KERALA FEDERATION OF OBSTETRICS & GYNECOLOGY

KFOG JOURNAL

INFERTILITY AND PREGNANCY

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CONTENTS

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Dear Seniors and friends

I take this opportunity to congratulate Dr Suchitra Sudhir, Editor and Dr Shyama Devadasan, Associate Editor for bringing out an exemplary journal on the theme "**Minding the Minds**". Included here are articles on infertility and pregnancy which have been written in a quite lucid and comprehensive style. This will help the members update their knowledge tremendously.

We are thankful to have achieved a MMR of 29 in 2020, but the Covid deaths and suicides this year, have proved exceedingly worrisome. We need to give much stress and considerable efforts towards achieving perinatal mental health goals.

We have been living with Covid since some time now and are getting tuned to this being the new normal. It has also been quite a long time since we have all met each other. I fervently hope and pray that the present calamity may tideover soon and we could start physical meetings and conferences before long.

I would like to thank you for the incredible service that you have all rendered withstanding the trials and tribulations of this pandemic. I hope that we will continue all our endeavours with the same vigour and zeal, standing hand in hand during these difficult times.

With best wishes

Dr Ajith S

Dr Venugopal
Secrertary KFOG

SECRETARY'S MESSAGE

Dear KFOGites,

Hope all of you are holding out well as slowly and steadily we are finding our way out of the pandemic. This edition of KFOG bulletin has some varied contributions focused on Infertility and Pregnancy. Dr Suchitra and team have taken a lot of effort in compiling the articles which are of great relevance in our daily practice. Congratulations to each one who contributed to this edition of the bulletin. The bulletin showcases the energy and enthusiasm of our members and the attempt to give an opportunity to new faces in KFOG is laudable. I urge all members to enthusiastically contribute to the future editions of the publication because creativity always brings positive energy. During the pandemic the bulletin has played an important role in keeping our members updated and i am sure it will continue to do so in the future. Best wishes and hope all of you and families are done with the vaccination and taking all steps to stay safe, healthy and happy.

Dr Venugopal

FORWORD

Dr. P K Sekharan
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Hearty congratulations to Dr.Suchitra Sudheer, the editor and Dr .Shyama Devadasan, the Associate editor, for bringing out the second issue of the Journal of the Kerala Federation of Obstetrics and Gynaecology. The editorial team of our journal is having a special style of working by bringing out articles of current practical importance from authors belonging to a group of societies and clubs of our Federation giving regional representation.

This issue is dedicated to infertility and labor management. The lead article is by Dr. Duru Shah, the Past President of FOGSI and Founder President PCOS Society of India, on PCOS and Infertility. Dr Duru Shah is one of the authorities on PCOS and the article gives very valuable and practical tips in the diagnosis and management of Infertility related to PCOS.The other articles on infertility management are by Dr Divya Nair on Endometriosis and infertility and complications of infertility management by Dr.Aswathy Kumaran.

On the labour management, the article by Dr. Betsy Thomas on use of ultrasonography as an invaluable tool in Obstetric Emergencies, especially the intrapartum ultrasonography is quite informative.Dr. Megha Jayaprakash gives the recent evidences on elective induction of labour at 39 completed weeks as a safe procedure without increasing the section rate. The other articles are use of Metformin in the management of GDM by Dr.M K Geetha and the importance of providing mental wellbeing counselling during pregnancy, labour and puerperium, especially during this COVID-19 Pandemic, by Dr Simi Kurian.

Once again, I congratulate the Journal committee of the Kerala Federation for bringing out this volume on Infertility and Labour management and wish them all the best in the future endowers also. Wishing happy reading to all our members!

EDITORS DESK

Dear KFOG colleagues,

It is with immense pleasure that we place before you the second volume of the KFOG Journal of this year. The topics are Infertlity and Pregnancy. The Quartet of Perinthalmanna, Thrissur Societies and Vadakara and Palghat Clubs are the contributors, in this issue. As before, we will have an event, wherein experts will give their valuable ideas on these topics.

My sincere thanks to our President Dr Ajith and Secretary Dr Venugopal for their support. My own professor, the evergreen Dr PK Sekharan is the patron of this issue. My heartfelt appreciation to Dr Shyama Devadasan, my Associate Editor, who did a marvellous job of coordinating the articles and the event. Please read, take part and enjoy the hot topics of Infertilty and Pregnancy!

With loving regards,

Dr Suchitra Sudhir
Editor, KFOG Journal 2021

Respected Seniors and friends,

Warm greetings to you all. Hope all are hale and healthy in the midst of the pandemic. We are happy to bring out the second issue of the KFOG journal which deals with relevant topics from the segment "Infertility and Pregnancy", keeping in mind the Presidential theme of the year "Minding the Mind". With the blessings of our patron for this edition, Prof. Dr. P.K. Sekharan sir; it was possible for us to bring forth an interesting read to our KFOGians.
I thank each one of the authors, for their valuable contributions to the Journal. Also, I express my gratitude to our KFOG office bearers and Editor Dr. Suchitra, for giving me an opportunity to be a part of this issue as Associate Editor.
Happy reading to all.
Warm regards

Dr. Shyama Devadasan
Associate Editor, KFOG journal (2021)

PCOS
ITS EFFECT ON INFERTILITY

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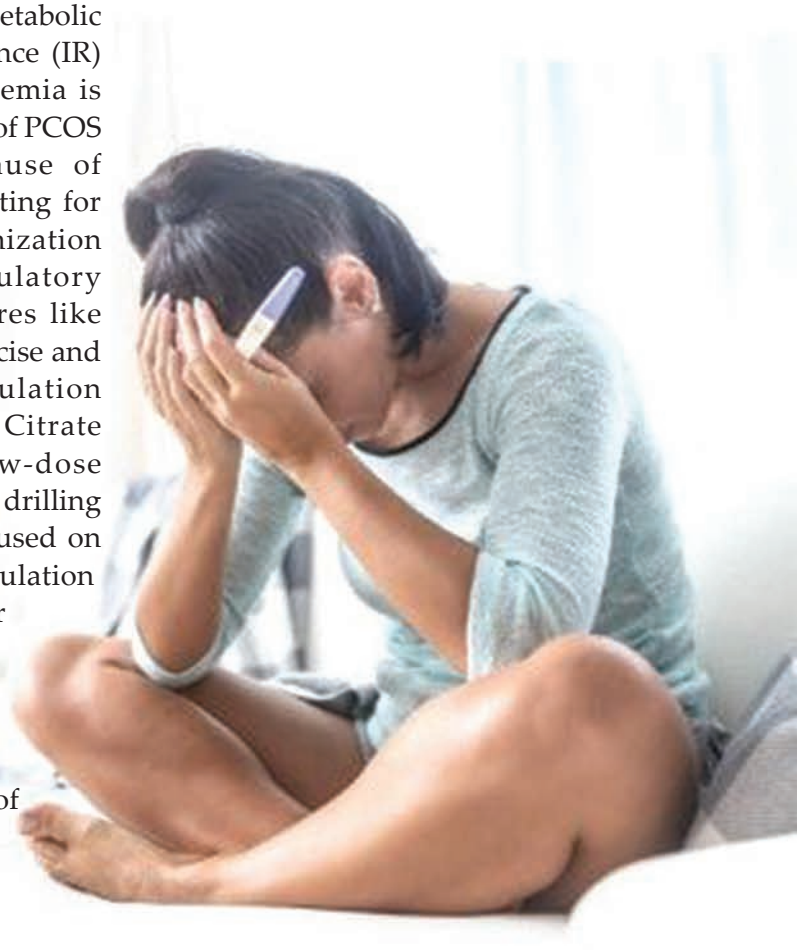
Introduction

Polycystic Ovary Syndrome (PCOS) is a complex endocrine spectrum disorder ranging from anovulation to metabolic syndrome (1) - Insulin resistance (IR) and consequent hyperinsulinemia is central to the pathophysiology of PCOS (2). PCOS is the major cause of anovulatory infertility, accounting for >80% of World Health Organization (WHO) Group II of anovulatory infertility. If lifestyle measures like weight restriction, regular exercise and hypocaloric diet and ovulation induction with Clomiphene Citrate (CC) and Letrozole fail, low-dose gonadotropins (Gn) or ovarian drilling may be tried. Treatment is focused on lifestyle modifications and ovulation induction with clomiphene or letrozole. For those who still remain anovulatory, Assisted Reproductive Techniques (ART) is a reasonable option but with close supervision in view of highly sensitive ovaries(3).



PCOS and Subfertility

Pathophysiology

Anovulation is the leading cause of subfertility in women with PCOS but there may be other contributing factors like insulin resistance (IR), obesity, hormonal imbalances and inflammation worsening the oocyte quality. The oocyte competence is compromised leading to reduced fertilization, abnormal meiosis and embryo formation (6). IR and hyperinsulinemia lead to impaired glucose metabolism in the follicles, with detrimental effect on oocyte energy production. This is followed by an altered expression of key genes for oxidative phosphorylation, chromosomal alignment and segregation, further worsened by hyperandrogenic microenvironment. Ovarian hyperandrogenism triggers premature luteinization of granulosa cells, disrupts granulosa cell-oocyte interactions and impairs cytoplasmic and nuclear maturation. The follicular testosterone levels are elevated in PCOS patients leading to meiotic incompetence. Serum hyperandrogenemia causes a dose-dependent decrease in Glycodelin which is an endometrial receptivity marker protein (7, 8).

