative strategies to minimise risk or expedite diagnosis of a potential ovarian or breast cancer to improve survival.The alternative strategies to a RRBSO are:

2.1 Surgical

Tubal ligation has been associated with some risk reduction of ovarian cancer. There is enough evidence to suggest fallopian tube origin of ovarian cancer. Risk-reducing salpingectomy initially followed by a delayed oophorectomy has also been adopted in younger women with BRCA1 and BRCA2 mutations who desire risk reduction with avoidance of menopause. Delaying oophorectomy, however, negates the risk reduction for breast cancer and cancers arising from ovaries in these women.

2.2 Intensive screening and Early detection

The goal of surveillance is early detection of cancer.

Breast cancer surveillance[13,14]

In the case of breast cancer, this involves:

- Regular (monthly) self breast examination from age 18 years
- Annual or 6monthly clinical breast examination
- Annual mammography beginning at age 30 years
- Annual breast MRI beginning at age 30 years

The sensitivity of mammography to detect malignancy in women with a genetic predisposition to breast cancer is approximately 33%, MRI increases this to approximately 80%. Surveillance with alternating mammography and MRI six monthly has a sensitivity of 95% for the detection of breast cancer[15,16].

Ovarian cancer surveillance

Screening for the early detection of ovarian cancer involves:

- Annual or semi-annual transvaginal pelvic ultrasonography from age 35 years or at 5 years younger than the earliest ovarian cancer diagnosis in the family
- Annual CA-125 testing

These surveillance modalities are non-invasive, have no adverse impact on fertility and can be utilized till childbearing is complete. The disadvantage of these surveillance methods are that they do not lead to cancer risk reduction. There is no evidence that the recommended surveillance strategies reduce cancer-related mortality. Furthermore, there is an inherent level of anxiety associated with surveillance and both breast MRI and pelvic USS can yield false positives which increase this anxiety[17,18]. It has been recommended that women opting for surveillance should be provided with professional psychosocial support when necessary.

2.3 Chemoprevention

Tamoxifen is a selective oestrogen receptor modulator (SERM) used routinely used as adjuvant therapy in women with estrogen receptor positive breast cancer. The aim is to prevent the development of cancer in the contralateral breast and to

prolong disease free survival[19]. This drug has also been shown to reduce the risk of developing cancer in high risk women without prior breast cancer and can be used as a chemoprevention strategy to reduce the risk of invasive ER positive breast cancer[20].

Regarding BRCA1/BRCA2 mutation carriers specifically, tamoxifen use has been shown to reduce the incidence of contralateral breast cancer in BRCA mutation carriers with a prior history of breast cancer[21,22].A subgroup analysis of the NSABP-P1 data revealed that tamoxifen use did not appear to have a significant effect on breast cancer risk in women with BRCA mutations[23]. ASCO panel concluded that the "limited evidence precludes reliable evidence of Tamoxifen effects in this setting". However as it has a proven risk reduction benefit in BRCA patients with a history of breast cancer and in women with an increased risk of breast cancer, tamoxifen is frequently offered as chemoprevention to BRCA mutation carriers who do not choose to undergo prophylactic mastectomy[24].

Tamoxifen use has been shown to be associated with an increased risk of uterine malignancy, including early stage adenocarcinomas, endometrioid, mucinous, clear cell and uterine sarcomas. There are reports of vascular and thromboembolic events with tamoxifen use as well[25]. This risk of uterine malignancy could be avoided by a concomitant hysterectomy at the time of RRBSO.

3. Risk reducing bilateral salpingo-oophorectomy

3.1 Age at RRBSO

The clinical management of cancer risk in BRCA1 and BRCA2 mutation carriers is complex and multifactorial. The optimal timing of RRBSO is not clearly defined. Eisen et al reported compared risk reduction in BRCA positive mutation carriers under and over the age of 50 years. There was improved risk reduction before 50 years age[26]. NCCN currently recommends risk reducing salpingo-oophorectomy to BRCA positive women between ages 35 to 40 years, or when the woman has finished childbearing.

3.2 Preoperative evaluation and preparation – counselling, timing of surgery, preoperative evaluation, written informed consent

A clear and precise discussion about the risk reduction benefit as well as possible side effects and morbidity associated with an early menopause must take place between the physician and the woman. The evidence suggesting that RRBSO in women under the age of 45 years is associated with increased mortality, particularly in patients who do not receive hormone replacement therapy (HRT) must be highlighted[27].

