Volume 17; Issue No.10; February 2018

Price: ₹ 30 only

AOGD BULLETIN

AOGD Theme 2017-18

'Optimizing Women's Health Through Enhanced Skills and Best Practices'

Issue:

Endocrine Glands and Hormones in Pregnancy

AOGD SECRETARIAT

Room No 712, 7th Floor, Private Ward, MCH Block
Department of Obstetrics and Gynecology
Guru Teg Bahadur Hospital & University College of Medical Sciences
Dilshad Garden, Delhi-110095, India
secretaryaogd2017@gmail.com, info@aogd.org

www.aogd.org

AOGD Secretariat
Room No 712, 7th Floor, Private Ward, MCH Block
Department of Obstetrics & Gynaecology
Guru Teg Bahadur Hospital & University College of Medical Sciences
Delhi-110 095, India
www.aogd.org

AOGD BULLETIN
Volume 17-10, February 2018

Contents

Publisher/Printer/Editor
Dr Rashmi on behalf of Association of Obstetricians & Gynecologists of Delhi.

Printed at
Process & Spot C-112/3, Naraina Industrial Area, Phase-1, New Delhi 110 028

Published from
AOGD Office, Room No 712, 7th Floor, Private Ward, MCH Block, Department of Obstetrics & Gynaecology, Guru Teg Bahadur Hospital & University College of Medical Sciences, Delhi-110 095, India

Editor
Dr Rashmi
Ph. No. 011-22692505; Email: info@aogd.org

Total number of pages = 52

AOGD Office-Bearers

Dr Shalini Rajaram
President

Dr Kiran Guleria
Vice President

Dr Gita Radhakrishnan

Dr Amita Suneja

Scientific Advisors

Dr Abha Sharma
Hon. Secretary

Dr A G Radhika
Chairperson Skill Workshops

Dr Himshweta Srivastava

Dr Sandhya Jain

Joint Secretaries

Dr Alpana Singh
Treasurer

Dr Archana Chaudhary
Co Treasurer

Editorial Board

Dr Rashmi

Dr Bindiya Gupta

Editors

Dr Rachna

Dr Anshuja

Web Editors

Dr Richa Aggarwal

Dr Sruthi

Co-Editors

Committees

Dr Richa Sharma

Dr Sanjeeta Behera

Dr Bhanu Priya

Coordinators Skill Workshops

Dr Vishnu Bhartiya

Dr Shweta Prasad

Clinical Secretaries

Dr Rashmi Gupta

Dr Seema Prakash

Public Relations & Hospitality

President's Message

Dear Friends

January 2018 has just whizzed past but not without fanfare! AOGD members are dotting the FOGSI landscape with key posts. Dr. Pratima Mittal took over as VP, North zone and Dr. Ashok Kumar was elected council member and Editor ICOG. In addition our members have won several awards sweeping the Senior Corion & Junior Corion categories, best journal paper, CS Dawn prize, Imaging science award, endoscopy fellowship, RD Pandit prize for best thesis, Kamini Rao oration and many more. See the January Events centre-fold for colourful pictures.

We also saw the release of the FOGSI GCPR guidelines on Cervical Cancer Screening & Vaccination at the AICOG by Dr. Neerja Bhatla, Chairperson FOGSI Oncology Committee. Finally we have our own guidelines based on resources and depending on your practice you can choose what's available and affordable. Guidelines are available on the FOGSI website. I urge all members to please screen women over 30 and vaccinate all young girls between 9 and 14 years. There is enough new evidence to show that HPV vaccination has brought about a decline not only in CIN 3 but also cervical cancer. Screen positive women must be triaged and managed appropriately, and screen negatives seen once in 5 years.

Dr. Jaideep Malhotra as President FOGSI this year has conceptualised a number of activities during the year, each month having a theme. February is marked for 'Medicolegal issues in Obstetric & Gynecology Practice'. AOGD will be holding a skills workshop on 'Medico-legal Tips & Access to evidence for Safe practice in O&G' on the 10th February, 2018. The calender of events of FOGSI are given in this bulletin so activities can be planned around these dates avoiding a clash.

This issue on 'Endocrine glands and Hormones in pregnancy' takes you through commonly encountered problems in pregnancy namely diabetes and hypothyroidism. Understanding the newer insulins and keeping oneself abreast of recent therapies is essential. Likewise management guidelines for hypothyroidism and hyperprolactinemia are updated and make for good reading. Progesterone the central hormone of pregnancy and its uses in preterm labor and threatened abortion are discussed as is Atosiban. Deficiency of Vitamin D3 has been implicated in a number of conditions and supplementation in pregnancy is discussed.

Hope to see you all at the next Clinical meeting at Lady Harding Medical College on the 23rd February, 2018

Cheers!

Shalini Rajaram
President, AOGD (2017-18)

Vice President's Message

Dear Friends,

Greetings

Congratulations all AOGDians for big presence at FOGSI and getting so many prestigious awards. Another bulletin is here with few well chosen topics.

Having dealt in details the role of hormones in gynecological problems earlier, our current issue focuses on "Endocrine Glands and Hormones in Pregnancy". Maintaining a balanced hormonal milieu is essential for an optimal pregnancy outcome. Subclinical hypothyroidism, Diabetes mellitus, Recurrent pregnancy loss etc. are common hormone related conditions complicating pregnancy which when managed judiciously can avert adverse maternal and fetal outcomes.

The current issue deals with some of the common hormonal conditions affecting pregnancy and their evidence based management. Hope you all will find something of interest in this.

Enjoy the spring!!

Kiran Guleria
Vice President AOGD (2017-18)

From the Secretary's Desk.....

Dear AOGDians

Happy Basant!

The year started with the biggest extravaganza, FOGSI annual conference & it was heartening to see significant participation by AOGD members. Our best wishes to **Dr Pratima Mittal** for assuming charge of Vice President FOGSI (North Zone); under her dynamic leadership North Zone is bound to go places. My congratulations to all award winners of various prizes conferred at FOGSI Conference. Bringing laurels to AOGD both Senior & Junior **FOGSI Corion awards** were won by Delhi members Dr Garima Kachhawa, AIIMS & Dr Bindiya Gupta, GTB hospital respectively.

As we near the fag end of our tenure, our editors are striving to cover all important topics. The latest issue in your hands demystifies **"Endocrine Glands and Hormones in Pregnancy"**; this controversy has been raging for at least twenty years & I hope you will have some enlightenment after going through this issue.

Enjoy the days of beautiful sunshine & blooming gardens!

Happy Reading,

Abha Sharma
Secretary AOGD (2017-18)

Monthly Clinical Meet

Monthly Clinical Meet will be held at Lady Hardinge Medical College, New Delhi on **Friday, 23rd February, 2018** from 4:00-5:00pm.

From the Editorial Board

Respected Seniors and dear Friends,

Heartiest congratulations from us at the editorial board to all the winners at FOGSI 2018. After bringing out an issue on "Hormones in Gynecology" we realized it is equally or perhaps more important to take out February issue of AOGD bulletin on the "Endocrine Glands and Hormones in Pregnancy".

Pregnancy is an endocrinal state. The endocrinology of human pregnancy involves endocrine and metabolic changes that result from physiological alterations at the boundary between mother and fetus. It is not only about the placental hormones and the fetus, but the changes occur in all the endocrinal systems of the mother. On one had we have to have adequate steroid hormones to support pregnancy, on the other hand same hormones cause challenging situations for management of maternal conditions like Diabetes, Prolactionomas etc. As new evidence is coming up, the management of certain conditions keep changing like thyroid disorders in pregnancy. While progesterone supplementation remains controversial, preterm labour keeps pushing us to find new choices to tackle the problem. Another issue that has been recently recognized of a lot of importance in obstetrics is about Vit D.

So, we have tried to cover few of these topics trying to clear dilemmas with the recent evidence and recommendations. Use of antenatal steroids for fetal lung maturity had also been covered with latest evidence and recommendations. Hope you all will find something useful for clinical practice.

In the section on "Mind, Body & Soul" we have tried to bring your attention to the science of Mantras and basically about Gayatri Mantra. These ancient practices are very useful in the present day stressful life.

In the end, do attempt the quiz. We really appreciate Dr Anita Rajhoria who had been very consistent in answering all the quizzes we published and had always been the first to send answers. Congratulations.

Hope you all enjoy reading this bulletin. All feedbacks are welcome.

The Editorial Team
AOGD (2017-18)

Insulin Therapy in Pregnancy

Sruthi Bhaskaran
Assistant Professor, Department of Obstetrics & Gynecology, UCMS & GTB Hospital, Delhi

Insulin is often the treatment of choice for women with Gestational Diabetes Mellitus/ Type II DM who are unable to maintain glycaemic control with medical nutrition therapy (MNT) or other pharmacological therapies. The use of insulin to achieve glycemic targets among women with GDM has been shown to reduce fetal and maternal morbidity. Insulin does not cross the placenta due to its large molecular size, except at very high doses. With an excellent fetal safety profile, it is thereby considered to be the first-line therapeutic option.

The type of insulin, timing of administration, and frequency needs to be individualized based on the patient's blood sugar values.

Physiology[1]

The physiological insulin requirement has two parts: **the prandial requirement** and **the basal requirement**.

The basal requirement of insulin means the insulin level needs to adequately regulate the endogenous glucose production by the liver. In the fasting state glucose levels are maintained by endogenous glucose production through glycogenolysis and gluconeogenesis in the liver, which prevents hypoglycemia.

In diabetes any insulin regimen used should aim at adequately providing insulin to handle exogenous glucose loads (meals) and adequately managing endogenous glucose production, especially during the night.

However, insulin resistance also determines insulin requirement and there is a transient physiological rise in insulin resistance at the end of the night between 4 and 6 am. This rise is attributed to increasing levels of cortisol and growth hormone.

These considerations are important when designing the individual insulin therapy and help to choose between different insulin administration methods. Also, insulin resistance (and thus insulin requirement) increases after the 20th week of gestation and, in some individuals, insulin requirement is lower during the first weeks of pregnancy, leading to hypoglycaemia when insulin dose is not adjusted.

Types of Insulin

Regular human insulin (RHI) and neutral protamines Hagedorn (NPH) were considered standard insulins for treatment of diabetes in pregnancy. Regular insulin is prepared by adding zinc atoms to dimers. On subcutaneous injection of RHI, it self-associates to form hexamers, which further disassociates into the monomeric form for its absorption through the capillary wall and this is responsible for delayed absorption leading to a slower onset of action compared to endogenous insulin, resulting in increased risk of post-meal hyperglycemia. The same slow diffusion into circulation leads to delayed peak action as well as a longer duration of action compared to endogenous insulin.

Therefore, at times, the preprandial administration of RHI is unable to control the peak postprandial plasma glucose and at the same time delayed peak action and a longer duration of action may result in preprandial hypoglycemia.

NPH has duration of action about 16–18 h and is unable to provide once-daily basal insulin. Night-time administration of NPH results in an unphysiologic rise in insulin concentration in the early-morning hours and risk of hypoglycaemia. Prior to injection, the intermediate human insulin needs to be re-suspended adequately otherwise it may lead to inaccurate dosing and risk of hyper- and hypoglycaemia.[2]

Insulin analogues were designed to overcome these shortcomings and mimic insulin physiology more closely.

The current commercially available preparations of insulin can be either -

Human-derived insulin or recombinant engineered insulin analogues.

Classification of insulin has generally been made by the duration of action into: rapid acting insulin analogues (lispro, aspart, and glulisine), short-acting (regular insulin), intermediate-acting (neutral protamine Hagedorn, NPH) and long-acting analogues (detemir and glargine).

Short-acting insulin (e.g. Humulin, Novolin): should be injected 15 to 30 minutes before a meal, to cover the rise in blood glucose levels that occurs after eating. This insulin has a peak action of two to six hours, and can last for up to eight hours.

Rapid-acting insulin analogues (e.g. Aspart, Lispro): genetically engineered analogues of human insulin, which work like insulin that is normally produced with a meal. Onset of action is approximately 15 minutes, peaking at one hour, and lasting three to four hours. They can be injected shortly before, during, or immediately after meals.

Long-acting insulin analogues (e.g. Detemir, Glargine): genetically modified analogues, with an onset of action

at one to three hours; they plateau and last for 20 to 24 hours. Generally used once- or twice-daily to produce a constant flow of insulin, they are physiologically similar to normal endogenous basal insulin secretion.

Intermediate-acting (medium-acting) insulins (e.g. isophane or neutral protamine Hagedorn (NPH)): these have an onset of action of two to four hours, peak at six to seven hours, and last 20 hours. Isophane insulin is ideal for twice-daily insulin regimens, and can be mixed with soluble insulin.

Mixed insulin (Biphasic insulin): a combination of medium-acting and rapid-acting or short-acting insulin

Mixed analogue: a combination of medium-acting insulin and rapid-acting analogue.

Table 1: Insulin types[2]

Insulin	Onset of action (min)	Time to peak concentration (min)	Duration of action (h)
Short/rapid acting			
Regular insulin	30–60	90–180	8–12
Insulin lispro	10–15	30–90	3-4
Insulin aspart	10–15	30–70	2–4
Insulin glulisine	10–15	30-90	3–5
Long acting			
NPH	60–120	240–480	12–18
Insulin glargine	60–120	None	Up to 24
Insulin detemir	60–120	None	Up to 24

Regular insulin, NPH, lispro, aspart and detemir are considered safe to be used in pregnancy.

For short-acting insulin, Insulin lispro and insulin aspart should be used preferentially over regular insulin because both have a more rapid onset of action, enabling the patient to administer her insulin right at the time of a meal rather than 10–15 minutes before an anticipated meal. This provides better glycemic control and helps avoid hypoglycemic episodes from errors in timing**. (ACOG 2018, RCOG 2015)**[3,4]

Cochrane 2017 concluded that there was no evidence of any clear benefit of one insulin type or regimen over the other in pregnant women with pre-existing type 1 or type 2 diabetes, and that large, randomised trials of better methodological quality are required.[5]

When to start?

Insulin should be started in cases refractory to nutrition therapy and exercise (after 1- 2 weeks**). It is added to nutrition therapy if consistently FBG≥ 95 mg/dL 1-hour levels consistently ≥140 mg/dL, or if 2-hour levels consistently≥ 120 mg/dL.**[3]

RCOG recommends Metformin for women with GDM if blood glucose targets are not met using changes in diet and exercise within 1–2 weeks.

Insulin should be offered if metformin is contraindicated or unacceptable to the woman or insulin can be added to diet, exercise and metformin if blood glucose targets are not met.[4]

Immediate treatment with insulin, with or without metformin, as well as changes in diet and exercise should be offered for FBG ≥ 126 mg/dl or with fasting plasma glucose level of between 108-124 mg/dl with complications such as macrosomia or hydramnios.[4]

Govt of India Guidelines- Insulin is the treatment of choice if Post prandial blood glucose >120 mg/dl after 2 weeks of MNT.[6]

What Regimen?

In women with diabetes, insulin requirements gradually increase throughout pregnancy:[7]

First trimester- 0.7 units/kg/day

From week 18- 0.8 units/kg/day

From week 26- 0.9 units/kg/day

From week 36 until delivery- 1.0 units/kg/day

Various regimens for insulin administration are available and needs to be individualised. The commonly used regimens are

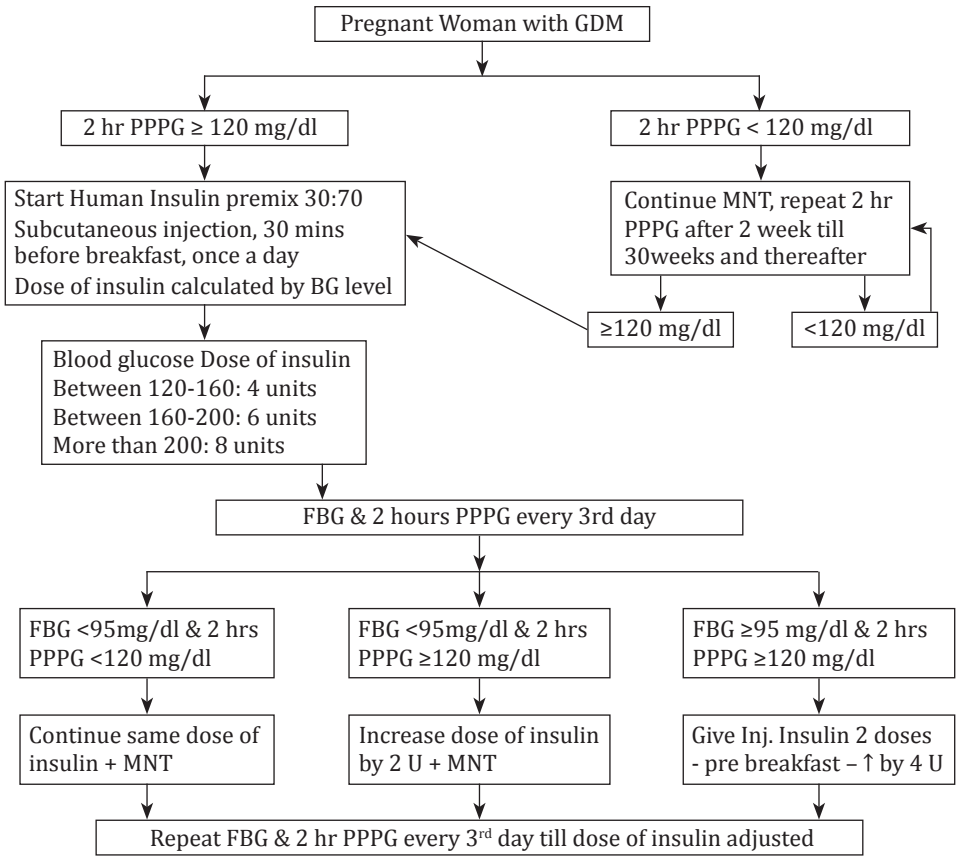
- B**asal-bolus regimen** - a long-acting or intermediate-acting dose and then separate injections of shorter rapid-acting insulin at each meal. This regimen is more common in those with type 1 diabetes. An advantage of this regimen is that it offers flexibility over timing of meals and variations based on different carbohydrate quantities in meals;
- **Twice daily dosing** with premixed human insulin or insulin analogues- Two-thirds of the total daily dose is to be given in the morning in a ratio of 2:1 NPH to regular human insulin (RHI). Remaining one-third is given in the evening in a ratio of 1:1 NPH to RHI.
- **Continuous subcutaneous infusion** which involves delivery of a consistent amount of rapid-acting insulin via an insulin pump. At meal times a bolus of insulin can be delivered to maintain glycaemic control.