Obesity is seen in nearly 40-70 % of PCOS patients. Gonadotropin resistance, oocyte yield, fertilization, clinical pregnancy and live birth rates are significantly lower in obese patients. (8)

Management of Subfertility

Ovulation Induction (OI):

OI in women with PCOS is a different ballgame and can change from no response to hyper-response in no time.

CC, introduced as an ovarian stimulant in 196,is a Selective Estrogen receptor modulator (SERM). CC causes prolonged depletion of hypothalamic-pituitary estrogen receptors, thus blocking the negative feedback, leading to a rise in release of pituitary Gn (9). CC achieves an ovulation rate of 70-92% but a pregnancy rate only ranging between 20-40%. Low pregnancy rates are explained by the antiestrogenic effect of CC on cervix, endometrium and tubal motility, decreased uterine blood flow and endometrium-embryo asynchrony (10).

Letrozole is a non-steroidal competitive inhibitor of aromatase. It blocks estrogen synthesis temporarily, releasing hypothalamic-pituitary block, and thus normalizing the pulsatile release of follicle stimulating hormone (FSH). There is no antiestrogenic effect on endometrium, cervix and tubes.

Clomiphene Citrate

Letrozole, Metformin:

In a systematic review and meta-analysis including 1833 PCOS patients, live birth rates (LBR) and pregnancy rates (PR) were found to be statistically significantly higher with Letrozole compared to CC (11). Another meta-analysis of 26 randomized controlled trials (RCTs) with 5560 PCOS women found Letrozole to improve PR and LBR compared to CC (12). A double-blind RCT of letrozole versus CC in PCOS women by Amer SA et al concluded the superiority of letrozole over CC as a primary ovulation induction agent,

with 40% increase in PR and with a shorter time-to-pregnancy interval (13). A recent meta-analysis of 57 RCTs with nearly 8000 participants concluded that compared to CC alone, both letrozole and combination of CC and metformin showed higher ovulation and PR. Letrozole was the only treatment with significantly higher LBR (14).

Controlled Ovarian Stimulation (COS) Strategies:

As far as different Gonadotropin preparations are concerned, there is no difference in the outcome between human menopausal gonadotropin (hMG) and recombinant- FSH (r-FSH). The number of oocytes retrieved, LBR, miscarriage, multiple pregnancy and ovarian hyperstimulation rates are not significantly different among various Gn preparations (15,16).

Gonadotropin Releasing Hormone-Antagonist (GnRH-ant) Protocol:

With no GnRH-receptor activation and a rapid suppression in secretion within hours of administration, GnRH ant regimens offer shorter treatments compared to GnRH- agonist regimens. A Cochrane review showed significantly lower incidence of OHSS in antagonist regimens with no difference in LBRs in PCOS patients (17). Lainas TG et al found an earlier follicular growth and higher estradiol levels during GnRH ant protocols compared to GnRH agonist long protocol. The oocyte yield, fertilization and clinical PRs were similar but the OHSs rates were significantly lower in the antagonist group (18). GnRH-ant regimens are the standard treatment of choice for all PCOS patients in view of marked reduction in incidence of OHSS.

Oocyte Maturation Triggers

GnRH Agonist Trigger

With the use of GnRH ant protocol, there is an advantage of using GnRH agonist trigger for ovulation. GnRH agonist displaces GNRH-ant from GnRH receptors and induces final oocyte maturation and development. This trigger has a shorter half-life compared to hCG (60 minutes vs. 32-34 hours) and a lower risk of OHSS. The various agonist triggers used are Buserlein- intranasal or subcutaneous, Triptorelin and Leuprolide subcutaneous. Agonist triggers produce comparable oocyte yield, embryo quality, and implantation and pregnancy rates (19, 20). However, a Cochrane review demonstrated an inferior LBR with reduced rates of OHSS with the use of agonist trigger (17). The low LBR was attributed to dramatically deficient luteal phase consequent to agonist trigger. Short half-life of LH, while being beneficial in reducing OHSS, is not able to sustain and support the corpus luteum for pregnancy (17).

The various strategies proposed and used for modifying and augmenting luteal phase support following an agonist trigger include a combination of low dose of hCG, and estradiol and progesterone supplementation. Various studies have reported equal LBR after modifying the luteal phase support (21, 22).

Recombinant LH trigger

Recombinant LH (r-LH) has a longer half-life compared to native LH and can be used to mimic the mid-cycle LH surge. R-LH is safer than hCG as far as OHSS is concerned (23). Compared to r-hCG, r-LH demonstrated lower rates of moderate to severe OHSS (24).

Kisspeptin Trigger

A novel agent for oocyte maturation trigger in high risk of OHSS is kisspeptin. Kisspeptins are hypothalamic peptides encoded by KISS-1gene and are potent stimulants of hypothalamic-pituitary-ovary axis. Kisspeptin 54 has been studied as an ovulation trigger in high responders and was found to be effective as well as safe (25).

Insulin Resistance (IR) and Insulin Sensitisers

Hyperinsulinemia consequent to IR causes hyperandrogenaemia besides being a harbinger of metabolic and cardiovascular diseases in women with PCOS. IR is best screened by 75 grams oral glucose tolerance test (26). Insulin sensitisers include Metformin, pioglitazone, and inositols.

Metformin

The evidence of Metformin in improving LBR in PCOS women undergoing IVF is conflicting. A Cochrane review of 5 RCTs comparing Gn plus metformin versus Gn alone concluded that metformin may increase the LBR among women undergoing ovulation induction with Gn (27). Abu Hashim RCTs and concluded that Metformin with CC should be considered as an effective option for CC-resistant PCOS. With Gn ovulation induction, metformin significantly increases LBR and PR with reduced risk of cycle cancellation. In women undergoing ART, metformin confers a beneficial effect on Clinical PR and reduces the risk of OHSS. There was no risk of major anomalies with the use of Metformin (28). A Cochrane review of Insulin sensitizing drugs in 4451 PCOs women with sub fertility suggested that metformin alone may be beneficial over placebo for LBR. Metformin plus CC showed a higher clinical PR and ovulation rate compared to CC alone (29).

Metformin treatment before and during IVF reduces the risk of OHSS (30).

Inositols

Inositols are being studied extensively for their use in PCOS. Treatment with the two isomers, myo (MI) and d-chiro inositols (DCI) shown promise in

improving hyperandrogenism, and metabolic syndrome, thus improving the cardiovascular risk (31, 32).While MI improves metabolic profile, DCI reduce s hyperandrogenism better. DCI at higher doses, however, is detrimental to the oocyte quality. Till there is conclusive evidence about the positive effect of inositols on reproductive outcomes in PCOS women, their use remains largely experimental, and is not currently recommended due to lack of strong evidence

In Vitro Maturation (IVM)

PCOS patients have hypersensitive ovaries which lead to an over-exaggerated response to supra physiological doses of Gn used for controlled ovarian hyperstimulation. This results in development of a large cohort of follicles being recruited, retrieval of immature oocytes and increased odds of Ovarian Hyperstimulation Syndrome (OHSS). Invitro Maturation (IVM) is a potentially effective alternative for women with PCOS, whereby early retrieval of immature oocytes at germinal vesicle stage is done either from unstimulated or minimally stimulated ovaries. These oocytes are isolated by washing the follicular aspirate, then matured in vitro in specially formulated IVM medium with melatonin at 37° C and 5% CO_2 for 24-48 hours. The oocytes are then fertilized with Intracytoplasmic sperm injection (ICSI) and assessed for fertilization 16-18 hours later (33). Due to prolonged culture, there is a hardening of zona pellucida, because of which ICSI is preferred even in the absence of male factor. A larger number of oocytes is retrieved from the Polycystic ovary compared to the normal ovary. The maturation and fertilization rates are comparable but pregnancy and live birth rates are significantly higher in PCOS patients compared to those with normal and polycystic ovaries (34). The oocyte yield and implantation rates are significantly lower from an IVM cycle compared to the conventional IVF. The pregnancy rates per transfer vary between 4 and 27% and implantation rates between 2 and 14%.This is attributed to reduced oocyte development potential, higher odds of abnormal meiotic spindles and chromosomal alignment, nuclear-cytoplasmic asynchrony, imperfect culture conditions and reduced endometrial receptivity (35, 36). In a Cochrane review to compare outcomes of IVM followed by either IVF or ICSI, it was concluded that there is still no evidence from RCTs upon which to base any practice recommendations regarding IVM. A meta-analysis of 11 trials with 268 PCOS, 100 PCO and 440 women with other causes of infertility, concluded that IVM appears to be a more efficient treatment option in women with PCOS in terms of clinical pregnancy, implantation and cycle cancellation rates (37). In view of poorer pregnancy outcomes with IVM compared to conventional IVF, it becomes a difficult decision for clinicians as well as patients to choose IVM over IVF.

Natural cycle IVM includes a baseline sonography on 2nd or 3rd day of periods

followed by another sonography on 6th or 8th day of periods to assess follicular growth and endometrial thickness. hCG trigger is given when the dominant follicle reaches a size of more than 12 and less than 14 mm and endometrium needs to be between 5 and 6 mm. (38). Some studies suggested that oocytes obtained after gonadotropin and hCG priming have better developmental competence and maturation rate (39, 40). Other studies were not able to prove this beneficial effect of Gn priming (41). Mild ovarian stimulation involves administration of 75 IU of Gn till follicles reach a size of 12 mm. hCG trigger of 10,000 IU is given at follicle size of 12 mm and oocytes retrieved 35-36 hours later. Since the follicular phase length is reduced, endometrial preparation with 6-12 mg of estradiol valerate is started on the day of oocyte retrieval. Progesterone support is begun from the day of oocyte retrieval (42). The obstetric outcome of babies born through IVM is comparable (43,44).

