THE TRICHY OBSTETRICS AND GYNAECOLOGICAL SOCIETY

28th ANNUAL CME

28th & 29th JUNE 2025

Optimizing Protocols,
Redefining Practices

Presidential Message

My dear friends,

I am extremely delighted to welcome you all to the 28th Annual Conference of Trichy O&G Society.

I have no words to express my gratitude to each and every one of EC members who have all contributed so much to our society throughout this year.

This E-Journal is brought out by our Editorial team with utmost sincerity and hard work. My heartfelt thanks to them.

All the articles are contributed by our own members with academic clarity and they are clinically useful to us.

Trichy O&G Society is known for its unity, organizing skills, academic work, and at the same time, fun and laughter with culture.

I wish the conference a grand success.

Long live TRIOGS

Dr. M. Thamilselvi

President, TRIOGS

Secretary Message

Dear Friends and colleagues,

Warm wishes from the secretary
Trichy Obstetrics and Gynaecological Society.

It's time again for our Annual meeting. We have our 28th Annual Conference on 28th and 29th of June 2025 in Courtyard by Marriott.

The theme this year is 'Optimizing protocols, Redefining practices.' We Continuously Unlearn and Relearn the newer concepts and newer Guidelines, so we practice in a better fashion in the forth coming years.

My Sincere thanks to all members of
Trichy O&G Society for their contribution to this 'E Journal'.

Congratulation to the 'Journal' team

Dr Uma Vaidhiyanathan
Dr Lavanya C

For their efforts in bring out journal.

God bless TRIOGS.

Dr. Uma Velmurugan

Secretary , TRIOGS

Editorial Message

Dear Readers,

It is our pleasure to present the latest issue of Triogs E-Journal of 28th Triogs annual conference, June 2025.

It offers a focused collection of articles from our members and faculty, and highlights the work of our postgraduate students.

Each article has its clinical relevance and potential to inform practice.

Among the highlights are a few insightful case reports that shed light on rare but important clinical scenarios, reminding us of the diagnostic challenges and nuanced decision making often required in patient care

We are immensely proud to publish such insightful contributions and acknowledge the hard work of authors, reviewers and editorial board members in putting this together.

We remain committed to maintaining the quality and integrity of the journal, and constantly strive to update ourselves to new paradigms in the rapidly evolving field of obstetrics and gynaecology.

We welcome your submissions, feedback, and continued support for the journal.

With warm regards

Dr. Uma Vaidhyanathan

Dr. Lavanya

CONTENTS

PHYSIOLOGY OF IMPLANTATION

PROF. DR. T. RAMANIDEVI, MD., DGO., FICS., FICOG., PH.D.,

Vice President FOGSI 2020
President TNFOG 2024
Director Ramakrishna Medical Centre LLP
Director Janani Fertility centre, Trichy & Patukkottai

DR AANANTHA LAKSHMI, MD

Physiology eshre certified and american college certified senior clinical embryologist
Jañani Fertility centre, Trichy

ABSTRACT:

Conservation of any species requires a fundamental process called reproduction. This process involves any events to achieve a successful pregnancy. Implantation and decidualization are the most important steps which involves maternal interactions with the developing embryo. This chapter highlights physiological process and the molecular mechanisms involved in implantation. Implantation of embryo involves the intimate interaction between a blastocyst which is competent and a uterus which is receptive. This occurs only in a limited period of time known as the window of implantation. Gene expression studies and genetically engineered mouse models have identified a numerous cellular events and molecular pathways involved in crosstalk between an embryo and the uterus. A complete understanding of the nature of implantation is still absent. Our aim is to provide the description of the process, molecular mechanism tangled in window of implantation and probable pathologies that could interrupt the blastocyst implantation and decidualization. This also enlightens about defective implantation and decidualization and its adverse outcome. New strategies to rectify implantation failure and improve pregnancy rates in women with recurrent pregnancy loss can be developed after understanding the underlying mechanisms governing embryo implantation.

KEYWORDS:

cytokines; decidualization; embryo; endometrium; gynaecological pathologies; implantation; miRNA; blastocyst activation; uterine receptivity; blastocyst attachment;

INTRODUCTION

The beginning of a new life involves a process called fertilization. The fusion of an oocyte with a spermatozoan is called fertilization.[1]. After fertilization, the zygote undergoes several cell divisions and morphological changes to form the blastocyst. This cell stage has two discrete cell lineages namely the outer specialized trophectodermal epithelium and the inner cell mass.[2,3] This blastocyst establishes a bidirectional crosstalk between uterus which is essential for normal implantation thus a successful pregnancy. Perturbations will generate adverse outcomes for subsequent development, including decidualization and placentation, with potential loss of the pregnancy. [4,5,6,7] Before pregnancy is recognized clinically, early pregnancy loss can occur during the peri implantation period in

humans.[3,8] The maximum chance of successful pregnancy occurring in a given menstrual cycle even in natural conception is limited to about 30% is an example. [9] According to Norwitz et al, only 50 to 60 percent of all conceptions advance beyond 20 weeks of gestation.[8] 75% of the cause is attributed to implantation failure.[10] Inspite of substantial developments in in vitro fertilization, success rates in achieving pregnancy remains relatively low. This is mainly due to implantation failure.[8,11,12]

Acquisition of implantation competency by the blastocyst and a receptive state in the uterine endometrium must be synchronised to get a successful implantation.[2,13,14] Ovarian oestrogen and progesterone regulate these two events.[15,16] These two hormones along with growth factors, cytokines, homeobox transcription factors, lipid mediators and morphogen genes, function through autocrine, paracrine and juxtracrine interactions to specify the complex process of implantation.[13] The blastocyst and the uterus can interact with each other only during a brief period called "window of implantation" . [17,18.]

