AOGD BULLETIN

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Safeguarding women and their Doctors

Issue Theme:
Miscarriage - The Bane

AOGD SECRETARIAT

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Foreword

It's a pleasure and an honour to write the foreword for this issue of AOGD bulletin. AOGD bulletins have maintained a high academic standard and provide easy to read, current practices of managing common obstetric and gynaecological conditions based on latest advancements.

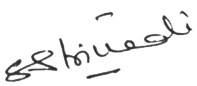
The August issue focuses on various aspects of miscarriage including recurrent pregnancy loss. Write up on prediction and prevention of this distressing condition will interest all the practising obstetricians and is very well described in this issue.

Progesterone has been widely used during pregnancy, usually empirically, for prevention of abortion and preterm labor. Results of high quality research quoted in this issue reassure us and give us confidence to use it rationally in various conditions.

The theme of AOGD 2022-23 is 'Safeguarding Women and their Doctors'. Working along these lines the article on "Violence Against Doctors" is of great help. Starting right from identifying different forms of violence and the roles and responsibilities of different segments of the society, media and the government, is a must know for all of us to effectively prevent and handle such untoward situations.

Editorial team of MAMC and all the authors have done a great job and this issue will provide an interesting and very useful reading.

My best wishes to all the AOGD members and AOGD team at Maulana Azad Medical College for a wonderful year ahead.



Prof Shubha Sagar Trivedi
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From the AOGD Office


Dr. Asmita M. Rathore


Dr. Y. M. Mala


Dr. Deepti Goswami

Warm greetings to all for the 75th Independence day !

August 15th was the day of commemoration of 75 years of glorious independence and is a proud moment for all Indians. We remember the struggle Indians faced and even lost many brave lives.

The present issue of bulletin is on miscarriage and Violence against doctors. Miscarriage can be multifactorial and many a times no cause could be found. It has an emotional impact on the woman and her family and is devastating if it is recurrent. The management of pregnancy loss has many controversial issues. In this bulletin various aspects have been covered and we hope it will be of use for all treating obstetricians.

Another important aspect covered is a grave issue, which is violence against doctors. As an association we should unite and fight for justice and strengthen laws to prevent such incidents. In case any member needs help they can approach AOGD Risk Management Support group.
Hoping for a safe work place environment for all doctors.

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From the Editor's Desk

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Greetings to all !

Dear Friends,

The editorial team is happy to present to you the AOGD Bulletin for the month of August 2022.

The torment of losing a pregnancy anytime is immense. Any treatment which can prevent is eagerly looked forward to equally by the expectant mother and the treating doctor. How much we all may want treatments to be helpful, medicine calls for evidence. Walking this road we bring to you the role of progesterone in miscarriage under the Game Changer section as progesterone support in miscarriage is widely practiced. The evidence brought forth by the PROMISE & PRISM RCTs alongside the Cochrane review 2021 make the picture clear.

In this issue we have attempted to bring forth topics which are of use in daily practice. The baggage that comes with a miscarriage is varied affecting both the physical and mental health of the woman. It can breach the sense of self-trust and self-compassion with overwhelming negative emotions and frustration with oneself.

What would be better than to be able to predict a miscarriage and also prevent it. Biomarkers and ultrasound findings may be of assistance in these unforeseen situations. Losing a pregnancy repeatedly is agonizing and baffling when no cause can be identified. The investigations in recurrent pregnancy loss have to be focused and justified and so should be the targeted management. We do not need to order the whole gamut of investigations or prescribe every possible treatment option available. Different progesterones are used during pregnancy for varying indications and which one to use when backed by evidence is what everyone wants to know.

All this has been covered very well by the authors and miscarriage being a very common occurence makes it interesting. I sincerely thank them for their contribution.

In August the article under the "Safeguarding the Doctors" is on "Violence against Doctors". The author walks us through various types of violence, predictors and the role society has to play to bring an end to this evil. A good insight into triggers so as to avoid such happenings. We need a shift towards a culture that does not recognize violence as a necessary component of behavior.

Your views and comments are welcome and these are important to improve with every issue.

Yours in health

Dr. Madhavi M Gupta
Editor

AOGD Risk Management Support [ARMS] Group

One of the ways to ensure the stress-free work environment and optimal patient care is mutual support among professional colleagues. We propose to form an advisory group of senior AOGD members that can be contacted if one of us is caught in a complex clinical dilemma / dealing with aggressive clients or is apprehensive about how to document or effectively troubleshoot a potential problem. This group will provide the timely advice and will be led by-

Convener- **Dr. Vijay Zutshi** - 9818319110

Co convener- **Dr. Aruna Nigam** - 9868656051

We invite suggestions from all members regarding functioning of this cell which will guide us forming the SOPs. Any member interested in being part of Advisory group may contact the convener.

Pl mail to aogdmamc2022@gmail.com

Game Changer:
Progesterone in Miscarriage -PROMISE & PRISM RCTs and Meta-analysis

Madhavi M Gupta*, Nalini Bala Pandey**
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Abstract of the research articles are available free at the journal websites and on PubMed (http://www.ncbi. nlm.nih.gov/pubmed

Miscarriage, defined as the spontaneous loss of a pregnancy before 24 weeks gestation, is common with approximately 25% of women experiencing a miscarriage in their lifetime, and 15% to 20% of pregnancies ending in a miscarriage.[1] Progesterone is essential to maintain a healthy pregnancy.[2] Several small trials have suggested that progesterone therapy may rescue a pregnancy in women with early pregnancy bleeding (threatened miscarriage), and to prevent miscarriages in asymptomatic women who have a history of three or more previous miscarriages (recurrent miscarriage).[1]

There is uncertainty about the effectiveness, safety, and side-effects of the available progestogens for preventing miscarriage in different groups of women. Guidance from the RCOG and a Cochrane review called for a definitive trial to test whether or not progesterone therapy in the first trimester could reduce the risk of miscarriage in women with a history of unexplained recurrent miscarriage (RM).[3] The findings and conclusion of the PROMISE study, the PRISM RCT, and two meta-analysis including the Cochrane Review have been briefly provided.

PROMISE RCT

PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages - a randomised, double-blind, placebo-controlled, international multicentre trial and economic evaluation

Coomarasamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S, Gupta P, Dawood F, Koot YE, Atik RB, Bloemenkamp KW, Brady R, Briley A, Cavallaro R, Cheong YC, Chu J, Eapen A, Essex H, Ewies A, Hoek A, Kaaijk EM, Koks CA, Li TC, MacLean M, Mol BW, Moore J, Parrott S, Ross JA, Sharpe L, Stewart J, Trépel D, Vaithilingam N, Farquharson RG, Kilby MD, Khalaf Y, Goddijn M, Regan L, Rai R. PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages - a randomised, double-blind, placebo-controlled, international multicentre trial and economic evaluation. Health Technol Assess. 2016 May;20(41):1-9

Trial registration: ISRCTN92644181; EudraCT 2009-011208-42; Research Ethics Committee 09/H1208/44.

It was a randomised, double-blind, placebo-controlled, international multicentre study conducted across 36 sites in the UK and 9 sites in the Netherlands. The intervention had two arms of women with unexplained RM (three or more first-trimester losses), aged between 18 and 39 years and conceived naturally. One arm received micronised progesterone at a dose of 400 mg (two vaginal capsules of 200 mg) and the second received placebo vaginal capsules twice daily, administered vaginally from soon after a positive urinary pregnancy test (and no later than 6 weeks of gestation) until 12 completed weeks of gestation (or earlier if the pregnancy ended before 12 weeks).

Main outcome measures: Live birth beyond 24 completed weeks of gestation (primary outcome), clinical pregnancy at 6-8 weeks, ongoing pregnancy at 12 weeks, miscarriage, gestation at delivery, neonatal survival at 28 days of life, congenital abnormalities and resource use.

Of the 836 women randomised between 2010 and 2013, 404 received progesterone and 432 received placebo. The follow-up rate to primary outcome was 826 out of 836 (98.8%). The live birth rate in the progesterone group was 65.8% (262/398) and in the placebo group it was 63.3%

(271/428), giving a relative risk of 1.04 (95% confidence interval 0.94 to 1.15; p = 0.45). There was no evidence of a significant difference between the groups for any of the secondary outcomes.

The authors concluded that there is no evidence that first-trimester progesterone therapy improves outcomes in women with a history of unexplained RM.

Limitations: This study did not explore the effect of treatment with other progesterone preparations or treatment during the luteal phase of the menstrual cycle.

PRISM RCT

Progesterone to prevent miscarriage in women with early pregnancy bleeding: the PRISM RCT

Coomarasamy A, Harb HM, Devall AJ, Cheed V, Roberts TE, Goranitis I, Ogwulu CB, Williams HM, Gallos ID, Eapen A, Daniels JP, Ahmed A, Bender-Atik R, Bhatia K, Bottomley C, Brewin J, Choudhary M, Crosfill F, Deb S, Duncan WC, Ewer A, Hinshaw K, Holland T, Izzat F, Johns J, Lumsden MA, Manda P, Norman JE, Nunes N, Overton CE, Kriedt K, Quenby S, Rao S, Ross J, Shahid A, Underwood M, Vaithilingham N, Watkins L, Wykes C, Horne AW, Jurkovic D, Middleton LJ. Progesterone to prevent miscarriage in women with early pregnancy bleeding: the PRISM RCT. Health Technol Assess. 2020 Jun;24(33):1-70.

Trial registration: Current Controlled Trials ISRCTN14163439, EudraCT 2014-002348-42 and Integrated Research Application System (IRAS) 158326.

It was a multicentre, double-blind, placebo-controlled, randomised trial with 48 hospitals in the UK participating. Women aged 16 – 39 years with early pregnancy vaginal bleeding were randomised in two arms, with one receiving twice-daily vaginal suppositories containing 400 mg of micronized progesterone and the second arm receiving matched placebo from presentation to 16 weeks of gestation.

Main outcome measures: The primary outcome was live birth at ≥ 34 weeks. A total of 4153 women received either progesterone (n = 2079) or placebo (n = 2074). The follow-up rate for the primary outcome was 97.2% (4038 out of 4153 participants). Altogether, 2972 participants had a live birth after at least 34 weeks of gestation The live birth rate was 75% (1513 out of 2025 participants) in the progesterone group and 72% (1459 out of 2013 participants) in the placebo group (relative rate 1.03, 95% confidence interval 1.00 to 1.07; p = 0.08). Although the live birth rate was 3% higher in the progesterone group than in the placebo group, there was statistical uncertainty about this finding. There were no significant differences in the rate of adverse events between the groups.

Conclusions: Progesterone therapy in the first trimester of pregnancy did not result in a significantly higher rate of live births among women with threatened miscarriage overall, but an important subgroup effect was identified.

However, it was observed that women with a history of one or more previous miscarriages and vaginal bleeding in their current pregnancy may benefit from progesterone.

For women with no previous miscarriages, the live birth rate was 74% (824 out of 1111 participants) in the progesterone group compared with 75% (840 out of 1127 participants) in the placebo group.

For women with one or more previous miscarriages, the live birth rate was 75% (689 out of 914 participants) in the progesterone group compared with 70% (619 out of 886 participants) in the placebo group.

The potential benefit appeared to be most strong for women with three or more previous miscarriages, who had a live birth rate of 72% (98 out of 137 participants) in the progesterone group compared with 57% (85 out of 148 participants) in the placebo group. Treatment with progesterone did not appear to have any negative effects.

Progestogens for preventing miscarriage: a network meta-analysis

Devall AJ, Papadopoulou A, Podesek M, Haas DM, Price MJ, Coomarasamy A, Gallos ID. Progestogens for preventing miscarriage: a network meta-analysis. ***Cochrane Database Syst Rev.*** 2021 Apr 19;4(4):CD013792.

The objective was this review was to estimate the relative effectiveness and safety profiles for the different progestogen treatments for threatened and recurrent miscarriage, and provide rankings of the available treatments

according to their effectiveness, safety, and side-effect profile.

This meta-analysis included seven randomised trials involving 5,682 women, and all provided data for meta-analysis. All trials were conducted in hospital settings. Across seven trials (14 treatment arms), the following treatments were used: three arms (21%) used vaginal micronized progesterone; three arms (21%) used dydrogesterone; one arm (7%) used oral micronized progesterone; one arm (7%) used 17-α-hydroxyprogesterone, and six arms (43%) used placebo.

The reviewers concluded that the overall available evidence suggests that progestogens probably make little or no difference to live birth rate for women with threatened or recurrent miscarriage when compared with placebo. However, vaginal micronized progesterone may increase the live birth rate for women with a history of one or more previous miscarriages and early pregnancy bleeding, with likely no difference in adverse events. Those women who had no previous miscarriages, but were now presenting with early pregnancy bleeding showed no improvement in live birth rate (high-certainty evidence). There is still uncertainty over the effectiveness and safety of alternative progestogen treatments for threatened and recurrent miscarriage.