Ovarian Hyperstimulation syndrome (OHSS)

OHSS is a serious iatrogenic complication of ovarian stimulation ranging from mild ovarian enlargement to severe life-threatening complications like pleural/pericardial effusion, adult respiratory distress syndrome, thromboembolic events and even death (45). PCOS is the strongest risk factor for the development of OHSS.

Etiopathogenesis of OHSS

OHSS is an utterly hCG-dependent condition, and consists of ovarian enlargement and massive production of ovarian hormones and vasoactive substances like rennin, prostaglandins, angiotensin II, vascular endothelial growth factor (VEGF), tumor necrosis factor and interleukins which promote neo angiogenesis and hyperpermeability state. VEGF levels correlate the best with disease severity (46).

Classification of OHSS

The syndrome is classified as early and late. Early OHSS occurs within 3-7 days of hCG triggering, and late OHSS

occurs more than 10 days after hCG trigger. Late OHSS only occurs in case of a pregnancy and accounts for 70% of all severe OHSS cases (47).

Based on severity, OHSS is classified as mild, moderate, severe and critical (See Table I) (48).

Table I: OHSS classification

Mild	Moderate	Severe	Critical
Bloating	Vomiting	Massive ascites	Tense ascites
Nausea	Abdominal pain	Hydrothorax	Hypoxemia, Pericardial effusion
Abdominal distension	Ultrasound evidence of ascites Hematocrit >41%	Hematocrit > 45%	Hematocrit >55%
Ovaries d"5 cm	Ovaries > 5cm	Ovaries enlarged variably	Ovaries enlarged variably
	Leucocyte (WBC) count >10,000/mm^3	WBC Count >15,000/mm^3	WBC count >25,000/mm^3
		Oliguria	Oliguria/anuria
		Serum creatinine 1-1.5mg/dl	Creatinine >1.5mg/dl
		Hepatic dysfunction	Renal failure, adult respiratory distress syndrome
		Anasarca	Thromboembolism

Prevention of OHSS

1. Definition of at-risk population is essential for following preventive strategies. The most important risk factor for OHSS is PCO on transvaginal ultrasound having a high antral follicle count with "necklace sign" or "string of pearls" appearance.
2. Chronic low-dose Step-up and Step-down methods of ovarian stimulation have been used. Chronic low dose regimen is more likely to significantly reduce OHSS. Step down protocol also allows more follicular atresia.
3. Coasting/ withholding gonado-tropin works by altering the VEGF production by granulosa cells. VEGF is the factor responsible for the release

of vasoactive substances leading to OHSS.There is conflicting evidence of coasting on oocyte yield and pregnancy rates (50-52).

4. GnRH antagonist cycles with agonist trigger and modified luteal phase support with best towards the preventive of OHSS (as discussed earlier in detail).
5. Blastocyst transfer- To assess the degree of OHSS before embryo transfer, it is advisable to do a blastocyst transfer. This is because a blastocyst transfer takes place on the 7th day of HCG injection and we can safely assess OHSS before transfer (48). Elective single blastocyst transfer is being widely advocated in women prone to develop OHSS to minimize the odds of multiple pregnancies (53).
6. Embryo Cryopreservation: For prevention of severe OHSS in patients showing early signs of hyperstimulation, freeze-all strategy may be employed (54).

Conclusions:

Women with PCOS undergoing treatment of infertility respond differently to women with normal ovaries. It is important for obese PCOS patients to lose weight, modify their lifestyle, and improve their general health which will benefit their reproductive outcome. Women with PCOS are at risk of OHSS, and with the introduction of GnRh antagonists and embryo freezing, the incidence and severity of OHSS can be drastically reduced. Metformin is a useful adjunct to reduce OHSS. IVM is a potential alternative but is yet to be adopted as a routine clinical entity.

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RED FLAGS
IN FERTILITY TREATMENT

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Fertility treatment revolutionized by Assisted Reproductive Technology (ART) is a safe and effective for people with fertility problems wanting to conceive. Like any other area in medicine, fertility management especially ART is not without risks, some associated with the treatment and the others associatedwith the outcome.

The problem areas in fertility management may be categorized as those associated with treatment, those associated with outcomes, or those areas where further research is required to decide regarding

what management techniques are ideal. Red flag zones in treatment for fertility problems include those in-patient selection, choosing the treatment technique is most appropriate, side effects of medicines used, differences in patient response to treatment, ovarian hyperstimulation syndrome, risks associated with sedation or anesthetic, risks associated with oocyte retrieval (hemorrhage and infection), surgical sperm recovery risks (infection, bleeding). The costs incurred, patient grievances and psychological adjustments to treatment as well as facing a negative result are other problematic areas.

Risks associated with outcomes include multiple pregnancy, ectopic and heterotopic pregnancy and higher incidence of obstetric complication in fertility treated conceptions. These also include the potential risk of increased developmental and congenital abnormalities in fertility treated children.

Further research is needed to asses risk for borderline ovarian tumor in women and childhood malignancy and imprinting errors in children conceived of fertility treatment.

Treatment decision red flags:

1. Do not offer self sperm IUI in Azoospermia
2. Do not offer more than 6 cycles of continuous ovulation induction
3. If three incremental ovulation inductions fail to result in ovulation, choose between Laparoscopic Ovarian drilling or Injectable Ovarian drilling
4. Opt for IVF if more than 3-4 IUI failures
5. Always discuss about non treatment options like adoption in all couples with infertility requiring ART so that they are aware about this option
6. Do not start any fertility treatment without Valid Informed Consent and ensure that they have understood the various aspects of the treatment they have chosen.
7. Give every couple a psychologic support when needed or facing accepting treatment failure, meeting treatment requirements.

Risks from treatment

A. Ovarian hyperstimulation syndrome

Mild OHSS occurs in up to one third of the women undergoing ART treatment. The severe form of OHSS is reported in 1–2% of ART cycles. Although a self-limiting condition, it may worsen and be accompanied by ascites, pleural and pericardial effusions, renal dysfunction and,sometimes, abnormal liver function test results. Recognized complications of OHSS are renal failure, venous and arterial thromboembolism, adult respiratory distress syndrome, hemorrhage from ovarian rupture and, very rarely, death. OHSS is best prevented than managed hence an antagonist stimulation protocol and agonist or dual trigger and freeze all strategy can prevent OHSS. Use of metformin and lower doses of gonadotropin during ovarian

stimulation reduces the risk in high risk women. Mild to moderate OHSS can be managed on an outpatient basis and spontaneous resolution of symptoms Patients with severe OHSS and those with significant pain or nausea that limits oral intake are usually managed as inpatients and more severe cases (critical OHSS) are admitted to an intensive care unit formanagement under a multidisciplinary team

B. Multiple pregnancy

The chance of a multiple pregnancy is almost 20 times higher with ART treatment than with spontaneous conception. UK data compiled in 2006 showed a staggering 24% multiple pregnancy rates. This led to promoting efforts in reducing the number of embryos transferred and adoption of theelective single embryo transfer (eSET) strategy has led to fall in the number of multiple pregnancies. Elective SET does not mitigate the increased risk of monozygotic twining (0.7–3.1%) compared to natural conceptions (0.4%).

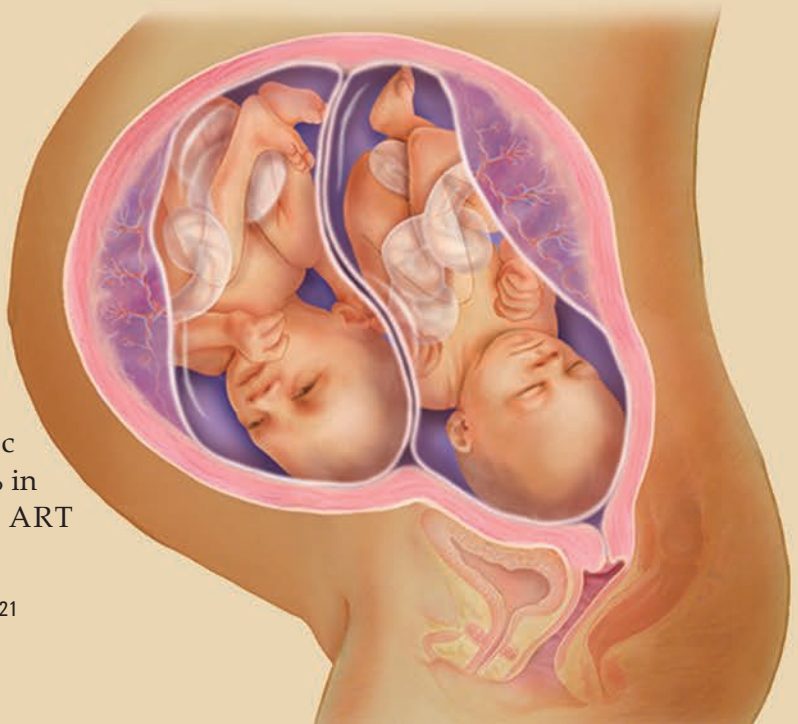
C. Ectopic pregnancy and heterotopic pregnancy

D. Pelvic inflammatory disease, previous ectopic

Pregnancy, endometriosis, and previous tubal surgery impair tubal function increase the risk of ectopic pregnancy The prevalence of ectopic pregnancy is as high as 8.6% in women undergoing ART treatment compared to 1–2% following natural conception. The incidence of heterotopic pregnancy is which is rare, 1 in 30 000 in the general population, increases to 8 in 1000 following ART treatment. Multiple embryo transfers, transfer techniques, alteration in the implantation environment in a stimulated cycle all may increase the risk of ectopic/heterotopic pregnancy.