The surrounding uterine stroma undergoes cellular transformation called decidualization, to accommodate embryonic growth and invasion. [19]

STAGES OF IMPLANTATION:

1. The process of summit of a blastocyst to the site of implantation in the endometrium is called apposition.
2. Blastocyst's trophectoderm cells get attached to the epithelium of the receptive endometrium is adhesion
3. The invading cells of the trophectoderm cross the basement membrane of the epithelium and invade the stroma of the endometrium by the process called invasion. [20]

MOLECULAR INTERACTION IN APPOSITION AND ADHESION

Morula enters the cavity of the uterus and the apposition process starts 2-4 days after this. The upper posterior wall of the uterus in midsagittal plane is the usual site of implantation. Implantation is a pro inflammatory reaction. Prostaglandins derived from Cyclo oxygenase pathway increases the vascularity of the endometrium at the implantation site. Increased level of Prostaglandin E2 is demonstrated at the site of implantation in both mice and human being. [21]. PG E2 also plays a vital role in invasion by activating other signalling proteins [22] Decidualization is a process by which the endometrial stromal cells that surrounds a blastocyst distinguish into decidual cells.[23]

Leukemia-inhibitory factor (LIF) is an important cytokine which belongs to interleukin-6 family. Action of Estrogen is mediated by LIF. In mice which has LIF gene knockout suffered from infertility, due to defective implantation and decidualization. This was treated by recombinant LIF. [24] In human the same has been demonstrated by Laird et al in 1997 that expression of LIF is higher in fertile female compared to infertile about the implantation time. [25,26].

There are many cell junction molecules that acts as a barrier to implantation of embryo. LIF causes down regulation of these molecules and favours proliferation of stromal cells through epidermal growth factor (EGF) pathway regulation. [27] Pollard et al established the importance of cross talk between Colony stimulating factor (CSF 1) receptor on the embryo and the CSF 1 receptor on the endometrium for attachment of the embryo. [28] Expression of vascular endothelial growth factor (VEGF) is stimulated by IL-1. This also regulates the expression of tissue inhibitors of metalloproteinases (TIMPs) and Matrix metalloproteinases (MMPs) [29]. Endometrial epithelial cell coculture system showed high level of Interleukin-6 (IL-6) [30.]

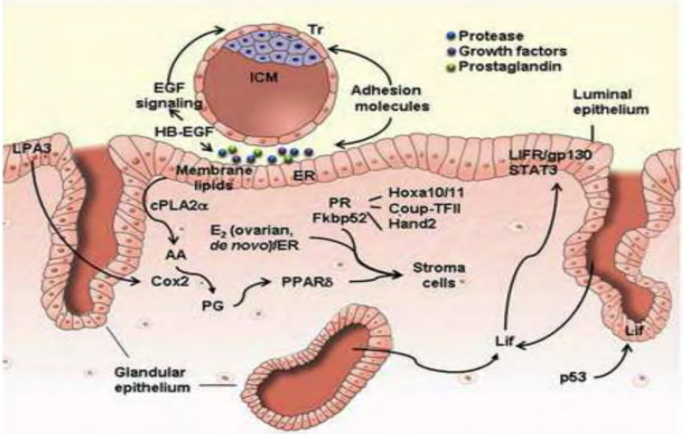
Heparin-binding epidermal growth factor-

like growth factor (HB-EGF) is a molecule studied by Cha et al in 2012 which plays a crucial role in attachment of the embryo. [32] HB-EGF is initially synthesized as a transmembrane protein later processed and release a growth factor which is soluble. Both the protein and growth factor form will influence the growth of the blastocyst as juxtracrine adhesion factor through the EGF family of receptors expressed on the surface of the embryo.[33] Integrins, cadherins, L.selectins and immunoglobulins are some of the cell adhesion molecules essential for implantation. They are expressed on the surface of the developing embryo. They interact with decidual ligands. [34]

Implantation window markers include Integrins which are specific to menstrual cycle are found upregulated in the mid-luteal phase of the endometrium and also it is expressed in trophoblast cells [35, 36] Klentzeris et al in 1993 have found a relation between lack of integrin and unexplained infertility. [37]

E -Cadherins are glycoproteins important for the initial attachment process and they act via cell adhesion mechanism which is Ca2+ - dependent. [38]

L-selectin is found to be expressed in pinopodes and its interaction with the trophoblast cells forms the basis for initial step of implantation. [39]



INVASION OF BLASTOCYST

The process by the trophoblastic cells of the embryo invade the decidua of the mother's uterus and migrate into it is called invasion. The trophoblastic cells differentiate into cytotrophoblast and syncitiotrophoblast at the implantation site. Eventually, the blastocyst which is invading destroys spiral arteries wall. sinusoidal sacs are formed from the arterial wall. The walls of these sinusoids are very flaccid lined by endovascular trophoblast. [40] Thus at the end all high resistance flow vessels are converted to low resistance flow vessels. All these are regulated by Vascular Endothelial growth factor VEGF.

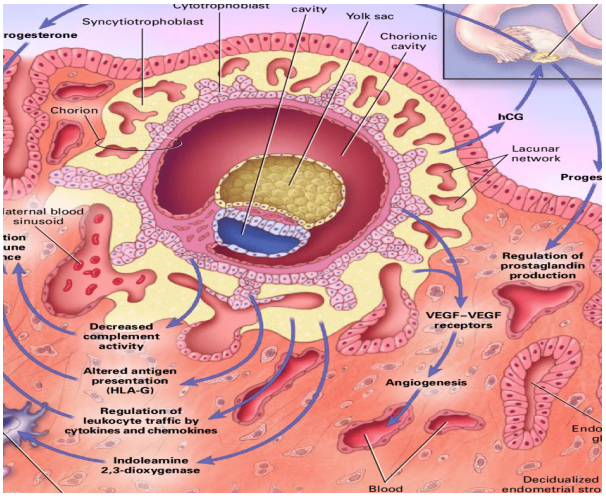
Trophoblastic invasion plays a major role in foetal viability and placental efficiency in late gestational age. Trophoblastic invasion deficiency can lead to Intrauterine growth restriction (IUGR) and preeclampsia as an adverse effect.[41]