According to **ACOG (2018)**[3]

- When fasting and postprandial hyperglycemia are present after most meals- starting total **dosage is 0.7–1.0 units/kg daily should be used** in multiple daily doses.
- This dosage should be divided in multiple injections using long-acting or intermediate acting insulin in combination with short-acting insulin.
- If only isolated abnormal values at a specific time of day- insulin regimen to correct the specific hyperglycemia is preferred.

According to National guideline for management of GDM Only Injection human premix insulin 30/70 to be used subcutaneously. (Fig-1)

Figure 1: **Insulin therapy**[6]



How to monitor

RCOG recommends women with type 2 diabetes or gestational diabetes on a multiple daily insulin injection regimen to test their fasting, pre-meal, 1-hour post-meal and bedtime blood glucose levels **daily** during pregnancy.[4]

However **ACOG** recommends daily glucose monitoring four times a day, once after fasting and again1 hour or 2 hours after each meal.[3]

- Long acting insulin at night controls the fasting glucose levels.

However when FBG is too high-

1) it can be as a consequence of too low dose of insulin
2) or it can be the consequence of nocturnal hypoglycaemia due to too high a dose leading to acute adrenergic response in combination with a surge in glucagon, cortisol and growth hormone causing a rapid rise in blood glucose values, leading to hyperglycaemia **(the Somogyi phenomenon)- Insulin dose needs to be decreased**
3) **Dawns phenomenon**- The autonomous rise in plasma glucose caused by a rise in cortisol and growth hormone levels between 4 and 6 am leads to rise in blood glucose levels which needs increase in insulin dosage.

Target Blood glucose

Fasting glucose ≤ 95 mg/dl

1 hour after meals ≤ 140 mg/dl

2 hours after meals ≤ 120 mg/dl

plasma glucose level should be maintained above 72 mg/dl

During labour[6]

- Morning dose of insulin is withheld the day of induction of labor and 2 hourly plasma glucose monitoring should be done (1 hourly- RCOG)4
- Target for glucose control during labor and delivery- 72–126 mg/dL
- Intravenous dextrose and insulin infusion should be considered for women with type 1 diabetes from the onset of established labour
- Use intravenous dextrose and insulin infusion during labour and birth for women with diabetes whose capillary plasma glucose is not maintained between 72–126 mg/dL
- IV infusion with normal saline (NS) to be started & regular insulin to be added according to blood glucose levels as per the Table-2

Table 2[6]: Insulin Therapy During Labour

Blood glucose (mg/dl)	Amount of insulin added in 500 ml NS	Rate of NS infusion
90-120	0	100ml/hr(16dps/min)
120-140	4U	100ml/hr(16dps/min)
140-180	6U	100ml/hr(16dps/min)
>180	8U	100ml/hr(16dps/min)

During Postpartum Period

After delivery, insulin requirement falls sharply and the insulin dose should be decreased to 25–40% of the pre-delivery dose to prevent hypoglycaemia. This is the more important in women after a caesarean section who do not eat or are not allowed to eat for hours to days. Breast-feeding which should be stimulated as much as possible, leads to even lower insulin requirements and insulin dose should be decreased further if necessary to prevent hypoglycaemia. Hypoglycaemia unawareness may occur in this setting. The period of acceptable lesser control may extend for a number of months. Insulin analogues can be safely used in lactation.

Side effects:

Hypoglycemia:

- Hypoglycemia is diagnosed when blood glucose level is < 70 mg/dl
- Especially frequent during the first trimester
- ***Early symptoms*** - 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 - Confusion, abnormal behaviour or both, visual disturbances, nervousness or anxiety, abnormal behaviour.

Uncommon - Seizures and loss of consciousness

Treatment

- If 50-80 mg/dL may give po- 20 gm of simple carbohydrate (60 calories)
- if <50 mg/dL or unable to tolerate orally - ½ amp 50% dextrose IV or IM glucagon 1 mg s/c or I/M
- Repeat FSBG in 15 minutes

References

1. H.W. de Valk, G.H.A. Visser / Best Practice & Research Clinical Obstetrics and Gynaecology 25 (2011) 65–76
2. Lambert K, Holt RI. The use of insulin analogues in pregnancy. Diabetes Obes Metab. 2013;15(10):888–900.
3. Gestational diabetes mellitus. ACOG Practice Bulletin No. 190. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;131:e49–64.
4. Diabetes in pregnancy: management from preconception to the postnatal period. NICE guideline. 25 February 2015 nice.org.uk/guidance/ng3
5. Insulin for the treatment of women with gestational diabetes (Review) Copyright © 2017 The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.
6. National Guidelines for Diagnosis & Management of Gestational Diabetes Mellitus. December 2014. Maternal Health Division Ministry of Health & Family Welfare Government of India.
7. Seshiah V, Balaji V. Insulin therapy during pregnancy. J Assoc Phys India. 2007;55(Suppl):

Winner of Quiz - January Issue

Dr Anita Rajorhia

Answer Key to Quiz in January Issue

1: a. T, **b.** F, **c.** T, **d.** T
2: a. GnRH anlogues and Ullipristal acetate, **b.** 25 mg OD for 3-6 months **c.** non-enhancement with contrast, more than 5 fibroids and size >10cm, inaccessible and calcified fibroids **d.** Adhesion, accrete, hemorrhage e. (ESHRE study into the evaluation of oocyte euploidy by microarray analysis) **e.** ESHRE study into the evaluation of oocyte euploidy by microarray analysis f. 38% AND 7-18%
3. Metaphase comparative genomic hybridization; array comparative genomic hybridization (aCGH); genome wide single nucleotide polymorphism analysis; PCR-based detection and next generation sequencing (NGS)
4. b **5.** b

Hypothyroidism in Pregnancy: What's new?

Himsweta Srivastava
Assistant Professor, Department of Obstetrics and Gynecology, UCMS & GTB Hospital, Delhi

Introduction

Thyroid dysfunction is the commonest endocrine disorder in pregnancy apart from diabetes. Thyroid hormones are essential for fetal brain development in the embryonic phase. Maternal thyroid dysfunction during pregnancy may have significant adverse maternal and fetal outcomes such as preterm delivery, preeclampsia, miscarriage and low birth weight

For these reasons thyroid function is frequently assessed during the gestation period. However, accurate assessment of maternal (and fetal) thyroid function during pregnancy remains difficult, and interpretation of laboratory testing differs from the nonpregnant patient. Placental human chorionic gonadotropin (hCG) stimulates thyroid hormone secretion, often decreasing maternal thyrotropin (TSH) concentrations, especially in early pregnancy. But while such transiently suppressed maternal TSH concentrations are often observed and deemed safe, defining the upper reference limit for serum TSH in this population has remained controversial.

Physiological Changes in Thyroid Function during Pregnancy

Normal pregnancy is associated with an increase in renal iodine excretion, an increase in thyroxine binding proteins, an increase in thyroid hormone production, and thyroid stimulatory effects of hCG. All of these factors influence thyroid function tests in the pregnant patient. The healthy thyroid adapts to these alterations through changes in thyroid hormone metabolism, iodine uptake, and the regulation of the hypothalamic-pituitary-thyroid axis.

A downward shift of the TSH reference range occurs during pregnancy, with a reduction in both the lower (decreased by about 0.1–0.2 mU/L) and the upper limit of maternal TSH (decreased by about 0.5–1.0 mU/L), relative to the typical nonpregnant TSH reference range. The largest decrease in serum TSH is observed during the first trimester because of elevated levels of serum hCG directly stimulating the TSH receptor and thereby increasing thyroid hormone production. Thereafter, serum TSH and its reference range gradually rise in the second and third trimesters, but nonetheless remain lower than in nonpregnant women. This downward shift varies greatly among different racial and ethnic groups. Initially, studies on pregnant women led to the earlier recommendation for a TSH upper reference limit of 2.5mU/L in the first trimester, then 3.0 mU/L in 2nd and 3rd trimester. However, recent studies (involving women from Asia, India, Netherlands) found only a modest reduction in upper reference limits. Hence, the upper reference limit has been set at 4.0mU/L in early pregnancy as per American Thyroid Association Guidelines 2017. The recommendation is ***"When possible, population –based, trimester- specific reference ranges for serum TSH should be defined through assessment of local population data representative of a healthcare provider's practice***" If the local upper reference limit is not available then **4.0mU/L** to be taken.[1,2]

Universal Screening

There is still no clear guidelines regarding advocacy of universal screening of thyroid status in all women before or during pregnancy. Considerations of cost, effectiveness and proper interpretation of the test results are a major deterrent to advocating a universal screening test.

To date, studies evaluating this question appear to demonstrate mixed conclusions. However, some physician groups recommend checking a woman's TSH value either before becoming pregnant (pre-pregnancy counseling) or as soon as pregnancy is confirmed. This is especially true in women at high risk for thyroid disease, such as those with prior treatment for hyperthyroidism, a positive family history of thyroid disease and those with a goiter. Clearly, woman with established hypothyroidism should have a TSH test once pregnancy is confirmed, as thyroid hormone requirements increase during pregnancy, often leading to the need to increase the levothyroxine dose. If the TSH is normal, no further monitoring is typically required.

Therefore, testing for serum TSH in following high risk women is recommended –

- A history of hypothyroidism/hyperthyroidism or current symptoms/signs of thyroid dysfunction
- Known thyroid antibody positivity or presence of a goiter
- History of head or neck radiation or prior thyroid surgery
- Age >30 years
- Type 1 diabetes or other autoimmune disorders
- History of pregnancy loss, pretermdelivery, or infertility
- Multiple prior pregnancies (‡2)
- Family history of autoimmune thyroid disease or thyroid dysfunction
- Morbid obesity (BMI ‡40 kg/m2)
- Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
- Residing in an area of known moderate to severe iodine insufficiency

Hypothyroidism in Pregnancy

Primary overt maternal hypothyroidism is generally defined as the presence of an elevated TSH and a decreased serum FT4 concentration during gestation, with both concentrations outside the (trimester-specific) reference ranges. Thyroid autoantibodies can be detected in approximately 30%–60% of pregnant women with an elevated TSH concentration. Increasingly, there appears to be a greater risk for adverse events in women who are TPOAb positive compared to those who are TPOAb negative, even when thyroid function is identical. The reasons for this difference remain unclear.

Adverse Outcomes

Overt maternal hypothyroidism has consistently been shown to be associated with an increased risk of adverse pregnancy complications as well as detrimental effects upon fetal neurocognitive development. These include preterm birth, low birth weight (mostly related to preterm delivery), perinatal death, pregnancy induced hypertension, pre-eclampsia, placental abruption, anaemia and postpartum haemorrhage. Hypothyroidism has also been associated with adverse effects on intelligence quotient (IQ) and neuropsychological development.[3] Fetal loss and gestational hypertension was estimated to be 60% and 22% in studies by Abalovich[4] and Leung[5] respectively, in pregnant women with overt hypothyroidism.

Treatment

Treatment with oral levothyroxine is recommended worldwide. The goal is to target a TSH in the lower half of the trimester-specific reference range. When this is not available, it is reasonable to target maternal TSH concentrations below 2.5 mU/L.

Dose Adjustments in Prenatal Hypothyroid women already on levothyroxine: It is recommended that the levothyroxine adjustment should be made as soon as possible after pregnancy is confirmed to reduce the probability of hypothyroidism. Normalization of TSH concentrations throughout gestation is the goal. For women receiving levothyroxine preconception, a prospective, randomized study has provided evidence that supports a single dose-adjustment strategy. A recommendation to increase by two additional tablets weekly (nine tablets per week instead of seven tablets per week, giving a 29% increase) can effectively mimic gestational physiology and thus prevent maternal hypothyroidism during the first trimester[6]. Another option is to increase the dosage of daily LT4 by approximately 25%–30%.

Subclinical Hypothyroidism: When to treat

Subclinical hypothyroidism is defined as an elevated TSH level (TSH 2.5–10.0 mU/L) with normal levels of free thyroxine. It can affect 0.25–2.5% of all pregnancies

Adverse outcomes associated with subclinical hypothyroidism are broadly classified into three categories –

i) Pregnancy Loss

ii) Adverse perinatal outcomes (Premature delivery, Hypertensive disorders)

iii) Adverse neurocognitive outcomes in offspring

A benefit of treatment, especially as it applies to reducing pregnancy loss in TPOAb-positive women is seen in several studies. Therefore, it seems reasonable to recommend or consider levothyroxine treatment for specific subgroups of pregnant women with subclinical hypothyroidism.[7,8]

Role of Thyroperoxidase Antibody (TPOAb) testing

Several studies have reported a significantly higher pregnancy loss rate in TPOAb-negative women with TSH concentrations between 2.5 and 5.0 mU/L compared to those with TSH concentrations below 2.5 mU/L. Also subclinical hypothyroidism increases the risk of pregnancy complications in TPOAb-positive women. In women classified as low risk for hypothyroidism, treatment of TPOAb-positive women with TSH >2.5 mU/L resulted in a significant reduction of pregnancy complications compared to no treatment. Hence the recommendation is to evaluate TPO antibody status in women with TSH concentration above 2.5mU/L and treatment to be started as per the guidelines given below.

Management Guidelines

Subclinical hypothyroidism in pregnancy should be approached as follows:

As per **American Thyroid Association Guidelines, 2017**

(a) LT4 therapy is recommended for

- TPOAb-positive women with a TSH greater than the pregnancy-specific reference range.
  (Strong recommendation, moderate-quality evidence)
- TPOAb-negative women with a TSH greater than 10.0 mU/L. (Strong recommendation, low-quality evidence).

(b) LT4 therapy may be considered for

- TPOAb-positive women with TSH concentrations >2.5 mU/L and below the upper limit of the pregnancy-specific reference range. Weak recommendation, moderate-quality evidence.
- TPOAb-negative women and TPOAb-negative women with TSH concentrations greater than the pregnancy specific reference range and below 10.0 mU/L.. Weak recommendation, low-quality evidence.

(c) LT4 therapy is not recommended for

- TPOAb-negative women with a normal TSH (TSH within the pregnancy-specific reference range or <4.0 mU/L if unavailable). Strong recommendation, high-quality evidence.

Conclusion

In conclusion, maternal hypothyroidism is a disorder with great potential to adversely affect maternal and fetal outcomes and is also associated with multiple other conditions which can affect maternal and fetal health. If the condition is detected early, it is easy to treat, with very little detriment to the mother and the fetus. Hence, this condition needs early detection, prompt initiation of treatment, adequate follow-up and most importantly, sufficient education of the doctors and the patients regarding these objectives, the importance of this condition and the ease and advantages of prompt management.

Treatment of subclinical hypothyroidism is associated with a lower risk of pregnancy loss, especially in women with TSH concentrations of 4.1 to 10 mU/L prior to treatment. And pregnant women with TSH concentrations >2.5 mU/L should be evaluated for TPOAb status. Decisions for levothyroxine treatment should be based upon both serum TSH measurements and TPOAb status.

References

1. Erik K. Alexander, Elizabeth N. Pearce et.al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid.2017; Volume 27, Number 3.
2. Medici M, Korevaar TI, Visser WE, Visser TJ, Peeters RP. Thyroid function in pregnancy: what is normal? Clin Chem. 2015; 61:704–713.
3. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. J Clin Endocrinol Metab.2010; 95:E44–E48.
4. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid. 2002; 12:63–68.
5. Leung AS, Millar LK, Koonings PP, Montoro M, Mestman JH. Perinatal outcome in hypothyroid pregnancies. Obstet Gynecol.1993; 81:349–353.
6. Yassa L, Marqusee E, Fawcett R, Alexander EK . Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. J Clin Endocrinol Metab.2010; 95:3234–3241.
7. Wang S, Teng WP, LiIX, Wang WW, Shan ZY. Effects of maternal subclinical hypothyroidism on obstetrical outcomes during early pregnancy. J Endocrinol Invest 2012; 35:322-5
8. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. J Clin Endocrinol Metab 2010; 95:1699-707.

Prolactinomas in Pregnancy

Anju Bala[1], Rashmi[2]

[1]Senior Resident, [2]Assistant Professor, Department of Obstetrics & Gynaecology, UCMS & GTB Hospital, Delhi

Prolactinomas are pituitary adenomas that express and secrete prolactin (PRL) to variable degrees, are almost invariably benign, but are nevertheless frequently clinically significant and may be challenging to manage. They are most common pituitary tumor constituting ~40% of all pituitary adenomas. The diagnosis of prolactinoma requires both radiographic evidence of pituitary adenoma and laboratory analyses documenting the presence of sustained hyperprolactinaemia. In general, serum prolactin levels parallel tumour size. Most patients with PRL levels over 150µg/l (~3000 mIU/l) (five times higher than the normal values) will have a prolactinoma.[1]

Prolactinomas occur with a prevalence of 60–100 cases per million. It is more common in women, particularly during the reproductive period. The highest incidence rate is found in women between 25 and 34 years of age. 90% of prolactinomas are microadenomas while rest 10% are macroadenomas (≥10 mm). Incidence in pregnancy has not been reported in literature.

Approximately 90% of premenopausal women with prolactinoma present with oligo/amenorrhoea, and up to 80% also exhibit galactorrhoea and may also manifest anovulatory infertility.[1] Neurological manifestations are common in patients with macroadenomas or giant adenomas, because they are space-occupying lesions and with possible compression of the optic chiasm. Neurological symptoms include headaches, visual impairment ranging from quadrantanopia to classical bitemporal hemianopia or scotomas. Blindness due to an expanding prolactinoma is an exceptional event, but may occur in the setting of pituitary apoplexy.

Prolactinoma and Infertility

Hyperprolactinemia decreases luteinizing hormone (LH) pulse amplitude and frequency through suppression of gonadotropin-releasing hormone (GNRH) and is associated with loss of the positive estrogen feedback on gonadotropin secretion at mid-cycle making most hyperprolactinemic women anovulatory with resultant amenorrhea and infertility.

Management of Prolactinoma

It is very important to understand that the goals of treating prolactinoma before pregnancy and during pregnancy are very different. The aim of treating before pregnancy is to restore ovulatory menses and fertility in most premenopausal women with prolactinoma apart from reduction in size of tumor. Achieving a normalization of PRL levels and a tumor size<10 mm is recommended before conception. In anovulatory women with Prolactinomas, choices to restore fertility include use of dopamine agonists or transsphenoidal selective adenomectomy.