There are a number of considerations which must be taken into account when planning and counselling a patient for RRBSO

1. Risk reduction benefit for breast cancer
2. Risk reduction benefit for ovarian cancer
3. Timing of surgery
4. Surgical approach
5. Adverse effects of surgical menopause
6. Risks and benefits of concomitant hysterectomy
7. Need for hormone replacement therapy (HRT) it's risks and benefits
8. Reproductive options[12] – prenatal diagnosis, pre-implantation diagnosis,

assisted reproduction for couples who express concern for their offspring in view of BRCA1/2 mutation carrier status

Clinical predictors of RRBSO include:

1. Family history of ovarian cancer
2. Personal history of breast cancer
3. Woman's perception of her own health and the risk of ovarian cancer

Women considering RRBSO face complex information regarding cancer risk and the risk/benefit profile of prophylactic surgery including factors such as surgical risk, hormonal deprivation and residual cancer risk. It is important that patients are supported in processing this information in order to help them make the best individual decision.

3.3 Technique

After RRSO, there remains a small risk for developing primary peritoneal cancer.

The specific protocol for RRSO for high-risk women involves[28,29]

1. Exploration of the pelvic organs for any evidence of cancer
2. Peritoneal wash
3. Complete removal of the ovaries and fallopian tubes

The 'Intensive' RRSO protocol includes[28,29]

1. Bilateral salpingo-oophorectomy and removal of entire length of the fallopian tubes
2. Cytologic examination of peritoneal washings
3. Random peritoneal and omental biopsies

Minimally invasive versus Open Technique

The advantages of laparoscopy over the traditional open surgery or laparotomy have made it the preferred modality of surgical approach for RRBSO. Improved visualisation of the pelvic peritoneum, avoidance of a large abdominal incision, shorter hospital stay, decreased post-operative pain and a rapid recovery time have been observed by most surgeons[30,31].

The decision of a concomitant hysterectomy is influenced by a longer operative time, increased morbidity and longer recovery time. The use of minimally invasive techniques in radical surgeries for carcinoma cervix and endometrium has demonstrated comparable surgical and oncologic outcomes to laparotomy[32,33].

Laparoscopic assisted vaginal hysterectomy combined with RRBSO is a feasible minimally invasive approach to risk reducing surgery in patients with BRCA1/2 mutations[34,35]. RRBSO by laparoendoscopic single-site surgery (LESS) utilizes a single port which accommodates the camera and operating instruments, needing only a single incision[36].

LESS was pioneered by Escobar and colleagues in the Cleveland Clinic who have reported its use in benign and malignant gynaecologic conditions[37-40]. They reported a retrospective series of 58 patients at high risk for breast/ovarian cancer who underwent LESS RRBSO with (n=13) and without (n=45) hysterectomy[38]. Larger prospective studies are required to validate these results. This single–port laparoscopic approach represents an advance in minimally invasive gynaecologic surgery that may become an attractive option for BRCA mutation carriers and breast cancer patients due to the favourable cosmetic outcome and rapid recovery time.

3.4 Role of concomitant prophylactic hysterectomy

The advantages of performing a concomitant hysterectomy with RRBSO in BRCA mutation carriers could be:

1. Theoretically reduce risk of cancer in the cornual fallopian tube[41]
2. Other gynecologic reasons such as fibroids or abnormal Pap smears
3. For women taking tamoxifen to reduce risk of endometrial cancer[42]
4. Facilitation of postoperative hormonal therapy; if hysterectomy were performed, only estrogen would be needed, which confers lower risk of hormone therapy complications compared to combined therapy with estrogen and progestin

Follow-up will vary based on whether or not a hysterectomy will be performed and whether or not hormone replacement therapy is prescribed. Generally, it has been suggested that patients with BRCA1 and BRCA2 mutations are not at increased risk of developing uterine carcinoma, although data have suggested a small increased risk of serous endometrial cancer[43]. The argument against hysterectomy is a small increase in recovery time and surgical complications associated with the addition of hysterectomy to salpingo-oophorectomy.

Generally, the decision to include hysterectomy with RRSO in BRCA1 and BRCA2 mutation carriers should be based on a full discussion of risks and potential benefits in shared decision-making between the patient and her surgeon.