Matrix metalloproteinases (MMPs) and collagenases helps in tissue degradation and thus this remodelling of tissues lead to placental villi formation. [42]

REGULATORS OF INVASION PROCESS

Plasminogen → plasmin (urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA)) Extracellular Matrix is destroyed by this plasmin. Trophoblast cells have Plasminogen activator receptors. The process of invasion should be under strict control and should confine only to the placental site. Activating growth factors, enzymes, inhibiting growth factors, and cytokines should be in a balance to maintain this limitation. The decidual cells produce Plasminogen activator inhibitor-1 (PAI-1)[43]

Transforming growth factor (TGF)-β present in the decidual cells converts invasive cytotrophoblasts into non-invasive syncitiotrophoblast and the tissue inhibitors of MMPs (TIMPs) regulate the invasion[44,45]. Decorin is a proteoglycan which binds to TGF-β present in decidua. All these process controls invasion, migration and proliferation of trophoblast cells.



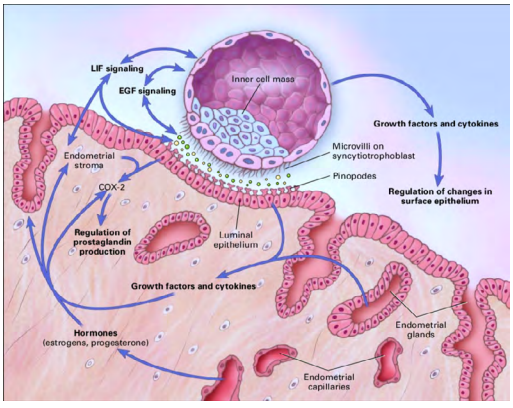


Figure 1 : Norwitz, Errol & Schust, Danny & Fisher, Susan. (2001). Implantation and the Survival of Early Pregnancy. The New England journal of medicine. 345. 1400-8. 10.1056/NEJMra000763.

NEW CONCEPT

The fate of ongoing pregnancy is dependent on the quality of implantation is the recent emerging concept of implantation. Our understanding about the implantation physiology has been advanced but it is only the tip of iceberg. Recent studies shows that the quality of ongoing pregnancy is determined by the implantation quality. Any errors at this early stage will profoundly contribute to early pregnancy loss or various pregnancy complications. [13]

Conclusion

15% of couples at reproductive age are at the risk of infertility. Only about 30% success rate are there for natural conception in each menstrual cycle , while implantation is a major limiting factor. Therefore, unscrambling the complexities of implantation will help to address these issues globally. A receptive uterus exchanges a complex dialogue between a competent blastocyst and this dialogue continues throughout the period of implantation. Assisted reproductive techniques serves as a boon for many infertile couples to overcome the problems. But, implantation of the blastocyst still remains a major limiting step in the success of In Vitro Fertilization and Embryo Transfer. Molecular pathway of implantation must be thoroughly studied to improve the diagnosis and treatment of infertility. Imperfect implantation and decidualization problems must be identified to fight against the problem of infertility.

References

4. Wassarman PM. Mammalian fertilization: molecular aspects of gamete adhesion, exocytosis, and fusion. Cell. 1999; 96(2):175–183. [PubMed: 9988213]
5. Wang H, Dey SK. Roadmap to embryo implantation: clues from mouse models. Nat Rev Genet. 2006; 7(3):185–199. [PubMed: 16485018]
6. Cockburn K, Rossant J. Making the blastocyst: lessons from the mouse. J Clin Invest. 2010; 120(4): 995–1003. [PubMed: 20364097]
7. Chen Q, Zhang Y, Peng H, Lei L, Kuang H, Zhang L, Ning L, Cao Y, Duan E. Transient {beta}2- adrenoceptor activation confers pregnancy loss by disrupting embryo spacing at implantation. J Biol Chem. 2011;

286(6):4349–4356. [PubMed: 21148315]