Dopamine Agonists Therapy

For both Micro and Macro prolactionamas, primary treatment is medical therapy with dopamine agonists (DA). Correction of hyperprolactinemia with DAs restores ovulation in over 90% of women with amenorrhea and anovulation. Treatment with dopamine agonist not only reduces the prolactin level but also reduces the size of the tumor. Results of various studies indicate that bromocriptine decreases pituitary tumor size by approximately 50% in two thirds of patients, compared with a 90% decrease with cabergoline. Overall 80% of Prolactinomas treated with dopamine agonist reduce to 25% of their original size.[1] Hence a good duration of treatment with dopamine agonist before pregnancy can cause sufficient shrinkage of tumor and avoid unnecessary problems antepartum.

Role of Surgery

With either dopamine agonists or surgery, successful pregnancy can be achieved in over 85% of patients. Transsphenoidal surgery results in a permanent normalization of PRL levels in only 60% of cases and is associated with some morbidity and mortality. Surgical resection of tumor can cause other anterior pituitary defects including gonadotropin deficiency which can further affect the fertility and does not completely eliminate the risk of tumor enlagement (~ 7%) in pregnancy and need for bromocrptine therapy.[2] 7–50% of surgically resected prolactin-secreting tumors recur. Side effects of surgery include hypopituitarism, diabetes insipidus, cerebrospinal fluid leak, and local infection. Hence, a routine surgical resection is generally not recommended these days.[3] Transsphenoidal surgery may be an option in women with microadenoma or macroadenoma intolerant or refractory to dopamine agonists, and in those with macroadenoma that does not decrease in size with drug treatment.[4]

Radiotherapy

Radiotherapy is rarely used for prolactinomas. Standard radiotherapy achieves a normalization of PRL levels in only 34.1% of patients, and most often after a long latency period with significant side effects (the risk

of hypopituitarism, the occurrence of secondary intracranial neoplasms, cerebral injury, optic nerve damage). Radiotherapy should be used only in patients with big tumors who are not candidates for surgery and who do not respond to dopamine agonists or cannot be treated with them, and in patients with aggressive prolactinoma or carcinoma.

Which Dopamine Agonist to Choose?

Various dopamine agonists which can be given for treatment of prolactinomas are Bromocriptine, Cabergoline and Quinagolide. Quinagolide does not appear to be safe for the fetus, so it is not used when fertility is desired. ***Cabergoline*** has higher efficacy in normalizing prolactin levels, as well as a higher frequency of pituitary tumor shrinkage. Because the incidence of unpleasant side effects is lower with cabergoline, drug compliance is superior for this medication. Though cabergoline is considered as first-line treatment for patients with prolactinoma because of its greater efficacy (both in terms of normalization of PRL levels and tumor size decrease and better tolerability),[3] approximately 10% are resistant to that drug. On the other hand, approximately 25% are resistant to bromocriptine and 80% of these patients may achieve prolactin normalization on cabergoline. Therefore, Cabergoline is the preferred drug in prolactinomas. But due to large safety data of bromocriptine on use during pregnancy, it is recommended that in planning before pregnancy, cabergoline should be discontinued and bromocriptine should be introduced, although this also crosses the placental barrier.

Bromocriptine: It is a D2 selective dopamine agonist and D1 antagonist. Bromocriptine is the drug of choice in pregnancy because of the greater cumulative experience with it, but it is less well tolerated than cabergoline. Side effects such as nausea, vomiting, postural arterial hypertension, and headache are very common, increase with high doses, and often limit treatment compliance.

Whichever Dopamine agonist is used for infertility, it is generally recommended to stop the drug as soon as pregnancy is confirmed as both the drugs are transmitted through placenta.

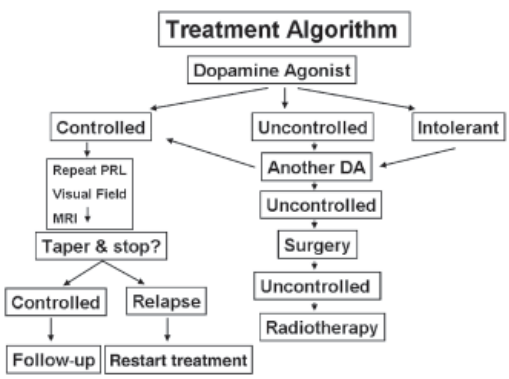


Figure 1: Management of Prolactinomas

Management of Prolactinomas during Pregnancy

When patients with prolactinomas become pregnant, clinicians are confronted with two major issues:

1) Possible growth of the Prolactinoma during pregnancy due to high circulating levels of estrogen,
2) Use of Dopamine agonist during pregnancy and their impact on the fetus.

Effect of Pregnancy on Prolactinoma

The increasing amount of estrogen produced by the placenta stimulates lactotroph hyperplasia and a gradual increase in PRL levels over the course of pregnancy. Prolactinomas can enlarge during pregnancy as a result of both the stimulatory effect of these high estrogen levels and the discontinuation of the dopamine agonist that might have caused tumor shrinkage. The pituitary gland increases in volume more than 2-fold during pregnancy. Size of the prolactinoma before pregnancy is an important factor that will help predict the potential problems during pregnancy.[5]

Prolactin Levels in Pregnancy

During pregnancy, serum prolactin levels increase 10-fold reaching levels of 150 to 300 µg/liter by term. When dopamine agonists are discontinued at the start of pregnancy, serum prolactin levels increase, and subsequent increases in prolactin levels do not accurately reflect changes in tumor growth or activity. Moreover, serum prolactin levels may not increase during pregnancy in all patients with tumour enlargement. In contrast, the lack of a rise in PRL may be falsely reassuring in a patient with headaches or other evidence of tumor enlargement. Periodic checking of PRL levels, therefore, is of no diagnostic benefit and can be misleading. It is therefore, ***not recommended to measure prolactin level during pregnancy.***

Management of Microprolactinoma during pregnancy

Microprolactinoma generally do not pose a threat during pregnancy. In a review of studies that included 457 pregnant women harboring microadenomas, 2.6% developed symptomatic tumor growth.[6] In studies that examined tumor growth using imaging techniques, the risk of tumor growth was observed to be somewhat higher (4.5–5%).[6] Because the risk of symptomatic tumor growth is so low, pregnant patients with microadenomas may be followed by clinical examination during each trimester. ***It is recommended to stop dopamine agonist once pregnancy is confirmed***. A close follow up of case of microprolactinoma during pregnancy with ***regular clinical assessment*** for symptoms of tumour expansion

like headache or visual disturbances is generally advised. Measurement of prolactin levels or MRI is not required in case of microprolactinoma.[3]

Management of Macroprolactinoma during Pregnancy

Management of macroprolactinoma is more complicated. The patients who had undergone debulking pituitary surgery or pituitary irradiation before pregnancy, the risk of symptomatic growth is only 2.8%, not substantially different from the microadenoma risk.[7] However, in patients with macroadenoma who did not undergo surgery or irradiation before pregnancy, the risk of symptomatic pituitary tumor enlargement was 31%.[6] Various studies have shown that risk of enlargement correlates with the pre conception tumour size. The potential problems of undertreated macroprolactinomas include visual compromise and pituitary apoplexy. Hence management of macroprolactinoma should begin with good planning before pregnancy.

The patient with a small intrasellar or inferiorly extending macroadenoma can probably be managed as those with microadenomas, i.e., with dopamine agonists. The risk that such a tumor will enlarge sufficiently to cause clinically serious complications is probably only marginally higher than the risk in patients with microadenomas. In such cases dopaminergic therapy is stopped as soon as pregnancy is diagnosed.

In woman with a larger macroadenoma, especially one with suprasellar extension an MRI should be done before pregnancy, if possible, to document any prior tumor shrinkage and to serve as a baseline for comparison with MRIs done during pregnancy. Pregnancy should be delayed for initial 3- 6 months of dopaminergic therapy so as to achieve tumour reduction before conception. As per Endocrine Society Clinical Practice Guidelines (2011), in patients with macroadenomas who become pregnant on dopaminergic therapy and who have not had prior surgical or radiation therapy or adequate Dopamine agonist therapy causing shrinkage of tumour, it may be prudent to continue dopaminergic therapy throughout the pregnancy, especially if the tumor is invasive or is abutting the optic chiasma.

Bromocriptine therapy is recommended in patients who experience symptomatic growth of a prolactinoma during pregnancy. In patients who cannot tolerate bromocriptine, cabergoline may be administered. If reinitiation of dopamine agonist therapy does not decrease tumor size and lead to improved symptoms, surgical resection may be indicated. If the fetus is near term, it may be reasonable to induce delivery before neurosurgical intervention is undertaken.[3]

For patients who have macroadenomas it is important to undertake more frequent clinical examinations and formal visual field testing. They should also be questioned for any new onset of headache or visual disturbances. Any such headache in patients with Prolactinoma during pregnancy must be taken seriously. Any evidence of visual field defects on perimetry, and/ or headache of mandates a MRI of the sella (without Gadolinium contrast).[3]

Postpartum

Management of prolactinoma postpartum depends on whether patient wants to continue breastfeeding. If patient is not going to breast feed the baby, the dopamine agonist may be restarted. If patient plans to breast feed, the dopamine agonist would interfere with lactation and hence it is not given. Growth of prolactinoma during lactation is not reported and presence of prolactinoma should not be considered as contraindication for lactation.[20] However, just like during pregnancy, prolactin levels may fluctuate postpartum and hence it is not recommended to monitor patient with prolactin level. Rather clinical and visual field assessment must be done during the postpartum period.

In some patients, postpartum PRL levels and tumor sizes are actually reduced as compared with values before pregnancy , but this has not been observed in all series. In a study, amongst the patients who were found harbouring the tumor antepartum, 27 % had complete resolution or cure of the tumor postpartum.[8] Therefore, many women may be ovulatory postpartum and would not need resumption of a dopamine agonist. It is recommended to measure serum PRL after 2 months of delivery and repeat a MRI Sella with contrast 2 months after stopping lactation.[9]

Effect of Dopamine Agonists on the developing Fetus

Bromocriptine has been shown to cross the placenta in human studies[22]; cabergoline has been shown to do so in animal studies but such data are lacking in humans. To limit the exposure time of the developing fetus to dopamine agonists, it should be stopped as soon as a woman misses her period and pregnancy is confirmed. In this way, the dopamine agonist will have been given for only about 3–4 weeks of the gestation. With such short-term exposure of generally <6 weeks, bromocriptine has not been found to cause any increase in spontaneous abortions, ectopic pregnancies, trophoblastic disease, multiple pregnancies, or congenital malformations. Experience with the use of cabergoline in pregnancy is more limited. Data has not shown an increased percentage of spontaneous abortion, premature delivery, or multiple births.[10,11,12] Long-term follow-up studies (up to 12 years) showed no abnormalities in physical or mental development in 83 children whose mothers received cabergoline to allow ovulation in one series.[13] Bromocriptine clearly has the largest safety

database and has a proven safety record for pregnancy. The database for the use of cabergoline in pregnancy is smaller, but there is no evidence at present indicating that it exerts deleterious effects on the developing fetus. The risk of malformations with either drug is not greater than that what is found in the general population.

Quinagolide does not appear to be safe for the fetus if used when pregnancy is desired as seen to be associated with abortions.

Conclusions

Treatment with dopamine agonists usually restores ovulation and fertility with cabergoline generally being preferred to bromocriptine because of its higher therapeutic efficacy/adverse effects ratio. But considering the large data regarding safety to the fetus, bromocriptine is recommended for infertility management and during pregnancy if required. Experience with both drugs shows no increase in spontaneous abortions, preterm deliveries, multiple births, or congenital malformations, compared with what is expected in the normal population. Dopamine agonist therapy is usually stopped as soon as pregnancy is confirmed except in situations where tumour is very large or close to optic chiasm. During pregnancy close follow up and visual field examination is recommended to detect any significant growth. If visual field defects or progressive headaches develop, an MRI should be done. Reinstitution of a dopamine agonist is usually successful in causing shrinkage should symptomatic tumor growth occur. Alternatively, if the pregnancy is sufficiently advanced, delivery is an option. Surgical debulking is rarely necessary.

A number of questions remain about women with prolactinomas who wish to become pregnant. About 18% of patients are resistant to cabergoline and require larger than conventional doses to achieve normal PRL levels and to ovulate. Additional safety information is needed when cabergoline is given in larger than conventional doses for both short- and long-term. A large macroadenoma that has been greatly reduced in size by dopamine agonists represents a particular safety issue if the dopamine agonist is stopped abruptly at the same time as estrogen levels are increasing. Additional safety information is needed for doing MRIs and for administering gadolinium during pregnancy.

References

1. Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, Brue T, Cappabianca P, Colao A, Fahlbusch R, Fideleff H. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clinical Endocrinology. 2006 Aug 1;65(2):265-73.
2. Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. Endocr Rev2006 Aug; 27(5): 485-534.
3. Melmed S, Casanueva FF, Hoffman AR, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab2011 Feb; 96(2):273-88.
4. Molitch M. Prolactinomas and pregnancy. Clin Endocrinol (Oxf). 2010;73:147-8.
5. Molitch ME. Endocrinology in pregnancy: management of the pregnant patient with a prolactinoma. European Journal of Endocrinology. 2015; 172(5):R205-13.
6. Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. Endocr Rev. 2006;27: 485–534
7. Molitch ME. Pituitary disorders during pregnancy. Endocrinol Metab Clin North Am. 2006; 35:99–116, vi
8. Bronstein MD. Disorders of Prolactin secreation and Prolactinomas. In: Jameson JL, Groot LD, editors. Endocrinology Adult and Pediatric: Saunders Elsevier; 2010. p. 333-58.
9. Karaca Z, Tanriverdi F, Unluhizarci K, Kelestimur F. Pregnancy and pituitary disorders. Eur J Endocrinol 2010; 162(3): 453-75.
10. Molitch ME. Prolactinoma in pregnancy. Best Practice & Research. Clinical Endocrinology & Metabolism 2011 25 885–896.
11. Auriemma RS, Perone Y, Di Sarno A, Grasso LF, Guerra E, Gasperi M, Pivonello R & Colao A. Results of a single-center 10-year observational survey study on recurrence of hyperprolactinemia after pregnancy and lactation. Journal of Clinical Endocrinology and Metabolism 2013 98 372–379.
12. Domingue M-E, Devuyst F, Alexopoulou O, Corvilain B & Maiter D. Outcome of prolactinoma after pregnancy and lactation: a study on 73 patients. Clinical Endocrinology 2014 80 642–648.
13. Ono M, Miki N, Amano K, Kawamata T, Seki T, Makino R, Takano K, Izumi S, Okada Y & Hori T. High-dose cabergoline therapy for hyperprolactinemic infertility in women with micro- and macroprolactinomas. Journal of Clinical Endocrinology and Metabolism 2010 95 2672–2679.

Calendar of Monthly Clinical Meetings 2017-2018

Months	Name of the Institute
23rd February 2018	Lady Hardinge Medical College
March 2018	UCMS & GTB Hospital
April 2018	Apollo Hospital, Sarita Vihar
May 2018	DDU Hospital

Vitamin D Supplementation during Pregnancy: An update

Bindiya Gupta
Assistant Professor, Obstetrics & Gynecology, UCMS & GTB Hospital, Delhi

Introduction

The prevalence of low vitamin D status has been reported to be high amongst women with rates varying significantly worldwide between 1–96% depending on their ethnic background.[1] In 2010, dietary reference intakes for vitamin D from the Institute of Medicine (IOM) were based solely on bone health— particularly in young children (for instance, rickets) and older adults (for instance, osteoporosis).[2] The IOM recommended 400 IU/d (10 μg) for infants, 600 IU/d (15 μg) for children, adolescents and adults, and 800 IU/d (20 μg) for adults aged over 70 years to maintain a desirable 25(OH)D concentration.[2] The minimal 25 (OH) D concentration of 20 ng/mL (50 nmol/L) was considered to be physiologically adequate. However, the institute's report did not recommend higher intake during pregnancy and lactation.

Evidence states that vitamin D deficiency in pregnancy is common in high risk groups including vegetarians, women with limited sun exposure (living in cold climates, northern latitudes, wearing winter protective clothing) and ethnic minorities, especially those with darker skin.[3] Neonatal vitamin D reflect maternal vitamin D status.[3] Over the last decade, studies associating vitamin D insufficiency in pregnancy with a wide range of adverse maternal, fetal and neonatal health outcomes have been accumulating in the epidemiological literature, with a number of systematic reviews and metaanalyses also attempting to summarize the available evidence. This article will summarize the latest reviews and guidelines on role of Vitamin D supplementation in pregnancy.

Vitamin D Metabolism in Pregnancy

Vitamin D3, or cholecalciferol, is formed in the skin upon exposure to ultra- violet light or is acquired through dietary supplementation. Once in the circulation, vitamin D is then converted into 25-hydroxyvitamin D [25 (OH)D], primarily in the liver and 25(OH)D is finally converted into the hormonal form of the vitamin—1,25-dihydroxyvitamin D3 [1,25(OH)2D]—in the kidney for endocrine function and other tissues for autocrine/ paracrine function. [4] By 12 weeks of gestation, 1,25(OH)2D serum concentrations are more than twice that of a non-pregnant adult and continue to rise two- to threefold from the non-pregnant baseline rising to over 700 pmol/ L.

Vitamin D besides an important regulator of calcium homeostasis, is also an important immune modulator and has an anti inflammatory role.[5] In many disease states, low circulating 25(OH)D are associated with multiple inflammatory diseases, such as cardiovascular, arthritis, multiple sclerosis, cancer, childhood asthma and sepsis. Early studies involving pregnant women with preeclampsia, placental dysfunction, respiratory maturation; a clinical picture of inflammation and vasculitis, vitamin D deficiency has been implicated.[5] Some studies have also reported that vitamin D supplementation can induce genomic changes during pregnancy by altering the maternal transcription which in turn might influence the fetal gene expression profiles that are related to fetal immune imprinting, neurogenesis and inflammation.[6] Vitamin D also has a role in prevention of infections during pregnancy due to its immunomodulatory action.