3.5 Pathology evaluation

Ovarian cancer in BRCA carriers may begin in the fallopian tubes. It is therefore important to remove the tubes in BRCA-mutation carriers and to perform 'serial sectioning' of the fallopian tubes to exclude occult cancers or serous intra-epithelial tubal carcinomas (STIC). In the SEE-FIM protocol (Sectioning and Extensively Examining of the Fimbriated end), the greatest surface area of the tube is histologically examined, based on the suggestion that multiple deeper sections should be examined, if the initial haematoxylin and eosin (H&E) sections are negative.

Originally developed by the Division of Women's and Perinatal Pathology, Brigham and Women's Hospital, the "sectioning and extensively examining the fimbriated end (SEE-FIM)" protocol is an easy means of standardizing grossing procedure. Although the protocol was created for BRCA-positive RRSO specimens, it's modification is applied to any prophylactic salpingo-oophorectomy specimen (regardless of known BRCA status) as well as all staging oophorectomies. Following this protocol assures that the entire specimen is submitted with the greatest surface area available for histologic review

Grossing Protocol for Prophylactic Salpingo-Oophorectomies[44]

1. Specimen is fixed before grossing to minimize exfoliation.
2. Distal 2 cm of the fallopian tube is separated from the rest of the tube
3. Distal 2 cm of the fallopian tube is then cut longitudinally and submitted on edge.
4. Remainder of the fallopian tube is subjected to cross section at _3 mm intervals.
5. Ovaries are cut at _3 mm interval.
6. The entire specimen is submitted for histologic review.

3.6 Follow up – postoperative care, surveillance for peritoneal cancer

The risk of a subsequent primary peritoneal cancer following RRSO is 1%–4%.

Pelvic ultrasound and CA-125 may have limited usefulness in surveillance for primary peritoneal cancer but alternatively should be used to evaluate symptoms. The Society of Gynecologic Oncology and the National Cancer Care Network endorse pelvic exams for ongoing monitoring of menopausal symptoms, consideration of short-term HRT, and related medical issues.

(Semi)-annual CA 125 monitoring is recommended; however, the evidence is insufficient to demonstrate that surveillance facilitates earlier detection of subsequent primary peritoneal cancer or provides a survival benefit, given its rare occurrence.

3.7 Benefits

RRBSO prevents approximately 80% of ovarian/fallopian tube and peritoneal cancer in women who carry BRCA1 and BRCA2 mutations.

Delaying RRBSO until mid-forties in women with BRCA2 mutations may be considered because the incidence of ovarian cancer is approximately 1 percent for women under age 50.

Breast cancer risk may also be reduced by premenopausal RRBSO.

3.8 Adverse Effects and Impact on Quality of Life (QOL) - Issues related to early surgical menopause

Following RRBSO, premenopausal women face an immediate consequence of surgical menopause. Surgical menopause significantly affects a woman's quality of life (QOL), including vasomotor and urogenital symptoms, sexual dysfunction, sleep disturbances, and mood changes. These women are at risk of long-term sequelae such as osteoporosis, cardiovascular diseases, and cognitive impairment[45].

The positive quality of life changes reported after RRBSO are[46,47]

1. Reduced perception of ovarian cancer risk
2. Reduced anxiety levels
3. Increased sense of control over ones' health

The majority of women, particularly the younger ones, complain of side effects related to hormonal deprivation, including hot flushes, vaginal dryness, decreased sexual interest and decreased sexual pleasure[47]. Women with a BRCA mutation have a unique risk and benefit profile which must be considered when making recommendations regarding the use of HRT following RRBSO in the premenopausal age-group. HRT remains the most effective strategy for the management of postmenopausal symptoms and sequelae such as osteoporosis and cardiovascular risk in young females undergoing sudden surgical menopause. Post-PSO HRT does not appear to increase the risk of cancer in premenopausal women who undergo PSO[48]. However, unopposed oestrogen does pose a substantial risk of uterine cancer while combined HRT has been shown in the Women's Health Initiative studies to increase the risk of breast cancer[49-51].

Hysterectomy at the time of RRBSO would negate the uterine cancer risk facilitating the use of unopposed oestrogen as HRT in these patients.

The PROSE study group in a prospective multicentre study of 462 patients with BRCA mutation found that the breast cancer risk reduction/protective effect attained following prophylactic bilateral oophorectomy was not significantly changed by the use of HRT[48]. Similarly, Eisen et al observed no increased risk of breast cancer associated with HRT use in patients following PSO[26].The short term use of HRT does

not appear to increase breast cancer risk, and should be considered in young patients to alleviate menopausal symptoms which may interfere with quality of life[52]. In high-risk patients carrying a BRCA mutation, estrogen-only HRT is preferable[52]. In women where a concomitant hysterectomy has been performed, estrogen alone HRT can be safely used to alleviate menopausal symptoms and adverse effects.