8. Song H, Lim H, Paria BC, Matsumoto H, Swift LL, Morrow J, Bonventre JV, Dey SK. Cytosolic phospholipase A2alpha is crucial [correction of A2alpha deficiency is crucial] for 'on-time' embryo implantation that directs subsequent development. Development. 2002; 129(12):2879– 2889. [PubMed: 12050136]
9. Wilcox AJ, Baird DD, Weinberg CR. Time of implantation of the conceptus and loss of pregnancy. N Engl J Med. 1999; 340(23):1796–1799. [PubMed: 10362823]
10. Ye X, Hama K, Contos JJ, Anliker B, Inoue A, Skinner MK, Suzuki H, Amano T, Kennedy G, Arai H, Aoki J, Chun J. LPA3-mediated lysophosphatidic acid signalling in embryo implantation and spacing. Nature. 2005; 435(7038):104–108. [PubMed: 15875025]
11. Norwitz ER, Schust DJ, Fisher SJ. Implantation and the survival of early pregnancy. N Engl J Med. 2001; 345(19):1400–1408. [PubMed: 11794174]
12. Zinaman MJ, Clegg E, Brown CC, O'connor J, Selevan S. Estimates of human fertility and pregnancy loss. Fertil Steril. 1996; 65(3):503. [PubMed: 8774277]
13. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence of early loss of pregnancy. N Engl J Med. 1988; 319(4):189–194. [PubMed: 3393170]
14. Miller PB, Parnell BA, Bushnell G, Tallman N, Forstein DA, Higdon HL, Kitawaki J, Lessey BA. Endometrial receptivity defects during IVF cycles with and without letrozole. Hum Reprod (3). 2012; 27(3):881–888. [PubMed: 22246449]
15. Wilcox LS, Peterson HB, Haseltine FP, Martin MC. Defining and interpreting pregnancy success rates for in vitro fertilization. Fertil Steril. 1993; 60(1):18–25. [PubMed: 8513941]
16. Dey SK, Lim H, Das SK, Reese J, Paria BC, Daikoku T, Wang H. Molecular cues to implantation. Endocr Rev. 2004; 25(3):341–373. [PubMed: 15180948]
17. Tranguch S, Daikoku T, Guo Y, Wang H, Dey SK. Molecular complexity in establishing uterine receptivity and implantation. Cell Mol Life Sci. 2005b; 62(17):1964–1973. [PubMed: 16143898]
18. Conneely OM, Mulac-Jericevic B, DeMayo F, Lydon JP, O'Malley BW. Reproductive functions of progesterone receptors. Recent Prog Horm Res. 2002; 57:339–355. [PubMed: 12017551]
19. Curtis Hewitt S, Goulding EH, Eddy EM, Korach KS. Studies using the estrogen receptor alpha knockout uterus demonstrate that implantation but not decidualization-associated signaling is estrogen dependent. Biol Reprod. 2002; 67(4):1268–1277. [PubMed: 12297545]
20. Ma WG, Song H, Das SK, Paria BC, Dey SK. Estrogen is a critical determinant that specifies the duration of the window of uterine receptivity for implantation. Proc Natl Acad Sci U S A. 2003; 100(5):2963–2968. [PubMed: 12601161]
21. Paria BC, Huet-Hudson YM, Dey SK. Blastocyst's state of activity determines the "window" of implantation in the receptive mouse uterus. Proc Natl Acad Sci U S A. 1993; 90(21):10159– 10162. [PubMed: 8234270]

22. Lim HJ, Wang H. Uterine disorders and pregnancy complications: insights from mouse models. J Clin Invest. 2010; 120(4):1004–1015. [PubMed: 20364098]
23. Bischof P, Campana A Trophoblast differentiation and invasion: its significance for human embryo implantation. Early Pregnancy 1997; 3:81-95
24. Van der Weiden RM, Helmerhorst FM, Keirse MJ Influence of prostaglandins and platelet activating factor on implantation. Hum Reprod 1991; 6:436-442
25. Nicola C, Chirpac A, Lala PK, Chakraborty C Roles of Rho guanosine 5'-triphosphatase A, Rho kinases, and extracellular signal regulated kinase (1/2) in prostaglandin E2-mediated migration of first-trimester human extravillous trophoblast. Endocrinology, 2007; 149:1243-1251.
26. Ramathal CY, Bagchi IC, Taylor RN, Bagchi MK. Endometrial decidualization: Of mice and men. Semin Reprod Med 2010; 28:17-2
27. Stewart CL, Kaspar P, Brunet LJ, Bhatt H, Gadi I, Kontgen F, Abbondanzo SJ (1992) Blastocyst implantation depends on maternal expression of leukaemia inhibitory factor. Nature 359:76-79
28. Laird SM, Tuckerman EM, Dalton CF, Dunphy BC, Li TC, Zhang X The production of leukaemia inhibitory factor by human endometrium: presence in uterine flushings and production by cells in culture. Hum Reprod 1997; 12:569-574.
29. Hambartsoumian E Endometrial leukemia inhibitory factor (LIF) as a possible cause of unexplained infertility and multiple failures of implantation. Am J Reprod Immunol 1998; 39:137-143
30. Hantak AM, Bagchi IC, Bagchi MK Role of uterine stromal-epithelial crosstalk in embryo implantation. Int J Dev Biol 2014; 58:139-146.
31. Pollard JW, Hunt JS, Wiktor-Jedrzejczak W, Stanley ER .A pregnancy defect in the osteopetrotic (opop) mouse demonstrates the requirement for CSF-1 in female fertility. Dev Biol 1991; 148:273-283.
32. Krüssel JS, Bielfeld P, Polan ML, Simón C Regulation of embryonic implantation. Eur J Obstet Gynecol Reprod Biol 2003;110:S2-S9
33. Dominguez F, Gadea B, Mercader A, Esteban FJ, Pellicer A, Simon C Embryologic outcome and secretome profile of implanted blastocysts obtained after coculture in human endometrial epithelial cells versus the sequential system. Fertil Steril 2010a; 93:774-782.
34. Dominguez F, Meseguer M, Aparicio-Ruiz B, Piqueras P, Quinonero A, Simon C., New strategy for diagnosing embryo implantation potential by combining proteomics and time-lapse technologies. Fertil Steril 2015 b; 104: 908-914
35. Cha J, Sun X, Dey SK Mechanisms of implantation: strategies for successful pregnancy. Nat Med 2002; 18:1754- 1767
36. Raab G, Kover K, Paria BC, Dey SK, Ezzell RM, Klagsbrun M Mouse preimplantation blastocysts adhere to cells expressing the transmembrane form of heparin-binding EGF-like growth factor. Development 2006, 122:637-645