Supplementation of Vitamin D during pregnancy: Evidence

Cochrane in 2016 [7]published a meta-analysis of 15 trials assessing a total of 2833 women, out of which nine trials compared the effects of vitamin D alone versus no supplementation or a placebo and six trials compared the effects of vitamin D and calcium with no supplementation. Results showed that supplementing pregnant women with vitamin D in a single or continued dose increases serum 25hydroxyvitamin D at term and may reduce the risk of preeclampsia (RR 0.51; 95% CI 0.32 to 0.80), low birthweight (RR 0.40; 95% CI 0.24 to 0.67) and preterm birth (8.9% versus 15.5%; RR 0.36; 95% CI 0.14 to 0.93). However, when vitamin D and calcium are combined, the risk of preterm birth is increased (RR 1.57; 95% CI 1.02 to 2.43). There were no major adverse effects reported. ***The authors concluded that the evidence on whether vitamin D supplementation should be given as a part of routine antenatal care to all women to improve maternal and infant outcomes remains unclear. While there is some indication that vitamin D supplementation could reduce the risk of preeclampsia and increase length and head circumference at birth, further rigorous randomized trials are required to confirm these effects.***[7]

Amegah A et al (2017)[8] in a systematic review of eighteen longitudinal studies published till June 2015, showed that serum 25(OH)D levels <75 nmol/l was associated with 83% (95% CI: 1.23, 2.74) and 13% (95% CI: 0.94, 1.36) increased risk of preterm birth (PTB) measured at <32–34 weeks and <35–37 weeks, respectively. Serum 25(OH)D levels <75 nmol/l was associated with 11% increased risk of spontaneous PTB (<35–37 weeks; RR = 1.11; 95% CI: 0.75, 1.65) with a doseresponse relation noted. Vitamin D

insufficiency was not associated with risk of spontaneous abortion and stillbirth (RR of 1.04 [95% CI: 0.95, 1.13] and 1.02 [95% CI: 0.96, 1.09], respectively), as well as short gestational length (ES = 0.24, 95% CI: 0.69, 0.22), and low Apgar score. **They concluded that *the overall experimental evidence uncovered was small and weak. Hence, the benefits of vitamin D supplementation during pregnancy should be further evaluated through rigorous intervention studies.*[8]**

Given the numerous trials on prenatal vitamin D published since 2015 and the restricted scope of the 2016 Cochrane review, Roth DE et al in 2018[9] published another updated systematic review of vitamin D in pregnancy to assess the current and future state of the evidence from randomized controlled trials. 43 trials (8406 participants) were eligible for metaanalyses and median sample size was 133 participants. Results showed that Vitamin D increased maternal/cord serum concentration of 25hydroxyvitamin D, but the doseresponse effect was weak. Maternal clinical outcomes were rarely ascertained or reported, but available data did not provide evidence of benefits. Overall, vitamin D increased mean birth weight of 58.33 g (95% confidence interval 18.88 g to 97.78 g; 37 comparisons) and reduced the risk of small for gestational age births (risk ratio 0.60, 95% confidence interval 0.40 to 0.90; seven comparisons), but findings were not robust in sensitivity and subgroup analyses. There was no effect on preterm birth (1.0, 0.77 to 1.30; 15 comparisons). There was strong evidence that prenatal vitamin D reduced the risk of offspring wheeze by age 3 years (0.81, 0.67 to 0.98; two comparisons). ***They concluded, that the evidence to date seems insufficient to guide clinical or policy recommendations.*** Future trials should be designed and powered to examine clinical endpoints, including maternal conditions related to pregnancy (such as pre-eclampsia), infant growth, and respiratory outcomes.[9]

Supplementation of Vitamin D during pregnancy: Recommendations

NICE 2017 guidance*[10] *states that all health care providers have the responsibility to take action and to promote and encourage all women to take vitamin D supplements during pregnancy. NICE recommends that 10 microgram vitamin D should be taken daily by all women throughout pregnancy. The recommended daily intake of vitamin D during pregnancy is considered both safe and cost-effective. Universal screening for vitamin D deficiency in pregnant women is not advised, with replacement rather than standard supplementation of vitamin D being required for confirmed vitamin D deficiency.

Citing the 2016 Cochrane review, ***the World Health Organization guidelines*[11]** for antenatal care advise against routine vitamin D supplementation in pregnancy to improve maternal and fetal outcomes.

***ACOG committee opinion in 2011 (reaffirmed in 2017)*[3]** states that there is insufficient evidence to screen all pregnant women for Vitamin D deficiency. When vitamin D deficiency is identified during pregnancy, 1000-2000 IU/ day of Vitamin D is safe**.** Higher dose regimens for treatment of vitamin D deficiency have not been studied. Routine supplementation during pregnancy beyond that contained in a prenatal vitamin is not recommended and more randomized trials are needed for the same. There is insufficient evidence to recommend vitamin D supplementation for prevention of preterm birth or preeclampsia.

Conclusion

Routine supplementation of Vitamin D in pregnancy to prevent antenatal complications is still unclear. There is no role of universal screening of Vitamin D levels in pregnancy. Thirty-five planned/ongoing randomized controlled trials could contribute 12,530 additional participants to future reviews and recommendations.

References

1. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol 2014; 144:138–45.
2. Ross AC, Taylor CL, Yaktine AL, Del Valle HB. Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. The National Academies Press, 2010.
3. ACOG committee on obstetric practice. ACOG committee opinion NO. 495: Screening and supplementation during pregnancy. Obstet Gynecol 2011;18(1): 197-8.
4. Hollis BW, Wagner CL. The role of the parent compound vitamin D with respect to metabolism and function: why clinical dose intervals can affect clinical outcomes. J Clin Endocrinol Metab 2013;98(12):4619-4628.
5. Hollis BW,Wagner CL. New insights into the vitamin D requirements during pregnancy. Bone Research 2017; 5: 17030
6. Al-Garawi A, Carey VJ, Chhabra D, Mirzakhani H, Morrow J, Lasky-Su J, et al. The role of vitamin D in the transcriptional program of human pregnancy. PLoS One 201611:e0163832.
7. De-Regil LM, Palacios C, Lombardo LK, Peña-Rosas JP. Vitamin D supplementa- tion for women during pregnancy. Cochrane Database Syst Rev 20161:CD008873.
8. Amegah AK, Klevor MK, Wagner CL (2017) Maternal vitamin D insufficiency and risk of adverse pregnancy and birth outcomes: A systematic review and metaanalysis of longitudinal studies. PLoS ONE 12(3): e0173605.
9. Roth DE, Leung M, Mesfin E, etal. Vitamin D supplementation during pregnancy: state of the evidence from a systematic review of randomised trials. BMJ 2017;359:j5237
10. National Institute for Health and Care Excellence. Vitamin D: increasing supplement use in at-risk groups. PH56. 2014. Last updated August 2017.
11. World Health Organization. Recommendations on Antenatal Care for a Positive Pregnancy Experience. WHO, 2016. Available at: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/ancpositive-pregnancyexperience/en/. Accessed 20th January 2018.

AOGD Sub Committee Nomination (2018-20)

Nominations are invited for the post of chairperson of the following sub-committees for the year 2018-20

1. Breast Cancer Awareness Committee
2. Cervical Cancer Awareness and Prevention Committee
3. Infertility Committee
4. Rural Health Committee
5. Multidisciplinary Patient Sub-committee

Eligibility Criteria

1. Person should be a member of AOGD and have at least 10 years standing in the profession with at least 5 years duration of holding senior position in the respective institutions.
2. Chairperson of a subcommittee has to be a member of any subcommittee earlier for at least 1 year.
3. No repeat nomination will be considered after one term of two years.
4. In case of two people applying for the same post, the decision of the executive will be fi nal.
5. In case of any deviation, the decision would be taken by executive committee.
6. Two posts cannot be held by any member at one particular time.

The nominations on plain paper should reach: AOGD Secretariat: Room No. – 712, 7th Floor Seminar Room, Department of Obstetrics and Gynaecology, MCH Block, GTB Hospital, New Delhi by 20th March, 2018 along with the bio-data stating the eligibility

Forthcoming Events

1. Next AOGD Clinical Meeting will be at Medical Education Hall, First Floor, Swarn Jayanti Auditorium Complex, Lady Hardinge Medical College on 23rd February at 4:00pm
2. Training Course in Minimally Invasive Gynaecology organised by Department of Obstetrics & Gynaecology, All India Institute of Medical Sciences will be held from 5th - 10th March, 2018. For further details please contact: Prof. Alka Kriplani, M. 9810828717, Prof. K K Roy, M. 9811317011
3. North Zone Yuva FOGSI will be held from 27th-29th April 2018 at Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun.

Events Held in January 2018

- Antenatal Care and Anemia Awareness Programme for Rural Women under aegis of AOGD on 03rd January 2018 at Community Centre, Ghazipur Delhi.


- **FOGSI Day Celebration:** Community Awareness Campaign on Adolescent Health Care under aegis of AOGD on 06th January 2018 at Community Centre, Ghazipur Delhi



- **FOGSI Day Celebration:** Community Awareness Campaign on Antenatal Care under aegis of AOGD on 06th January 2018 at Gynae OPD, UCMS & GTB Hospital

- **AOGD representation at AICOG 2018 at Bhubaneshwar**

Dr Shalini Rajaram (President) & Several other members of AOGD were invited faculty at FOGSI annual conference at Bhubaneshwar

FOGSI GCPR guidelines on cervical cancer screening and prevention were released in the managing committee meeting and FOGSI oncology committee workshop

Congratulation to **Dr Pratima Mittal** for her induction as Vice President FOGSI

Dr Ashok Kumar from MAMC was inducted as Governing council member for 3 year of ICOG & also edited the first issue of ICOG campus 2018

FOGSI President "Rallis Oration" at 61st AICOG, Bhubaneshwar was delivered by **Dr Alka Kriplani** on "Evolution and Advances in Minimally Invasive Gynaecology"

Dr A.G. Radhika
Best paper published in FOGSI Journal 2016 in open category (third prize)

Dr Richa Sharma
Pravin Mehta Laparoscopy Fellowship Award, FOGSI Imaging Science Award, Dr. CS Dawn 1st Prize for Free Communication on contraception

Dr Bindiya Gupta
FOGSI Corion award Junior Category

Dr K Aparna Sharma
Kamini Rao orator North Zone 2017, Junior Corion second runner up

Dr Garima Kachhawa
Senior FOGSI Corion second runner up
Second prize Dr CS Dawn for best paper on theme topic

Dr Neetu Chowdhary
RD Pandit prize for best thesis

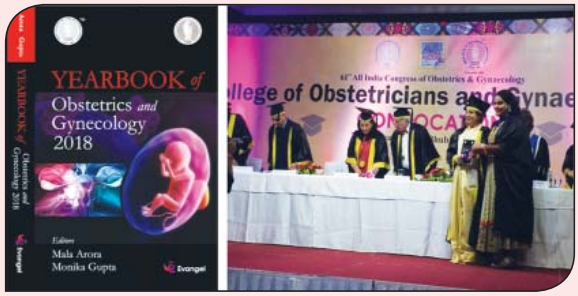
Dr Kavita Agarwal
FOGSI – Dr Kamini A. Rao Orator for the year 2018, North Zone

Dr Suman Lal
Third prize Dr CS Dawn for best paper on theme topic

Dr Neha Palo Chandel
Best paper published in FOGSI Journal during the year 2016 in Junior category - 2nd Prize

Dr Neerja Sharma
Dr Amarendra Nath Dan Prize (third) for best paper on MCH Care

- Dr Mala Arora & Dr Monika Gupta released year book in Obstetrics & Gynaecology at ICOG convocation.



- A book "Clinical Guidelines for Management of Diabetes in Pregnancy" Editor in Chief - Dr Pikee Saxena, Editors - Dr Alka Pandey, Dr Anupam Prakash, released in 61st AICOG 2018 at Bhubaneshwar by the President FOGSI.

- AOGD Monthly Clinical Meeting on Thursday, 25th January 2017 at Dr R.M.L Hospital, New Delhi

DGES-ESGE 2018

Delhi Gynaecological Endoscopists Society – Annual
European Society of Gynaecological Endoscopy – Regional

Date: **16th,17th, 18th, 19th August, 2018**
Venue: **Hotel Le Meridien, New Delhi**

Making a Difference with Endoscopy
in
Gynae Surgeries, Urogynaecology, Oncosurgery, Infertility

International Faculty

Prof. Dr Dr Rudy Leon De Wilde
Oldenburg, Germany

Dr Hugo. C Verhoeven
Düsseldorf, Germany

Dr Rajesh Devassy
Oldenburg, Germany

Prof. Dr Sven Becker
Frankfurt, Germany

National Faculty

Dr Alka Kriplani
Dr B Ramesh
Dr Dinesh Kansal
Dr Dipak Limbachiya
Dr Hafeez Rahman
Dr Malvika Sabharwal
Dr P G Paul
Dr Prakash Trivedi
Dr Prashant Mangeshikar
Dr Rajendra Sankpal
Dr Sanjay Patel
Dr Shailesh Putambekar
Dr Shivani Sabharwal
Dr S Krishna Kumar
Dr Vineet Mishra

Highlights

- Understanding Pelvic Anatomy
- TLH made easy - with different vessel sealers
  Large Uterus/ Scarred Abdomen/ Endometriosis
- Changing Trends in Laparoscopic Onco Surgeries
- Advancement in Urogynaecology
- Fertility Enhancing Surgeries
- Setting benchmarks in Infertility
- Transumblical Laparoscopy
- Non descent Vaginal Hysterectomy
- Transvaginal Laparoscopy
- Sentinel Lymphadenectomy
  with ICG Flurescence Mapping

Save the Date
16th,17th, 18th,19th August, 2018

Call For Abstracts/Posters Last 15th July 2018

Exciting Prizes Quiz

Cadaveric Pelvic Anatomy Workshop on 16th August: Dr Alka Kriplani, Dr Garima Kachhawa, AIIMS, Delhi

Dates	DGES Members	Non Members	PG	Foreign Delegate
Upto 1st July 2018 (early bird)	9000 INR	9900 INR	6000 INR	300 USD
1st July-1st Aug 2018	9500 INR	10400 INR	6500 INR	400 USD
Late & Spot	10500 INR	11400 INR	7000 INR	500 USD

Includes Three Lunches + Conference kit + Live Surgical Workshop on 17th Aug. 2018 + Scientific Session on 18th, 19th Aug. 2018
*Taxes Extra if Applicable
Banquet on 18th August at Hotel Le Meridien, 2500 INR

Organising Chair

Dr Malvika Sabharwal
President, Delhi Gynaecological Endoscopists Society

Prof. Dr Dr Rudy Leon De Wilde
Director of the ESGE (European Society for Gynaecological Endoscopy)

Dr Shivani Sabharwal
Secretary, Delhi Gynaecological Endoscopists Society

Office Secretariat:
Jeewan Mala Hospital
67/1 New Rohtak Road, New Delhi-110005
(M): 9212150571, 9811557511, E-mail: dgesjmh2017@gmail.com
Website: www.dges.in

DR DASH'S 'HANDS ON' COURSE ON

BASIC AND ADVANCED GYNAE LAPAROSCOPIC & HYSTEROSCOPIC SURGERY

Course Highlights:

- Focused hands on training on creating pneumoperitoneum, port placement
- Orientation and hands on to basic and advanced laparoscopic and hysteroscopic surgeries
- Hands on Pelvi-trainer

Proposed Schedule:

26th - 31st March, 2018

8:00 am to 12:00 pm

- Live surgery 2-3 cases every day
- Diagnostic laparoscopy and hysteroscopy
- Hysteroscopic polypectomy & septal resection
- Total laparoscopic hysterectomy
- Laparoscopic myomectomy
- Laparoscopic adhesiolysis (depending upon availability of cases)

8:00 am to 12:00 pm

- Interactive lectures on laparoscopic instruments & energy sources
- Video sessions discussing critical steps of surgery, managing bleeders, dealing with complications

3:00 pm to 5:00 pm

- Pelvic trainer exercises including hand-eye coordination
- Laparoscopic suturing & knot tying

Registration fee: INR 29,000/-

Secretariat / Correspondence:

REJOICE FERTILITY & GYNAE ENDOSCOPY CLINIC

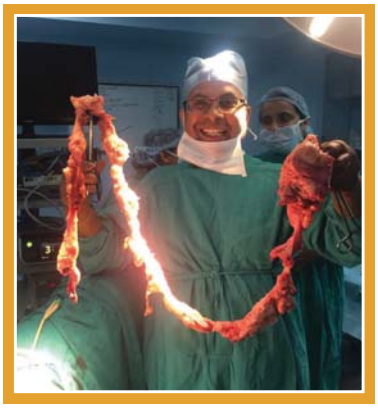
A-28, South Extension Part-II, New Delhi-110049

Ph- 011-26261352, 9212397781

Website: www.gynelaparoscopy.in, Email- bishulee@gmail.com

FACULTIES:

Dr B B Dash, Dr Sonia Chawla



Organised By: Rejoice Clinic and Sukhmani Hospital, New Delhi

Day of the Month:

World Cancer Day

February 4th every year is celebrated as World Cancer Day. Commemorated internationally, it was founded under the direction of the Union for International Cancer Control (UICC) with the aim of supporting the World Cancer Declaration goals written in 2008. People across the world have ever since come together on this day to ensure optimal awareness and significantly reduce illness and deaths caused by cancer by 2020. World Cancer Day unites the world's population in the fight against cancer. It aims to save millions of preventable deaths each year by raising awareness and education about the disease, pressing governments and individuals across the world to take action. Nearly every family in the world is touched by cancer, which is now responsible for almost one in six deaths globally. On World Cancer Day (4 February) WHO highlights that cancer no longer needs to be a death sentence, as the capacity exists to reduce its burden and improve the survival and quality of life of people living with the disease.

For 2016-2018, the theme for observing World Cancer Day is ***'We Can.I can.'*** Under this theme, people are expected to, individually and collectively, understand and work towards lessening the impact and harmful effects of the condition globally. The theme will mobilize people to work towards generating more discussions on and about cancer and for making it an issue of highest concern in terms of political discussions as well. The Empire State building in United States is lit blue and orange, after the colours of the UICC — the eighth year in a row. **World Cancer Day is a chance to reflect on what you can do, make a pledge and take action**. Whatever you choose to do 'We can. I can.' make a difference to the fight against cancer.