Summary and Recommendations

Most of the evidence is consensus based (category 2A, NCCN 2017)[12]

1. Prophylactic bilateral salpingo-oophorectomy (PBSO) is also known as risk-reducing salpingo-oophorectomy (RRSO)
2. Any woman must not be offered genetic testing despite of meeting the genetic testing criteria before a pre-test counselling by a team of clinicians including a genetic counsellor, medical geneticist, oncologist
3. An elaborate post-test counselling session must be performed before taking any decision for performing risk reducing surgeries. Risks, benefits and alternatives must be discussed with the woman and her family
4. The optimal timing of performing RRBSO for BRCA carriers before age 40 years or after completion of child-bearing.
5. The decision to perform a concomitant hysterectomy will be individualized depending on co-existing gynaecological conditions, concurrent tamoxifen use, in younger women who may need HRT for long time
6. Detailed preoperative counselling regarding timing, approach of surgery, cancer risk reduction benefits, need for surveillance, alternative strategies, need for concomitant hysterectomy, need for HRT and consequences of early menopause, possibility of primary peritoneal carcinoma post RRBSO, need for follow up must be discussed in detail and documented with a clear written informed consent
7. All women undergoing RRBSO must have the specimen grossed by SEE-FIM protocol to identify precursor lesions or occult cancers in the fallopian tube
8. Women with a BRCA mutation have a unique risk and benefit profile which must be considered when making recommendations regarding the use of HRT following RRBSO in the premenopausal age-group.

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NCCN Categories of Evidence and Consensus

Category 1: Based upon high level evidence, there is uniform NCCN consensus that an intervention is appropriate

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate

Category 3: Based upon a level of evidence, there is major NCCN disagreement that the intervention is appropriate

Risk Reducing Salpingectomy

Urvashi Miglani, Rupinder Sekhon

Background

Ovarian cancer has emerged as one of the most common malignancies affecting women in India and has shown an increase in the incidence rates over the years[1]. Fatality due to ovarian neoplasm is high due to nonavailability of an effective screening tool, early peritoneal dissemination and absence of symptoms in the early stage of the disease. The patients can broadly be divided into 2 groups: 1) Those at high risk for hereditary ovarian cancer (BRCA mutation carriers) and 2) Those at population risk (no genetic predisposition for ovarian cancer)

In the absence of an effective screening tool in the high risk women, removal of the ovaries and fallopian tube i.e. Risk-reducing salpingo-oophorectomy (RRSO)—is recommended for prevention with strong evidence supporting this approach. It results in a 75% to 96% decrease in ovarian cancer risk and a 50% decrease in breast cancer risk in BRCA mutation carriers[2,3]. However, RRSO is accompanied by a hazardous impact on cardiovascular and bone health, as well as quality of life (hot flashes, vaginal dryness, dyspareunia, and changes in sexual function and body image) due to surgical menopause[4,5]. In women with BRCA mutations, RRSO is generally recommended by age 40 years, or when childbearing is complete. These adverse effects can probably be circumvented in women at population risk of ovarian cancer and to some extent in high risk women by the emerging role of bilateral salpingectomy in the prevention of ovarian cancer.

Evidence

The tubal paradigm: Recent evidence strongly indicates that fallopian tube is the site of origin of majority of high grade serous ovarian and peritoneal carcinomas[6-10]. The Sectioning and Extensive Examining of the Fimbria (SEE-FIM) protocol has revealed tubal involvement in up to 70 % of unselected women diagnosed with ovarian or primary peritoneal High Grade Serous Carcinomas HGSC (with and without BRCA 1/2), including the presence of fimbrial Serous Tubal Intraepithelial Cancer STICs in 40–60 % of these women. Importantly, STICs have not been observed in women with non-gynaecologic or benign conditions Based upon these findings, it has been proposed that tubal neoplasia is the primary lesion in HGSC and that these lesions spread to the ovary and peritoneum.

Also, genetic studies show that these tubal lesions express a common TP53mutation, as do high-grade serous, high-grade endometrioid, and undifferentiated carcinomas. In addition, gene expression of high-grade serous carcinomas is more closely related to the fallopian tube morphology than the ovarian surface epithelium[6-10]. However, since not all serous ovarian carcinomas are accompanied by STIC lesions, it is possible that not all high-grade serous EOCs arise in the fallopian tube, and that alternative pathways of carcinogenesis exist.