37. Lyall F Mechanisms regulating cytotrophoblast invasion in normal pregnancy and pre-eclampsia. Aust N Z J Obstet Gynaecol 2006; 46:266-273.
38. Lessey BA, Damjanovich L, Coutifaris C, Castelbaum A, Albelda SM, Buck CA Integrin adhesion molecules in the human endometrium. Correlation with the normal and abnormal menstrual cycle. J Clin Invest ; 1992 ; 90:188-195
39. Sutherland AE, Calarco PG, Damsky CH Developmental regulation of integrin expression at the time of implantation in the mouse embryo. Development, 1993; 119: 1175-1186.
40. Klentzeris LD, Bulmer JN, Trejdosiewicz LK, Morrison L, Cooke ID Infertility: Beta-1 integrin cell adhesion molecules in the endometrium of fertile and infertile women. Hum Reprod 1993; 8:1223-1230
41. Rowlands TM, Symonds JM, Farookhi R, Blaschuk OW Cadherins: Crucial regulators of structure and function in reproductive tissues. Rev Reprod; 2000, 5:53-61.
42. Nejatbakhsh R, Kabir-Salmani M, Dimitriadis E, Hosseini A, Taheripanah R, Sadeghi Y, Akimoto Y, Iwashita M Subcellular localization of L-selectin ligand in the endometrium implies a novel function for pinopodes in endometrial receptivity. Reprod Biol Endocrinol 2012; 10:46.
43. Burrows TD, King A, Loke Y Trophoblast migration during human placental implantation. Hum Reprod Update 1996; 2:307-321.
44. Hunkapiller NM, Gasperowicz M, Kapidzic M, Plaks V, Maltepe E, Kitajewski J, Cross JC, Fisher SJ A role for Notch signaling in trophoblast endovascular invasion and in the pathogenesis of pre-eclampsia. Development 2011;138:2987-2998.
45. Cohen M, Meisser A, Bischof P Metalloproteinases and human placental invasiveness. Placenta 2006; 27:783-793.
46. Schatz F, Aigner S, Papp C, Toth-Pal E, Hausknecht V, Lockwood CJ Plasminogen activator activity during decidualization of human endometrial stromal cells is regulated by plasminogen activator inhibitor 1. J Clin Endocrinol Metab 1995; 80:2504-2510.
47. Karmakar S, Das C Regulation of trophoblast invasion by IL-1β and TGF-β1. Am J Reprod Immunol 2002; 48: 210-219.
48. Graham CH, Lysiak JJ, McCrae KR, Lala PK (Localization of transforming growth factor-β at the human fetal-maternal interface: role in trophoblast growth and differentiation. Biol Reprod 1992; 46:561-572

PRE-CONCEPTIONAL COUNSELLING

DR. PRIYADHARSHINI MOHANASUNDARAM
MD,MRCOG,MICOG,FRM,
ASSISTED CONCEPTION- BRITISH FERTILITY SOCIETY.

ABSTRACT:

Preconception counseling is a form of preventative care which includes counseling and education about the state of a women's health prior to pregnancy. This involves determining a women's overall health status as influenced by her clinical, environmental and psychosocial status followed by identifying a set of interventions. The preconception period is often defined as the 3 months before conception because this is the average time to conception for fertile couples.

Benefits of intentionally preparing for pregnancy are supported by data indicating that unfavorable maternal and fetal outcome associated with pre-existing maternal conditions can be avoided through pregnancy intervention. Preconception care should begin during the adolescent years in the form of life skill development where young women are educated about the importance of factors such nutrition, contraception, tobacco/alcohol use, rubella immunization, sexually transmitted infections and safe sex practice for future health.

Factors such as increasing obesity rates and delaying pregnancy until women are older means that more women are entering pregnancy with acquired medical conditions such as hypertension, diabetes and renal disease. Furthermore, advances in medical care mean that women with complex medical and surgical disease are able to have successful pregnancies.

INTRODUCTION

Obstetrician–gynecologists have a prime opportunity to improve maternal and fetal outcomes through pre-pregnancy counseling. Like a well-woman visit, the pre-pregnancy visit (when the patient presents to discuss a potential future pregnancy) provides an excellent opportunity to counsel patients about maintaining a healthy lifestyle and minimizing health risks. The goal of pre-pregnancy care is to reduce the risk of adverse health effects for the woman, fetus, and neonate by working with the woman to optimize health, address modifiable risk factors, and provide education about healthy pregnancy. Pre-pregnancy counseling should include a review of a patient's immunizations, an assessment for immunity, and other screenings and tests, as appropriate. All those planning to initiate a pregnancy should be counseled, including heterosexual, lesbian, gay, bisexual, transgender, queer, intersex, asexual, and gender nonconforming individuals.

Pregnancy complications may be reduced by appropriate identification and mitigation of risk factors, while genetic screening may allow a couple to make informed decisions regarding family planning. Management of preexisting medical conditions may be optimized during the pre-pregnancy period, reducing the chances of pregnancy-related complications. Additionally, understanding aspects of patient 's social context during pre-pregnancy counseling may identify ways to help improve prenatal care usage, including understanding barriers that patients may face when accessing health care.

TIMING OF PRE-PREGNANCY COUNSELLING

Counseling can begin with the following question: "Would you like to become pregnant in the next year ?" Pre-pregnancy counseling is appropriate whether the reproductive-aged patient is currently using contraception or planning pregnancy. Because health status and risk factors can change over time, pre-pregnancy counseling should occur several times during a woman's reproductive lifespan, increasing her opportunity for education and potentially maximizing her reproductive and pregnancy outcomes.

The American College of Obstetricians and Gynecologists and ASRM support coverage for and access to recommended pre-pregnancy counseling and services as a core component of women's health care.

The American College of Obstetricians and Gynecologists (ACOG) and the American Society for Reproductive Medicine (ASRM) make the following recommendations and conclusions:

- Any patient encounter with nonpregnant women or men with reproductive potential (eg, not post-hysterectomy or post-sterilization) is an opportunity to counsel about wellness and healthy habits, which may improve reproductive and obstetric outcomes should they choose to reproduce.
- The goal of pre-pregnancy care is to reduce the risk of adverse health effects for the woman, fetus, and neonate by working with the woman to optimize health, address modifiable risk factors, and provide education about healthy pregnancy.
- Women should be counseled to seek medical care before attempting to become pregnant or as soon as they believe they are pregnant to aid in correct dating and to be monitored for any medical conditions in which treatment should be modified during pregnancy.
- Many chronic medical conditions such as diabetes, hypertension, psychiatric illness, and thyroid disease have implications for pregnancy outcomes and should be optimally managed before pregnancy.
- All prescription and nonprescription medications should be reviewed during pre-pregnancy counseling. This review also should include nutritional supplements and herbal products that patients may not consider to be medication use but could affect reproduction and pregnancy.
- Women who present for pre-pregnancy counseling should be offered screening for the same genetic conditions as recommended for pregnant women.
- Women of reproductive age should have their immunization status assessed

annually for tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap); measles–mumps–rubella; hepatitis B; and varicella.