Individuals can:

- Make healthy lifestyle choices that include avoiding tobacco, getting plenty of physical activity, eating a healthy diet, limiting alcohol, and staying safe in the sun.
- Know about signs and symptoms of cancer and early detection guidelines because finding cancer early often makes it easier to treat.
- Support cancer patients and survivors with the physical and emotional impacts of cancereven after treatment ends.
- Share stories about their own cancer experiences, communicate with decision-makers, and join support groups to help make positive change for all people affected by cancer.
- When possible, return to work after cancer treatment to restore normality, routine, stability, social contact, and income.

Communities can:

- Call on governments to commit adequate resources to reduce cancer deaths and provide a better quality of life for patients and survivors.
- Educate people about the link between lifestyle behaviors – including smoking, poor diet, and lack of physical activity – and cancer risk.
- Dispel myths that lead to stigma and discrimination against people with cancer in some communities.
- Encourage schools and workplaces to implement nutrition and physical activity policies that can help people to adopt healthy habits for life.
- Improve access to affordable cancer health care for all populations.

Progesterone for Short Cervix

Richa Agarwal
Assistant Professor, Department of Obstetrics and Gynecology, UCMS & GTB Hospital, Delhi

Preterm birth is a major health problem for the neonate, family, country, and society in general. Despite many risk factors being identified for women destined to deliver preterm, short cervical length (CL) detected on transvaginal ultrasound (TVU) is the most plausible, practical and sensitive risk factor for prediction of spontaneous preterm birth (sPTB).

A short CL is a good screening predictor as it heralds onset of preterm delivery weeks prior, to allow for intervention to prevent it. In addition, short CL can be diagnosed reliably and easily by ultrasound which can be performed at the time of an already scheduled visit for fetal anatomic survey. The infrastructure and equipment for TVS already exist in most centers performing fetal ultrasounds though may not be in certain geographic areas. The shorter the sonographic cervical length, the higher the risk of spontaneous preterm birth

The accepted definition of short cervix is ≤2.5 cm in the midtrimester of pregnancy[1]. In addition, the risk of sPTB for a particular CL varies depending on the gestational age it was measured. For example, a CL of <25 mm at 20 weeks has a 40% chance of sPTB < 35 weeks compared to 70% if detected at 16 weeks. Other important factors affecting the predictability of CL include number of fetuses, patient symptoms, and prior history of sPTB.

Short TVU CL can be detected by screening, or incidentally. TVU CL screening is recommended in women with singleton gestations and prior spontaneous PTB. A short TVU CL can also be detected in women with singleton gestations but WITHOUT prior spontaneous PTB. This scenario is often called 'universal CL screening.' The issue of universal transvaginal ultrasound CL screening of singleton gestations without prior PTB for the prevention of PTB remains an object of debate. Current SMFM guidelines state CL screening in singleton gestations without prior PTB cannot yet be universally mandated. Nonetheless, implementation of such a screening strategy can be viewed as reasonable, and can be considered by individual practitioners[1].

Progesterone is considered a key hormone for pregnancy maintenance, and a decline of progesterone action is implicated in the onset of parturition. If such decline occurs in the midtrimester, cervical shortening may occur, and this would predispose to preterm delivery. Therefore, an untimely decline in progesterone action has been proposed as a mechanism of disease in the "preterm parturition syndrome".

Administration of vaginal progesterone was proposed for the prevention of preterm birth in women with a sonographic short cervix in the mid-trimester based on its biologic effects on the cervix, myometrium, and chorioamniotic membranes. In 2007, Fonseca et al. reported that the administration of vaginal progesterone in women with a cervical length ≤15 mm was associated with a significant 44% reduction in the rate of spontaneous preterm birth before 34 weeks of gestation[2]. Similar findings were reported by DeFranco et al. in a secondary analysis of a randomized clinical trial of vaginal progesterone in women with a prior history of preterm birth in which the cervix was measured[3]. Hassan et al. reported that vaginal progesterone, when administered to women with a cervical length of 10–20 mm, reduces the rate of preterm birth at < 33 weeks[4]. The safety for mother and fetus, and tolerability of vaginal progesterone, particularly the gel form, is also well established. Vaginal progesterone is a minimally invasive intervention that is not painful and is very safe, with reasonable cost where the benefits (even if argued to be small) clearly outweigh the risks.

***Singleton gestations without a prior spontaneous PTB and with a short TVU CL before 24 weeks*:** Randomized trials have shown that vaginal progesterone, either 200 mg or 90 mg gel, may prevent PTB[6]. Vaginal progesterone is associated with a 42% significant reduction in the rate of preterm birth <33weeks, a significantly lower rate of respiratory distress syndrome (6.1% vs 12.5% in the placebo group); a 43% decrease in composite neonatal morbidity and mortality; lower admission rates to NICU (20.7% vs 29.1%) and use of mechanical ventilation (8.5% vs 12.3%); fewer neonates with a birthweight <1500g (8.8% vs 16.5%); a non-significant difference in maternal adverse events (13.8% vs 13.4%), discontinuation of therapy (2.6% vs 2.6%), congenital anomalies (1.5% vs 1.7%), and neurodevelopmental disability at 18 months of age (3.8% vs 3.7%). The results were significant when the analyses were restricted to patients with a singleton gestation; in patients with a twin gestation, there was a non-significant trend towards reduction of the rate of preterm birth <33 weeks of gestation[5]. However, in twins, there was a significant reduction in the risk of composite neonatal morbidity/mortality which was observed in both women with no and without history of spontaneous preterm birth.

There is insufficient evidence that any of the vaginal preparations or doses is superior, as they have not been compared. CL, cost, availability, and other factors may influence preferred dosing. As there are no effective interventions to prevent PTB in multiple gestations with short CL, screening for short CL should not be performed in these pregnancies[7].

Singleton gestations with a short CL less than 25 mm before 24 weeks and one or more prior PTBs:

In asymptomatic women with a past history of one second trimester pregnancy loss/extremely preterm birth (ie, <28 weeks) associated with no or minimal mild symptoms, serial transvaginal ultrasound (TVU) measurement of cervical length is performed beginning at around 14 weeks, with repeat screening every two weeks until 24 weeks as long as cervical length is ≥30 mm[8]. If cervical length is 26 to 29 mm, weekly screening is done as long as the length remains in this range. If the cervical length becomes ≤25 mm before 24 weeks, cerclage placement (called ultrasound-based or ultrasound-indicated cerclage) should be done. If the woman develops symptoms of cervical insufficiency, an ultrasound examination for cervical length should be performed promptly because a normal physical examination cannot reliably exclude the diagnosis of cervical insufficiency. TVU screening is discontinued at 24 weeks of gestation, as cerclage is rarely performed after this time.

In singleton gestation with prior SPTB, progestogen administration starting at 16 weeks is beneficial in preventing PTB. Although there is limited data comparing the different preparations of progestogens, there is at present stronger evidence of effectiveness for 17P than for vaginal progesterone. Therefore, 17-alpha-hydroxy-progesterone caproate (17P), 250 mg IM weekly starting at 16-20 weeks until 36 weeks should be recommended to women with singleton gestations and prior SPTB. In cases in which 17P is unavailable, other progesterone preparations may be considered. If the cervix shortens <25 mm by TVU <24 weeks in such a woman, it is reasonable to continue 17P until 36 weeks, and to offer cervical cerclage[7].

To conclude, vaginal progesterone use in women with midtrimester short cervix decreases sPTB. Adding to this benefit is the fact that it has no significant adverse effects for mother or the neonate. Data suggests that approximately 11 women need to be treated to prevent one SPTB. This one prevented SPTB will result in insurmountable benefits not only to that neonate, but also to that family, and the society not only monetarily but also emotionally and intellectually and lighten the burden of chronic diseases. Overall the risk–benefit ratio balance tips towards vaginal progesterone use in women with short CL especially as there are no significant side effects.

References

1. Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. The role of routine cervical length screening in selected high- and low-risk women for preterm birth prevention. *Am J Obstet Gynecol*. 2016;215(3):B2–B7
2. Fonseca EB, Celik E, Parra M, et al. Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med. 2007;357:462–469.
3. DeFranco EA, O'Brien JM, Adair CD, et al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a randomized, doubleblind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2007;30:697–705.
4. Hassan SS, Romero R, Vidyadhari D, et al. for the PREGNANT Trial, authors. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2011;38:18–31.
5. Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and meta-analysis of individual patient data. Am J Obstet Gynecol 2012;206:124.e1-19. Level I
6. Preterm labour and birth. NICE guideline Published: 20 November 2015
7. Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. *Am J Obstet Gynecol*. 2012; 206: 376–386
8. Committee on Practice Bulletins—American College of Obstetricians and Gynecologists.Practice bulletin no. 130: prediction and prevention of preterm birth. *Obstet Gynecol*. 2012; 120: 964–973

Atosiban for Preterm Birth

Garima Kachchawa[1], Anju Singh[2]
Associate Professor[1], Senior Resident[2], All India Institute of Medical Sciences, Delhi

Introduction

Preterm birth is one of the important causes of neonatal deaths and long–term neurological morbidities. Besides gestational age, perinatal morbidity and death also depends on whether or not steroids have been administered antenatally, and the preterm infant has been transferred to a tertiary care center in utero or ex utero. Therefore, postponing delivery for at least 48 hours in order to allow maximal effect of antenatal corticosteroids and transportation to a center with neonatal intensive care unit (NICU) facilities are the primary indications of tocolytic therapy in management of preterm labour.

Traditionally, β-adrenergic-receptor agonists and calcium channel blockers are the most commonly used tocolytic agents. However, oxytocin (OT) receptor antagonists have also gained popularity due to comparable efficacy and fewer maternal side effects. Atosiban is the first clinically tested OT receptor antagonist which can be used as a labor tocolytic to halt preterm labor. It was developed by Ferring Pharmaceuticals in Sweden and first reported in the literature in 1985[1].Though not US-FDA approved, but it is licensed for use as a tocolytic in Europe and other parts of the world.

Mechanism of Action

Oxytocin is a potent uterotonic hormone that is secreted from the posterior pituitary gland and is responsible for the initiation of labour via the interaction with the OT receptors. Atosiban, 1-(3-mercaptopropanoic acid)-2-(O-ethylD-thyrosine)-4-threonine-8-L-ornithine-oxytocin, is a synthetic cyclic nonapeptide that behaves as a vasopressin/oxytocin receptor antagonist (VOTra). The oxytocin molecule has been modified at positions 1, 2, 4 and 8, and can thus inhibit the uterotonic action of oxytocin competitively and dose dependently. It inhibits the oxytocin-mediated release of inositol trisphosphate from the myometrial cell membrane. As a result, there is reduced release of intracellular, stored calcium from the sarcoplasmic reticulum and reduced influx of Ca^{2+} from the extracellular space through voltage gated channels. In addition, it also suppresses oxytocin-mediated release of prostaglandins from the decidua. All these actions antagonise uterine contractions and induce uterine quiescence.

Indications

It is indicated to delay imminent pre-term birth under following conditions:

- Regular uterine contractions of at least 30 seconds duration at a rate of ≥ 4 contractions per 30 minutes
- Cervical dilation of 1 to 3 cm and effacement of ≥ 50%
- Gestational age from 24 until 33 completed weeks
- Normal fetal heart rate

Dosage and administration

It is available in two forms: 6.75 mg/0.9 ml solution for bolus injection and as 37.5 mg/5 ml concentrate. It is administered intravenously in three successive stages:

- 6.75mg bolus, direct intravenous, in 0.9mL saline;
- followed by infusion @ 300 μg/min in a 5% glucose solution for 3 hours (using 37.5 mg/5 ml concentrate)
- followed by infusion @ 100 μg/min for 15–45 hours.

The total dose given during one full course of atosiban therapy should preferably not exceed 330.75 mg and duration not more than 48hrs. If uterine contractions persist during treatment with atosiban, alternative tocolytic therapy should be considered.

Pharmacokinetic properties

Peak plasma concentrations of atosiban are achieved at 2 to 8 minutes following intravenous (IV) administration. This enables rapid onset of uterus relaxation; uterine contractions being significantly reduced within 10 minutes to achieve stable uterine quiescence. Steady state plasma concentrations are reached within one hour following the start of the infusion. The clearance, volume of distribution and half-life are independent of the dose. At the completion of infusion, plasma levels decline in a bi-exponential manner with initial and terminal half lives of 13 ± 3 and 102 ± 18 minutes, respectively[2]. Two metabolites have been identified, M1 and M3, in the plasma and urine of women. No dose adjustment is needed in patients with renal impairment, since only a small extent of atosiban is excreted in the urine. But in patients with impaired hepatic function, it should be used with caution. It is also excreted in breast milk. It does cross the placenta but in little amount. A dose of 300 mcg/min administered at term to a healthy pregnant woman gives a fetal/maternal atosiban concentration ration of 0.12 and does not accumulate in fetus[2].

Efficacy

The efficacy and safety of atosiban has been evaluated and compared to other tocolytics in a number of clinical trials which are discussed as follow:

Atosiban vs placebo

Romero et al[3] found that compared to placebo, the proportions of the women with preterm labour who were successfully treated were significantly higher in the atosiban group: 73% versus 58% at 24 hours, 67% versus 56% at 48 hours and 62% versus 49% at 7 days. Compared to placebo, this tocolytic effect of atosiban on prolongation of pregnancy up to 7 days was more evident in pregnancies more than 28 completed weeks of gestation (65% versus 48%) and not as effective at gestational age less than 28 weeks (51% versus 59%).

Valenzuela et al[4] concluded that after successful treatment of acute phase, the use of Atosiban as maintenance therapy resulted in a statistically significant prolongation of uterine quiescence, compared to placebo (median of 32.6 days versus 27.6 days). Except for more injection site reactions in atosiban group (70% versus 48%), adverse event profiles in two groups were comparable.

Atosiban vs Beta agonists

In a number of randomized controlled trials, the clinical effectiveness of atosiban have been found to be comparable to conventional beta-adrenergic agonist therapy, with an added advantage of few maternal cardiovascular side effects. No statistical differences in neonatal/infant outcomes were observed with either study medication. (Table 1)

Atosiban vs Nifedipine

Recently published Assessment of Perinatal Outcome after Specific Tocolysis in Early Labour (APOSTEL-III), a multicentre randomized controlled trial[8] found similar rates of adverse perinatal outcomes and maternal outcomes while comparing tocolysis with nifedipine versus atosiban in women with threatened preterm birth (Table 2); however, NICU admittance rates were lower in the nifedipine group (52%) than in the atosiban group (62%). Unexpectedly, a non-significant higher perinatal mortality rate was found in the nifedipine group which warrants further evaluation.

Similarly Kashanian et al[9] did not find a significant difference in the effectiveness of tocolysis between atosiban and nifedipine at 48 hours (82.5% vs. 75%) or at 7 days (75% vs. 65%). In another randomized controlled trial by Al Omari et al[10] , no significant difference in rates of delivery at 48 hours (77.4% vs. 81.3%; P = 0.474) and 7 days (74.2% vs. 70.96%; P = 0.421) were found in the atosiban group compared to nifedipine group respectively. Similar tocolytic effectiveness between two drugs has also been found in meta-analysis by Coomarasamy et al[11] However at gestational age less than 28 weeks, nifedipine was significantly more effective than atosiban. Cardiovascular side-effects like hypotension (27.5%), palpitations (7.5%) and maternal tachycardia (7.5%) were reported more in the nifedipine group as compared to atosiban group (0%).

Table1: Results of Randomized Trials comparing Atosiban with Beta-agonists

Study details and outcomes	**The Worldwide Atosiban versus Beta-agonists Study Group[5]**		**The European Atosiban Study Group[6]**		**Australian Study Group[7]**	
Drugs Compared	Atosiban	Ritodrine	Atosiban	Terbutaline	Atosiban	Salbutamol
No of patients	128	124	116	129	119	122
Prolongation of pregnancy >48h (%)	84.9	86.9	86.1	85.3	93.3	95
Prolongation of pregnancy >7 days (%)	73	76	75.6	67.4	89.9	90.1
Gestational age at delivery (wks)	35.1	35.2	35.8	35.2	36.5	36.3
Maternal adverse effects (%)	4.0	84.3*	4.3	75.2*	16	80.3*
Discontinuation of t/t due to side -effects (%)	0.8	29.8*	1.7	13.2*	0.8	10.7*
NICU admission (%)	20.5	16.3	28	33	20.9	20.3
Perinatal mortality (%)	2	1	3	7	1	4

*p <0.05 compared with atosiban group i.e significant difference

Table 2: Results showing Adverse Perinatal and Maternal Outcomes of APOSTEL III Trial

Outcome measure	**Atosiban Group**	**Nifedipine Group**
Number of women analysed	255	248
Number of babies analysed	294	297
Adverse perinatal composite outcome (primary outcome)	45 (15%)	42 (14%)
Gestational age at delivery (weeks)	32.4 (30.1–35.8)	33.1 (30.5–37.0)
Prolongation of pregnancy (time to delivery) Continuous (days) ≥48 h ≥7 days	 4 168 (66%) 116(45%)	 7 169 (68%) 127 (51%)
NICU admittance	182 (61.9%)	155 (52.2%)
Perinatal deaths	7 (2%)	16 (5%)

Others

Cochrane 2014 review[12] did not demonstrate superiority of oxytocin receptor antagonist (ORA) mainly atosiban compared with placebo, betamimetics or CCBs in terms of pregnancy prolongation or neonatal outcomes, although it does mention that ORA was associated with less maternal adverse effects.

RCOG has also stated that the most commonly used beta-agonist, ritodrine, 'no longer seems to be the best choice', and has suggested the oxytocin receptor antagonist atosiban or calcium channel blockers as a first line agent in the management of preterm labor[13].

Contraindications

There are certain conditions in which tocolysis with atosiban is contraindicated which include

- Gestational age <24 or >33 wks,
- Severe pre-eclampsia, eclampsia,
- Intra-uterine growth retardation,
- Abnormal foetal heart rate,
- Intra-uterine foetal death,
- Suspected intra-uterine infection,
- Placenta praevia, abruptio placentae.
- Premature rupture of membranes

Side effects

The most common maternal side effects are headache, vomiting and nausea, occurring in about 10% of the patients. Other less common side effects are dizziness, flushes, tachycardia, hypotension, hyperglycaemia, injection site reaction, insomnia, pruritus, rash, pyrexia. Rarely, it can lead to uterine atony and postpartum hemorrhage.