Efficacy of progesterone on threatened miscarriage: an updated meta-analysis of randomized trials

Yan Y, Chen Z, Yang Y, Zheng X, Zou M, Cheng G, Yuan Z. Efficacy of progesterone on threatened miscarriage: an updated meta-analysis of randomized trials. Arch Gynecol Obstet. 2021 Jan;303(1):27-36.

This meta-analysis was conducted with the purpose to evaluate the correlation between progesterone and improving pregnancy outcomes in women with threatened miscarriage. It included nine randomised controlled involving 4,907 women, aimed to demonstrate the efficacy of progesterone on the threatened miscarriage pregnancy. The outcomes were miscarriage, preterm birth, and live birth.

Compared with placebo or no treatment, progesterone supplementation had a relationship with a reduction in the rate of miscarriage [RR 0.70 95% CI (0.52, 0.94)]. However, there was no significant difference between progesterone supplementation and placebo or no treatment in preterm birth [RR 0.87 95% CI (0.52, 1.47) and live birth (RR 1.02 95% CI (0.98, 1.07)].

Progesterone supplementation had a relationship with a reduction in the rate of miscarriage among threatened miscarriage pregnancy compared with placebo or no treatment arm. However, there was no significant difference between progesterone supplementation and placebo or no treatment in preterm birth [RR 0.87 95% CI (0.52, 1.47) and live birth (RR 1.02 95% CI (0.98, 1.07).

The authors concluded that progesterone supplementation did not significantly improve the incidence of preterm and live birth, so progesterone treatment of threatened miscarriage may be unhelpful.

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Miscarriage - Can we predict and prevent?

Sumitra Bachani* Bijoya Mukherjee **
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Miscarriage refers to the spontaneous loss of intrauterine pregnancy before 20 weeks of gestation. The word 'Miscarriage' includes terminologies such as an-embryonic pregnancy, embryonic demise, fetal demise and missed abortion/asymptomatic pregnancy loss. Nearly 10-15% of pregnancies undergo miscarriage, however, a rising trend in miscarriages has been observed in the recent COVID 19 pandemic in some populations.[1] Early pregnancy loss upto the first trimester is more common and second trimester losses comprise 1% of the total losses. The unplanned loss of pregnancy can be challenging to the women, both physically and mentally and also poses diagnostic challenge to the obstetricians. In this article, we throw light on the prediction and early diagnosis of miscarriage, the various possible preventive measures and its management.

PREDICTION: Miscarriage is an unexpected and unwanted event that can happen despite all measures. It is difficult to predict which pregnancy can result in a miscarriage. Studies have reported that combination of maternal risk factors, hormonal levels and ultrasonographic features may be used in predicting subsequent miscarriage in a live embryo, but there is still an element of error and it needs further validation.

Maternal factors:

1. Maternal age: Advancing maternal age (>35 years) has been linked with the increasing rate of aneuploidies, a decline in both the number and quality of the remaining oocytes, which contribute to the increased chances of miscarriage.[2] There is also controversial evidence regarding decline of progesterone support in early pregnancy in advanced maternal age.[2] Advanced paternal age (>40 years) has also been identified as a risk factor for miscarriage.[3]
2. Race and Ethnicity: Genetic and environmental factors affect implantation and placentation for which it has been noted that Africans have almost 60% more miscarriage rates than Caucasians.[2] This difference may not be truly biologic and could likely be due to the impact of the cumulative stressors of systemic racism, social determinants of health, and unavoidable occupational and/or environmental exposure to potential toxins.
3. Smoking, alcohol and illicit drugs: Causes placentation defect and is linked with increased rates of miscarriage. Smoking, caffeine, and alcohol consumption in general appear to increase the risk of pregnancy loss in a dose-related manner. Some studies have also reported increased risk with cocaine or methamphetamines. Substance abuse is also associated with poor health status of the individual which can be a contributory factor.
4. Environmental factors and exposures: While exposure to ionising radiation is definitely related to miscarriage excessive lead, arsenic and environmental pollutants have also been implicated for pregnancy loss by causing cell death, altering growth of normal tissues, or interfering with normal cellular differentiation.
5. Medications: Drugs with a known teratogenic effects can result in loss of pregnancy depending on the agent, dose and timing of exposure. The COVID -19 vaccination taken in the preconception period or early pregnancy does not seem to increase the risk of pregnancy loss. Detailed information regarding the impact of specific drugs on the risk of miscarriage is available at the United States National Library of Medicine toxicology data network site.
6. Body Mass Index (BMI): A BMI of more than 25 can increase the odds of miscarriage by 70% upto 20 weeks in spontaneous or assisted conceptions.
7. Previous miscarriage: Each miscarriage increases the chance of pregnancy loss in subsequent pregnancy, reaching 40% after 3 consecutive pregnancy loss irrespective of maternal age.[3] It has been observed to occur in subsequent generations thus having a

possibility of an inheritable component.

8. Medical conditions including infections: Endocrinopathies, cardiovascular and metabolic disorders have been implicated in early pregnancy loss, however these are modifiable and if well controlled can improve outcomes. Untreated syphilis leads to a 21% increased risk of fetal loss and stillbirth. Maternal viral infections have been associated with fetal loss rates nearly 8 % for parvovirus B19, 6 % for Zika virus, and 2.5 % for cytomegalovirus.
9. Stress: Both acute and chronic stress can increase the risk of pregnancy loss. Chronic stress leads to increased cortisol, decreased immunity and susceptibility to infections and it can be associated with other factors such as financial constrains or physical trauma which can aggravate the health condition. Physical trauma including intimate partner violence has been implicated in loss of pregnancy.
10. Antiphospholipid syndrome: The antiphospholipid antibodies inhibit trophoblastic function and differentiation and activate the complement pathways at the maternal–fetal interface resulting in a local inflammatory response. This can result in recurrent miscarriage.[3]
11. Inherited thrombophilia: The mechanism is not clear however it has been postulated that Factor V Leiden mutation, deficiencies of protein C, protein S, antithrombin III, hyperhomocysteinaemia and prothrombin gene mutation cause placental thrombosis which can lead to miscarriage.[3]
12. Congenital uterine malformations: Septate uterus has the highest risk of miscarriage, mostly in 1st trimester while arcuate uterus is associated with miscarriage in the second trimester.
13. Cervical weakness: An established cause of miscarriage in the second trimester is cervical shortening.
14. Parental chromosome abnormalities like balanced or Robertsonian translocation which can be inherited as unbalanced translocations by the fetus thus resulting in miscarriages.[3]
15. Chromosomal abnormalities of the fetus including monosomies and trisomies are an important cause of miscarriage.

Hormones: Serum estradiol, progesterone and Human chorionic gonadotrophin (HCG) levels increase with gestational age during 5–9 weeks. Serum estradiol and immune cells work together in pregnancy to maintain normal environmental milieu. Studies have reported that low serum estradiol levels at 5–6 and 7–9 weeks and progesterone at 7–9 weeks, specific to the gestational age, can serve as early predictors of miscarriage. B-HCG or progesterone level alone has little predictive value, but their combination with estradiol could improve its efficacy. β-HCG or progesterone combined with estradiol at 5–6 weeks of gestation and combination of estradiol and progesterone at 7–9 weeks of gestation can serve as good predictors of risk of miscarriage.[4]

Ultrasonographic features: Amongst the markers in early ultrasound, bradycardia {fetal heart rate (HR)<80 beats per minute(bpm)} at 6 weeks and <100 bpm at 7 weeks has been found to be the most sensitive marker for prediction of miscarriage, specially for threatened miscarriage.[5] Crown rump length (CRL)< 5th centile is a predictive marker of early pregnancy loss. Gestational sac diameter (GSD) <5th centile for gestational age and yolk sac diameter(YSD) >95th centile for gestational age are also reported to be strong predictors of early miscarriage. Small GSD for CRL is indicative of impaired placentation.[4] Subchorionic hematoma has variable outcomes and it not a strong predictor. Abnormal appearance/ rupture of amnion, deformed, wrinkled or calcified yolk sac have been associated with miscarriage though there is no definitive value in its prediction.[6]

There is evidence that combination of maternal age, racial origin, cigarette smoking, history of vaginal bleeding and the measurements of HR, GSD and YSD corrected for CRL is able to predict 86% of subsequent miscarriages. This is applicable to all pregnant women, irrespective of method of conception or history of menstrual cycles. Thus, one can advise women at high risk to undergo subsequent scan at 1-2 weeks interval to assess the progress of pregnancy while women at low risk can wait till 12 weeks of gestation.[2]

Diagnosis :

1. Clinical features: The presence of vaginal

bleeding with or without abdominal cramps along with history of amenorrhoea is suggestive of threatened pregnancy loss.

2. Ultrasonographic features: A pregnancy should be classified as being of 'unknown viability' when transvaginal ultrasonography has depicted the following, irrespective of the date of a woman's last menstrual period:[7]
   A) An intrauterine gestational sac seen with a Mean sac diameter (MSD) of 16-24 mm without a visible yolk sac or embryonic pole.
   B) An intrauterine gestational sac with MSD of less than 25mm with a yolk sac seen without a visible embryonic pole.
   C) An intrauterine gestational sac with an embryo with a CRL measuring less than 7 mm with no visible heartbeat.

In such cases a follow-up transvaginal ultrasound scan and a diagnosis of pregnancy failure may be made on the basis of the following findings.

1. Embryo with a CRL of more than 7 mm with no heartbeat.
2. Mean gestational sac diameter of more than or equal to 25 mm with no embryo.
3. An absence of an embryo with a heartbeat if more than two weeks has elapsed following a scan that depicted a gestational sac without a yolk sac.
4. An absence of an embryo with a heartbeat more than 11 days after a scan that depicted a gestational sac and yolk sac.

Missed miscarriage: Definitive diagnosis is based on the following ultrasound features:

1. MSD >25mm without any yolk sac or embryo
2. CRL>7mm without any heartbeat

If there is no visible heartbeat when the CRL is measured or If there is no visible fetal pole and the MSD is measured using a transabdominal ultrasound, a second scan is to be performed a minimum of 14 days after the first before confirming a diagnosis.

Incomplete miscarriage : On ultrasonography, an incomplete miscarriage may be defined as the finding of irregular heterogeneous echoes within the endometrial cavity and the diagnosis is based on the subjective impression of the examiner and the clinical findings. Power Doppler may have value in these circumstances by depicting significant vascularity in the event of retained tissue being present as opposed to a blood clot.[8]

Complete miscarriage : diagnosed on ultrasound when there is no evidence of intrauterine pregnancy wherein a previous scan had diagnosed a live pregnancy.

Threatened miscarriage: ultrasound depicts viable intrauterine pregnancy in presence of vaginal bleeding.

Prevention:

1. NICE recommends use of progesterone as prevention of miscarriage in women who have experienced vaginal bleeding in early pregnancy and has at least one previous miscarriage, though evidences does not suggest absolute efficacy in each pregnancy. The dose needed is 400 mg twice daily till 16 weeks of gestation.[9]
2. Premarital and Preconception counselling can play a major role in optimising the woman's health. Genetic factors, inheritance of familial disorders can be investigated. Avoiding known miscarriage risk factors - such as smoking, drinking alcohol and illicit drug use.
3. Limiting caffeine intake.
4. Folic acid supplementation 0.4mg daily to be started in preconception period as folate deficiency is linked to early miscarriage.[10]
5. Preconception control of endocrinopathies and optimisation of cardiovascular disorders.
6. Use of low dose aspirin and low molecular weight heparin helps in prevention of miscarriages in thrombophilias.
7. Surgical correction of uterine anomalies where indicated.
8. Cervical cerclage if there is history of previous three spontaneous loss of pregnancy or history of miscarriage along with ultrasound evidence of cervical shortening. It can be carried out preconceptionally also.[11]
9. Seeking regular prenatal and antenatal care.
10. Seeking psychosocial support in conditions of chronic stress such as intimate partner violence.

Impact on Mental Health:

Pregnancy and birth is a joyful state which women share with family. The unexpected loss of pregnancy causes sudden shock to the pregnant woman, resulting in intense emotional distress. They suffer from social isolation by grieving alone while 20% develop depression after this period. In majority of them, symptoms of anxiety or depression persist for 1-3 years, thereby affecting quality of life and subsequent pregnancies.[12] Obstetricians are generally focused on physical management of miscarriage, while the psychological aspect is often ignored. It is therefore of utmost importance to utilize the Patient Health Care Questionaire-2 (PHQ 2) for screening of depressive symptoms and if found to be severe, patient should undergo rigorous follow up and assessment. Many women feel guilt regarding fetal loss, so they should be properly enquired about self blame.[13]

After a miscarriage, many women want information about why their miscarriage occurred and how it affects future pregnancies. The initial counselling should start within 1 week of miscarriage as distress is most marked during this time. It is recommended to wait for 6 months after miscarriage before planning the next pregnancy in order to allow time for physical and mental recovery.[13] Tender loving care must be offered to patients and they should be allowed to grieve with a support system in order to resume normalcy in daily lives.