E. Complications of the oocyte retrieval procedure-

Transvaginal oocyte retrieval is generally very safe but may be rarely complicated by minor vaginal bleeding (1.4–18.4%), pelvic infection (0.1–0.6%) or severe intra-abdominal bleeding (0.05–0.2%). Though these complications occur very rarely we must take all precautions to avoid them as the affected woman suffers from significant morbidity.



F. Cancer risk

Current evidence shows that there is no increased risk in hormone independent cervical cancer. There breast cancer risk is similar in general population and women undergoing fertility treatment.

Pooled evidence reveals that, after removing the confounding effect of infertility, the risk of ovarian cancer in general population and those undergoing controlled ovarian stimulation is the same. But there is a small increased risk for borderline ovarian tumours.

G. Risk of Early menopause

Many are concerned whether undergoing COS will lead to depletion of ovarian follicular cohort quickly culminating in early menopause. This is because COS do not act on primordial follicles but on FSH sensitive antral follicles which would have undergone atresia unless recruited.

H. Perinatal outcomes

Fertility treated pregnancy is associated with increased risk adverse pregnancy outcomes compared to pregnancies in fertile women. The present evidence points to the fact that it is the subfertility causing factors rather than the fertility treatment that accounts for the higher morbidity associated with singleton pregnancy. Fertility treatment predisposes to multiple pregnancy and higher risk due to this. Hence the goal of fertility treatment should be to achieve singleton pregnancy.

I. Risks to offspring

Analysis of available evidence suggests that there are a 30-40% increased risk congenital anomalies in ART conceived pregnancies, although it is not very clear whether the higher risk is due to factors relating to subfertility or the treatment. Compared to a background prevalence of 5% the absolute risk of anomalous birth is low; i.e. 6.5-7%. There is an increased risk of offspring with imprinting errors. Yong ICSI conceived males have a higher prevalence of male subfertility.

J. Risk for Childhood cancer

Most of the evidence suggests possible increased risk in childhood cancer but again whether it is due to subfertility itself or fertility treatment is not clear. Ovarian stimulation does not seen to be associated with increased cancer risk, but exposure to maternal progesterone markedly increased the risk of acute lymphocytic leukaemia and sympathetic nervous system tumours.

K. Affordability and psychological factors

Always choose a patient tailored treatment strategy keeping in mind their feasibility to undergo treatment. Couple evaluation and appropriate patient counselling is mandatory part of all fertility treatment programs.

Risk associated with treatment outcomes

Treatment outcomes are dependent on the age of the woman, ovarian

reserve, number of eggs retrieved, fertilization method, number of embryos transferred, Life style, body mass index, prior obstetric history and male factors.

Interventions like endometrial scratching in women with prior IVF failures, Day 5 Blastocyst PGS, Time lapse assessment of embyogenesis and embyoselection, Hyaluronic acid, oocyte activation with calcium ionophore are interventions that are promising as per available evidence.

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CARING FOR MATERNAL MIND IN COVID TIMES

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"Happiness in minds can be found even in the darkest of times, if one only remembers to turn on the Light ".

Finding out oneself is pregnant can be a very exciting time .But, it can also make a woman feel uncomfortable, unwell and worried about how she shall cope with the pregnancy. And it doesn't stop even when the baby arrives. Some find it easy to adjust to life with a new baby, but others don't. It will be much more difficult if one had a bad experience before, like a miscarriage or a fetal loss.

Perinatal Mental Health problems are those which occur during pregnancy or in the first year following the birth of a child. It covers a wide range of conditions. These disorders include depression, anxiety disorders and postpartum psychosis which usually manifests as bipolar disorder.

How big is the problem?

Worldwide, about 10% of the pregnant women and 13 % of the women who have just given birth, experience a mental disorder. In developing countries, this is even much higher, ie 15.6% during pregnancy and 19.8% after child birth. In severe cases, the suffering might be so severe that they may even commit suicide.

Perinatal depression and anxiety are the most common problems during pregnancy. Postpartum blues are common, but a less severe manifestation of postpartum affective disturbances. Women with history of bipolar disorder and family history of postpartum psychosis in the first degree relative have 75% chance of psychosis.

Who is at increased risk?

Virtually, all women can develop mental disorders during pregnancy and in the first year after delivery.

- High risk pregnancies, Older mothers, Pregnancies with assisted reproduction, Previous pregnancy loss
- Psychosocial factors – Ongoing conflicts with the partner, poor social support, financial problems, stressful life events, natural disasters etc
- Past history of depression, anxiety or bipolar disorder.

All these factors play a key role in developing mental health problems.

What are the consequences if untreated?

Maternal depression during pregnancy is an independent risk factor for low birth weight and preterm labour. But other illnesses such as anxiety disorders, eating disorders and psychotic illness may also predict adverse birth outcomes. Systematic reviews and meta-analysis have found significant association between poor antenatal mental health and impaired neonatal cognitive development. After giving birth, the mother with depression suffers a lot and may fail to adequately eat, bathe or care for herself. The risk of suicide is also a consideration and in psychotic illnesses, the risk of infanticide, though rare, must be taken into consideration. Prolonged or severe mental illness also hampers the mother- infant attachment, breast feeding and infant care.

Why can't it be ignored?

Psychiatric symptoms and diagnosis are often undetected and underreported in pregnant women receiving antenatal care. Suicide is now a leading cause of maternal death in developed countries. Even in Kerala, the suicide death rate during pregnancy have seen an alarming rise and is the single most leading cause of maternal death in last two years. Unlike the West, where suicides are predominantly as a result of postpartum depression, in Kerala, pregnancy in unmarried women and lack of family support seem to be the major cause for the suicides.

How to tackle the situation?

Maternal mental health can be integrated into the general health care including women's health, maternal and child health care, reproductive health care and other relevant services. Our state Kerala has developed a state wide maternal mental health programme, AMMA MANASU, an initiative to address psychiatric disorders among women during pregnancy and post-delivery. Mothers will be assessed during their antenatal and postnatal visits by JPHNs, who are trained to provide first level interventions. Referral pathways are established for stepped care and include doctors in the primary care and the District Mental Health Programme. However, we as clinicians must also make a dedicated effort to take a proper history and look for any warning signs. Maintaining a good rapport with the patient can go a long way in preventing untoward consequences.

ENDOMETRIOSIS AND INFERTILITY

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Defined as the presence of endometrial tissue outside the uterine cavity, endometriosis remains an enigma–a chronic, progressive, recurrent and debilitating immune mediated disease.

PREVALENCE:

The prevalence of endometriosis is 25% to 50% in women with infertility, and 30% to 50% of women with endometriosis have infertility. The fecundity rate in normal reproductive-age couples without infertility is 15% to 20%, whereas the fecundity rate in women with untreated endometriosis is 2% to 10%.

PATHOGENESIS:

What we know:

1. Retrograde menstruation—endometrial tissue transported in a retrograde fashion through patent fallopian tubes into the peritoneal cavity during menstruation, gets attached to mesothelial cells, establish blood supply, proliferate and form endometrial implants.
2. Coelomic metaplasia—undiffe rentiated peritoneal cells differentiate into endometrial cells.
3. Metastatic spread— menstrual tissue travels from endometrial cavity through lymphatic channels and veins to distant sites that shall explain extra-pelvic endometriosis.
4. Altered immunity—women with endometriosis have altered immunity that leads to decreased clearing of endometrial implants that reach the peritoneal cavity through retrograde menstruation. There is an increase in the number of leukocytes and macrophages around endometrial implants and in the peritoneal fluid. These cells secrete cytokines and growth factors (IL- 1, 6 and 8, TNF, RANTES, VEGF) into the peritoneal milieu, which then recruit surrounding capillaries and leukocytes leading to proliferation of endometriosis implants with increased vascular supply.

What is new:

1. **Stem cells**:

   During organogenesis, some of the genes involved in the differentiation of the urogenital tract might become dysregulated, leading to anatomical abnormalities, as well as misplacement of the stem cells. Non-endometrial stem cell source can result in endometrial cells in both the uterus and ectopic implants. Studies using murine models suggest that bone marrow derived stem cells (BMDCs) can localize to eutopic and ectopic endometrium and contribute to endometriosis. Ectopic differentiation of stem cells may be a novel mechanism of disease.

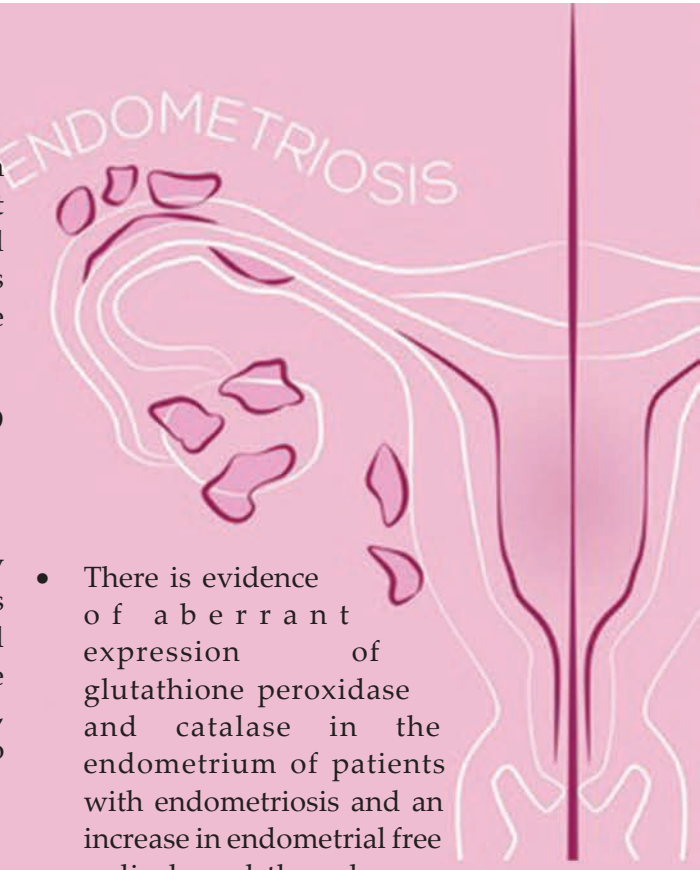
2. **Genetics:**

   Endometriosis has a familial tendency. Women who have a first degree relative affected by the disease have a 7 times higher risk of developing endometriosis. KRAS gene is mutated in several cancers and can lead to increased cell proliferation, survival and migration. Polymorphism in the KRAS gene and change in the mRNA expression patterns of the endometrial stromal cells could be involved in the pathogenesis of endometriosis.