The fetal concerns regarding its use are mainly based on study by Romero et al[3], which found a higher rate of fetal-infant deaths in the atosiban treated group compared to placebo. However, 7 of the 10 infant deaths were newborns with birth weights ,0.650 kg suggesting that extreme prematurity could have played a rather large role in these adverse outcomes[3].Further trials of atosiban with other tocolytics have shown a comparable neonatal outcome[8]. It is neither oncogenic nor mutagenic in in-vitro and in -vivo studies

Conclusion

Despite the debate in literature regarding best tocolytic agent, there is enough evidence of good efficacy and few maternal side–effects of atosiban. In a low-income country like India, high cost, parenteral administration and need of hospitalization may be a barrier in its wide-spread use. However, it may be preferred as tocolytic of choice particularly in women with cardiovascular problems and who are not tolerating conventional agents like beta-agonists and calcium-channel blockers due to adverse effects.

Other oxytocin antagonists such as Retosiban which can be used orally, have displayed better tocolytic action are under further research.

Reference

1. Akerlund M, Carlsson AM, Melin P, Trojnar J (1985). "The effect on the human uterus of two newly developed competitive inhibitors of oxytocin and vasopressin". Acta Obstet Gynecol Scand. 64 (6): 499–504
2. Atosiban. Summary of Product Characteristics. Ferring Pharmaceuticals Ltd. 2000 Jan.
3. Romero R, Sibai BM, Sanchez-Ramos L, Valenzuela GJ, Veille JC, Tabor B et al. An oxytocin receptor antagonist (atosiban) in the treatment of preterm labour: a randomised, double blind, placebo-controlled trial with tocolytic rescue. Am J ObstetGynae. 2000;182(5):1173–8
4. Valenzuela GJ, Sanchez-Ramos L, Romero R, Silver HM, Koltun WD, Millar L, et a Mantenance treatment of preterm labor with the oxytocin antagonist atosiban. The Atosiban PTL-098 Study Group. American Journal of Obstetrics and Gynaecology. 2000;182:1184–90.
5. Moutquin JM, Cabrol D, Fisk NM. Effectiveness and safety of the oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of preterm labour. The Worldwide Atosibanversu Beta-agonists Study Group. BJOG. 2001; 108: 133–142.
6. The European Atosiban Study Group. The oxytocin antagonist atosiban versus the β-agonist terbutaline in the treatment of preterm labour: a randomised, double-blind, controlled study. ActaObstet Gynecol Scand 2001; 80:413–22.
7. French/Australian Atosiban Investigators Group. Treatment of preterm labor with the oxytocin antagonist atosiban: a double-blind, randomized, controlled comparison with salbutamol. Eur J Obstet Gynecol Reprod Biol 2001; 98: 177-85.
8. Elvira OG van Vliet, EwoudSchuit, Karst Y Heida et al. Nifedipine versus atosiban in the treatment of threatened preterm labour (Assessment of Perinatal Outcome after Specific Tocolysis in Early Labour: APOSTEL III-Trial). BMC Pregnancy Childbirth. 2014 3;14:93.
9. Kashanian M, Akbarian AR, Soltanzadeh M. Atosiban and nifedipin for the treatment of preterm labor. Int J Gynaecol Obstet. 2005; 91:10–14.
10. Al-Omari WR, Al-Shammaa HB, Al-Tikriti EM, Ahmed KW. Atosiban and nifedipine in acute tocolysis: a comparative study. Eur J ObstetGynecolReprod Biol. 2006;128:129–134.
11. Coomarasamy A, Knox EM, Gee H, Song F, Khan KS. Effectiveness of nifedipine versus atosiban for tocolysis in preterm labor: a metaanalysis with an indirect comparison of randomised trials. BJOG. 2003;110:1045–1049
12. Flenady V, Reinebrant HE, Liley HG, Tambimuttu EG, Papatsonis DNM. Oxytocin receptor antagonists for inhibiting preterm labour. Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD004452. DOI: 10.1002/14651858.CD004452.pub3
13. Royal College of Obstetricians and Gynaecologists. Tocolytic Drugs for Women in Preterm Labour. Clinical Guideline No. 1(B), 2002

Role of Progesterone in Threatened Abortion

Anshuja Singla[1], Prerna Gupta[2]

[1]Assistant Professor, [2]Senior Resident, Department of Obstetrics and Gynecology, UCMS & GTB Hospital, Delhi

Threatened abortion is a condition in pregnancy before the 20th week of gestation which is characterised by uterine bleeding and cramping, sufficient to suggest that miscarriage may result. Threatened abortions occur in up to 20% of early pregnancies of which half progress to inevitable abortion.

Mechanism of action of progesterone in maintenance of pregnancy

Progesterone plays a crucial role in maintenance_of pregnancy. It is produced by the corpus luteum until the placenta takes over its function at 7-9 weeks of gestation, just after the expression of MHC (Major histo-compatibility complex) antigens is suppressed in extra-embryonic foetal tissue. Inadequate secretion of endogenous progesterone in early pregnancy has often been linked to recurrent miscarriage. Progesterone induces secretory changes in the endometrium essential for endometrial maturation & stabilization ,embryo implantation and proper regulation of inflammatory mediators to create adequate positive immune response in early pregnancy by enhancing uterine quiescence, thus preventing pregnancy loss.

Myometrial contractility is controlled by the balance of two major endogenous regulators that exert opposing effects. Contractility is increased by prostaglandins, and inhibited by progesterone. Progesterone binds calcium and consequently raises the threshold of excitability of the myometrium, whereas prostaglandins exert the opposite effect, when progesterone is absent.

Progesterone might play a significant role in establishing an adequate immune environment for the early stages of pregnancy. Progesterone at concentrations comparable to those present at the materno-foetal interface during pregnancy, is a potent inducer of Th2-type cytokines (i.e. IL-4 and IL-5), and also of LIF and M-CSF production by T lymphocytes, thus progesterone present in the microenvironment of the decidual T cells could be responsible, at least in part, for the Th2-biased cytokine production by these cells and a favourable response to pregnancy.

Literature review

A meta-analysis by Wahabi et al(2011)on the effect of vaginal progesterone on miscarriage compared to placebo showed a point estimate which suggested a reduction of miscarriage rate with the use of progesterone (RR 0.47; 95% CI 0.17 to 1.30.

Musrat and colleagues (2012) in their study on 60 women with threatened miscarriage enrolled over a period of 1 year and divided into groups of 30 each (oral dydrogesterone vs no treatment) reported no significant improvement with the use of progesterone in threatened miscarriage.

Yassaee etal (2014) in their single-blinded clinical trial study done on 60 pregnant women with threatened abortion randomly divided into 2 groups (400 mg progesterone suppository vs no treatment) demonstrated a reduction in abortion rate in women treated with progesterone suppository though it was not statistically significant.

A questionnaire based survey conducted over a period of 1 month by Maria Ayub and colleagues (2015) showed a 100% response rate with progesterone and a successful pregnancy rate of 90% in women with threatened abortion.

Lee etal (2017) in their systematic review and meta analysis of nine randomized control trials including 913 pregnant women with usage of different forms of progesterone and controls concluded that Progesterone therapy, especially oral dydrogesterone can effectively prevent miscarriage in pregnant women experiencing threatened abortion.

A randomized interventional clinical trial is going on in US by Omar etal with an estimated enrolment of 290 participants will see the efficacy of vaginal progesterone in threatened abortion , the results of which will be out by February 2018.

Cochrane review

Cochrane review in 2011 concluded that the use of progestogens is effective in the treatment of threatened miscarriage with no evidence of increased rates of pregnancy-induced hypertension or ante-partum haemorrhage as harmful effects to the mother,nor increased occurrence of congenital abnormalities on the newborn. However, the analysis was limited by the small number and the poor methodological quality of eligible studies (four studies) and the small number of the participants (421), which limit the power of the meta-analysis and hence of this conclusion..

The limited evidence suggests that the use of a progestogens does reduce the rate of spontaneous miscarriage. Two trials reported that treatment with progestogens did not increase the occurrence of congenital abnormalities in the newborns and the women did not have any significant difference in incidence of pregnancy-induced hypertension nor antepartum haemorrhage. Further larger studies are warranted for firmer conclusions.

FOGSI position statement on the use of Progestogens

Based on the available clinical data, progesterone support (vaginal micronized progesterone and dydrogesterone) is beneficial in women presenting with a clinical diagnosis of threatened miscarriage with relative risk reduction in the miscarriage rate of 47% with the use of progesterone (RR 0.53; 95% CI 0.35 to 0.79).

The argument for use of progesterone (vaginal micronized progesterone & dydrogesterone) is that there is no evidence of harm and some evidence of benefit, although not coming from huge multi centric trials. The decision should be based on clinician's discretion until strong evidence is available to recommend routine use. There is no role of progesterone supplementation in normal healthy pregnant women for prevention of miscarriage.

Available evidence strongly supports the safety of progesterone when used in pregnancy (based on the available clinical data on vaginal progesterone and dydrogesterone). There is no statistically significant difference in the congenital abnormalities seen in the clinical studies between the newborns of the mothers who received progesterone and those who did not."

To conclude, based on the data available, there is evidence to support the routine use of progesterone for the treatment of threatened miscarriage though the information about potential harms to the mother or child, or both, with the same is lacking. Further multi centric studies are the need of the hour.

Suggested reading

Wahabi HA, Fayed AA, Esmaeil SA, Al Zeidan RA. Progestogen for treating threatened miscarriage. Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD005943. DOI: 10.1002/14651858.CD005943.pub4.

Raghupathy R et al. Modulation of cytokine production by dydrogesterone in lymphocytes from women with recurrent miscarriage. BJOG: an International Journal of Obstetrics and Gynaecology 2005;112:1096-1101

Bartho JS, Wilczynski JR Basta P Kalink J

Role of progesterone and progestin therapy in threatened abortion and preterm labour Frontiers in Bioscience 13, 1981-1990, January 1, 2008

Akhtar M, Fatima N, Jabeen S, Akram M

Role of Progesterone in the Management of Threatened Miscarriage. P J M H S VOL .6 NO.1 JAN – MAR 2012 261

"Body, Mind and Soul"

Mantras & Pregnancy

Rashmi
Asstt Professor, Deptt of Obstetrics & Gynaecology, UCMS & GTB Hospital, Delhi

"Vedic chants or veda mantras are the very breath of God"

The mantras are special composed chants to bring about patterns of resonant waves to achieve the desired result. They are the part of a broad science called Tantra Shatsra. Mantra chanting uses vibration and sacred sound to connect to the most infinite aspect of being, to open the heart, to quiet the mind, and to elevate the circumstances for both mother and child.

It is said in four Vedas that, "Mother is the creator of child's future." It is in her hands that how she builds her child's future. It is very important on how mothers keep their thoughts and actions when they are pregnant. Mothers are gifted with a powerful strength and power - the power to give life it's form. As such, they are also capable of moulding the nature of the child. We know from our scriptures that Abhimanyu learnt the secrets of entering the chakravyuh in the Kurushetra war when he (Abhimanyu) was still in the womb. The foetus or child inside the womb listens to whatever the mother hears/speaks and grasps. It is said that the children of teachers are usually bright and intelligent- due to the reason that they grasp the words of the lessons orated by the mothers while being still enclosed in the womb.

For someone going through the tremendous changes of pregnancy and motherhood, mantra is a powerful tool for peace and joy. Not only does mantra chanting give babies the soothing comfort of hearing mom's voice, but it also can uplift the mother herself. Using mantra in pregnancy and in birth can create a high vibration and a deep, loving peace for mother and baby. What a great way to welcome a soul!!!

There are many options available to a pregnant mother – Chanting of Om, Gayatri Mantra, Garbh-Sanskar, Vedic chants

Garbh sanskar is an ancient Indian Ayurvedic practice that helps to shape the personality and character of the fetus inside the mother's womb. Various practices like yoga, meditation, chanting mantras, listening to music etc are done by the expecting mother. There are various Garbh Sanskar mantras for chanting/ listening during pregnancy.

An important and powerful mantra that can be practiced by everyone including pregnant ladies is the Gayatri Mantra.

Gayatri Mantra is one of the most known and beneficial of the ancient Sanskrit mantras. Gayatri is a mantra of physical, emotional, and mental healing, purifying the subtle karmas, protection from the onslaught of obstacles, and of spiritual awakening or Self-realization. The Gayatri is a universal prayer given in Vedas. This may be considered as having three parts: Adoration, Meditation and Prayer. First the Divine is praised, then it is meditated upon in reverence and finally an appeal is made to the Divine to awaken and strengthen the intellect, the discriminatory faculty of man.

The History and Significance of the Gayatri Mantra

The Gayatri Mantra has been chronicled in the Rig Veda, which was written in Sanskrit about 2500 to 3500 years ago, and the mantra may have been chanted for many centuries before that. The ancient Hindu scriptures describe how the sage Vishwamitra was given the Gayatri mantra by the Supreme Being as a reward for his many years of deep penance and meditation. This was to be a gift for all humanity. It is said that this sacred prayer spirals through the entire universe from the heart of the chanter, appealing for peace and divine wisdom for all. In very basic but beautiful language, it says "May the divine light of the Supreme Being illuminate our intellect, to lead us along a path of righteousness".

The Vedas say:

To chant the Gayatri Mantra
purifies the chanter.
To listen to the Gayatri Mantra
purifies the listener.

It calms the mind, improves immunity, concentration, stress tolearance. It also has healing effects on heart, lungs, skin and brain. Apart from that the vibrations from chanting the mantra stimulate the penial body and help in the release of endorphins and other relaxing hormones that help keep depression at bay. It has been to help in treatment of people with depression and epilepsy.

Chanting The Gayatri Mantra

It is quite important that you chant it with the correct pronunciation and with the deepest integrity of intent. This of course, means that one needs to know the meaning of the words behind the mantra. The Sanskrit words of the Gayatri carry tremendous power when chanted correctly and with the purest of hearts.

Om Bhur Bhuva Swaha (Om Bhoor Bhoova Swa-Ha)

Om Tat Savitur Varenyam (Om Tat Sa-Vidoor Va-rain-yam)

Bhargo Devasya Deemahi (Bhaargo They-Vas-Ya Dee-Mahi)

Deeyo Yo Naha, Prachodayaat (Thee-Yo Yo-Na-Ha, Pra-Cho-Da-Yaat)

OM is considered the primeval sound from which all sounds emerge. OM is Brahma and a metaphor for Source Energy or the Supreme Being.

Om Bhur Bhuva Swaha is actually a preamble to the main mantra and means that we invoke in our prayer and meditation the One who is our inspirer, our creator and who is the abode of supreme Joy. It also means, we invoke the earthly, physical world, the world of our mind, and the world of our soul.

Tat Savitur Varenyam……Tat meaning THAT, again denoting the Supreme Being. Savitur meaning the radiating source of life with the brightness of the Sun; and Varenyam, meaning that most adorable, most desirable.

Bhargo Devasya Deemahi……Bhargo meaning luster and splendor, Devasya meaning Divine or Supreme and Deemahi meaning "We meditate upon".

Deeyo Yo Naha, Prachodayaat……Deeyo meaning our understanding of reality, our intellect, our intention. Yo meaning He Who, and Naha meaning Our. Finally, Prachodayaat, meaning May he Inspire, Guide.

Put together, we could say:

"We meditate on that most adorable, desirable and enchanting luster and brilliance of our Supreme Being, our Source Energy, our Collective Consciousness.... who is our creator, inspirer and source of eternal Joy. May this warm and loving Light inspire and guide our mind and open our hearts."

The Gayatri can be listened to, chanted, or even thought. There is power and potency in all three approaches. One should choose the approach that one is most comfortable with. Pregnant ladies should be encourages for practices like Mantraa chanting or listening for the dual effect on herself as well as the growing fetus inside.

It's More Than Saying I Love You

We give on this day candy and flowers,
But we never stop to say thank you for the many hours.

You have stood by my side and gave a smile,
As if to tell our hearts it's been worth every mile.

No need to buy a teddy bear or even a card,
It's pretty simple and not at all hard.

Just put your arms around me and hold me tight,
And say without words that in your heart all is right.

You may say I Love You throughout the year,
But on this day you need to make sure.

The words so sweet and straight from your heart,
That your life would be lonely without my part.

So put forth the effort and take the time,
Look me in the eye and say I'm glad you're mine.

(From internet)

Antenatal Corticosteroid Therapy for Fetal Lung Maturity

Bindiya Gupta
Assistant Professor, Department of Obstetrics and Gynecology, UCMS & GTB Hospital, Delhi

Introduction

Preterm birth is defined as live births occurring before 37 completed weeks of gestation. An estimated 14.9 million neonates were born preterm in 2010, accounting for 11.1% of live births worldwide. The majority of all preterm births occur in the late preterm period (34 to <37 weeks)—for example, in USA more than 70% of preterm births in 2014 were born in the late preterm period. It is estimated that more than 60% of the world's preterm births occur in sub-Saharan African and South Asian countries. Preterm infants experience higher rates of respiratory distress syndrome, bronchopulmonary dysplasia, necrotising enterocolitis, kernicterus, hypoglycaemia, periventricular leucomalacia, seizures, intraventricular haemorrhage, cerebral palsy, infections, feeding difficulties, hypoxic ischaemic encephalopathy, retinopathy of prematurity, as well as visual and hearing loss. Those preterm neonates who survive are at increased risk of a wide range of respiratory, infectious, metabolic and neurological morbidities.

Respiratory distress syndrome (RDS) is one of the most important causes of early neonatal morbidity and mortality and it affects about 20% of low birthweight infants and 30% of extremely low birthweight infants. Besides preterm birth, cesarean delivery is also a risk factor for the development of neonatal respiratory complications, including RDS. Respiratory failure occurs as a result of surfactant deficiency, poor anatomical development of lung, as well as immaturity in other organs. Neonatal survival after preterm birth improves with length of gestation, reflecting improved maturity of organ systems.

Ever since the NIH consensus panel of 1995, antenatal steroids are used as a part of management protocol of preterm labour. In a Cochrane 2017 review of 30 studies (7774 women and 8158 infants), treatment with antenatal corticosteroids (compared with placebo or no treatment) was associated with a reduction in the most serious adverse outcomes related to prematurity, including perinatal death (average risk ratio (RR) 0.72, 95% confidence interval (CI) 0.58 to 0.89; neonatal death (RR 0.69, 95% CI 0.59 to 0.81; moderate/severe RDS (average RR 0.59, 95% CI 0.38 to 0.91; intraventricular haemorrhage (IVH) (average RR 0.55, 95% CI 0.40 to 0.76; necrotising enterocolitis (RR 0.50, 95% CI 0.32 to 0.78; need for mechanical ventilation and systemic infections in the first 48 hours of life (RR 0.60, 95% CI 0.41 to 0.88). There was no obvious benefit for: chronic lung disease, mean birthweight; childhood death; neurodevelopment delay in childhood or death into adulthood.