Management :

As per NICE guidelines, the management of miscarriage is outlined as follows:[9]

a) Expectant management for 7 to 14 days is the first-line management for women with a confirmed diagnosis of miscarriage. A repeat scan may be done if bleeding and pain has not not started or symptoms continue to persist or exacerbate, suggestive of incomplete miscarriage.

b) Medical management:

1. Threatened miscarriage: Routine antenatal care is followed if bleeding stops within few days, but if bleeding persists beyond 14 days the patient should follow up with the obstetrician. She is advised to take 400mg vaginal progesterone twice daily till 16weeks if she also had a prior miscarriage.
2. Missed miscarriage: A single dose of 800µg of Misoprostol is advised vaginally or orally. Mifepristone should not be offered to such cases.
3. Incomplete miscarriage: A single dose of 600µg of Misoprostol is advised vaginally. Oral route can also be offered. Mifepristone is not given in incomplete miscarriage.
4. Medications for pain relief and antiemetics are also advised if needed.
5. Urine pregnancy test at home is advised after 3 weeks of medical management. If she has worsening of symptoms or a positive urine pregnancy test, she is asked to follow up with the obstetrician for further management.

c) Surgical management: In patients with worsening of symptoms or positive pregnancy test after 3 weeks of medical management, molar or ectopic pregnancy should be judiciously ruled out. In such cases and those with persistent vaginal bleeding, patients are offered surgical management.

1. Manual vacuum aspiration is done as outpatient setting or can also be done in operation theatre under anaesthesia.
2. Dilatation and evacuation is carried out in the second trimester.

The expelled tissue should always be sent for histo-pathological examination.

d) Anti-D immunoglobulin should be offered to all patients with surgical management and those with medical management >12 weeks of gestation.

e) Psychological support, pre and post procedure counselling and details of follow up should be conveyed in order to reduce the anxiety and fear associated with miscarriage.

Conclusion:

Miscarriage is a common condition in obstetric practice. Early prediction and prevention of miscarriage is of utmost importance to save couples from mental agony and further research is needed in this arena. The obstetricians must also focus upon the psychological needs of

the mother undergoing this tormenting event and provide supportive care to her in order to prevent long term mental health consequences. Improvements in these aspects can further enrich our obstetric practice and provide women with the precious moments of motherhood.

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Recurrent Pregnancy Loss- Investigations & Management

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Overview

1. When to investigate: Defining Recurrent pregnancy loss (RPL)
2. What is the etiology of RPL: Evidence-based investigations
3. Managing Idiopathic RPL
4. Summary of Work up and diagnosis: Do's and Don't's

1. When to investigate: Defining RPL

Providing a definition of RPL is important because the whole battery of investigations available is quite exhaustive and before a couple plunges into the financially and emotionally difficult journey there should be an agreement that it was required in the first place. Various organisations have given slightly varying definitions of RPL. The French practice guidelines defined RPL by the occurrence of three or more consecutive miscarriages before <14 weeks of gestation.[1]

There also has been an attempt to separately define the early and late pregnancy losses as they have a varied etiology resulting in management implications. So early recurrent pregnancy loss has been defined as 3 consecutive losses <10 weeks gestation & late recurrent losses as >10wk-< 16wks of gestation.[2]

ESHRE 2018 guidelines define Recurrent pregnancy loss (RPL) as the loss of two or more pregnancies.[3]

2. Prevalence and etiology of RPL: Evidence based investigations and treatment

2.1 Prevalence

Approximately 15 percent of pregnant women experience sporadic loss of a clinically recognized pregnancy. Just 2 percent of pregnant women experience two consecutive pregnancy losses and only 0.4 to 1 percent have three consecutive pregnancy losses.[4]

2.2 Etiology of RPL

These etiological factors have been associated with recurrent pregnancy losses. Despite extensive research , the definitive association has been proven only with a limited number of causes and almost 50% of cases remain idiopathic. Fig 1 shows the various causes implicated in RPL:

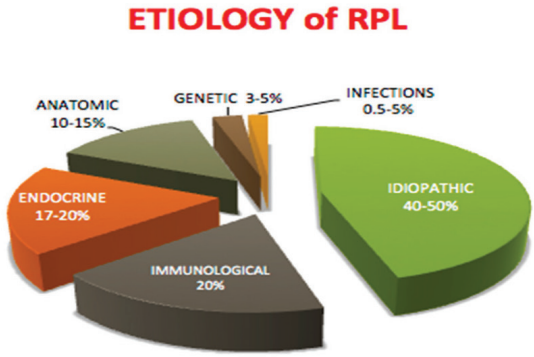

Figure: 1 : Etiology of RPL

2.2.1 Anatomic factors implicated in pregnancy losses

Various congenital and acquired uterine abnormalities have been implicated in causing pregnancy losses.

2.2.1.1 Pathophysiology

Congenital Anomalies

The prevalence of uterine anomalies in the general population is 4.3% while that in women with RPL has been reported to be 13%.[5]

The septate uterus is the uterine anomaly associated with the poorest reproductive outcome and the most common uterine abnormality associated with RPL.[6]

A history of first trimester losses was found in 42% of the women with a subseptate uterus and 16% of women with arcuate uterus. History of second-trimester loss was slightly more frequent among women with an arcuate uterus (8% vs. 4%).[7]

The etiology of pregnancy loss in uterine anomalies has not been clearly established. Uterine cavity distortion, poor implantation or even cervical insufficiency could be the

underlying cause but it has not been established.

Acquired Causes

Conditions like intrauterine adhesions, submucous fibroid, endometrial polyp and cervical incompetence are certain conditions that can affect the uterine cavity and hence can result in pregnancy losses.

2.2.1.2 Diagnosis

The options for uterine evaluation include techniques like hysterosalpingography, hysteroscopy, saline infusion sonography, 3D ultrasound and MRI.

- Sonohysterography: it shows the internal contours of the uterine cavity and also provides details of outer surface and wall of the uterus. It provides information on tubal patency and can distinguish between the septate and bicornuate uterus.
- Hysterosalpingography: It provides information on the uterine contour and cavity and also tubal patency but not about the outer surface and wall of the uterus, therefore it cannot reliably differentiate between a septate and a bicornuate uterus.
- Hysteroscopy — Hysteroscopy is the gold standard for the diagnosis of intrauterine abnormalities and also provides the option of treatment in the same sitting.
- 2D Ultrasound : It can provide information on uterine abnormalities and associated renal abnormalities. It can also delineate the number, size and location of fibroids.
- 3D Ultrasound : It can accurately diagnose various uterine anomalies. The availability and cost is an issue.
- MRI: MRI is useful for distinguishing between a septate and bicornuate uterus suspected on ultrasonography or HSG. It is less invasive and less expensive than laparoscopy for this purpose.

The preferred modality would depend on the availability and access for each provider and the patient. Hysteroscopy remains the gold standard for evaluating the uterine cavity but is more invasive than other modalities. Newer techniques like 3D USG and MRI are quite sensitive but are expensive.

The logical approach would be a 2-stage procedure in which :

Step 1: 2D USG, HSG, sonohysterography, hysteroscopy

Step2: If anomaly suspected: 3DUSG/MRI

2.2.1.3 Treatment of Uterine anomalies

The aspect of treatment of congenital and acquired anomalies has been a matter of debate. Although small individual trials have shown promising results on the benefits of interventions, there are no randomised controlled trials.

- A recent review[8] of hysteroscopic metroplasty for septate uterus has concluded that the overall success reported indicates its efficacy and reaffirms the place of minimally invasive treatment such as hysteroscopic metroplasty as the standard criterion and method of choice for treatment of this septate uterus.
- Hysteroscopic polypectomy may be considered for women with RPL if the polyp is large and where other possible causes have been excluded.
- For women with early RPL who have submucosal fibroids, myomectomy should be considered if no other causes have been identified.

Although direct evidence is not available, surgical removal of adhesions should be recommended for women with RPL who have no other known causes, with great precaution taken to prevent recurrence.

The paucity of randomized trials should remind practitioners to approach corrective procedures with the knowledge that surgery may not always improve a patient's chances for successful pregnancy.

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- All women with RPL should have an assessment of the uterine anatomy (Strong Recommendation)
- The preferred technique to evaluate the uterus is transvaginal 3D ultrasound (3D US), which has a high sensitivity and specificity, and can distinguish between septate uterus and Bicornuate uterus uterus with normal cervix (Conditional Recommendation)
- Sonohysterography (SHG) is more accurate than hysterosalpingography (HSG) in diagnosing uterine malformations. It can be used to evaluate uterine morphology when 3D ultrasound (3D US) is not available, or when tubal patency has to be investigated (Conditional Recommendation)
- If a Müllerian uterine malformation is diagnosed, further investigation (including investigation of the kidneys and urinary tract) should be considered (Conditional Recommendation)
- MRI is not recommended as first line option for the assessment of uterine malformations in women with RPL, but can be used where 3D ultrasound (3D US) is not available (Conditional Recommendation)

2.2.2 Genetic factors implicated in pregnancy losses

Genetic factors are implicated in RPL in 4-5% of cases. The purpose of estatblishing a genetic etiology in RPL is to be able to predict the chance of recurrence. Genetic abnormalities can be of two types:

a. Aneuploidies

b. Structural chromosomal rearrangements

   a. Aneuploidies: these are implicated as the underlying genetic cause more often in sporadic losses as compared to RPL (70% vs 30%). Of these Trisomy 16, monosomy X and polyploidies are the most frequent causes. Diagnosis requires a karyotype of the conceptus. Cells from chromosomally abnormal abortuses, especially trisomy 7 and triploidy, are less likely to grow in culture, thereby skewing the results of cohort studies of the frequency of aneuploidy in products of conception from spontaneously aborted pregnancies. Array comparative genomic hybridization (array-CGH) does not require dividing cells, and therefore can be useful in fetal demise with culture failure. Microarray however, cannot be presently recommended routinely for evaluation of RPL.

   b. Structural chromosomal rearrangements:

Parental balanced translocations affect 3% to 4% of couples with RPL. The most common types of balanced translocations are reciprocal translocations, which involve the exchange of genetic material from one chromosome to another, and Robertsonian translocations, whereby the long arms of 2 acrocentric chromosomes erroneously share a centrosome. Carriers of balanced translocations are typically asymptomatic, as they have the normal quantity of genetic material at all loci. However, during gametogenesis, the segregation of chromosomes may result in unbalanced gametes, which can lead to an increased miscarriage rate or ongoing conception with congenital anomalies. Although parental carriers of structural rearrangements have increased reproductive loss rates, similar to patients with unexplained RPL, most carriers of parental translocation will succeed in having successful pregnancies without intervention.

Practice Points :

- Knowledge of the karyotype of products of conception allows an informed prognosis for future pregnancy outcome
- Risk of miscarriage due to fetal aneuploidy decreases with an increasing number of pregnancy losses
- If the karyotype of miscarried pregnancy is abnormal, there is a better prognosis for the next pregnancy

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- Genetic analysis of pregnancy tissue is not routinely recommended but it could be performed for explanatory purposes (Conditional Recommendation)
- For genetic analysis of the pregnancy tissue, array-based comparative genomic hybridization (array-CGH) is recommended based on a reduced maternal contamination effect (Strong Recommendation)
- Parental karyotyping is not routinely recommended in couples with RPL. It could be carried out after individual assessment of risk (Conditional Recommendation)

2.2.3 Immunological factors implicated in pregnancy losses

Acquired Thrombophilias

Antiphospholipid antibody syndrome (APS)

Antiphospholipid antibody syndrome (APS) is one of the most established and treatable causes of recurrent pregnancy loss. The presence of antiphospholipid antibodies like lupus anticoagulant (LAC) and antiCardiolipin Antibodies (aCL) increase the risk of pregnancy loss. These antibodies lead to various pathophysiological changes like platelet aggregation, activation of coagulation cascade and complement system, stimulation of pro-inflammatory cytokines from the endothelial cells and also affect the placental trophoblastic cell growth and invasion.