3. **Hormonal factors:**

   Endometriosis is an estrogen dependent disorder. But it is also a disorder of progesterone resistance. Disordered progesterone signalling in the endometrium plays a role in impaired decidualization and establishment of ectopic endometrial implants. Progesterone decreases inflammation in the endometrium, and abnormal progesterone signalling results in a proinflammatory phenotype.

Conversely, chronic inflammation can induce a progesterone-resistant state. Chronic peritoneal inflammation in endometriosis further exacerbates progesterone resistance.



ENDOMETRIOSIS ASSOCIATED INFERTILITY:

What we know:

In severe disease, pelvic anatomy becomes distorted. Pelvic adhesions interfere with oocyte release and pick-up, alter sperm motility, cause disordered myometrial contractions, impair fertilization and embryo transport.

What is new:

- Inflammatory cytokines, growth and angiogenic factors, and aberrantly expressed genes are all being explored as potential etiologic factors of endometriosis-associated infertility.
- Inflammatory effects of endometriomas affect both oocyte production and ovulation in the affected ovary.
- Inflammation impairs tubal function and decreases tubal motility. Disordered myometrial contractions associated with endometriosis can also impair gamete transport and embryo implantation.
- The increased number of inflammatory cells in the peritoneal fluid will damage the oocytes and sperms, apart from having toxic effects on the embryo.
- There is evidence of aberrant expression of glutathione peroxidase and catalase in the endometrium of patients with endometriosis and an increase in endometrial free radicals and these have a negative effect on embryo viability.
- It is proposed that there is likely bi-directional movement of cells between the eutopic and ectopic endometrial tissue. The reprogrammed and abnormally located cells likely that have 'returned' to the endometrium generate the signal that leads to aberrant gene expression (Hoxa10/ HOXA10 gene, Wnt7agene) and implantation failure. Normal epithelial stromal polarity required for implantation is also disturbed.
- Progesterone receptor dysregulation in endometriosis leads to a luteal phase disruption. Progesterone target genes are affected, which in turn leads to decreased endometrial receptivity.

- Down-regulation of progesterone receptors is seen prior to implantation in normal endometrium but is delayed in the endometrium of endometriosis. Also, both eutopic and ectopic endometrium have been shown to be resistant to progesterone, causing an unopposed estrogen state which is likely not suitable for implantation.
- Progesterone resistance in endometriosis leads to persistent high levels of matrix metalloproteinases (MMPs) causing matrix breakdown.
- It has been shown that abnormal levels of aromatase are present in both endometriotic implants as well as eutopic endometrium where it is normally absent, resulting in increased estradiol production, leading to abnormal development and impaired receptivity of endometrium.
- In endometriosis, there is a reduced expression of the adhesion molecule áâ-integrin, interfering with embryo attachment.

MANAGEMENT OF ENDOMETRIOSIS ASSOCIATED INFERTILITY:

Investigations-

1. Examination- Symptoms of dysmenorrhoea, dyspareunia, dyschezia, dysuria, abnormal uterine bleeds, difficulty to conceive and non cyclical pelvic pain mandate a pelvic examination.
1. Trans-vaginal sonography helps diagnose ovarian cysts.
2. Sonographic features vary from simple cysts to complex cysts with internal echoes to solid masses, usually devoid of internal vascularity but shows peri cystic flow with high resistance.
3. MRI helps detect lesions as small as 1 cm, and differentiate from dermoid cysts, also helpful in recto vaginal lesions.
4. Laparoscopy is the gold standard with or without histopathological evidence.
5. CA 125 may be helpful in diagnosing malignancies as well as in treatment follow up.

TREATMENT:

Age of patient, severity and duration of symptoms, stage of disease, previous treatment taken, and male factor should be taken into account when treating endometriosis associated infertility.

- **Medical management** of endometriosis which causes ovulation suppression holds no value in treatment of women with infertility.

  Super ovulation and IUI improves fertility compared to expectant management.
- **Surgical management:** Laparoscopic ablation or excision and adhesiolysis improves pregnancy rate when compared to

diagnostic laparoscopy alone in stage I and II endometriosis. Excision/cystectomy is recommended to increase spontaneous pregnancy rates instead of drainage and coagulation. Operative laparoscopy is indicated in stage III and IV endometriosis compared to expectant management to increase spontaneous pregnancy rate. Excision is also indicated when there is suspicion of malignancy and in case of rupture or torsion of the cyst. Decision for repeat surgery should be done carefully and women should be counselled regarding the possibility of reduction of ovarian reserve following surgery. Adjunctive hormonal therapy has no value before or after surgery in improving spontaneous pregnancy rates.

- **IVF or ICSI**: This is indicated if tubal function is compromised, in advanced reproductive age, male infertility and other treatment failures. COS using GnRh agonists or antagonists is effective in IVF patients with mild to moderate endometriosis and in those with endometrioma who did not undergo surgery. Ultra-long protocol of GnRh agonists for a period of 3 – 6 months before ART improves the clinical pregnancy rates. Previous ovarian surgery results in longer stimulation, higher FSH requirement, decreased oocyte number but no difference in fertilization, pregnancy outcome in subsequent ART cycles.
- In infertile women with endometrioma smaller than 3 cm cystectomy prior to ART does not improve pregnancy rates. If endometrioma is larger than 3 cm, cystectomy is indicated prior to ART when it is associated with pain or inaccessibility of follicles. Surgical management of endometrioma does not significantly increase IVF pregnancy rate and ovarian response to stimulation.
- In women with endometrioma, antibiotic prophylaxis should be given at the time of oocyte retrieval to reduce the risk of ovarian abscess. In women undergoing IVF, stage III and IV is associated with poor implantation and lower clinical pregnancy rate. IVF does not have

any effect on risk of recurrence. The sSurgical removal of the deeply infiltrating lesions does not have much effect on pregnancy outcome after ART.

To summarize, IVF appears to be the most successful treatment option for patients with all stages of endometriosis.

TREATMENT MODALITIES IN FUTURE:

1. **Immunoconjugates (ICON)-**They act on aberrantly expressed tissue factor on endometrial endothelium. They have the potential to destroy preexisting implants in a nontoxic, non-hormonal manner, probably by devascularisation and improve fertility rates.
2. **Aromatase inhibitors**- They inhibit the aromatase present in eutopic endometrium and may improve implantation.
3. Potential future treatments would be aimed to correct altered molecular pathways and **correcting abnormal methylation of HOXA 10gene, estrogen and progesterone receptors**.
4. Replacement of endometrium with a **stem cell-based therapy** may be the optimal way to restore normal endometrial function and implantation in women with endometriosis.

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WHEN TO DELIVER IN A LOW RISK PREGNANCY?

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Elective induction of labour before 41 weeks has generally been discouraged by all professional bodies up until recently .They have asserted that it could only be considered earlier than that for exceptional logistical or psychosocial reasons and never before 39 weeks. Elective induction means induction without a medically dictated maternal or fetal indication in essentially a low risk pregnancy.

Historically the key concerns surrounding such induction practices have been an increase in cesarean section rates as well as possible adverse maternal and perinatal outcomes. Such recommendations were based on small retrospective observational studies which reported increase in cesarean section rates .These studies were often with flawed methodology comparing induction with spontaneous labour and not induction with expectant management.

One of the first studies to compare outcomes of elective induction of nullipara with unfavourable cervix at 39 weeks with expectant management beyond 39 weeks was by Osmundson et al (Am J Obstet Gynecol 2011) and the conclusion was there was no significant difference in cesarean section rates or maternal or perinatal outcomes between the two groups. This was followed in 2012 by a study from Cheng et al (Am J Obstet Gynecol 2012 Dec) that compared outcomes of elective induction at 39 weeks with delivery at later gestational ages in low risk nulliparae. They found that those induced at 39 weeks had a lower risk of cesarean and labor dystocia. Their neonates had lowered risk of having 5-minute Apgar <7, meconium aspiration syndrome and admission to neonatal intensive care unit.

A much larger study(sample size- 362154) by Darney et al (Am J Obstet Gynecol 2013) retrospectively looked at maternal and perinatal outcomes in those who were electively induced at 37, 38, 39 and 40 weeks compared to expectant management at later gestational ages. Interestingly the odds of cesarean delivery were lower among women with elective induction compared to expectant management across all gestational ages (37, 38 and 39 weeks) and parity. Elective induction was also not associated with increased odds of adverse maternal or perinatal outcome at any term gestational age. These seemingly confusing results on effects of elective induction prompted a systematic review of published studies and was carried out by Woods et al (BJOG 2014). It determined that a policy of induction was associated with a reduction in the risk of caesarean section compared with expectant management (OR 0.83, 95% CI 0.76-0.92) but opined that further trials were needed.