Drugs used for steroid therapy

A single course of antenatal corticosteroids could be considered routine for preterm delivery to accelerate fetal lung maturation in women at risk of preterm birth. Betamethasone is given as12 mg in 2-doses at a 24h interval while dexamethasone is administered in 4-doses of 6 mg treatment at 12h intervals achieve similar receptor occupancy.

Betamethasone versus Dexamethasone

The drugs are similar fluorinated corticosteroids with primarily glucocorticoid and minimal mineralicorticoid effects. The only structural difference is the isomeric position of a methyl group on position 16 of the ring structure. There are two approaches to evaluating the relative benefits or risks of these drug treatments: a direct analysis of trials that randomized women to betamethasone or dexamethasone, or an indirect analyses of the trials that compared each drug with placebo and then a comparison of the outcomes relative to the placebo controls (Table 1).

Table 1: Dexamethasone vs. Betamethasone Risk Ratio (95% Confidence Incidence)

Outcomes	Direct Comparison	Indirect Comparison
RDS	1.06 (0.88–1.28)	1.44 (1.14–1.78)
Severe IVH	0.40 (0.13–1.24)	0.47 (0.09–2.33)
Feta/Neonatal Death	1.28 (0.46–3.52)	0.96 (0.71–1.30)

The indirect comparison identified less RDS with the betamethasone as the only significant difference. Another large recent series reported significantly less RDS and bronchopulmonary dysplasia for betamethasone than dexamethasone exposed infants The direct comparison qualitatively favors dexamethasone for the outcome of severe IVH. There has been a concern that maternal dexamethasone phosphate treatments may increase periventricular leucomalacia in the newborns because of sulfites used for preservative, but it is not proven. No definitive recommendation can be made in favor of one drug treatment over the other. According to Cochrane

2017, both are equally effective and further information is required concerning the optimal corticosteroid to use.

Timing of admistration

According to ACOG Committeee opinion 2017, steroids should be offered to women between 24 0/7 weeks and 33 6/7 of pregnancy who are in suspected, diagnosed or established preterm labour, including for those with ruptured membranes and multiple gestations. It also may be considered for pregnant women starting at 23 0/7 weeks of gestation who are at risk of preterm delivery within 7 days, based on a family's decision regarding resuscitation, irrespective of membrane rupture status and regardless of fetal number. Biologic evidence supports the benefit of steroid therapy in 22 and 26 weeks' gestation as the fetal lung is in the canalicular stage of development, conducting airways are formed, epithelial differentiation occurs, air–blood barrier starts to form and surfactant begins to appear in the type 2 alveolar cells and within the airway spaces.

Use of antenatal corticosteroids in the late preterm period (34+0-36+6weeks)

The most notable respiratory morbidities in late-preterm infants include respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTN), particularly as pulmonary maturation continues through the late preterm period into early childhood.

The Antenatal Late Preterm Steroids (ALPS) trial was a double-blind, placebo-controlled randomized clinical trial conducted at 17 MFMU centers across the United States from 2010 to 2015. Investigators evaluated the use of antenatal betamethasone for pregnancies at high risk for delivery in the late preterm period, between 34 weeks 0 days and 36 weeks 6 days of gestation. The primary outcome was a composite end point describing the need for respiratory support within 72 h after birth. There was a significant decrease in the primary outcome in the betamethasone group compared with placebo (RR = 0.80; 95% CI: 0.66–0.97). A larger decrease was demonstrated for severe respiratory complications (a composite outcome of CPAP or high-flow nasal cannula for at least 12 continuous hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least at least 24 continuous hours, ECMO or mechanical ventilation, stillbirth, or neonatal death within 72 h after delivery), from 12.1% in the placebo group to 8.1% in the betamethasone group (RR = 0.67, 95% CI: 0.53–0.84, $P < 0.001$). There were also significant decreases in the rates of transient tachypnea of the newborn (TTN), bronchopulmonary dysplasia (BPD), a composite of respiratory distress syndrome, TTN and RDS, and the need for postnatal surfactant. Infants exposed to betamethasone were less likely to require immediate postnatal resuscitation. Prolonged neonatal intensive care/special care nursery stays were also decreased in the betamethasone group. There was no difference in proven neonatal sepsis, chorioamnionitis, or endometritis.

In another systematic meta-analysis in 2016, infants of mothers who received antenatal betamethasone at 34^0-36^6weeks' gestation had a significantly lower incidence of transient tachypnea of the newborn (relative risk 0.72, 95% confidence interval 0.56 to 0.92), severe RDS (0.60, 0.33 to 0.94), and use of surfactant (0.61, 0.38 to 0.99).

ACOG committee opinion in 2017 endorsed this trial and recommended that administration of betamethasone may be considered in pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation who are at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids.

For term fetus (at or more than 37 weeks)

The rate of neonatal respiratory complications is increased after delivery by cesarean section. In a systematic meta- analysis by Saccone G 2016 of three trials including 2498 women undergoing planned cesarean delivery; infants of mothers undergoing planned cesarean delivery at ≥37 weeks' gestation who received prophylactic antenatal corticosteroids 48 hours before delivery had a significantly lower risk of RDS (0.40, 0.27 to 0.59), mild RDS (0.43, 0.26 to 0.72), moderate RDS (0.40, 0.18 to 0.88), transient tachypnea of the newborn (0.38, 0.25 to 0.57), and mechanical ventilation (0.19, 0.08 to 0.43), and significantly less time receiving oxygen (mean difference -2.06 hours, 95% confidence interval -2.17 to -1.95), lower percentage of maximum inspired oxygen concentration (-0.66%, -0.69% to -0.63%), shorter stay in neonatal intensive care (-7.44 days, -7.44 to -7.43), and a higher APGAR score at one and at five minutes.

Antenatal Steroids for Term Elective Caesarean Section (ASTECS) trial, also confirmed the benefits of antenatal glucocorticoids up to 39 weeks of gestation.

According to RCOG recommendation, elective lower segment caesarean section should normally be performed at or after 39+0 weeks of gestation to reduce respiratory morbidity. Corticosteroids should be given to reduce the risk of respiratory morbidity in all babies delivered by elective caesarean section prior to 38+6 weeks of gestation.

The appropriate dosing regimen: Is there a need for repeat courses?

The NIH consensus panel of 1994 suggested that the optimal benefit of antenatal corticosteroid treatment was seen 24 h to 7 days after initiation of treatment and recommended further investigation to determine whether the beneficial effects diminish after 7 days and whether additional treatment is necessary for infants that remain in utero.

Despite the dearth of evidence regarding the utility of additional steroids, use of repeat courses became widespread. In various surveys across the world in 1990's 85-98% of specialists prescribed multiple courses of antenatal corticosteroids. In 2001, a second NIH steroid consensus panel concluded that there was insufficient scientific data from randomized trials regarding the safety and efficacy of repeat corticosteroids to recommend either for or against their use. They suggested limiting administration of repeat courses to patients enrolled in randomized trials only. The largest randomized, double-masked, placebo controlled, and multicenter clinical trial (BEARS—for beneficial effects of repeat steroids) was performed by 18 MFMU network centers in UK. The primary outcome was a composite of[1] severe respiratory distress syndrome (RDS),[2] grade III or IV intraventricular hemorrhage,[3] periventricular leukomalacia,[4] chronic lung disease, or[5] stillbirth or neonatal death. The final results of the study showed no difference in the primary outcome between repeat and single course steroids (RR=0.88 955 CI;0.49–1.57). However, surfactant use, need for mechanical ventilation, need for pressure or volume support, and occurrence of a pneumothorax were all significantly reduced in the repeat steroids group. Overall the primary results of the trial were somewhat inconclusive as there was suggestion of both benefit and harm.

In a systematic metaanalysis of 10 trials (a total of 4733 women and 5700 babies) treatment of women who remain at risk of preterm birth seven or more days after an initial course of prenatal corticosteroids with repeat dose(s), compared with no repeat corticosteroid treatment, showed a reduced risk of infants experiencing the primary outcomes respiratory distress syndrome (risk ratio (RR) 0.83, 95% confidence interval (CI) 0.75 to 0.91, and serious infant outcome (RR 0.84, 95% CI 0.75 to 0.94) with multiple courses. Treatment with repeat dose(s) of corticosteroid was also associated with a reduction in mean birth weight (mean difference (MD) -75.79 g, 95% CI -117.63 to -33.96). However, outcomes that adjusted birthweight for gestational age (birthweight Z scores, birthweight multiples of the median and small-for-gestational age) did not differ between treatment groups. At early childhood follow-up, no statistically significant differences were seen for infants exposed to repeat prenatal corticosteroids compared with unexposed infants for the primary outcomes (total deaths; survival free of any disability or major disability; disability; or serious outcome) or in the secondary outcome growth assessments. In women, for the two primary outcomes, there was no increase in infectious morbidity of chorioamnionitis or puerperal sepsis, and the likelihood of a caesarean birth was unchanged. They concluded that, the current available evidence reassuringly showed no significant harm in early childhood, although no benefit except for non significant short term gains and further research was needed on the long-term benefits and risks for the woman and baby.

ACOG committee opinion in 2017 states that a single repeat course of antenatal corticosteroids should be considered in women who are less than 34 0/7 weeks of gestation who are at risk of preterm delivery within 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously. Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario.

Contraindications to the use of antenatal corticosteroids?

Caution should be exercised when giving corticosteroid therapy to women with systemic infection including tuberculosis or sepsis and cases of overt chorioamnionitis. In women with diabetes mellitus, additional insulin should be given according to an agreed protocol and be closely monitored.

Effect of antenatal steroids on intraventricular hemorrhage

Intraventricular hemorrhage (IVH) is a significant cause of preterm morbidity and mortality, with approximately 12,000 infants developing IVH every year in the United States. IVH occurs in nearly half of infants born at extremely low birth weight (500-750 g). Infants who survive a severe IVH (Grade III or IV) may be at higher risk of significant long-term or permanent neurological injuries/deficits, including cerebral palsy, mental retardation, and post-hemorrhagic hydrocephalus.

A Cochrane review in 2006 consisting of a meta-analysis of randomized trials demonstrated a reduced risk of IVH (relative risk 0.54, 95% confidence interval 0.43 to 0.69) with antenatal steroid therapy. In a recent observational study, in 25,979 very low birth weight infants, antenatal steroid use was associated with a reduction in incidence of any grade of intraventricular hemorrhage (odds ratio = 0.51, 95% confidence interval: 0.45, 0.58) and a reduction in incidence of severe intraventricular hemorrhage (odds ratio = 0.62, 95% confidence interval: 0.57, 0.67).

Conclusion

To conclude a single course of antenatal steroids either betamethasone or dexamethasone is recommended for both early and late preterm births and women undergoing cesarean section <39 weeks. Although ACOG committee opinion 2017 suggests a repeat course, a universal consensus of all societies on repeat course of steroids is still to be arrived. Continued surveillance of long-term outcomes after in utero corticosteroid exposure should be supported. Quality improvement strategies to optimize appropriate and timely antenatal corticosteroid administration are encouraged.

Suggested reading

1. Wei JC, Catalano R, Profit J, Gould JB, Lee HC. Impact of Antenatal Steroids on Intraventricular Hemorrhage in Very Low Birth Weight Infants. *J perinatol* 2016; 36(5):352-6.
2. Wapner R, Jobe AH. Art and Science, Clinics in Perinatology. 2011; 38(3): 529-45.
3. Wapner RJ, Gyamfi-Bannerman C, Thom EA; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. What we have learned about antenatal corticosteroid regimens. Semin Perinatol. 2016;40(5):291-7.
4. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2017; 3: CD004454.
5. Saccone G, Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials. BMJ. 2016; 355: i5044.
6. Stutchfield P, Whitaker R, Russell I. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomized trial. BMJ 2005;331:662-662
7. RCOG Green top guideline No.7. October 2010. Antenatal Corticosteroids to Reduce Neonatal Morbidity and Mortality
8. El-Sayed YY, Borders AE, Gyamfi-Bannerman C. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice; Society for Maternal– Fetal Medicine. Committee Opinion No. 713 Summary: Antenatal Corticosteroid Therapy for Fetal Maturation. Obstet Gynecol. 2016; 128(4): e187-94.
9. C. Gyamfi-Bannerman, E.A. Thom, S.C. Blackwell, *et al.* Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med 2016; 374 (14): 1311-20

Block Your Dates for FOGSI Events

Date	Place & Venue	Congress	Coordinators	Contact No.	Email
03 - 04 February	Varanasi	FOGSI for Fraternity Conclave	Dr Anuradha Khanna Dr Archana Shah Dr Anjali Rani Dr Ruchi Pathak Dr Sangeeta Rai	9415343904 8052922000 9936044220 9839603421 9621591247	dr_anuradhakhanna@gmail.com dr.archana.sah@gmail.com anjaliraniimsbhu@gmail.com drruchipathak@gmail.com dr.sangeeta1975@gmail.com
17 - 18 March	Manesar	Adbhut Matrutva	Dr BK Subhada Neel Dr Nitika Sobti	9820676002 9899045401	dr.spneel@gmail.com drnikitasobti@gmail.com
27 - 29 April	Dehradun	YUVA FOGSI North Zone	Dr Pratima Mittal Dr Vineeta Gupta Dr Luna Pant	9810027762 9758284395 9997572306	drpratima@hotmail.com lunapant@gmail.com
29 April	Dehradun	M.C.M.	Dr Jaydeep Tank Dr Neharika Malhotra Bora	9820106354 8055387886	drjaydeeptank@gmail.com dr.neharika@gmail.com
18 - 20 May	Ahmedabad	Conference on "Multiple Pregnancy & Medical Disorders"	Dr M C Patel Dr Jayprakash Shah	9825027818 9426356198	drmcp54@yahoo.co.in rajnijp@yahoo.com
01 - 03 June	Delhi	International Women's Health Summit	Dr Narendra Malhotra Dr Anupam Gupta Dr S N Basu	9837033335 9837030836 9429617556	mnmhagra3@gmail.com attocagra@gmail.com ssndoasu@gmail.com
23 - 24 June	Patna	FOGSI - ISPAT GFMCON (Genetics Conference)	Dr Narendra Malhotra Dr Abha Rani Sinha Dr Pragya Mishra Choudhary Dr Saurabh Dani	9837033335 9835273668 9869069200	mnmhagra3@gmail.com pragyamishra@hotmail.com dr.saurabh.dani@gmail.com
29 June - 01 July	Bangalore	Conference on Critical Care in Obs (FOGSI Endorsed)	Dr Shoba Gudi Dr Alpesh Gandhi	9980140778 9825063582	sngudi@yahoo.co.in gandhialpesh@gmail.com
28 - 29 July	Hotel Centre Point, Nagpur	Conference on Gestosis (FOGSI Endorsed)	Dr Suchitra N Pandit	9820416474	suchipan56@gmail.com
20 - 22 July	Udaipur	YUVA FOGSI West Zone	Dr Lila Vyas Dr Madhubala Chauhan Dr Lata Rajoria Dr Sudha Gandhi Dr Nupoor Hooja	9829099039 9352506105 9828086792 9413417037 9828025302	lilavyas_149@yahoo.com yuvafogsiwest2018@gmail.com
04 - 05 August	Indore	BREASTCON	Dr Kawita Bapat Dr Anju Dorbi	9826055666 9826657666 9826057666	bapatkawita@gmail.com info@breastcon.com anjudorbi@gmail.com
17 - 19 August	Manesar	Leadership Summit & Capacity Building	Dr Jaideep Malhotra Dr Neharika Malhotra Bora Dr Deepak Gupta	9897033335 8055387886	jaideepmalhotraagra@gmail.com drjaideepmalhotra@gmail.com dr.neharika@gmail.com
07 - 09 September	Vijaywada	YUVA FOGSI South Zone	Dr Jayam Kanna Dr Avimeni Sasibala	9382828429 9848128252	drjayamkannan@rediffmail.com sbavimeni@gmail.com
22 - 23 September	Mumbai	FOGSI MCM	Dr Jaydeep Tank Dr Madhuri Patel	9820106354 9869042132	drjaydeeptank@gmail.com drmadhuripatel@gmail.com
14 - 19 October	Rio, Brazil	FIGO Rio	Group Travel to Rio Dr Narendra Malhotra	 9837033335	 mnmhagra3@gmail.com
27 - 28 October	Kanpur	Women Health for Women Empowerment Conference	Dr Meera Agnihotri Dr Kiran Pandey Dr Kalpana Dixit	9838004050 9415050322 9832202687	drmeeraagnihotri@rediffmail.com dr.kiranpandey@gmail.com drvikasdikshit@yahoo.co.in
16 - 18 November	Hyderabad	ICOG Conference	Dr Shantha Kumari Dr Parag Biniwale	9848031857 9822023061	drshanthakumari@yahoo.com parag.biniwale@gmail.com
22 - 24 Novermber	Gangtok	YUVA FOGSI East Zone	Dr Rajat Kumar Ray Dr Hafizur Rehman	9438391319 9733400336	rajatkuray@rediffmail.com dr_hafizurrose86@rediffmail.com
08 - 09 December	Chennai	FWCON 2018 Adolescent Conference	Dr Jayam Kannan Dr Sampath Kumari	9382828429 9382828429	drjayamkannan@rediffmail.com drskumari@yahoo.co.in

Journal Scan

Bindiya Gupta
Assistant Professor, Department of Obstetrics & Gynecology, UCMS & Guru Teg Bahadur Hospital, Delhi

1. Hormones (Athens). 2017 Jul;16(3):282-290.

Maternal serum placental growth hormone, insulin-like growth factors and their binding proteins at 20 weeks' gestation in pregnancies complicated by gestational diabetes mellitus

Liao S, Vickers MH, Taylor RS, Fraser M, McCowan LME, Baker PN, Perry JK

Objective

To investigate whether maternal serum concentrations of placental growth hormone (GH-V), insulin-like growth factor (IGF) 1 and 2, and IGF binding proteins (IGFBP) 1 and 3 were altered in pregnancies complicated by gestational diabetes mellitus (GDM).