2.2.3.1 Diagnosis

The diagnosis of APS can be made on the basis of at least one of the clinical and laboratory criteria as shown below :

Clinical Criteria:

- Vascular thrombosis- ≥1 episode of arterial, venous & small vessel thrombosis
- Pregnancy morbidity
- **≥1 Unexplained death of morphologically normal fetus at or beyond 10 wk**
- **≥1 premature birth of morphologically**

normal neonate before 34wks d/t severe preeclampsia or recognized f/o placental insufficiency

- **≥3 unexplainable consecutive sp. abortions before 10 wks**

Laboratory Criteria

- Anticardiolipin antibodies IgG or IgM on ≥2 occasions, at least 12 wks apart (>40GPL)
- Anti β2-glycoprotein on ≥2 occasions, at least 12 wks apart
- Lupus anticoagulant (LAC) on ≥2 occasions at least 12 wks apart

2.2.3.3 Management

Current recommended therapy for women with positive RPL diagnosed with APS and no history of prior thrombosis is prophylactic or intermediate dose unfractionated heparin (UFH) or prophylactic dose low–molecular weight heparin (LMWH) in combination with low-dose aspirin (LDA). The LDA may be started preconceptionally, and the heparin is started once a potentially viable pregnancy is identified (usually around 6 or 7wk gestation). One meta-analysis exploring the use of prophylactic heparin in conjunction with LDA suggested a 50% reduction in pregnancy loss compared with prednisone or LDA alone.[9] In women with APS and a history of prior thrombosis, full dose (therapeutic) regimens of UFH or LMWH should be used as depicted in table 1.

Table 1: Suggested Protocol for management of APS with RPL

APS in pregnancy without prior thrombosis
• Low dose aspirin (75-150mg OD) • Start pre-conceptionally • Stopped 4 weeks prior to EDD
• Heparin • Start at diagnosis of pregnancy • Stopped when: - Goes into spontaneous labour - Night before scheduled induction/LSCS
• Corticosteroid and Intravenous immunoglobulins –not recommended.

Hereditary Thrombophilias

Hereditary thrombophilias are a group of inherited conditions which accentuate the naturally procoagulant state in pregnancy and predispose to vascular thrombotic events. Although their association with thrombosis is well established, their role in obstetric mishaps is not yet clearly defined. The common conditions which have been associated with adverse pregnancy outcomes are:

- Factor V Leiden mutation
- Prothrombin G20210A mutation (PGA)
- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency
- Methyl tetrahydrofolate reductase deficiency (MTHFR)

Treatment of Hereditary Thrombophilias

Large trials have not validated the use of heparin to prevent adverse pregnancy outcomes in hereditary thrombophilias (TIPPS trial, 2014[10]). The present evidence does not support screening or treatment of hereditary thrombophilias in women with recurrent pregnancy losses.

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- For women with RPL, we suggest not to screen for hereditary thrombophilia unless in the context of research, or in women with additional risk factors for thrombophilia. (Conditional recommendation)

Other Immunological Factors

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- HLA determination in women with RPL is not recommended in clinical practice. (Conditional)
- Cytokine testing should not be used in women with RPL in clinical practice (Strong)
- Cytokine polymorphisms should not be tested in women with RPL (Strong)
- Antinuclear antibodies (ANA) testing could be considered for explanatory purposes (Conditional)
- There is insufficient evidence to recommend natural killer (NK) cell testing of either peripheral blood or endometrial tissue in women with RPL (Strong)
- Testing anti-HLA antibodies in women with RPL is not recommended (Strong)

2.2.4 Endocrine factors implicated in pregnancy losses

2.2.4.1 Thyroid disorders

Severe hypothyroidism and hyperthyroidism in pregnancy are associated with sporadic pregnancy loss and thyroid autoimmunity as documented by the presence of thyroid auto antibodies is specifically associated with RPL.

The role of subclinical hypothyroidism (TSH increased with normal T4) is still debated as a causative factor for RPL. A meta-analysis demonstrated the association of antithyroid antibodies in euthyroid women and recurrent pregnancy loss which when subsequently

treated, led to improved pregnancy outcomes.

2.2.4.2 Luteal Phase defects

Early pregnancy is supported by progesterone from the corpus luteum during the luteal phase till the time placenta takes over the function. The definition of abnormalities of the luteal phase known as the luteal phase defect is not standardized and there is no consensus. Studies have estimated the incidence of LPD to be between 17% and 28% in women with RPL. Many treatment options have been proposed for suspected LPD such as ovulation induction, hCG supplementation, and progesterone supplementation alone or in combination, but without any clear effect.

It has been seen that a low progesterone level in early pregnancy does not necessarily justify progesterone supplementation because it might simply reflect an abnormal secretion of hCG by a nonviable or ectopic pregnancy rather than LPD.[11]

Other endocrine factors:

- Obesity, hyperinsulinemia and hyperandrogenism are inherent risk factors for RPL
- Investigating for PCOS and insulin resistance and the role of metformin is not presently defined
- Treatment with cabergoline/bromocriptine can improve outcomes in women with hyperprolactinemia and RPL

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- Thyroid screening (thyroid-stimulating hormone [TSH] and thyroid peroxidase [TPO]-antibodies) is recommended in women with RPL (Strong recommendation)
- Abnormal thyroid-stimulating hormone (TSH) and thyroid peroxidase [TPO]-antibody levels should be followed up by thyroxine (T4) testing in women with RPL (Strong recommendation)
- Assessment of polycystic ovary syndrome (PCOS), fasting insulin and fasting glucose is not recommended in women with RPL to improve next pregnancy prognosis (Strong recommendation)
- Prolactin testing is not recommended in women with RPL in the absence of clinical symptoms of hyperprolactinemia (oligo/ amenorrhoea) (Conditionalrecommendation)
- Ovarian reserve testing is not routinely recommended in women with RPL
- (Strong recommendation)
- Luteal phase insufficiency testing is not recommended in women with RPL (Strong recommendation)

3. Managing Idiopathic RPL

3.1 Etiology

Unexplained RPL accounts for a significant proportion of women with RPL. Even this group is a highly heterogeneous group.

In up to 50% of women with RPL no cause can be found. Although, a certain proportion can be attributable to chance, a reasonably good prognosis can be expected with tender loving care with a live birth rate of 40-65%.

Possible etiologies could be ovarian ageing with a resultant decline in oocyte quality, sperm factors like Y chromosome microdeletions, oxidative stress and DNA fragmentation, endometrial factors and potential immunological factors like uterine and peripheral NK cells.

3.2 Treatment

3.2.1 Role of Progesterone

There is a large and conflicting data on the role of progesterone in idiopathic RPL. A meta-analysis by Coomarasamy[12] in 2011 and a Cochrane review[13] in 2013 reported that progesterone supplementation reduces the risk of abortion in RPL. However, the recent PROMISE trial14 has questioned the very role of progesterone in RPL.

The PROMISE study, which included 836 women with idiopathic RPL, found no difference in the live birth rate after progesterone supplementation (65.8% for progesterone vs. 63.3% for placebo). Currently, the role remains controversial till further evidence becomes available.

3.2.2 Immunotherapy for unexplained RPL

A Cochrane review 15 in 2014 looked at the evidence of various proposed immunological therapies like paternal cell immunization, third-party donor cell immunization, trophoblast membrane infusion and intravenous immunoglobulin. There was no significant benefit over placebo and these treatments should not be recommended.

3.2.3 Heparin in unexplained RPL

A review of more than 800 women from 9 studies did not find a benefit of using aspirin, heparin or a combination of both in women with unexplained RPL.[16] Hence this treatment should not be offered to women.

4. Summary of Work up and diagnosis: Do's and Don't's[17]

Evaluating RPL : The Do's

- Test for LAC , aCL, anti- **β-**2-GP1(IgG & IgM)
- Evaluate for uterine malformations with Imaging modality i.e SSG, HSG , MRI, Hysteroscopy
- Karyotype of conceptus should be obtained for etiological evaluation. Chromosomal microarray yields better results than conventional karyotype.
- Check for Thyroid, prolactin abnormalities (if symptomatic).

Evaluating RPL : The Dont's

- Test aPL antibodies other than LAC, aCL & anti-b2-GP1
- Perform endometrial biopsies
- Measure luteal phase progesterone levels
- Test Peripheral blood for immunological causes
- Obtain vaginal, cervical, or endometrial cultures
- Perform Serological titers TORCH
- Screen for inherited thrombophilias.
- Obtain semen analyses in absence of infertility

Treating RPL : The Do's

- Treat APS with heparin low-dose aspirin
- Consider surgically correcting uterine septa /fibroids polyps/adhesions
- Genetic counselling, consideration for IVF with PGD (limited evidence)
- Treat persistent hyperprolactinemia with dopamine agonist.
- Treat thyroid disease
- Offer frequent office visits & USG to ensure fetal viability

Treating RPL : The Dont's

- Treat women without APS with heparin
- Treat women with progesterone in unexplained RPL
- Treat with Immunomodulatory agents i.e IVIG, intralipids, prednisone, or immunizations

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Progesterone Use in Obstetrics

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Introduction

Progesterone word is derived from a Latin word 'gestare' which means "to bear" or "carry. It is one of the widely used molecule by obstetricians, discovered by Allen in 1935. Progesterone (21 carbon steroid) is derived from cholesterol and it can either be natural or synthetic. Synthetic progestins are used for contraception and gynaecological purposes.

For obstetrics purpose stereoisomer of progesterone (retro progesterone) called Dydrogesterone is used, which is metabolized in liver and it's metabolite dihydrodydrogesterone is active on the progesterone receptor. Progesterone is a naturally occurring steroid hormone that acts through its receptor ligand–activated nuclear transcription regulators to establish and maintain a pregnancy.

Progesterone uses in Obstetrics

Progesterone can be used by various route Oral, Vaginal, Deep intramuscular in obstetrics.

1. **Natural Progesterones (Micronized Progesterone):** These can be administered by oral, vaginal, rectal, and intramuscular or transdermal routes. Oral water soluble preparations are available. Dose- 200 to 800mg daily in divided doses.
2. **Synthetic Progestins:** 17α-hydroxy progesterone is administered as 250-500mg deep intramuscular injection.
3. **Progesterone derivatives:** Dydrogesterone is administered as oral tablets. Dose- 10 to 30mg daily.

Threatened Abortion/ miscarriage

Progesterone is most widely used in threatened abortion. It is a common complication affecting more than 20% of pregnancy. Progesterone is an essential hormone secreted by corpus luteum that provides support to early pregnancy up to 10 weeks, till placenta takes over the function. It is proved in clinical studies that low level of progesterone is linked with threatened abortion and vaginal bleeding in early pregnancy. Also progesterone support have showed improved outcomes for women with threatened abortion.

How progesterone helps?

1. Progesterone helps the endometrium in the process of implantation.
2. The pre-ovulatory increase in the secretion of 17 α-estradiol (E2) promotes the proliferation and differentiation of uterine epithelial cells. Then the production of progesterone takes place causing the proliferation and differentiation of stromal cells.
3. Progesterone acts on the endometrium via specific receptors.
4. It causes conversion of TH1 to TH2; as a response producing progesterone induced blocking factor (PIBF) and performs reduction of NK cells activity. Corpus luteum is the only source of progesterone during the luteal phase of the normal/routine menstrual cycle and in pregnancy.[1]

Low level of progesterone is thought to cause miscarriage but its whole and sole role is unclear. A Cochrane review done by Wahabi A et all that included seven randomized controlled trials, involving total of 696 participants from different countries, concluded that progesterone "probably reduces the risk of miscarriage" with a relative risk (RR) of 0.64 and a confidence interval CI of 0.47 to 0.87. The quality of evidence was considered moderate, and the trials included those with a small sample size (the largest trial included 191 participants; the smallest trial 35 participants). In addition, the route of progesterone administration and the dosage varied widely. A subgroup analysis indicated that treatment with oral progesterone reduced the miscarriage rate when compared with no treatment, whereas treatment with vaginal progesterone did not. A subgroup interaction analysis, however, showed no difference when comparing the route of administration.[2]

The 2019 PRISM trial, a large multicenter,

randomized, double-blind, placebo-controlled trial also was done to study the role of progesterone in miscarriages and recurrent pregnancy loss. The study involved 4153 women aged 16 to 39 years, who presented with vaginal bleeding in the presence of an intrauterine pregnancy of less than 12 weeks gestation. The RR of ongoing pregnancy at 12 weeks with 400 mg of twice-daily vaginal micronized progesterone was 1.04 (95% CI, 1.01-1.07) and of live births after at least 34 weeks, 1.03 (95% CI, 1.00-1.07; P = .08). A more pronounced effect was seen in those with a history of 3 or more miscarriages (RR, 1.28; 95% CI, 1.08-1.51; P = .007). The live birth rates in this subgroup were 72% in the treated group and 57% in the placebo group. Because the analysis was done on a prespecified study subgroup of 285 women, the authors stated that their observation required validation.[3]

A subsequent meta-analysis comprising 8 studies, including the PRISM trial, and 4833 patients found the RR of miscarriage to be lower in women taking progesterone (RR, 0.7, 95% CI, 0.52-0.94). The quality of evidence, however, was considered very low, and when limiting the analysis to only studies reporting live birth rates, no significant difference was found with or without progesterone supplementation.[4]

Recurrent pregnancy loss

The American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) define recurrent pregnancy loss (RPL) as the spontaneous loss of 2 or more pregnancies.[5,6] Earlier definitions required 3 or more pregnancy losses hence studies comparing treatment outcome differ with regard to RPL definition.