Results of ARRIVE (A Randomized Trial of Induction Versus Expectant Management) multicentric trial (Grobman et al) conducted in USA funded by NICHD was published in NEJM in 2018. 3062 low risk nulliparous women were randomized to elective induction of labour at 39+0 to 39+4 weeks and 3044 women to expectant management (defined as the induction from 40 weeks 5 days to 42 weeks 2 days or spontaneous or medically indicated delivery on or before 42 weeks 2 days. The primary perinatal outcome was not significantly different between the induction of labor and expectant management groups whereas the major secondary outcome of cesarean delivery was significantly less common in the induction of labor group. It concluded that one cesarean delivery may be avoided for every 28 deliveries among low-risk nulliparous women who plan to undergo elective induction of labor at 39 weeks.

A secondary analysis of the ARRIVE trial was done by El Sayed et al(ACOG 2020)funded by NICHD and MFMU network in order to evaluate the association between patient characteristics and maternal and perinatal adverse outcomes among women who participated. On multivariate analysis, they found that intended labor induction at 39 weeks of gestation was associated with a reduction in the adverse perinatal composite outcome and no characteristics identified a subgroup of women who would preferentially benefit from undergoing expectant management.

In a meta-analysis by Grobman and Caughey (Am J Obstet Gynecol 2019) that included 66,019 women undergoing elective labor induction at 39 weeks and 584,390 undergoing expectant management, it was found that elective induction of labor at 39 weeks, compared with expectant management beyond that gestational age, was associated with a significantly lower risk of cesarean delivery, maternal peripartum infection, and perinatal adverse outcomes, including

respiratory morbidity, intensive care unit admission, and mortality.

Although Cochrane Database Systematic Review in 2018 opined that a policy of labour induction at or beyond 40 weeks compared with expectant management is associated with fewer perinatal deaths and fewer caesarean sections, Cochrane Database was updated again in 2020 with a systematic review by Middleton et al. They found that there is a clear reduction in perinatal death with a policy of labour induction at or beyond 37 weeks compared with expectant management, though absolute rates are small (0.4 versus 3 deaths per 1000). The number needed to treat for an additional beneficial outcome (NNTB) with induction of labour, in order to prevent one perinatal death, was 544. There were also lower caesarean rates without increasing rates of operative vaginal births and there were fewer NICU admissions with a policy of induction. The review concluded that optimal timing of offering induction of labour to women at or beyond 37 weeks' gestation needs further investigation and offering women tailored counselling may help them make an informed choice.

In July 2021 NICE UK incorporated the latest evidence on elective IOL in the draft for revising IOL guidelines.NICE advises health professionals to consider IOL from 39 weeks in women with otherwise uncomplicated pregnancies who are at increased risk, including those aged 35 and over, those with a BMI over 30, and those with Black, Asian and minority ethnic backgrounds.

ACOG also has revised their recommendations and advises that one should make sure the gestational age is atleast 39 weeks before offering IOL.

Practice points-

- FOGSI Good Clinical Practice Guidelines 2018 were based mainly on the results of the ARRIVE trial and recommend offering elective induction of labour at 39 weeks in low risk pregnancies after counselling and informed consent.
- KFOG protocol development committee under the stewardship of Prof. V.P. Paily had advocated offering elective induction at 39 weeks as early as 2017, drawing from experience with a large case series spanning many years. 39 weeks was chosen as many studies have reported that there is a continuous relationship between gestational age and neonatal morbidity from early pregnancy onward, with a nadir at about 39 weeks.

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METFORMIN IN GESTATIONAL DIABETES

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The use of metformin in gestational diabetes is increasing worldwide as randomised control trials (RCT) have emerged - demonstrating its safety and efficacy. There is an increased prevalence of pre-existing diabetes in pregnant women. The morbidity of GDM is also on the rise in the recent years. About 17% of all pregnancies are complicated by GDM.

The Metformin in Gestational Diabetes (MiG-RCT) study had postulated that metformin has similar pregnancy outcomes to insulin therapy with less maternal weight

gain and a higher degree of acceptability. It is an effective, safe and rational option for reducing insulin resistance in pregnant women with gestational diabetes mellitus (GDM), Type 2 diabetes, polycystic ovarian syndrome, etc.

GDM has been defined as any degree of glucose intolerance with onset during pregnancy. It is the most frequent complication of pregnancy and is associated with several adverse outcomes both short and long term for both mother and offspring. Maternal complications include an increased risk for pre-eclampsia, caesarean section and increased risk of developing type 2 diabetes after pregnancy. There is increased risk of neonatal death, congenital defects, stillbirths, etc resulting from excessive mother to foetus glucose transfer. Macrosomia is another complication and also neonatal hypoglycaemia immediately after birth. The influence of intrauterine hyperglycaemic environment can affect children later in life. Thereby, the early detection of GDM and proper treatment to reduce adverse pregnancy outcomes must be advocated.

Diet therapy, exercise, oral hypoglycaemic agents or insulin are necessary to reduce the complications of GDM. In all high risk pregnancy and patients with family history of diabetes, previous history of GDM or history of giving birth to babies weighing more than 3.5 KG etc should have GCT or GTT test in the first antenatal check-up itself.

If GDM is detected, i.e.Fasting Glucose more than 95 mg/dl or GCT 140 or above or PPBS more than 120 after 2 hours, diet and exercise modifications are initiated. If blood glucose levels do not come to normal within two weeks with diet and exercise, oral hypoglycaemic agents like metformin should be started.

Insulin therapy has several disadvantages, like multiple injections, risk of hypoglycaemia, and maternal weight gain. It requires modification based on patients body mass index, glucose levels, and lifestyle. Detailed guidance for dose adjustment is necessary to ensure safe self-administration of insulin. The cost of drug is also to be considered. Hence safe and effective oral therapy would be acceptable for women with GDM.

Mechanism of Action of Metformin:

Metformin improves insulin sensitivity, reduces hepatic gluconeogenesis and increases peripheral glucose uptake resulting in lowering of blood glucose with minimal risk of hypoglycaemia and weight gain. During pregnancy there is a physiological increase in secretion of several counter regulatory hormones including cortisol, growth hormone and human placental lactogen, progesterone and prolactin. This results in a state of insulin resistance. The rise in insulin resistance is compensated by an increase in insulin secretion and most women remain normoglycemic due to the adequate beta cell compensation.GDM develops if beta cell function is decreased or fails to compensate for the rise in

insulin resistance. Metformin therefore, seems to be a logical treatment for GDM.

Pharmacokinetic Considerations:

Metformin is a hydrophilic and positively charged biguanide and hence it requires transporter proteins to cross cell membranes. The predominant proteins involved in metformin transport include Organic CATion Transporters (OCT), Plasma membrane monoamine transporters etc.

Placental tissue expresses several OCTs including OCT 2 and metformin has been shown to freely cross the placenta. Several other transporters are also expressed in the human syncytiotrophoblast including P-Glycoprotein. The transport of metformin across placenta is regulated by these proteins and seems to be bidirectional.

The renal clearance of metformin is significantly increased by about 29% in mid and late pregnancy parallel to increase renal plasma flow and glomerular filtrations during pregnancy. Hence patients may require higher doses of metformin at that time. Metformin dose ranges from 500 to 2000 mg/day. The dose exceeding 2500 mg/day is detrimental to the safety of maternal and foetal health.

Side effects of metformin include nausea, vomiting giddiness etc. due to gastrointestinal effects like delayed intestinal glucose absorption, enhanced secretion of gastrointestinal hormones and effects on bile acid metabolism.

The role of metformin in GDM has gained acceptance following the publication of MiG trial in 2008. MiG trial was a randomized multicentre open-label trial comparing metformin versus insulin in 751 women diagnosed with GDM between 20 and 33 weeks of gestation. The glycaemic control was comparable to insulin group but 46.3% of patience on metformin required insulin. Maternal weight gain for was lower with metformin than with insulin. Birthweight was similar in metformin group versus insulin group, but incidence of neonatal hypoglycaemia was lower with metformin. The incidence of premature groups was slightly higher in metformin group. Neonatal complications like respiratory distress, need for phototherapy etc. was same in both the groups.

Predictors of poor response to metformin and those who needed insulin supplementation include:

1. Higher fasting glucose level at diagnosis.
2. Early detection of GDM.
3. Past history of GDM.
4. Older age at diagnosis.
5. Higher baseline HbA1c.
6. Elevated BMI.

Effect of Metformin on Maternal Outcome:

Trials have shown that there are no adverse maternal outcomes with the use of metformin and is rather beneficial and associated with lower maternal weight gain and lower risk of preeclampsia. Additional benefits include lower risk of maternal hypoglycaemia compared to insulin. Two meta-analysis studies where

metformin was continued throughout pregnancy showed lower risk of early pregnancy losses.

Long Term Safety Data of Metformin Use in Pregnancy:

Use of metformin during pregnancy can result in significant foetal exposure, but the long term effects on exposed offspring are currently unknown. Metformin may improve foetal insulin sensitivity by altering foetal programming and reduce the long term risk of obesity and cardio metabolic risk in the offspring. The 2 year follow up of offspring born to mothers in the MiG trial, the offspring follow up MiG TOFU generated better hope as there were no increased adverse outcomes. Metformin can sometimes result in vitamin B12 deficiency if used for longer periods, due to inhibition of thiamine uptake and this need to be evaluated further.