- All patients should receive an annual influenza vaccination; those women who are or will be pregnant during influenza season will have additional benefits.
- Assessment of the need for sexually transmitted infection (STI) screening should be performed at the time of pre-pregnancy counseling.
- All patients should be routinely asked about their use of alcohol, nicotine products, and drugs, including prescription opioids and other medications used for nonmedical reasons.
- Screening for intimate partner violence should occur during pre-pregnancy counseling.
- Female pre-pregnancy folic acid supplementation should be encouraged to reduce the risk of neural tube defects (NTDs).
- Patients should be screened regarding their diet and vitamin supplements to confirm they are meeting recommended daily allowances for calcium, iron, vitamin A, vitamin B12, vitamin B, vitamin D, and other nutrients.
- Patients should be encouraged to try to attain a body mass index (BMI) in the normal range before attempting pregnancy, because abnormal high or low BMI is associated with infertility and maternal and fetal pregnancy complications.

FAMILY PLANNING AND PREGNANCY SPACING

Counseling patients about optimal intervals between pregnancies may be helpful to reduce future complications. Women should be advised to avoid interpregnancy intervals shorter than 6 months and should be counseled about the risks and benefits of repeat pregnancy sooner than 18 months. Short interpregnancy intervals also are associated with reduced vaginal birth after cesarean success for women undergoing labor after cesarean (also referred to as trial of labor after cesarean).

For infertile women planning to use assisted reproductive technology to become pregnant, a pregnancy interval less than 18 months but greater than 6 months may be advisable.

An ovulatory woman who is younger than 35 years who desires pregnancy and who does not have a clearly identifiable risk factor for infertility should be expeditiously evaluated if she has not become pregnant after 12 months of unprotected intercourse. A woman who is 36 years and older should be evaluated after 6 months

Referral to a fertility specialist for males and females may be considered at any point if the infertility etiology, indicated treatment, or attempted treatment failures exceeds the expertise of the obstetrician–gynecologist.

PRE-CONCEPTIONAL HEALTH EVALUATION

NUTRITION AND WEIGHT MANAGEMENT
• Diet • Folic acid/multivitamin use • Ideal body weight
FAMILY HISTORY
• Heritable conditions • Previous birth defects

SOCIAL
• Pregnancy intention/access to care • Occupational hazards • Mental health conditions such as depression • Use of alcohol, tobacco, recreational drugs • History of physical or psychological abuse
MEDICAL DISEASE
• Diabetes • Respiratory • Renal conditions • Lupus • Thyroid disease • Cardiac disease • Epilepsy
REPRODUCTIVE HISTORY
• Uterine/cervical anomalies • One or more fetal deaths • Previous small-for-gestational-age infant • 2 or more previous miscarriages • Previous preterm birth • One or more infants with a birth defect
MEDICATION
• Drugs that must be stopped/ changed
INFECTIONS/VACCINATIONS
• Sexually transmitted diseases • Immunity against rubella/varicella • IV and prevention of mother-to-child-transmission

REVIEW OF CURRENT MEDICATIONS

All prescription and nonprescription medications should be reviewed during pre-pregnancy counseling. This review also should include nutritional supplements and herbal products that patients may not consider to be medication use but could affect reproduction and pregnancy. The pregnancy safety of each medication and supplement should be discussed. Medications with potential teratogenicity should be reviewed and the specific risks of each individual medication discussed in detail. The importance of reliable contraception should be emphasized when a patient is taking potentially teratogenic medications.

The lowest effective doses of the safest medications should be used whenever it is medically reasonable to do so.

Male partners should be screened for the use of androgens, such as testosterone. Androgen use is associated with azoospermia and infertility in males, which may be reversible in some cases with cessation

REVIEW OF FAMILY AND GENETIC HISTORY

A genetic and family history of the patient and her partner should be obtained This may include family history of genetic disorders, birth defects, mental disorders, and breast, ovarian, uterine, and colon cancer. When any genetic disease carrier status is diagnosed in one or both partners, full medical records review and genetic counseling are recommended to educate the patient on the effects of the disease and the potential options for pre-pregnancy and early pregnancy screening of offspring.

REVIEW OF MEDICAL, SURGICAL, AND PSYCHIATRIC HISTORIES

Many chronic medical conditions such as diabetes, hypertension, psychiatric

illness, and thyroid disease have implications for pregnancy outcomes and should be optimally managed before pregnancy (Table 2). Consideration may be given to referral to a maternal–fetal medicine specialist. Data are insufficient to recommend for or against universal screening for subclinical thyroid disease; however, screening may be appropriate for patients with risk factors (e.g., age greater than 30 years, morbid obesity, history of pregnancy loss, preterm delivery, or infertility.