The most common cause of early pregnancy loss is chromosomal abnormalities. They account for approximately 60% of early miscarriages, with a lower prevalence in women with more advanced gestation and among those with RPL.[7] Other possible etiologies of RPL include anatomical factors, immunological factors such as the antiphospholipid syndrome, and endocrinological factors. Yet even after comprehensive examinations, the cause for RPL can be determined only in less than 50% of couples.[8]

As progesterone is required for both implantation and the maintenance of pregnancy, it has been postulated that a dysfunction in progesterone secretion or action could contribute to RPL. The condition related to insufficient progesterone action is known as luteal phase deficiency.

Luteal phase insufficiency or Luteal phase deficiency (LPD) was first described by Georgeanna Jones in 1949.[9] It is defined as a condition in which there is either deficient production of endogenous progesterone by corpus luteum or suboptimal response of the endometrium to otherwise normal progesterone concentrations.[10] Hence there is inadequate secretory changes of the endometrium after the ovulation of the dominant follicle.[11,12] It could be primary, in which no cause is found (idiopathic), or secondary to other pathologies including thyroid or prolactin disorders.

The first approach to treatment of potential LPD is the correction of any underlying condition like hypothalamic dysfunction, thyroid dysfunction or hyperprolactinemia. Empirical treatment of LPD is neither justified nor warranted as per the present evidence. Although it is given to promote endometrial maturation, to increase endometrial receptivity and to support implantation and development of early pregnancy.

Ovulation inducing drugs like clomiphene treat LPD by improving the quality and quantity of follicle, as suggested by few studies. There is no evidence that progesterone is beneficial in natural, unstimulated cycles. They are useful in controlled ovarian stimulation cycles for IVF.[13-15]

ASRM guidelines suggest a clinical diagnosis of luteal phase deficiency when a luteal phase lasts for 10 days or less.[16] The guidelines also state that short luteal phases have been diagnosed in fertile women and luteal phase deficiency has not been proved as a cause of RPL.

Several studies have evaluated the effect of progesterone supplementation in women with RPL. Kumar et al evaluated dydrogesterone (20 mg/day orally) in 360 women with a history of 3 or more pregnancy losses in a double-blind, randomized, placebo-controlled study.[17]

As seen in PROMISE trial, the largest trial which evaluated 836 women between the ages of 18 and 39 with a history of 3 or more pregnancy losses, the risk for another miscarriage was

higher in the placebo group (RR, 2.4; 95% CI, 1.3-5.9). Patients in the study group received 400 µg of micronized progesterone twice daily from the time of a positive urinary pregnancy test until 12 gestational weeks. The RR for live births after 24 weeks of gestation in the progesterone-treated group was 1.05 (95% CI, 0.94-1.15). The live birth rate in the progesterone group was 66% and in the placebo group 63%. The neonatal outcomes were comparable. No effect was found in the subgroups defined according to maternal age or number of previous miscarriages (3 or >4). The subgroup analysis by the number of previous miscarriages (3, 4, 5, or >6) showed a nonsignificant trend toward increased efficacy with increasing number of previous miscarriages.[18]

Clearly, no universal agreement exists regarding the use of progesterone in women with a history of RPL. The ASRM 2012 guidelines on the evaluation and treatment of RPL state that "in patients with 3 or more consecutive miscarriages immediately preceding their current pregnancy, empiric progesterone administration may be of some potential benefit."

ACOG guidelines [19] state that "women who have experienced at least 3 prior pregnancy losses may benefit from progesterone therapy in the first trimester." ESHRE guidelines on RPL state that "vaginal progesterone does not improve live birth rate in women with unexplained RPL" and "there is insufficient evidence to recommend the use of progesterone to improve live birth rate in women with RPL and luteal phase insufficiency."[20]

In July 2021, National Institute for Health and Care Excellence.[21] issued guidelines regarding progesterone administration in threatened miscarriage and recurrent pregnancy loss:

1. Offer vaginal micronized progesterone 400 mg twice daily to women with intrauterine pregnancy, confirmed by a scan, if they have vaginal bleeding and have a previous miscarriage.
2. If fetal heart beat is confirmed, continue progesterone until 16 completed weeks of pregnancy.
3. No benefit of vaginal/oral progesterone in women with early pregnancy bleeding but with no previous miscarriage, nor in women with previous miscarriage but no early pregnancy bleeding in current pregnancy
4. No overall benefit of progesterone in any form for use in recurrent miscarriage.
5. Also there is no evidence of any harm to fetus by progesterone use.

Role of progesterone in Prevention of Preterm Labor

Keirse (1990) suggested that supplemental administration of progesterone might reduce the rate of preterm birth in women at increased risk.[22]

Two randomized placebo-controlled trials whose findings were published in 2003 found that progesterone, administered as either weekly intramuscular injections of 250 mg of 17α-hydroxprogesterone caproate or daily progesterone vaginal suppositories,reduced the rate of recurrent preterm delivery by about a third.[23,24]

When these data were combined with data from earlier trials of supplemental progesterone in meta-analyses, the risk of recurrent preterm birth was reduced by 40 to 55 percent (in the study of Dodd et al. [2005] the RR was 0.58 and the 95 percent CI was 0.48 to 0.70; in the study of Sanchez-Ramos et al [2005] the RR was 0.45 and the 95 percent CI was 0.25 to 0.80). Unlike strategies targeted at a specific risk factor such as infection, supplemental progesterone treatment was effective at reducing the rates of preterm birth in women chosen only because of a prior preterm birth.[25,26]

This suggests three possibilities:

(1) that progesterone is effective in inhibiting a pathway shared by diverse causes of preterm birth,

(2) that progesterone has diverse effects that act on several different pathways, or

(3) that progesterone is very effective against one highly prevalent pathway or cause.

Although progesterone supplementation is promising, several questions about its use remain incompletely answered.

How does progesterone work?

The original rationale for progesterone prophylaxis was that it is a uterine relaxant, but some studies suggest it may act through an effect

on the inflammatory response.[27,28] The optimal dose, interval, and duration of treatment have also not been determined. Pharmacokinetic, pharmacodynamic, and pharmacogenetic studies of progesterone are urgently needed. The mechanism by which progesterone given to high-risk women is able to maintain uterine quiescence and prevent preterm birth is unknown. There is increasing evidence that the withdrawal of progesterone is associated with normal parturition and progesterone maintains this at the level of the uterus.

Petrini et al. (2005) projected that use of 17α-hydroxyprogesterone in women with a prior preterm birth would have a small but significant effect on the rate of preterm birth in the US(12.1% to 11.8% [p < .001])[29]

Multiple trials have evaluated the use of various progesterone preparations for the prophylaxis of recurrent preterm birth. 17α-hydroxyprogesterone caproate has been studied the most recently for the prevention of preterm birth.

The American College of Obstetrics and Gynecology recommends that if progesterone is to be given for the prevention of preterm birth, it is only indicated in women with a history of spontaneous preterm birth at <37 weeks' gestation.[30]

Progesterone is rapidly absorbed from the intramuscular site, reaching peak levels in ~8 hours. It is almost exclusively bound to plasma proteins, especially albumin and is metabolized by the liver and excreted renally.

As per the RCOG Guidelines[31] for prophylactic vaginal progesterone and prophylactic cervical cerclage (Nice Guidelines: NG25: PRETERM LABOUR AND BIRTH):

1. Offer a choice of prophylactic vaginal progesterone or prophylactic cervical cerclage to women who have both:
   - a history of spontaneous preterm birth (up to 34+0 weeks of pregnancy) or loss (from 16+0 weeks of pregnancy onwards), and
   - results from a transvaginal ultrasound scan carried out between 16+0 and 24+0 weeks of pregnancy that show a cervical length of 25 mm or less.
   - Discuss the risks and benefits of both options with the woman, and make a shared decision on which treatment is most suitable. [2019, amended 2022]
2. Consider prophylactic vaginal progesterone for women who have either:
   - a history of spontaneous preterm birth (up to 34+0 weeks of pregnancy) or loss (from 16+0 weeks of pregnancy onwards), or
   - results from a transvaginal ultrasound scan carried out between 16+0 and 24+0 weeks of pregnancy that show a cervical length of 25 mm or less.[2019, amended 2022]
3. When using vaginal progesterone, start treatment between 16+0 and 24+0 weeks of pregnancy and continue until at least 34 weeks. [2019]
4. Consider prophylactic cervical cerclage for women when results of a transvaginal ultrasound scan carried out between 16+0 and 24+0 weeks of pregnancy show a cervical length of 25 mm or less, who have had either:
   - preterm prelabour rupture of membranes (P-PROM) in previous pregnancy
   - a history of cervical trauma [2015, amended 2019]
5. If prophylactic cervical cerclage is used, ensure a plan is made and documented for removal of the suture. [2019, amended 2022]

Recommendations by SOGC Clinical Practice Guideline[32] in June 2020 on the use of progesterone for prevention of spontaneous preterm birth:

1. In women with a singleton pregnancy and a short cervical length (≤25 mm by transvaginal ultrasound between 16 and 24 weeks), vaginal progesterone therapy for prevention of spontaneous preterm birth is recommended (strong/moderate).
2. In women with a previous spontaneous preterm birth, vaginal progesterone therapy for prevention of spontaneous preterm birth is recommended (strong/moderate).
3. In women with a twin pregnancy (and by extrapolation of data, with a higher-order multiple pregnancy) and with a short cervical length (≤25 mm by transvaginal ultrasound between 16 and 24 weeks), vaginal progesterone therapy for prevention of spontaneous preterm birth is recommended (strong/moderate).

4. In patients with a singleton pregnancy and a previous spontaneous preterm birth or a cervical length ≤25 mm between 16 and 24 weeks in the current pregnancy, if a cerclage is being considered, vaginal progesterone should be offered as an effective and potentially superior alternate therapy (strong/moderate).
5. In patients using progesterone for prevention of spontaneous preterm birth, additional therapies such as a cervical cerclage (with exception of a rescue cerclage for an examination-based diagnosis) or a pessary are not recommended (strong/moderate).
6. In patients at increased risk of spontaneous preterm birth due to a previous preterm birth, a short cervical length in the current pregnancy, or a multiple pregnancy, bed rest or reduced activity is not recommended (strong/moderate).
7. When indicated for prevention of spontaneous preterm birth in a singleton pregnancy, vaginal micronized progesterone in a daily dose of 200 mg is recommended (strong/moderate).
8. When indicated for prevention of spontaneous preterm birth in a multiple pregnancy, vaginal micronized progesterone in a daily dose of 400 mg is recommended (conditional [weak]/low).
9. When indicated, vaginal progesterone therapy should be initiated between 16 and 24 weeks gestation, depending on when the risked factor is identified (strong/moderate).
10. With consideration of individual patient risk factors, vaginal progesterone therapy can be continued up to 34–36 weeks gestation (strong/moderate).

Side effects include skin site reactions, fever, insomnia, nausea, cerebral edema, cerebral thrombosis, edema, depression, somnolence, changes in cervical secretions, and cholestatic jaundice

Contraindications: Hypersensitivity to progesterone or any of its by-products, current history of venous or arterial thrombosis, carcinoma of the breast or genital tract, or active thrombophlebitis.

Safety of progesterone in pregnancy

One factor that plays a role in a clinician's decision-making process, apart from the specific treatment, is treatment safety. In a case control study, progesterone supplementation was associated with an increased risk of hypospadias (odds ratio [OR], 3.7; 95% CI, 2.3-6.0). The risk remained elevated even among cases that did not report any additional subfertility procedures or treatment (OR, 2.2; 95% CI, 1.0-5.0).[33]

The PROMISE and PRISM trials found no evidence for an increased risk of congenital malformations in women taking micronized vaginal progesterone. Although the studies were not powered to do so, this finding is reassuring. Despite limited data and low quality, both Cochrane reviews regarding threatened abortion and RPL found no increase in congenital anomalies in women treated with progesterone. In addition, controlled trials have shown no increased risk of congenital anomalies, including genital abnormalities resulting from progesterone exposure in early pregnancy.

The ASRM concluded that there is no evidence indicating that maternal exposure to progesterone increased the risk of birth defects.[34]

In an overview of birth defects reported between 1977 and 2005, 28 cases of a potential link between dydrogesterone use and congenital birth defects were reported.[35] The type of defects showed no specific pattern, suggesting that an association between dydrogesterone use and birth defects is unlikely.

More importantly, an estimated 10 million pregnant women received dydrogesterone during this period, also supporting the safety of dydrogesterone in pregnancy. Clinical studies of progesterone use during pregnancy, both oral and vaginal, support its tolerability and relatively minimal adverse effects.