Method

In a nested case-control study, GDM cases (n=28) and matched controls (n=28) were selected from the Screening for Pregnancy Endpoints (SCOPE) biobank in Auckland, New Zealand. Maternal serum hormone concentrations at 20 weeks of gestation were determined by enzyme-linked immunosorbent assay (ELISA).

Results

There was no significant difference in maternal serum GH-V concentration in the GDM group compared to the control group (1.64 ± 0.11 ng/ml vs. 1.38 ± 0.10 ng/ml, p=0.079). However, GDM cases who delivered large for gestational age (LGA) babies had significantly higher serum GH-V concentrations compared to non-diabetic control cases. Maternal IGF-1 concentrations in GDM pregnancies were significantly higher than in controls (275.7 ± 11.5 ng/ml vs. 218.5 ± 11.1 ng/ml, p <0.001). Maternal IGFBP-1 concentrations were significantly lower in GDM pregnancies than in controls (41.04 ± 3.42 ng/ml vs. 67.58 ± 6.17 ng/ml, p <0.001). There were no significant differences in serum IGF-2 and IGFBP-3 concentrations between groups.

Conclusion

Concentrations of IGF-1 and IGFBP-1 in maternal serum were altered in GDM pregnancies compared to controls, suggesting that the IGF axis plays a role in the development of this condition. GH-V may be associated with macrosomia as increased maternal GH-V was observed in GDM cases who delivered LGA babies

2. Eur J Endocrinol. 2018 Feb;178(2):191-199.

Pregnancy outcomes are not altered by variation in thyroid function within the normal range in women free of thyroid disease

Veltri F, Kleynen P, Grabczan L, Salajan A, Rozenberg S, Pepersack T, Poppe K

Objective

In the recently revised guidelines on the management of thyroid dysfunction during pregnancy, treatment with thyroid hormone (LT4) is not recommended in women without thyroid autoimmunity (TAI) and TSH levels in the range 2.5-4.0 mIU/L, and in a recent study in that particular group of pregnant women, more complications were observed when a treatment with LT4 was given. The objective of the study was therefore to investigate whether variation in thyroid function within the normal (non-pregnant) range in women free of thyroid disease was associated with altered pregnancy outcomes?

Design

Cross-sectional data analysis of 1321 pregnant women nested within an ongoing prospective collection of pregnant women's data in a single centre in Brussels, Belgium.

Methods

Thyroid peroxidase antibodies (TPO-abs), thyroid-stimulating hormone (TSH), free T4 (FT4) and ferritin levels were measured and baseline characteristics were recorded. Women taking LT4, with TAI and thyroid function outside the normal non-pregnant range were excluded. Pregnancy outcomes and baseline characteristics were correlated with all TSH and FT4 levels within the normal range and compared between two groups (TSH cut-off < and ≥2.5 mIU/L).

Results

Tobacco use was associated with higher serum TSH levels (OR: 1.38; CI 95%: 1.08-1.74); P = 0.009. FT4 levels were

inversely correlated with age and BMI (rho = -0.096 and -0.089; P < 0.001 and 0.001 respectively) and positively correlated with ferritin levels (rho = 0.097; P < 0.001). Postpartum haemorrhage (>500 mL) was inversely associated with serum FT4 levels (OR: 0.35; CI 95%: 0.13-0.96); P = 0.040. Also 10% of women free of thyroid disease had serum TSH levels ≥2.5 mIU/L.

Conclusions

Variation in thyroid function during the first trimester within the normal (non-pregnant) range in women free of thyroid disease was not associated with altered pregnancy outcomes. These results add evidence to the recommendation against LT4 treatment in pregnant women with high normal TSH levels and without TPO antibodies.

3. Minerva Endocrinol. 2017 Dec 21. doi: 10.23736/S0391-1977.17.02792-4. [Epub ahead of print]

Prolactinomas: how to handle prior to and during pregnancy?

Glezer A, Bronstein MD

Prolactinomas are the most common cause of pathological hyperprolactinemia, leading to central hypogonadism and, therefore, a frequent etiology of infertility. Treatment, usually with dopamine agonist (DA), can reverse hyperprolactinemia and hypogonadism, allowing pregnancyin the majority of cases. Bromocriptine is still the DA of choice for such purpose. Important issues in DA-induced pregnancies include fetal exposition, both malformations and neuropsychological development and tumor size increase. Regarding microprolactinomas and intrasellar macroprolactinomas, DA should be withdraw as soon as pregnancy is confirmed. In expansive/invasive macroprolactinomas, DA maintenance should be individualized. Patient follow up includes periodically clinical evaluation, sellar imaging only indicated in the presence of tumor mass effects related symptoms. Neurosurgery, both before and during gestation, is indicated in cases in which DA treatment failed. Breastfeeding is usually allowed. As tumor volume decrease and remission of hyperprolactinemia may occur after pregnancy, serum prolactin levels and tumor status should be reevaluated.

4. Eur J Endocrinol. 2018 Jan;178(1):131-137

Metformin in gestational diabetes mellitus: predictors of poor response

Gante I, Melo L, Dores J, Ruas L, Almeida MDC

Objective

Metformin can be regarded as a first-line treatment in gestational diabetes mellitus (GDM) due to its safety and effectiveness. However, a proportion of women do not achieve adequate glycemic control with metformin alone. We aim to identify predictors of this poor response to metformin.

Design and Methods

Retrospective multicentre cohort study of women with GDM who started metformin as first-line treatment. The assessed cohort was divided into a metformin group and metformin plus insulin group. Biometric and demographic characteristics, glycemic control data, obstetric, neonatal and postpartum outcomes were compared between groups and analysed in order to identify predictors of poor response to metformin. Data were analysed using STATA, version 13.1.

Results

Of the 388 women enrolled in the study, 135 (34.8%) required additional insulin therapy to achieve the glycemic targets. Higher age (aOR: 1.08 (1.03-1.13), $P = 0.003$), higher pre-pregnancy body mass index (BMI) (1.06 (1.02-1.10), $P = 0.003$) and earlier introduction of metformin (0.89 (0.85-0.94), $P < 0.001$) were independent predictors for insulin supplementation. Regarding all the analysed outcomes, only cesarean delivery rates and postpartum glucose levels were higher in women requiring insulin supplementation.

Conclusions

Although almost 35% of women did not achieve adequate glycemic control with metformin, insulin supplementation was not associated with poor neonatal outcomes. Higher age, higher pre-pregnancy BMI and earlier introduction of metformin could be used as predictors of poor response to metformin.

Proceedings of AOGD Monthly Clinical Meet

AOGD Monthly Clinical Meeting was organized at Ram Manohar Lohia Hospital, New Delhi on 25th January 2017. It was attended by 60 Gynaecologists from all over NCR. The meeting was initiated with a welcome note by the HOD, Dr Bani Sarkar. Dr Shalini Rajaram, President AOGD, addressed the gathering followed by a brief outline of AOGD achievements and forth coming events by secretary, Dr Abha Sharma.

1. Peripartum Cardiomyopathy

Ananta Kanwar, P. Singh, Poonam Yadav, Sushma Rani, Shikha Sharma, Kamna Datta

Pregnancy is a unique physiological state. It is not uncommon to encounter cases of dyspnea, pedal edema, tachycardia and increased BP especially in late pregnancy or postpartum period. The obstetricians with restricted armamentarium investigate for these symptoms, and once basic investigations are normal, these symptoms are attributed to pregnancy which may not be the case as happened in the present cases.

Case1: A 24yrs parous female with first uneventful live birth who underwent elective LSCS and developed acute pulmonary edema in immediate postoperative period. She was incubated, kept on inotropes for 6 days and was diagnosed with peripartum cardiomyopathy (PPCM) on 2D ECHO. Now she is recovering and following in Cardiology OPD.

Case 2: A 34yrs G3P1L1A1 with previous LSCS underwent elective caesarean and was discharged satisfactorily. She was admitted again after 5 weeks of delivery in medicine emergency with complaints of breathlessness and orthopnea. 2D ECHO done showed ejection fraction of 25% and confirmed PPCM. Currently she is waiting for heart transplant in AIIMS.

PPCM is a form of dilated cardiomyopathy of unclear etiology affecting women without pre-existing heart disease during the last month of pregnancy or during the first 5 months postpartum. Speculated etiologies include inflammation, apoptosis, abnormal prolactin metabolism. Patient presents with symptoms of cardiac failure with changes in 2D ECHO. Management includes a multidisciplinary approach with involvement of cardiologist, anesthetist and obstetrician.

2. Managing placenta percreta with bladder invasion: an abstruse challenge

Veena Ganju Malla, Indu Chawla, Nidhi Garg

A 35 year old G5 P1 L1 A4 with previous history of one cesarean section, 2 surgical MTPs & 2 D&Es for missed abortion, was diagnosed as having low lying anterior placenta at first trimester scan followed by suspected placenta percreta with bladder invasion at 25 weeks scan which was later confirmed by MRI. Patient underwent preterm classical cesarean section at 34 weeks with bilateral internal artery ligation followed by subtotal hysterectomy with bladder repair with a multidisciplinary team of senior obstetricians, urologists, CTVS surgeons, anesthetists, hematologists and pediatrician. Patient required massive transfusion intraoperatively. Postoperative period was marked by acute kidney injury treated with dialysis. Mother and baby were discharged happy and healthy on postoperative day 25.

Placenta percreta, the rarest and most severe form of placenta accreta, can involve the urinary bladder with an occurrence of 0.3-1 per 10000 births. Because of its propensity for severe hemorrhage, it is a potentially life-threatening condition, with a high mortality rate of 5.6-10%. Women at greatest risk of morbidly adherent placenta are those who have myometrial damage caused by previous cesarean delivery with either an anterior or posterior placenta previa overlying the uterine scar. Although commonly discovered at the time of delivery, antenatal diagnosis may be achieved with ultrasound, magnetic resonance imaging, and/or cystoscopy. The optimum gestational age for scheduled delivery is between 34-36 weeks to reduce the risk of patient needing emergency surgery. .Antenatal corticosteroids are administered as per standard guidelines. Management by a multidisciplinary team and delivery in a tertiary care facility improve the outcome and lower the complication rates. The management options are planned preterm classical cesarean delivery with cesarean hysterectomy with placenta in situ or conservative and may be individualized.

3. A Case Report of Uterine Arterio-Venous Malformation

Parul Sharma, Bani Sarkar

A 48 year old P1L1A1 presented to Gynae OPD with complaints of heavy menstrual bleeding since 10 yrs. Despite being offered cyclic progesterone therapy, patient's condition did not improve. Patient went to AIIMS for the same, where she was investigated and diagnosed as a case of Uterine arterio-venous malformation(AVM) on USG color Doppler. She was advised embolisation but patient wanted definitive treatment. So she came to Dr. RML Hospital, where she was worked up and prepared for definitive surgery. Hysterectomy was done. HPE report confirmed Uterine AVM.

Uterine AVM is a potentially life threatening but treatable condition. Conservative management in the form of embolisation is a safe and effective method in women desirous of future childbearing. However, the definitive treatment remains Hysterectomy.

Quiz Time: *Tick it, Fill it, Click it, Whatsapp/ Email it*

Rashmi, Bindiya Gupta

Assistant Professor, Department of Obstetrics & Gynecology, University College of Medical Sciences & Guru Teg Bahadur Hospital, Delhi

Q1. Regarding insulin therapy in pregnancy, mark true or false

a) Regular human insulin has increased risk of post meal hypoglycemia (T/F)

b) NPH has duration of action 16-18 hours (T/F)

c) Insulin Glargine can be used in pregnancy(T/F)

d) Insulin Lispro and Aspart should be given 15-30 minutes before meal (T/F)

Q2. Insulin should be started in GDM when despite MNT and Exercise

a) Fasting blood glucose > ----------

b) 1 hour Postprandial blood glucose >----------

c) 2 hour postprandial blood glucose >----------

Q3. According to ACOG insulin therapy if required in pregnancy, starting dose is

.....

Q4. According to American Thyroid Association Guidelines 2017, the upper reference limit for Serum TSH is

.....

Q5. Write the full forms of the following trials

a. APOSTEL-III

b. ALPS

c. BEARS

d. ASTECS

Q 6. Fill in the blanks:

a. Mechanism of action of atosiban is ……. ……..

b. Dose of betamethasone for lung maturity is ……..……..

c. Dosage schedule of atosiban is ……...

d. Three conditions besides RDS for which antenatal steroids are useful:

a. ……..……..

b. ……..……..

c. ……..……..

Q7. What is true about prolactinomas in pregnancy:

a. Serum prolactin levels should be repeated in each trimester

b. Dopamine agonist therapy should be stopped as soon as pregnancy is confirmed in Macroprolactinomas

c. If there is enlargement of macroadenoma during pregnancy with pressure on optic chiasm, urgent transshenoidal surgery is indicated

d. Dopamine agonist therapy should be restarted in all women with prolactinoma after delivery

Q8. What are the recommendations regarding Vit D Supplementation in pregnancy:

a. NICE 2017: ……..

b. WHO : ……..

c. ACOG: ……..

Q9. What is the accepted definition of short cervical length:

……..

Q10. What is false regarding progesterone therapy in pregnancy:

a. In singleton pregnancy with short cervix & no prior PTB, vaginal progesterone gel of 90mg may prevent PTB

b. Screening for short cervix should be performed in multiple pregnancies

c. Singleton pregnancies with prior spontaneous PTB, progesterone supplementation is started at 16 weeks

d. In Singleton pregnancy with past history of second trimester loss, TVU screening is stopped at 24 weeks

Tick the MCQs and fill in the blanks.
Click a pic and whatsapp or email to us
Whatsapp Nos.: 9810645212, 9810719002
Email: secretaryaogd2017@gmail.com

Refer page 12 for Previous answer key.

Royal College of Obstetricians & Gynaecologists
AICC Northern Zone India

Website: **www.aiccrcognzindia.com**

Chairperson: Dr Nirmala Agarwal: (n.menoky@gmail.com /9811888732)

Vice Chairperson	Hon. Secretary	Treasurer	Web Editor
Dr Anita Kaul	Dr Arbinder Dang	Dr Ranjana Sharma	Dr Anjila Aneja

RCOG UK Franchise MRCOG Final Preparation: Part II Written Course

Friday 1st – Sunday 3rd June 2018 (Total 3 Days)

Limited to 25 candidates only (First Come First Serve basis)

Overview

This revision course is aimed at candidates preparing for the next Part 2 MRCOG exam. It focuses on polishing your exam techniques to improve your chances of passing the written papers. Developed and taught by experienced MRCOG Examiners, this course reflects the new format and standards of the Part 2 MRCOG written exam from July 2018. You will hear about the exam question formats and will have ample opportunity to practice Single Best Answer Questions (SBAs) and Extended Matching Questions (EMQs). This course will map the RCOG core curriculum and the examination syllabus, and you will also have lectures from experts about current developments and hot topics in key curriculum areas.

We recommend you book early to avoid disappointment. There are a maximum of **25** places.

Who should attend?

- Candidate sitting the July 2018 Part 2 MRCOG exam

After completing this course, you will be able to:

- Gain familiarity with the new format of the part 2 MRCOG written papers
- Understand the standard of the required knowledge
- Understand core O&G topics in relation to UK practice
- Understand training within the NHS

Course Fee: Rs 30,000

Venue - RCOG North Zone Academic Centre
B-235, C R Park, New Delhi-110019, INDIA

UK Conveners of International Part 2 Revision Course - Ms Rhona Hughes
UK Course Organizer & Convener - Dr Sanjeev Sharma

India Conveners and Contacts for details - Dr Saritha Shamsunder (shamsundersaritha@gmail.com/9313826748)
Dr Sweta Gupta (swetagupta06@yahoo.com/8130140007)
Dr Mamta Sahu (mamta2sahu@yahoo.co.in/ 9810106470)

Certificate of attendance for this course will be provided by the RCOG UK

Registration Guidelines (Online registration available on website)

- Registration form to be downloaded from website www.aiccrcognzindia.com.
- Bank Transfer or Demand Draft must be made in favour of "RCOG NZ 2012 Plus" payable at New Delhi. (cheques not accepted).
- There will be no refunds on cancelation.
- Registration request along with Demand Draft to be posted to the Secretariat mailing address as given below:-

Mailing Address:
RCOG North Zone Secretariat
OT Complex 3rd Floor Sant Parmanand Hospital, 18 Shamnath Marg, Civil Lines, Delhi 110054
Mr Asif Muniri (Administrative Assistant) +919560069925 / 9716801190, Tel No - 91-11-23981260, 23994401-10 Ext 314
Email: rcog_nz2012@yahoo.com/ n.menoky@gmail.com/ arbidang@gmail.com

MEMBERSHIP FORM

ASSOCIATION OF OBSTETRICIANS & GYNAECOLOGISTS OF DELHI

Member's Name: .....

Surname: .....

Initial Name: .....

Middle Name: .....

Qualification: .....

Postal Address: .....

City: ..... State: ..... Pin code: .....

Place of Working: .....

Residence Ph. No. ..... Clinical/Hospital Ph. No. .....

Mobile No: ..... Email: .....

Gender: Male: ..... Female: .....

Date of Birth: Date ..... Month ..... Year .....

Member of Any Society .....

Proposed by .....

Cheque/DD No: .....

Enclosed: Cheque/Demand Draft should be drawn in favour of:

Association of Obstetricians and Gynaecologists of Delhi

For Life Membership : Rs. 11,000/-
For New Annual Membership* : Rs. 2,000/-
For Old Renewal Membership+ : Rs. 1,200/-

Encl.: Attach Two Photocopies of All Degrees and Two Photographs
***- Annual Membership is for the calendar year January to December.**
+ - In case of renewal, mention old membership number

Send completed membership form along with cheque to:

AOGD OFFICE

AOGD Secretariat: Room No 712, 7th Floor, Private Ward, MCH Block
Department of Obstetrics & Gynecology, Guru Teg Bahadur Hospital & University College of Medical Sciences
Dilshad Garden, Delhi-110095, India
Email: secretaryaogd2017@gmail.com
www.aogd.org

Postal Registration No. DL(E)-20/5525/2017-19
February 14-15, Date of Publication, February 7-8
Registered with Registrar of Newspapers for India
DELENG/2001/04547/8.25" x 11.25"