TABLE 1. CHRONIC MEDICAL CONDITIONS, RISKS, AND PRECONCEPTION INTERVENTIONS

Medical Problem	Risks	Interventions
Pregestational Diabetes	Miscarriage, congenital fetal anomalies, perinatal death.	• Optimize HbA1c prior to conception • (HbA1C ≤ 6%)
Chronic Hypertension	Preterm birth, placental abruption, intrauterine growth restriction, preeclampsia, fetal death.	• Good control with nonteratogenic medications Avoid ACE inhibitors, ARBs and atenolol. • Consider testing for ventricular hypertrophy, retinopathy and renal disease for women with longstanding hypertension.
Untreated Hypothyroidism	Preterm birth, low birth weight, placental abruption, fetal death.	• Medication dosages usually increases by 4-6 weeks of gestation.
Hyperthyroidism	Significant maternal and neonatal morbidity.	• Propylthiouracil preferred in first trimester while methimazole is preferred in second and third trimesters
Seizure Disorder	Miscarriage, low birth weight, developmental disabilities, microcephaly, hemorrhagic disease, and congenital anomalies.	• Monotherapy at the lowest dose possible should be used when able. Supplement with 4mg folic acid daily.
Overweight	Overweight Diabetes, gestational diabetes, and hypertension.	• Achieve healthy weight prior to conception, limit weight gain during pregnancy.
Underweight	Preterm birth, low birth weight, and gastroschisis.	• Obtain ideal weight prior to pregnancy.

Medical Problem	Risks	Interventions
Psychiatric Illness	Maternal suffering can lead to poor compliance with prenatal care, poor nutrition, substance abuse, or disturbed relationship between mother and infant.	• Women on medication with no or mild symptoms can be considered for a taper and discontinuation. Discontinuation of medication not advised for women with severe recurrent depressive disorders, psychosis, bipolar illness, psychiatric comorbidity requiring medication, or history of suicidal ideation.
Human Immunodeficiency Virus(HIV)	Vertical Transmission	• Anti-retrovial therapy should be instituted before and continued during pregnancy. • Viral load should be undetectable and should be managed in concordance with HIV care provider
Previous Thrombophilias	DVT / PE during pregnancy or postpartum period	• Consider and plan Thromboprophylaxis throughtout and during pregnancy and postpartum

EXPOSURE TO VIOLENCE, INTIMATE PARTNER VIOLENCE, AND REPRODUCTIVE AND SEXUAL COERCION

Screening for intimate partner violence should occur during prepregnancy counseling. The discussion regarding intimate partner violence should be framed by indicating that all patients in the practice are screened. Assurances of privacy and confidentiality are important components of intimate partner violence screening; however, some state laws place mandatory reporting requirements on health care providers for certain types of injuries or disclosures and for certain groups of patients. Sexual coercion includes a range of behavior that a partner may use related to sexual decision making to pressure or coerce a person to have sex without using physical force . If ongoing abuse is identified, assessment of the immediate safety of the patient and her family should be ascertained and community resources for victims should be provided.

ACHIEVING AND MAINTAINING A HEALTHY BODY WEIGHT

Patients should be encouraged to try to attain a BMI in the normal range before attempting pregnancy because abnormal high or low BMI is associated with infertility and maternal and fetal pregnancy complications. The reproductive risks of obesity include, but are not limited to, infertility, miscarriage, birth defects, preterm delivery, gestational diabetes, gestational hypertension, cesarean delivery, and thromboembolic events . Obesity also increases the risk of nonreproductive diseases, including stroke, heart disease, certain types of cancer, arthritis, high cholesterol, hypertension, and diabetes. Pregnant

women with low BMI are at risk of having small-for-gestational-age fetuses and low-birth-weight infants. Ideally, weight should be optimized before a woman attempts to becoming pregnant, although the health benefits of postponing pregnancy need to be balanced against reduced fecundity with female aging .

PREGNANCY DATING

Women should be counseled to seek medical care before attempting to become pregnant or as soon as they believe they are pregnant to aid in correct dating and to be monitored for any medical conditions in which treatment should be modified during pregnancy. Correct first-trimester pregnancy dating provides value in managing potential subsequent pregnancy complications and indications for delivery.

CONCLUSION

Maternal physiology, diet, body composition and lifestyle have profound effects on offspring health. Research has shown that the fetus is particularly vulnerable to adverse influences around the periconception period. The preconception time period therefore provides a perfect "window of opportunity" for intervening on a variety of health practices. Additional research is required, particularly in lower- and middle-income countries to determine how systems can support the provision of preconception care.

PRACTICE RECOMMENDATIONS

- The aim of preconception counseling is to optimize maternal health in preparation for pregnancy.
- A detailed history is important to determine pregnancy risk. This should include screening for mental health disorders.
- Women should be encouraged to book early. Antenatal care should be person-centered with the implementation of effective clinical practices.
- Folic acid supplementation should begin 1 month prior to conception.
- Women should be advised to lead a healthy lifestyle, abstaining from tobacco, alcohol and recreational drugs.
- Achieving a healthy weight with optimal glycemic control is important in reducing both maternal and fetal risk.

References

1. American College of Obstetricians and Gynecologists. Well-woman visit. ACOG committee opinion no. 755. Obstet Gynecol. 2018;132:e181-6.
2. Potter RG, Parker MP. Predicting the time required to conceive. Population studies. 1964 Jul 1;18(1):99-116.
3. Fleming TP, Watkins AJ, Velazquez MA, Mathers JC, Prentice AM, Stephenson J, Barker M, Saffery R, Yajnik CS, Eckert JJ, Hanson MA. Origins of lifetime health around the time of conception: causes and consequences. The Lancet. 2018 May 5;391(10132):1842-52.
4. Cefalo RC, Moos MK. Preconceptional health care: A practical guide. Mosby Incorporated; 1995.
5. Pattinson RC. Saving Mothers 2011-2013: Sixth report on confidential enquiries into maternal deaths in South Africa. Pretoria: Department of Health. 2014.
6. Knight M, Tuffnell D. A view from the UK: the UK and Ireland confidential

enquiry into maternal deaths and morbidity. Clinical Obstetrics and Gynecology. 2018 Jun 1;61(2):347-58.