Future role of progesterone is being evaluated in preeclampsia due to its immunomodulatory effects although currently no recommendation are available for its use. [36]

Progesterone and ART

Progesterone is also used widely in pregnancy by assisted reproductive technology. Progesterone is used routinely in most in vitro fertilization programs after egg retrieval to support the lining of the uterus. The theoretical basis for progesterone use rests on the assumption that a high level of estrogen requires more

progesterone to create an adequate uterine environment, and some of the progesterone producing potential of the ovary may be diminished after oocyte retrieval. In an early study on in vitro fertilization, pregnancy rates improved once progesterone was utilized. Although it is not known which patients require progesterone therapy during in vitro fertilization, most programs continue to use this medication for support of implantation.[37]

Progesterone treatment is recommended in ART cycles to enhance embryo implantation and decrease the risk of miscarriage.

1. In stimulated cycles, exogenous progesterone is highly recommended and should be initiated the day after oocyte retrieval.
2. In artificial cycles, exogenous progesterone is absolutely needed as no endogenous production of progesterone is present.
3. In natural cycles, exogenous progesterone might improve pregnancy outcomes.
4. Serum progesterone levels in the mid-luteal phase relate to the chances of pregnancy. Thus, monitoring progesterone levels and individualizing LPS is recommended.

Conclusion

Progesterone is an essential hormone in the process of reproduction. Once the therapeutic need of progesterone is established, the key factor is the decision of the best route to administer the hormone and the optimal dosage determination. Progesterone can be administered by many different routes, but the most utilized are oral, the vaginal and intramuscular administration. In obstetrics the most frequent uses of progesterone are in the treatment of threatened abortion, prevention of recurrent miscarriage, or in the support of the luteal phase in assisted reproduction programs, and in threatened preterm labor. Though guidelines are available for use in threatened miscarriage, recurrent pregnancy loss and preterm labor, proper dosage and protocols are yet to be made and measures should be taken for preventing unindicated usage of progesterone supplements.

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Calendar of Virtual Monthly Clinical Meetings 2022-23

26th August, 2022	All India Institute of Medical Sciences
30th September, 2022	Deen Dayal Upadhyay Hospital
28th October, 2022	PGIMSR & ESI Hospital
12th & 13th November, 2022	**44th Annual AOGD Conference (Physical)**
25th November, 2022	VMMC & Safdarjung Hospital
30th December, 2022	Sir Ganga Ram Hospital
27th January, 2023	ABVIMS & Dr Ram Manohar Lohia Hospital
24th February, 2023	UCMS & Guru Teg Bahadur Hospital
31st March, 2023	MAMC & Lok Nayak Hospital
28th April, 2023	LHMC & Smt. Sucheta Kriplani Hospital
26th May, 2023	Sitaram Bhartia Hospital

Risk Management- Violence against Doctors

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Introduction

Violence against doctors is a disease that is deep rooted into the mindset of people. It is an extreme manifestation of a worsening doctor patient relationship and reflects a deep crisis, arising from a socio-political breakdown. In its crudest form, it represents a mob mentality.

Though it is a global phenomenon, in India it has reached epidemic proportions. It has continued unabated despite the sacrifice of doctors in the recent corona pandemic.

Incidence

While Indian doctors have been winning accolades worldwide for their exemplary work, they have been facing a lot of hostility in their own country.

According to a study by the Indian Medical Association, about 75 percent of doctors have faced violence at work.

Types of violence

This violence may comprise

- Telephonic threats
- Intimidation
- Verbal abuse
- Physical but noninjurious assault
- Physical assault causing simple or grievous injury
- Murder
- Vandalism and arson

Effects of violence

Those who have suffered from violence have been known to develop-

- Psychological issues such as depression, insomnia, posttraumatic stress disorder, fear and anxiety leading to absenteeism[1]
- Many have suffered destruction of their clinics & hospitals, loss of practice with consequent financial losses
- Injured themselves and lost lives, both because of homicide and even suicide
- Loss of reputation

Risk factors

Health care professionals have been found to be at the highest risk of facing violence at work. Their risk of being injured and away from work is almost four times more compared to any other professional.[2]

A study of the risk factors has shown that following trends.[3]

- Age - Younger doctors face more violence
- Sex – Female doctors are more at risk
- Branch
  - o The department of Obstetrics & Gynaecology reported the highest rate of violence followed by Medicine with allied specialities and surgery with allied specialities
- Time
  - o The most common time of violence was during the visiting time
- Place
  - o The most common places that witnessed violence were the emergency area and the ICU. In the emergency almost 100 % doctors have reported some form of violence
- Type of violence
  - o The most common type of violence was verbal violence
- Cause
  - o The most common causes cited were long waiting time, delay in getting medical attention and denial of admission
- People involved
  - o In most cases it is not the patient but the relatives who resort to violence
  - o There could be goons, local politicians who can provoke people into violence against doctors

Violence faced by mental health professionals

About 45-50 % of psychiatrists have suffered violence, especially in the early phases of their career.[4] Their problem is unique as unlike other

specialities, they suffer violence not only at the hands of relatives but also from their patients who can get violent during treatment. In 2007, Dr Wayne S Fenton, Assistant Director of the National Institute of Mental Health was killed by his own schizophrenic patient who was undergoing treatment with him.[5] However, psychiatrists are better trained to deal with these situations.[3]

Factors responsible for violence against doctors

Policy issues

India spends less than 2 % of GDP on health care. This compares poorly to even the poorest countries in the world.

Over the years, rather than strengthening the primary health care and investing more on preventive medicine the focus has been more on developing tertiary care hospitals. With the entry of corporates into health care, it is now a flourishing health industry but is largely unaffordable to majority of population.

The government is responsible for only 20% of the health care delivery system. In majority places, it is the small nursing homes that are providing health care. Many of these may not be empanelled with insurance companies and patients pay out of their pockets leading to more grievances and violence.[6] These small set ups are many a times not equipped enough to handle all complication and may need to refer to higher centres. The problem is aggravated by the local goons who force them to treat the patients at their own place.

Even the government hospitals are not spared of violence. There are about 1 lakh doctors in government as compared to about 9 lakhs elsewhere. This along with a redundant infrastructure and a high patient load, translates to long strenuous duty hours especially of the resident doctors making them more susceptible to mistakes and prone to violence.[7] Further there is lack of security and surveillance, overcrowding and unrestricted access to almost all areas in a government hospital making them more vulnerable.

Socio- cultural factors

In India, doctors have been traditionally respected. But in the recent times too much has been spoken about profit booking, targets, writing tests and medicine just to make money, denting the image of doctors.

In a private hospital, doctors may be responsible for less than 20% of the bill, yet because it is their clinical decision that indirectly leads to the bill, the patients hold them responsible.[8]

The cost of medical care has increased globally but in India due to illiteracy and ignorance coupled with the irresponsible statements of influential people, people believe that their lives will be saved if they have paid more money.[9] There is an unrealistic expectation for a good outcome even in a high-risk situation.

Further media has almost always projected a negative image of medical professionals. Stings and sensationalism of news, often ignoring the crucial details that would otherwise exonerate a doctor in an incident of alleged medical negligence has further crippled the profession.

Viral videos every other day showing doctors getting beaten up by the relatives, with no video ever showing the perpetrators getting punished encourages people into resorting to violence whenever they feel cheated.

There are goons, local politicians who seize the death of a patient as an opportunity to display strength. There are rising number of notorious gangs, who openly solicit people to settle their hospital bills on a certain commission.

On 29th March 2022 in Dausa, Rajasthan, a meritorious doctor Dr Archana Sharma committed suicide after losing her patient to PPH. Local politician, journalist and police acting in collusion, held the hospital hostage over the dead body of the unfortunate patient merely to extort money from the doctor. They framed the doctor under section 302, murder, totally disregarding the Supreme Court's decision. Such cases are not in isolation, and portray the vulnerability of doctors working in remote areas.

Lack of civic responsibility amongst people, increasing intolerance and restlessness amongst youth, no fear of law, a general deterioration of

morality and ethics has further compounded the situation.

Medical Curriculum

Doctors have been taught clinical skills but are not given lessons on communication and empathy. Majority hospitals do not have a good grievance addressal system. Counselling or psychological support to relatives of critical patients or in case of death and bereavement is generally lacking.

Due to illiteracy amongst people and overburdened medical facilities these things have traditionally not been given importance in India but with increasing awareness amongst people, effective communication is a necessity and can improve patient satisfaction and doctor patient relationship.

Prediction of Violence

Lauretta Luck, researched in Australia and pointed that 'STAMP' violence assessment framework could be used to predict violence in hospitals and elsewhere.[10]

- S stands for Staring
  - o Staring has been found to be an early predictor and used to force a response from the health care professionals. Responding to this has averted violence in studies.
  - o Lack of eye contact has also been shown to mean anger and passive resistance.
- T for tone and volume of voice
  - o Raised voices, yelling, abusive language, caustic remarks have all been associated with violent behaviour.
- A for anxiety
  - o Anxiety in relatives of patients can escalate to violence and doctors should intervene before the anxiety reaches dangerous levels.
- M for mumbling
  - o Mumbling amongst relatives can denote heightened emotions and mounting agitation and should alert the health care professionals.
- P for pacing
  - o Pacing by relatives in wards or outside the doctor's clinic can again reflect mounting frustration that can explode into violence.
  - o Other physical indicators could be staggering, waving arms around or pulling away from the healthcare staff.

Prevention of violence against doctors

Defensive and fearful doctors are not in the best interests of a country that still suffers from a deficit of medical practitioners. There is an immediate need to rectify the situation.

Responsibility of the government

Providing affordable and quality health care is the responsibility of the government.

- The government should increase the health budget so that the health infrastructure improves along with better resources, staffing and an improved doctor-patient relationship leading to reduced violence.[11]
- Doctors are skilled professionals and should not be disrespected as a community through irresponsible statements especially in cases of alleged negligence without verifying facts.
- Government should come with initiatives such as easy loans to support young doctors and small hospitals, rather than exploit them through ambitious schemes that are difficult to sustain. Underpaid work neither gives job satisfaction nor can lead to a happy doctor-patient relationship.
- In cases of medical deaths or alleged negligence, the police should be sensitised to follow the Supreme Court ruling and not register FIR against the doctors under acts such as murder, cheating or arrest them. A medical board should be constituted, and their opinion sought. Erring police should be penalised.
- There is a tendency amongst people to allege negligence whenever there is a medical eventuality.[12] Such frivolous complains by people should be strongly deterred through legal provisions.
- There should be strong legislations and a political will to enforce the laws that protects health care professionals.
  - o The first law came into existence in Andhra Pradesh during the tenure of Chief Minister YS Raj Shekhar Reddy in 2007 who was a doctor himself. The law stated that any

violence against doctors would be treated as a nonbailable offense with a penalty of up to 50,000 rupees and a jail term of up to 3 years.[13]

- Around, 19 states of India have acts to protect medical professionals and health-care establishments from violence. However, till date no one has been penalised in such cases.[12]

Responsibility of media

Media should stop making doctors 'breaking news' to earn TRPs. Diagnosis is always hypothetical and there is always a risk of negative outcome.[11] Doctors cannot be held negligent for every eventuality.

Media should try to spread more positivity about the medical community. There should be legal deterrents against unscrupulous journalists indulging in wrongful and malicious reporting.

Responsibility of health professionals

- It is important to inculcate communication skills and develop empathy as part of medical curriculum. The MCI has introduced AETCOM (Attitude, Ethics & Communication) classes in medical schools for training young students.
- Doctors should regularly undergo assertiveness training, refusal skills, anger management, and stress management. Psychiatrists should be actively involved in such workshops.
- They should be trained into breaking bad news to family and there should be counsellors to deal with anxiety and bereavement of relatives.
- It is important for doctors not to overreach, timely refer patients, give time for proper counselling. There should not be any effort to either undermine or exaggerate the disease.
- Doctors should ensure proper documentation.
- They should update themselves regularly regarding legal provisions and acts pertaining to doctors.
- They should maintain a unified front with their own fraternity and reach out to each other in times of distress.
- There should be every effort to strike a healthy work life balance and destress regularly.

Role of professional bodies

- Professional and academic bodies should conduct regular meetings to update doctors, promote unity and harmony and reach out to them immediately in crisis.
- They should also be in regular contact with government and concerned authorities to ensure wellbeing of the medical community.