1. **Is salpingectomy safe?**

   A primary concern about routine salpingectomy is the potential effect on ovarian function, including its impact on the timing of menopause. Evidence suggests that salpingectomy does not have any deleterious influence on ovarian reserve or perioperative morbidity[11-13]. The safety of this procedure has been consolidated by a large cohort study from the Ovarian Cancer Research Program of British Columbia

(OVCARE) on the perioperative safety outcomes of 49,931 women who underwent hysterectomy with and without bilateral salpingectomy or BSO. They found that a bilateral salpingectomy was associated with a minimal increase in operative time (approximately 16 minutes more for hysterectomy with bilateral salpingectomy v/s without salpingectomy, and 10 minutes more for bilateral salpingectomy v/s tubal ligation. Besides this finding, no differences were observed in the risks of hospital readmission, blood transfusions, or length of hospital stay[14].

2. **Salpingectomy in the general population**
   Studies have shown that salpingectomy with hysterectomy at age 45 years was less costly and more effective (longer life expectancy gain for women who would have died prematurely from ovarian cancer) than hysterectomy alone or hysterectomy with bilateral salpigoophorectomy. This holds true for women who have hysterectomy at any time before age 50 years[15]. Further there is strong evidence that opportunistic salpingectomy is safe and does not incur additional risks[14].

   The subjects requiring tubal sterilization can be counselled about the option of salpingectomy, with the advantage of avoiding ectopic pregnancy in the latter option. However, there is no possibility of reversal of the procedure in case of salpingectomy in women who subsequently wish to regain their fertility and have to rely on in vitro fertilization approach[16].

   Also, the complications following retained tubes after hysterectomy and sterilization like hydrosalpinx, pelvic inflammatory disease, salpingitis, benign fallopian tube tumours, and tube prolapse can be avoided by performing salpingectomy at the time of hysterectomy and in lieu of tubal ligation[17].

   Thus, as salpingectomy becomes more prevalent in the benign gynaecology practice, it is crucial to continue to investigate its safety and efficacy; future studies should aim to determine the rate of preinvasive disease in the fallopian tubes of average-risk women, as well as the potential sequelae of leaving the ovaries in situ.

3. **Salpingectomy in the high risk population**
   Risk reducing salpingo-oophorectomy has shown to dramatically reduce incidence of ovarian cancer in the high risk subjects with a genetic predisposition.[18] 30 % of these genetically predisposed women are unwilling for removal of their ovaries due to concerns regarding future fertility or premature menopause.

   Recently the potential role of interval salpingectomy after the completion of childbearing followed by later oophorectomy in women with BRCA1and BRCA2 mutations who decline the standard recommendation for RRSO is being discussed. A recent study comparing cost for RRSO versus salpingectomy at the age of 40 years followed by oophorectomy at the age of 50 years showed that both strategies met standard cost-effective criteria, but RRSO was less costly. Further the latter approach was the most cost-effective for quality-adjusted life years.[19] But it needs to be emphasized that this theoretically attractive approach has not been validated to reduce cancer risk in randomised trials [18]. Salpingectomy followed by oophorectomy should be offered only to those who are unwilling to undergo salpingo-oophorectomy at the recommended age.

4. **Technique**
   In risk-reducing surgery for high-risk patients, peritoneal washings should be taken, and the entire fallopian tube should be removed up to the cornua when the uterus is being preserved. The fimbriae may be adherent to the adjacent ovarian capsule, and this may require excision of the adjacent capsule of the ovary in high-risk patients.

The utero-ovarian ligament, the infundibulo-pelvic ligament, and all vascular supply to the ovary should be preserved for pathology processing, the entire fimbriae should be embedded for microscopic examination in low-risk women, whereas in high-risk women, additional serial sectioning of the entire fallopian tube is required. p53 and Ki67 immunohistochemical stains may be used to characterize any subtle changes in high-risk (BRCA1 and BRCA2 mutation carrier) patients[20.]