Metformin in pregnancy does not increase congenital abnormalities and it's generally well tolerated. Metformin is now a preferred option if glucose targets are not attained with dietary measures. In GDM, it reduces the maternal weight gain when compared with insulin. As there are now increasing incidence of obesity, metformin is very useful in GDM. If glucose levels are not controlled despite the use of tis oral hypoglycaemic agent, lower doses of insulin may be supplemented.

Metformin when started before pregnancy and continued until term in women with PCOS has beneficial effects both for the mother and foetus like reducing GDM, gestational hypertension, preterm labour and also in reducing early pregnancy loss and foetal growth retardation.

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POCUS:
OUR THIRD EYE FOR OBG EMERGENCIES?

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POCUS – Point of Care Ultrasound is the most apt term to describe the bedside Ultrasound, which is considered as an extension to the clinical skills. It is an indispensable tool in the armamentarium of the OBGYN. It is only an extension of the clinical skills of the OBGYN with which a life threatening emergency to the mother or the baby can be picked up in the Emergency department, Labour Room, Operation Theatre or Bed side. The introduction of PUM (Portable *(and affordable)* Ultrasound Machine) brought about this revolution.

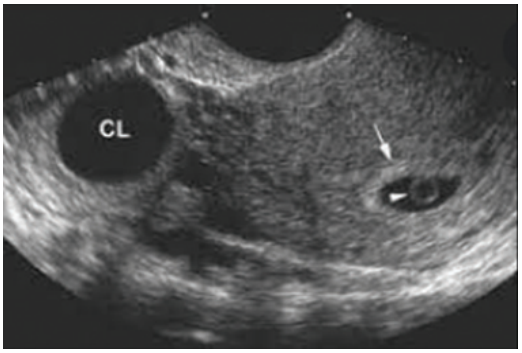
POCUS in Obstetric emergencies:

POCUS is handy in all Obstetric emergencies from the time of conception to delivery and beyond.

Scenario 1 :

A 22 year old Primi with regular cycles at 5 weeks of amenorrhoea presented with right lower abdominal pain. She is not pale, her vitals are within normal limits, abdomen is soft, bimanual examination shows a normal sized uterus with clinically normal adnexae and no tenderness. Routine blood and urine investigations are normal. UPT is weakly positive *(Beware UPT can be 'weakly' positive at very low as well as high values of serum Beta HCG).*

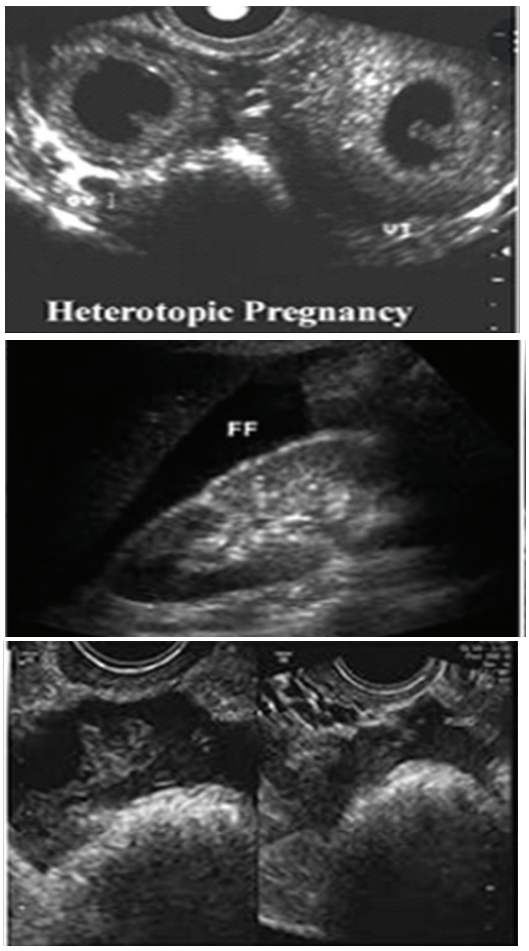
Fig : 1 Intra uterine sac with Right ? Corpus luteum cyst



Her Serum Beta HCG was 1848 mIU/mL. POCUS showed an intrauterine gestational sac with double decidual sac sign which differentiates intrauterine pregnancy from a pseudogestational sac, the decidua capsularis covering the gestational sac and the decidua parietalis lining the uterine cavity contributing to it (Fig 1). She was not discharged due to continuing abdominal pain. A repeat Beta HCG after 48 hours was 3918 mIU/Ml and she had spotting PV on day 5 along with persistent right sided abdominal pain. Clinical examination revealed a bulky uterus and right forniceal and cervical excitation tenderness.

The repeat USS showed a right ectopic pregnancy along with intrauterine pregnancy (heterotopic) (Fig 2). One would have been easily carried away by the initial USS and Doubling Beta HCG values. This shows the importance of repeated clinical examination with POCUS **;'The eyes don't see what the mind doesn't know' .**

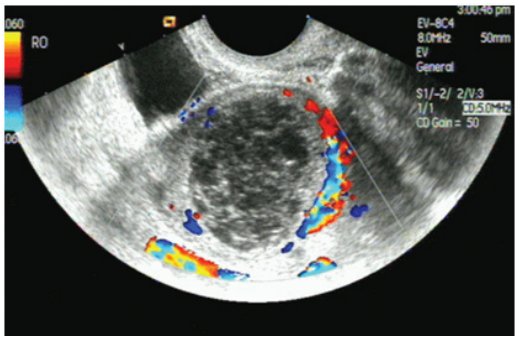
Fig: 2 Heterotopic pregnancy (Right ectopic with intrauterine pregnancy) with hemoperitoneum



In addition POCUS in the first trimester picks up other ectopic pregnancies, ruptured corpus luteum (ring of fire sign Fig.3), multiple pregnancy, vesicular mole, miscarriage, retained products of

conception, scar pregnancy, semi surgical emergencies like acute appendicitis etc.

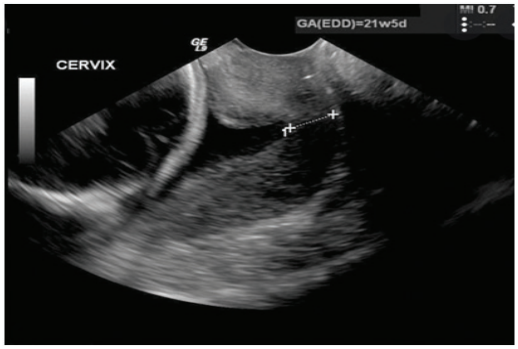
Fig: 3. Ring of fire sign (can be seen in both corpus luteum cyst and tubal ectopic)



Scenario 2:

A 27 year old Primi at 21^{+5} weeks of gestation presents with glary white mucus discharge and lower abdominal discomfort. Her TIFFA was normal. Clinical examination revealed an adequately growing baby and a suspicious short cervix with external os closed.

Fig: 4 : Bulging fetal membranes with short cervix



Scenario : 3

A 32 year old third gravida with 2 previous uneventful deliveries at 32 weeks, booked elsewhere was brought in an ambulance from her work place as she was found to have a bout of bleeding. She is clinically stable, Uterus is relaxed, FHS good and corresponds to the period of gestation. Local examination shows active bleeding. POCUS is shown in fig:5.

Fig: 5 Complete placenta previa

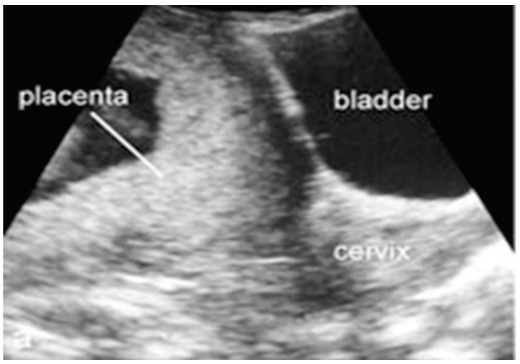
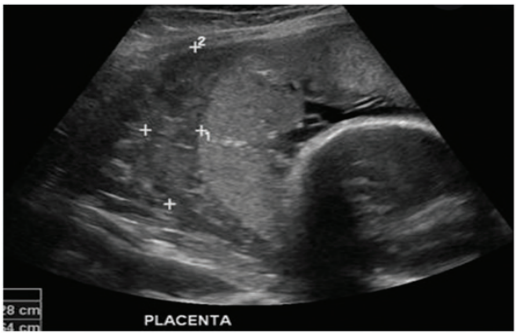


Fig: 6 Abruptio placenta



We might not be always fortunate in POCUS to get a picture of retroplacental haemorrhage like in Fig: 6 , but have to be on the lookout in cases of APH.

POCUS has a definite role in confirming presentation especially in labour, localising fetal heart sounds when it is not audible with stethoscope or hand held doppler, for second of twin vaginal delivery etc

Scenario : 4

A 35 year old Primi was in spontaneous labour. She become fully dilated 2 hours back and has been straining for almost an hour now. Abdominal examination reveals no fetal pole palpable, adequate contractions and good FHS. Per vaginal examination shows fully dilated cervix, absent membranes, large caput and adequate pelvis. Station and position could not be assessed due to large caput.