Responsibility of institutions

- Every hospital should have an effective security and closed-circuit television surveillance system.
- They should have their own protocols and mock drills to check their preparedness in dealing with violence.
- Worldwide SOPs such as 'code violet' is used to deal with such situations.[14]
  - The hospital should have a public address system to mobilise staff to the area of violence.
  - The staff should form a human chain around the professional under threat. They should maintain their calm and avoid any altercation with the relatives.
  - The security personnel should rush to the area and if needed police should be informed.
  - A senior member who is not part of the treating unit should communicate with the relatives and try to diffuse tension.
  - Once the situation is under control, the announcement should be made again on the public address system.
  - All institutes should have zero tolerance to workplace violence. Countries like UK and Australia have mandatory organisational and police reporting of violent acts.
  - They should ensure adequate staff, avoid overcrowding, limit number of relatives and their access to every place in the hospital.
  - Transparency in billing and a good financial counselling before admission reduces problems later.
  - Flag marking patients and relatives prone to violence has been suggested by clinicians but the practicality of this needs further evaluation.

Responsibility of people and society

People need to be sensitised about the travails

of medical community, medical laws and how to seek redressal. They need to understand that doctors are not God but are human and can make mistakes. However, there are stringent procedure to keep this in check and in case of any eventuality there is a procedure to seek redressal. Violence against doctors should be equated with an act of terror inviting penal action.

Conclusion

There is dearth of literature pertaining to violence against doctors. Even governments have failed to categorise it as a separate entity. There are laws in some states but the tendency of politicians and media to harp on public sympathy prevents the enforcement of these laws. We need to stop making doctors scapegoats and soft targets.

We need a shift towards a culture that does not recognise violence as a necessary component of behaviour and does not sacrifice doctors at the altar of duty and nobility.

Let's join hands together to put an end to this malady that infests our socio-political system, a raging fire called 'violence against doctors'.

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Events held in July 2022

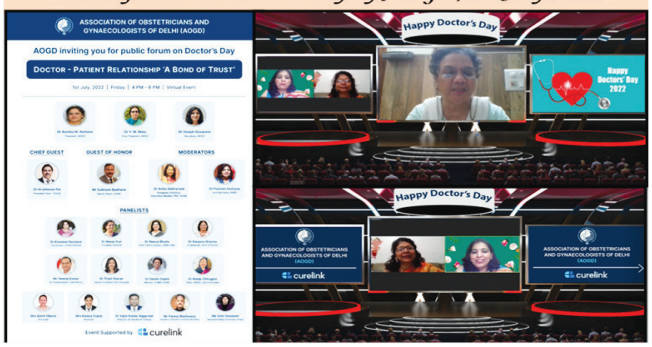
S no	Date	Events
1	01.07.2022	Webinar on Urodynamics for the beginner by Urogynaecology sub-committee
2	01.07.2022	Public form on Doctor's Day by AOGD
3	01.07.2022	Free Women Health Camp on cervical cancer awareness and pap smear by LBC under the aegis of Rural Health sub-committee
4	01.07.2022	CME by Safe motherhood sub-committee
5	02.07.2022	CME on "RPL & Threatened Abortion" by AOGD
6	06.07.2022	Webinar on adenomyosis under aegis of AOGD and ISOPARB in collaboration with SGRH
7	12.07.2022	Diagnosis and management of amenorrhea by Fetal medicine sub-committee (physical)
8	15.07.2022	CME on 'Women Health'" by DGF SW & DGF North under aegis of AOGD
9	16.07.2022	Public forum by Rural Health Committee
10	16.07.2022	Webinar on "Robotics in Gynae-oncology" by oncology sub-committee
11	18.07.2022	PG Forum on "Heart-disease in Pregnancy"
12	21.07.2022	CME by Infertility sub-committee
13	23.07.2022	Webinar on cervical cancer. by oncology sub-committee
14	23.07.2022	Awareness session on contraception at Muskan clinic by Dr Deepa Gupta
15	24.07.2022	Conference by IFS in association with AOGD
16	26.07.2022	Webinar on "A Stitch in time, prevents 9" by Breast and Cervical Cancer Awareness, Screening & Prevention sub-committee with DGF
17	28.07.2022	CME by Endoscopy sub-committee
18	29.07.2022	AOGD monthly clinical meeting at Army Hospital (R & R)
19	30.07.2022	Webinar on Critical care by multidisciplinary sub-committee with Safdarjung hospital

Forthcoming Events

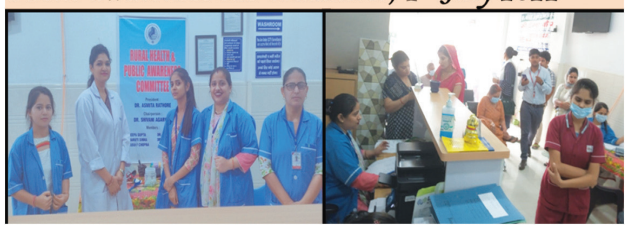
S. No.	Date	Events
	02.08.2022	Public forum on Breastfeeding awareness, Rural Health and Public awareness committee AOGD along with Adolescent sub-committee AOGD
	04.08.2022	CME by Infertility sub-committee & DGFS (physical)
	06.08.2022	Webinar on "Hyperglycemia in Pregnancy Interventions for Glycemic control" by AOGD
	07.08.2022	CME by Safe motherhood sub-committee with BLK Max Centre & NNFD
	13.08.2022	CME by oncology sub-committee with GTB
	15.08.2022	PG forum on Abdominopelvic mass by AIIMS & ESI
	17.08.2022	Webinar on "Preeclampsia screening" by Fetal medicine sub-committee
	21.08.2022	Public forum by Rural health sub-committee
	25.08.2022	CME by Endoscopy sub-committee
	25.08.2022	CME by endometriosis sub-committee
	26.08.2022	AOGD Monthly clinical meeting at AIIMS
	27.08.2022	Webinar breast and cervical cancer sub-committee
	27.08.2022	CME by Adolescent health sub-committee – (Physical)
	12th &13th NOV 2022	**ANNUAL AOGD CONFERENCE**

Events held under aegis of AOGD in July 2022

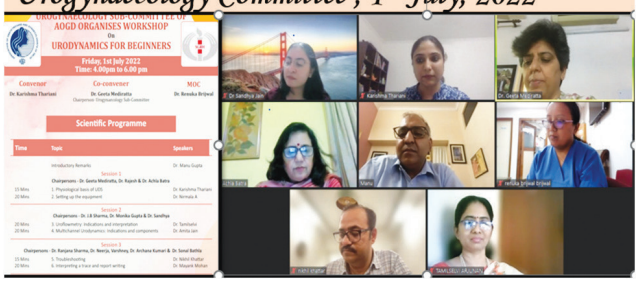
Public forum on Doctors day by AOGD, 1st July 2022



Public forum on Doctors day by Rural Health & Public awareness sub-committee, 1st July 2022

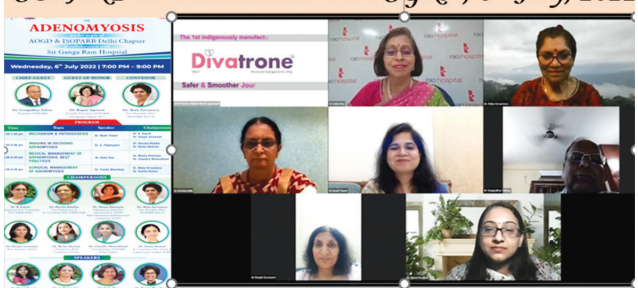


Webinar on Urodynamics for the beginner by Urogynaecology Committee , 1st July, 2022



CME on " RPL & THREATENED ABORTION" by AOGD, 2 July

Webinar on adenomyosis under aegis of AOGD and ISOPARB in collaboration with SGRH, 6th July, 2022

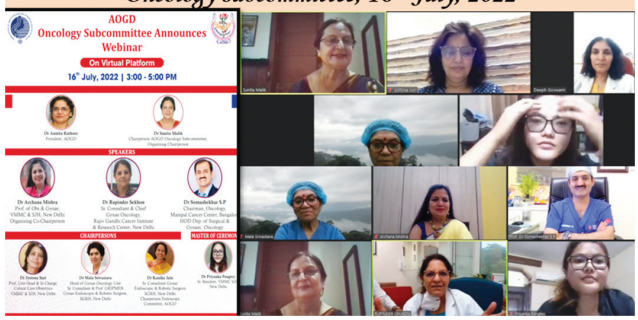


CME on Diagnosis and management of amenorrhea by Fetal medicine committee, 12 July, 2022

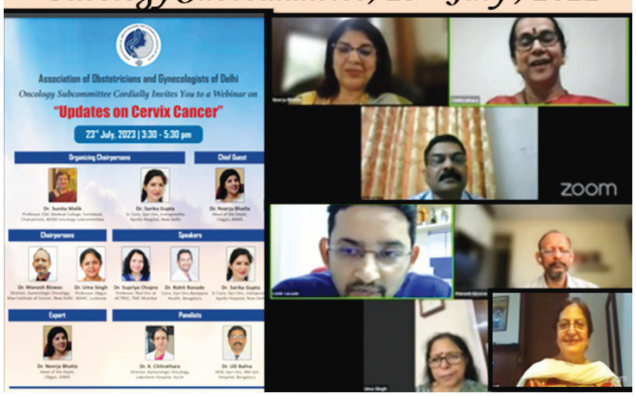
CME on "Women Health" by DGF SW and DGF North under aegis of AOGD, 15th July, 2022

Public forum by Rural Health Sub-committee, 16th July 2022

Webinar on Robotics in Gynae Oncology by Oncology subcommittee, 16th July, 2022



Webinar on Update on Cancer cervix by Oncology Subcommittee, 23rd July , 2022



PG Forum on "Heart Disease in Pregnancy"

Master classes in Reproductive Genetics by IFS with AOGD , 24th July 2022

Webinar on "A Stitch in time, prevents 9" by Breast and Cervical Cancer Awareness Screening & Prevention Subcommittee with DGF ,26th July, 22

AOGD Monthly Clinical Meeting Army Hospital (R&R), 29th July 2022

Webinar on Critical care by multidisciplinary subcommittee with Safdarjung hospital, 30th July, 2022

Cross Word Puzzle

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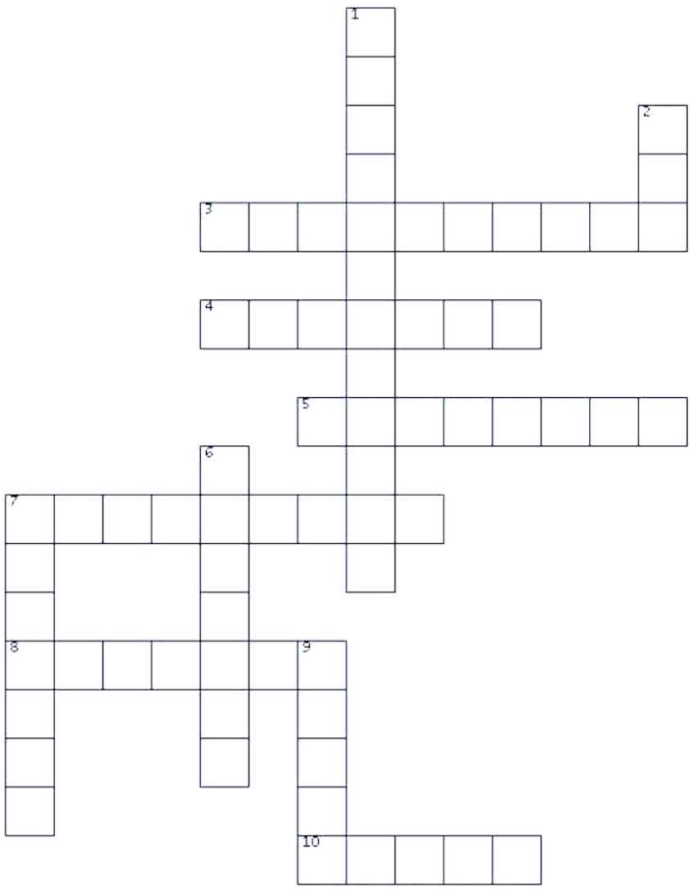

ACROSS
3. Mean sac diameter cutoff for anembryonic prregnancy is>=.....mm without embryo
4. Most common trisomy seen in spontaneous abortions
5. Which genetic test does not require dividing cells, and hence most helpful in fetal demise with culture failure
7. Method of vaginal cerclage where suture is taken near the level of internal os after pushing bladder
8. Trial which utilized first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages (2016)
10. Which trials have not validated the use of heparin to prevent adverse pregnancy in hereditary thrombophilia

DOWN
1. Termination of Pregnancy caused by rape comes under which clause of MTP Act
2. Predominance of which t helper cells is seen in recurrent miscarrianges
6. Syndrome caused by misoprostol intake due to teratogenicity in fetus
7. Criteria used in the diagnosis of Antiphospholipid Antibody Syndrome
9. Unsafe abortion constitutes what percentage of maternal mortality

Mail the answers to aogdeditor22@gmail.com. The correct answers and names of the three winners will be announced in the next issue.