5. Recommendations[21-25]

5.1 Women at population risk of ovarian cancer

- Women not at high risk who raise the possibility of risk-reducing bilateral oophorectomy should be offered appropriate information, and if seriously considering this option should be offered referral to the team that deals with women at high risk.
- The surgeon and patient should discuss the potential benefits of the removal of the fallopian tubes during a hysterectomy in women at population risk of ovarian cancer who are not having an oophorectomy.
- When counselling women about laparoscopic sterilization methods, clinicians can communicate that bilateral salpingectomy can be considered a method that provides effective contraception.However in India the updated NHM (National Health Mission) guidelines on standard of care for female sterilization have not incorporated salpingectomy as a modality for female sterilization. Hence in India, salpingectomy as a substitute for ligation can't be advocated till the NHM guidelines permit the same.
- Prophylactic salpingectomy may offer clinicians the opportunity to prevent ovarian cancer in their patients.(**Low quality evidence**). Currently there is no evidence from randomised controlled trials with respect to the effectiveness of bilateral salpingectomy alone in preventing ovarian cancer in low-risk women.
- The pathologic specimen processing in low risk women should include representative sections of the tube, any suspicious lesions, and entire sectioning of the fimbriae.
- Randomized controlled trials are needed to support the validity of this approach to reduce the incidence of ovarian cancer

5.2 Women at Genetic predisposition[20,24,26]

- Recommend risk-reducing salpingo-oophorectomy (RRBSO ideally in consultation with a gynaecologist oncologist), typically between 35 and 40 y, and upon completion of child bearing. Because ovarian cancer onset in patients with BRCA2 mutations is an average of 8–10 years later than in patients with BRCA1 mutations, it is reasonable to delay RRSO until age 40–45 years in patients with BRCA2 mutations who have already maximized their breast cancer prevention (i.e., undergone bilateral mastectomy) (**RCOGLevel of evidence III, NCCNGrade of recommendation IIA)**
- Counselling should include a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term hormone replacement therapy to a recommended maximum age of natural menopause, and related medical issues. (**NCCNGrade of Recommendation IIA)**
- RRBSO leads to 50-75 % reduction in incidence of breast cancer in high-risk women**(RCOG Level of evidence III, NCCN grade of Recommendation IIA**)
- For a risk-reducing bilateral salpingo-oophorectomy, all tissue from the ovaries

and fallopian tubes should be removed. Thorough visualization of the peritoneal surfaces with pelvic washings should be performed. Complete, serial sectioning of the ovaries and fallopian tubes is necessary, with microscopic examination for occult cancer.

- When women with no personal history of breast cancer have either a BRCA1 or BRCA2 mutation or a family history of breast cancer and they have had a bilateral salpingo-oophorectomy before their natural menopause, offer them: - combined HRT if they have a uterus - oestrogen-only HRT if they don't have a uterus until the time they would have expected natural menopause. Manage menopausal symptoms occurring when HRT is stopped in the same way as symptoms of natural menopause. (**RCOG 2013 Level of Evidence IV**))
- The use of HRT following oophorectomy may have an impact (negative) on the level of riskreduction, but there is no good evidence. (**Level of evidence IV**)
- Salpingectomy alone is not the standard of care in high risk women as no level I evidence is available. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. (**Grade of Recommendation IIA**).Salpingectomy can be considered at the completion of childbearing in women at increased genetic risk of ovarian cancer who do not agree to salpingo-oophorectomy. However, this is not a substitute for oophorectomy, which should still be performed as soon as the woman is willing to accept menopause, preferably by the age of 40 years. Women delaying or refusing risk-reducing oophorectomy should be counselled that they will not receive the breast cancer risk reduction provided by oophorectomy.
- Do not offer risk-reducing surgery to people with comorbidities that would considerably increase the risks of surgery. Do not offer risk-reducing surgery to people who have a limited life expectancy from their cancer or other conditions(**RCOG 2013**)

Risk reducing salpingectomy:knowledge gaps[27]

1. STIC lesions are identified in only 50% to 60% of sporadic HGSC; thealternate pathways of carcinogenesis for other 40% to 50% cancers are yet to be studied.
2. The mechanism underlying the apparent preference for tumour growth or metastasis and dominant mass development at the site of the ovary, despite cancer initiation in the fallopian tube remains unfolded
3. There are no data at this point that prove reduction in incidence of ovarian cancer, improved overall survival, or preservation of ovarian function with the two-stepped surgical approach of salpingectomy followed by oophorectomy in high risk and average risk women.

   Multicentric prospective randomised trials to address these issues are the need of the hour before salpingectomy replaces the current approach of salpingo-oophorectomy especially in high risk women

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