Fig: 7 LOA as demonstrated by intrapartum USS

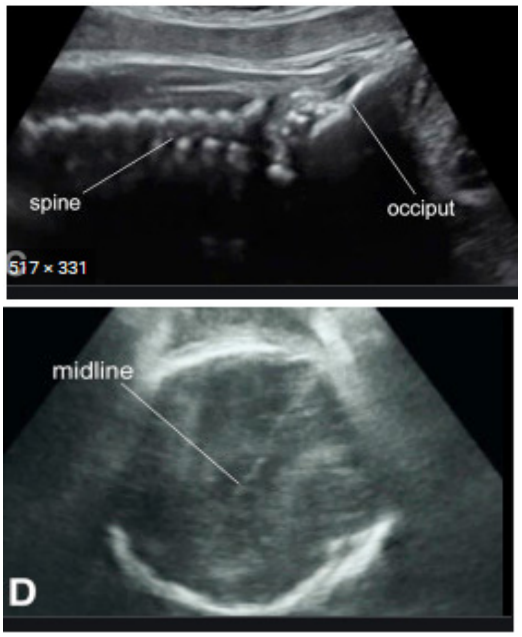
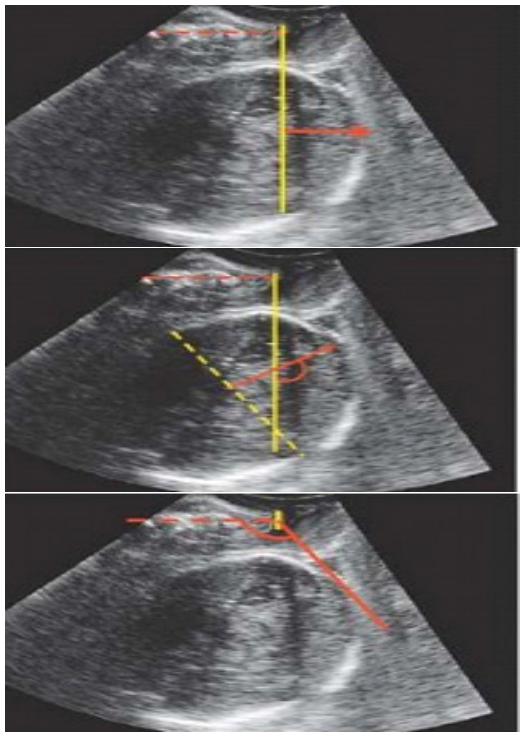


Fig:8 Intra partum USS with Progression distance, fetal head direction, angle of progression



Intra partum USS (IPS) has come to solve some of our clinical dilemmas as in this case. The position and station of fetal head in labour is a subject which has been studied so well and shows great interpersonal variation. Objective assessment of both is possible today with POCUS. Fig: 7 shows how to assess the position and Fig: 8 shows how to assess the fetal descent in labour. This is very handy for deciding on instrumentation.

Another special situation where USS has come to the author's help is to assess the position of condom tamponade, whether it is in situ or not. How much ever emergency the situation is, we should abide by the PNDT rules in Obstetric ultrasound. Management of the above mentioned ObGyn emergencies is beyond the scope of this article.

POCUS in Gynaec emergencies-

POCUS has an equal role in gynecological emergencies too. Failure to diagnose and manage any gynaecological emergency at the appropriate time may lead to serious and chronic consequences. Transvaginal ultrasound has developed as an essential tool in the assessment of the majority of emergency gynaecological cases.

Scenario : 5

A 18 year old girl was brought to Emergency Department with acute abdomen. Her LMP was 2 weeks ago. Clinically, there was tenderness in the left iliac fossa, UPT negative *(Do UPT in all reproductive age group women with abdominal pain irrespective of LMP and marriage status).*

POCUS is shown in Fig : 9 a . These two sonographic pictures differentiate between a simple ovarian cyst and a haemorrhagic one, the latter associated with reticulated spider web appearance. The sonological differential diagnoses would be hydrosalpinx

and tuboovarian abscess (Fig: 10 a and b). Hydrosalpinx has a tubular appearance with incomplete septae and cogwheel appearance in the transverse plane with thick wall. Tubo ovarian abscess has thick wall with mixed echogenicity and inhomogenous content.

Fig: 9 (a and b)Simple ovarian cyst vs Haemorrhagic ovarian cyst

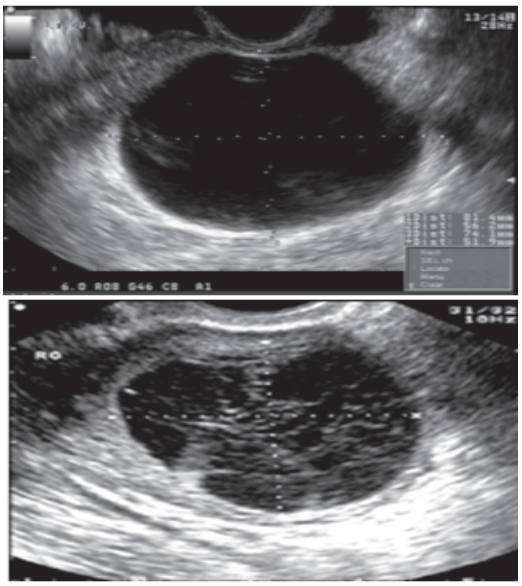
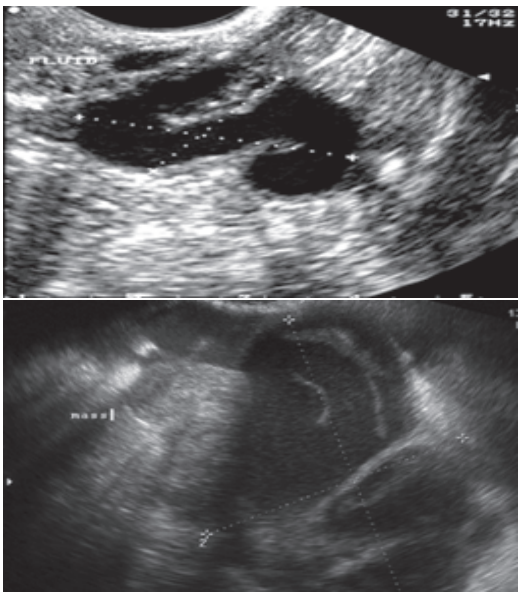
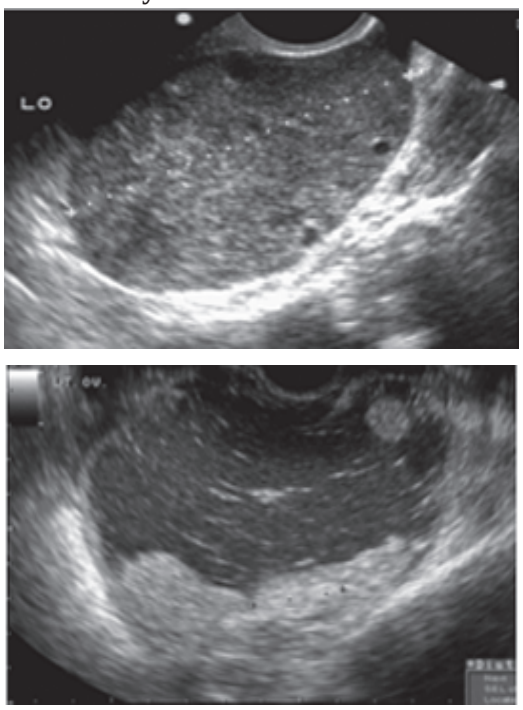


Fig : 10 (a and b) : Hydrosalpinx and tubo ovarian abscess



Yet another differential diagnosis is torsion ovary (Fig:11 a).The usual features are enlarged oedematous ovary, diffuse margins, peripheral follicles, limited vascularity with peritoneal fluid. The ovary can successfully be conserved by detorsion in 88–100% of cases of ovarian torsion, whatever the appearance of the ovary at surgery. Another differential diagnosis is dermoid cyst which is characterised with mixed echogenicity with posterior acoustic shadowing. It is usually cystic to dense with possible fluid and fine strands representing hair. Normal ovarian tissue may be visualised in the periphery (crescent sign)

Fig: 11 (a and b) Torsion ovary and Dermoid cyst

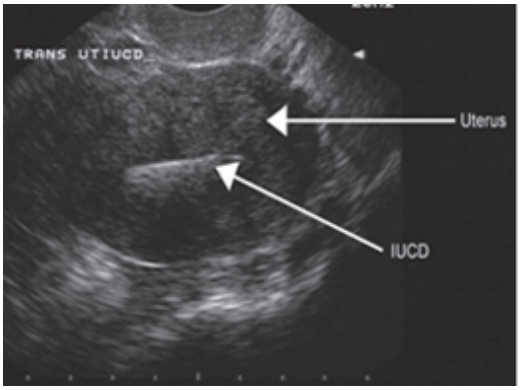


Scenario : 6

A 29 year old Para1 Live1 reports to OPD with lower abdominal pain of 2 months duration. Copper T was inserted 6 months back, LMP 2 weeks back.

General and abdominal examination did not reveal any positive findings. Per speculum and PV findings were also within normal limits. Cu- T thread was missing. Fig: 2 shows the POCUS.

Fig: 12 . Missing IUCD



Other uses of POCUS would be to pick up postoperative intraperitoneal bleed, OHSS etc. Ultrasound is a key investigation in emergency gynaecology, but we should beware findings of incidental pathology such as functional ovarian cysts or hydrosalpinges.

Conclusion

It is cent percent certain that there are so many other ObGyn emergency scenarios, where in my respected seniors and colleagues would have found POCUS handy. POCUS in ObGyn should be delinked from Radiologists and Emergency Physicians and be an extension of our Clinical skills. It should be part of our training of Undergraduates and Residents. POCUS is used as a diagnostic, interventional and Screening tool; all the same it is never a replacement for in depth antenatal or gynaecological ultrasound. So also by incorporating Telemedicine into PUM technology, it is possible to deliver quality Medical care to the remotest corners of the world.

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