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AOGD Monthly Clinical Meeting Held on 29th July 2022 at Army Hospital (Research & Referral), Delhi

A Case of Postpartum Maternal Collapse - An Anomalistic Presentation of ? Acute Sheehan Syndrome Without Inciting Factors

Lt Col (Dr) Anil Kumar Singh, Maj (Dr) Pranjali

A 24 years primigravida spontaneous singleton conception was registered at 10 weeks gestation. Her booking investigations were normal and there was nothing significant in history. We advised her to follow up with a first trimester scan and aneuploidy screening which was normal. Her blood pressure at 13 weeks was 144/94 mm Hg. Her spot urine albumin was negative and she was asymptomatic. We asked to follow up after one week with domiciliary resting BP records. Unfortunately, despite our thorough counselling she was lost to follow-up.

She returned at 27 weeks and 5 days period of gestation with a severe throbbing bitemporal headache, swelling of both feet reaching up to ankles and BP recorded this time was 166/100 mm Hg. We admitted her to our high dependency unit in the antenatal ward.

Her lab parameters revealed thrombocytopenia and transaminitis. Serum lactate dehydrogenase was elevated but peripheral smear did not show any features of hemolysis. 24 hour urine showed massive proteinuria. An obstetric ultrasound was done for fetal surveillance which was unremarkable and there was no evidence of uteroplacental insufficiency. Evaluation also ruled out any secondary cause of hypertension and absence of hypertensive retinopathy. We started her on anti-hypertensive therapy with tab Labetalol.

By second day, her blood pressures was poorly controlled despite oral labetalol 200 mg thrice daily and recordings were up to 180/120 mm Hg. She also started complaining of epigastric and right hypochondriac discomfort and had multiple episodes of vomiting. She was started on intravenous labetalol. With ongoing hypertensive crisis and impending eclampsia, termination of the pregnancy was the only option to primarily prevent a maternal catastrophe and secondarily aiming at salvaging the fetus. Emergency caesarean was carried out under general anaesthesia to deliver a 940 grams female neonate with a satisfactory APGAR score but was taken to NICU in view of prematurity.

Blood pressure recordings of patient continued to be in the range of 180-190/130-140 mm Hg in the immediate post-op period. There was no tachycardia and estimated blood loss during surgery was 750 ml. Labetalol infusion at 10 mg per hour was started. Patient under strict vital parameter surveillance was shifted to maternity ward. She was started on Magnesium sulfate by intravenous regime for seizure prevention. Suddenly the attending nursing staff noticed that the patient was unresponsive. Carotid pulse was not palpable and blood pressure was not recordable. She promptly recognized that the patient had a cardiac arrest. She immediately called for help. Hospital's code blue protocol alarm was activated. The resident in ward promptly started chest compressions. The Code Blue team arrived in no time and continued resuscitation as per adult ACLS protocol. Patient could be successfully revived after 15 minutes of intensive resuscitation and return of spontaneous circulation was achieved. She was shifted to ICU.

For ascertaining the cause of postpartum maternal collapse, she was evaluated. There was no evidence of hemorrhagic shock; her bedside point of care ultrasound (POCUS) done for evaluation of sudden collapse showed normal left ventricular function with no RA/RV dilation or pericardial collection. There was no evidence of DVT. Abdominal scan showed minimal fluid which in the post-op setting was considered insignificant. Serum magnesium levels were within the therapeutic range.

After 24 hours of ventilation, she was intermittently weaned off from sedatives and her vital parameters were stable. NCCT head raised suspicion of a pituitary apoplexy. Her mentation in the conscious phases were preserved. However, she had recurrent hypoglycemic episodes which were managed with intravenous infusion of 50 % Dextrose.

MRI done on 2nd day was consistent with hemorrhage in the pituitary. With low serum cortisol, LH and FSH and elevated insulin levels, the differentials considered were either primary adrenal failure or involvement of HPA axis. However, since there was no lactation suppression we thought of keeping Sheehan Syndrome as a retrospective diagnosis for subsequent surveillance.

While the ventilatory support continued, we started her on intravenous steroid therapy with Hydrocortisone. There was remarkable improvement in her clinical condition post steroid therapy. She was extubated after 36 hours of mechanical ventilation without any

neurological deficit. She was stepped down from ICU to the postnatal ward and continued on oral Prednisolone in tapering doses for further 3 weeks. She was normotensive in the postpartum period and could lactate her newborn.

She will continue to be under our surveillance. A follow up MRI to look for empty sella will be done if she manifests with pituitary amenorrhoea, lactational failure or any other cardinal features of Sheehan syndrome.

Muddling Lymphadenopathy in a Case of Carcinoma Endometrium

Lt Col (Dr) Vinod Kumar, Maj (Dr) Ashisha

- 62 year P2L2, post-menopausal woman, asymptomatic on routine evaluation was found to have thickened endometrial thickness on USG pelvis. She was evaluated further and endometrial biopsy revealed Endometroid Carcinoma. On further imaging, MRI Pelvis showed irregular intra-cavitary in-homogeneous soft soft tissue component measuring 1.31 x 1.53 cm in uterine corpus region. Super-facial (inner 1/2) myometrium involvement seen. Multiple enlarged lymph nodes involving lower para aortic lymph nodes on left side near bifurcation, b/L common Iliac lymph nodes, b/L Pelvic and b/L Inguinal lymph nodes measuring 1.5 to 3.1 cm, largest 3.1 x 1.8 cm, noted. Further, PET scan showed ill defined FDG avid (SUV max 4.8) soft soft tissue mass lesion seen arising from the endometrial cavity measuring 1.4 x 1.6 x 1.6 cm - suggestive of primary mitotic pathology. Multiple FDG avid (SUV max 4.14) para aortic, aorto-caval, bilateral common iliac, bilateral internal and external Iliac and bilateral inguinal lymph nodes seen. Multiple FDG avid (SUV max 3.58) bilateral axillary and bilateral retropectoral lymph nodes noted, largest in right axillary region measuring 1.6 x 1.9 cm.

  On eliciting a detailed history, patient revealed that she had Chikungunya infection three months back, from which she has recovered. After counselling she was taken for surgical staging with total abdominal hysterectomy with bilateral salpingo oophorectomy with infracolicomentectomy with pelvic and retroperitoneal lymph node dissection with Inguinal Lymph node dissection. In Pre-op patient counseling, the decision was taken not to proceed with biopsy of enlarged axillary lymph node and wait for final histopathological report. Her frozen section showed reactive Inguinal and Pelvic lymph nodes. Final HPE report showed it to be Endometroid Carcinoma Grade II, FIGO stage IB. She was started on three cycles of vaginal brachytherapy. On follow up after 03 months of completion of therapy, PET revealed no active metabolic focus, multiple FDG avid (SUV max 2.4) bilateral axillary and bilateral retropectoral lymph nodes, largest in the right axillary region measuring 1.6 x 2.1 cm- likely reactive/inflammatory. Patient is under follow up and asymptomatic until date.

Tubo Ovarian Abscess Unconforming Complication After Embryo Transfer

Surg Cdr (Dr) Hrishikesh Magdum, Sqn Ldr (Dr) Reena

My patient 32yrs old, a case of primary infertility underwent FET 10 days prior to presenting to us with complaints of fever and intermittent lower abdominal pain for 6 days. She underwent first In Vitro Fertilization and Embryo transfer (IVF-ET) in March 2022. Ovarian stimulation was done using long protocol. A total of 07 oocytes were retrieved, and 04 fertilized by Intracytoplasmic Sperm Injection (ICSI). Two day3 fresh embryos were transferred and remaining were frozen. However, she tested negative for pregnancy 18 days later. After 1 month she was reassessed on D2 and started for Frozen Embryo Transfer (FET) cycle by standard protocol. Two day3 frozen thawed embryos were transferred post which patient became symptomatic.

Her general physical examination was normal. Per abdominal examination showed no distention, however there was pain in the right iliac fossa on deep palpation. There was no guarding, rigidity and rebound tenderness. There was no tenderness at Mc Burney's point. No free fluid on percussion. Bowel sounds were present. Gynaecological examination revealed tenderness in right adnexa, however no apparent mass was felt.

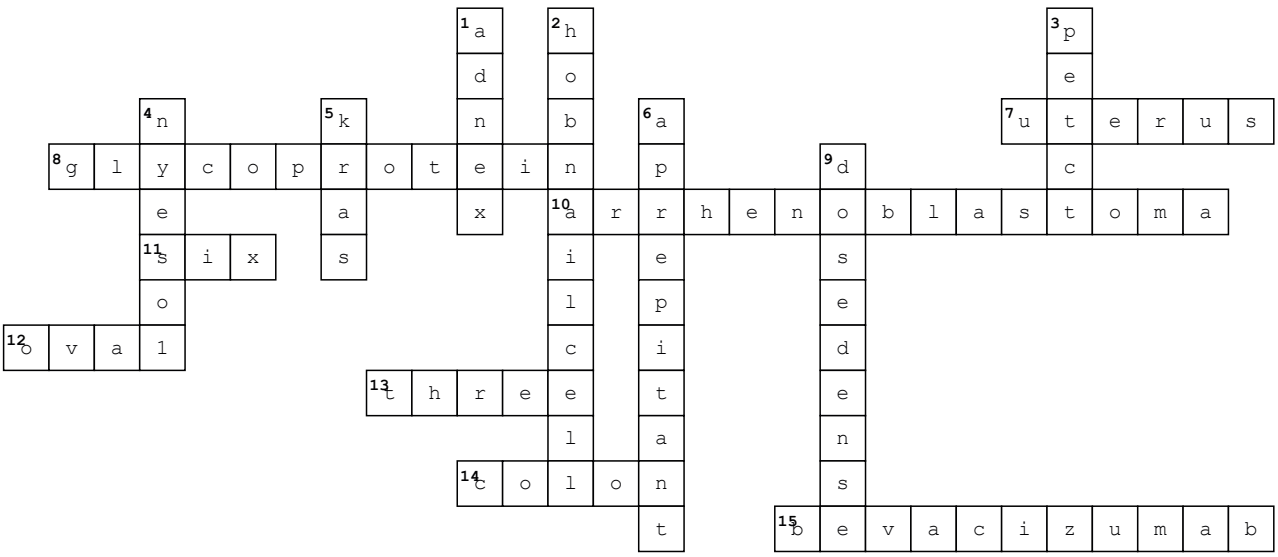
Transvaginal ultrasonography showed right ovarian size of 3.5x2.9 cm along with minimal periovarian fluid. A provisional diagnosis of Acute PID was made and a differential diagnosis of Acute Appendicitis and Right Ureteric Colic was considered. Lab investigation showed a raised TLC count of 28400 cells/mm3 (78% neutrophils and 15% lymphocytes) with toxic granules on peripheral blood smear suggesting an infective pathology. So, a clinical diagnosis of PID was made and patient started on injectable antibiotics (Inj ceftriaxone 1 g IV 12th hourly and Inj flagyl 500mg IV 8th hourly).

Patient continued to have on and off fever (100- 101.0 F) after admission. TLC's ranged between 25970 to 31100 cells/mm.^{3} On day 3 of admission, patient had

a temperature of 100.6 F along with intense nausea, vomiting and severe colicky abdominal pain. Her PR was 130/min and RR - 20/min. Per Abdominal examination showed tenderness with guarding in right iliac fossa. Repeat USG showed right adnexal mass of 6x4.5 cm with collection of fluid in the POD. CT scan showed right adnexal fluid collection of 200-400 ml with no evidence of obstruction/perforation/ischemia. A final diagnosis of Ruptured Tubo-ovarian abscess with sepsis was made and patient was taken up for laparoscopy under GA. 150 – 200ml of pus was drained and pus deposits were seen on uterus, lateral pelvic wall and liver surface. Appendix and right ovary could not be seen. Hyperemic thin-walled bowel was seen so manipulation of intestines was kept to minimum to avoid perforation. Pus was sent for culture and sensitivity.

Post extubation, patient was observed in ICU for 48 hours as she was in sepsis pre-op. Antibiotics were upgraded to Inj Piptaz 4.5gm IV 8th hourly and Inj Targocid 400mg IV OD. Her TLC count settled to 10,240 cells/mm^3. Three spikes of fever were recorded during the post op period. Pus culture was sterile. However, antibiotics were continued for 2 weeks. Ultrasonography on day of discharge did not show any collection in POD/adnexa.

Answer key of Quiz of July 2022



Winners of the monthly quiz, July Issue 2022

1. Dr Lekshmi
2. Dr Hansveen

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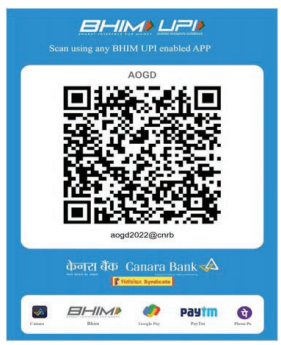

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