7. Frayne DJ, Verbiest S, Chelmow D, Clarke H, Dunlop A, Hosmer J, Menard MK, Moos MK, Ramos D, Stuebe A, Zephyrin L. Health care system measures to advance preconception wellness: consensus recommendations of the clinical workgroup of the National Preconception Health and Health Care Initiative. Obstetrics & Gynecology. 2016 May 1;127(5):863-72.
8. Abajobir A, Alati R, Kisely S, Najman JM. Antecedents and maternal health outcomes of unintended pregnancy: a systematic review. Ethiop Med J. 2017 Sep 20;55(4):325-54.
9. No CO. Female age-related fertility decline. Fertility and Sterility. 2014 Mar 1;101(3):633-4.
10. Rosario PW. Selective screening for thyroid dysfunction in pregnant women: How often do low-risk women cease to be treated following the new guidelines of the American Thyroid Association?. Archives of Endocrinology and Metabolism. 2018;62:641-3.
11. National Institute for Health and Care Excellence (Grande-Bretagne). Antenatal care for uncomplicated pregnancies. National Institute for Health and Clinical Excellence; 2008.
12. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. World Health Organization; 2016.
13. De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC, Rayco-Solon P. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. Cochrane database of systematic reviews. 2015(12).
14. Cuskelly GJ, McNulty H, Scott JM. Effect of increasing dietary folate on red-cell folate: implications for prevention of neural tube defects. The Lancet. 1996 Mar 9;347(9002):657-9.
15. Austin MP. Antenatal screening and early intervention for "perinatal" distress, depression and anxiety: where to from here?. Archives of women's Mental Health. 2004 Feb;7(1):1-6.
16. Mackie YO. The Effects of High Sucrose or High Fat Diet on Brain Macrostructure, Cognition, and Expression of Phosphorylated Tau (Master's thesis, Graduate Studies).
17. Berenson AB, Pohlmeier AM, Laz TH, Rahman M, Saade G. Obesity risk knowledge, weight misperception, and diet and health-related attitudes among women intending to become pregnant. Journal of the Academy of Nutrition and Dietetics. 2016 Jan 1;116(1):69-75.
18. Abara WE, Cha S, Malik T, DeSimone MS, Schumann B, Mallada E, Klemme M, Aguon V, Santos AM, Collier M, Kamb M. Hepatitis B Surface Antigen Screening Among Pregnant Women and Care of Infants of Hepatitis B Surface Antigen–Positive Mothers—Guam, 2014. Morbidity and Mortality Weekly Report. 2017 May 5;66(19):506.
19. DR Disease Watch Focus: Syphilis – WHO. https://www.who.int/tdr/publications/disease_watch/syphilis/en/ (accessed 3 June 2019)
20. Nielsen GL, Møller M, Sørensen HT. HbA1c in early diabetic pregnancy and pregnancy outcomes: a Danish population-based cohort study of

573 pregnancies in women with type 1 diabetes. Diabetes care. 2006 Dec 1;29(12):2612-6.

21. Nelson-Piercy C. Handbook of obstetric medicine. CRC press; 2020 Aug 26.
22. Chamberlain L, Levenson R. Addressing intimate partner violence, reproductive and sexual coercion. A Guide for Obstetric, Gynecologic and Reproductive Health Care Settings,. 2012.
23. American College of Obstetricians and Gynecologists. Reproductive and sexual coercion. Committee opinion No. 554. Obstet Gynecol. 2013 Feb;121(2):411-5.
24. Nelson-Piercy C. Handbook of obstetric medicine. CRC press; 2020 Aug 26.
25. College of Obstetricians and Gynecologists . Obstet Gynecol 2013 ; 121 : 411 – 5 .
26. American College of Obstetricians and Gynecologists. Neural tube defects. ACOG Practice Bulletin No. 187. Obstet Gynecol. 2017;130:e279-90.
27. Frayne DJ, Verbiest S, Chelmow D, Clarke H, Dunlop A, Hosmer J, Menard MK, Moos MK, Ramos D, Stuebe A, Zephyrin L. Health care system measures to advance preconception wellness: consensus recommendations of the clinical workgroup of the National Preconception Health and Health Care Initiative. Obstetrics & Gynecology. 2016 May 1;127(5):863-72.
28. Louis GM, Sapra KJ, Schisterman EF, Lynch CD, Maisog JM, Grantz KL, Sundaram R. Lifestyle and pregnancy loss in a contemporary cohort of women recruited before conception: The LIFE Study. Fertility and sterility. 2016 Jul 1;106(1):180-8.
29. American College of Obstetricians and Gynecologists. Challenges for Overweight and Obese Women. Committee Opinion No. 591. Obstet Gynecol. 2014 Mar;123:726-30.
30. Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. PloS one. 2013 Apr 16;8(4):e61627.
31. Artal R, O'Toole M, American College of Obstetricians and Gynecologists. Exercise during pregnancy and the postpartum period. Clin Obstet Gynecol. 2003;46(2):496-9.
32. No AC. Exposure to toxic environmental agents. Fertility and sterility. 2013 Oct 1;100(4):931-4.
33. McDiarmid MA, Gehle K. Preconception brief: occupational/ environmental exposures. Maternal and Child Health Journal. 2006 Sep;10(1):123-8.

AN INTERESTING CASE OF JOUBERT SYNDROME

DR.MALATHI G PRASAD

DR.VASANTHA KARUNYA.R

TRICHY FETAL MEDICINE CENTRE

This case has been presented because of rarity and for genotype and phenotype correlation.

INTRODUCTION:

Joubert syndrome (JS) is a rare autosomal recessive or X-linked congenital brain malformation with strong genetic heterogeneity. Joubert syndrome is characterized by absence or underdevelopment of vermis and malformed brainstem. Afterbirth, it may cause a series of neurological symptoms , even with retina , kidney, liver and other organ abnormalities , which is defined as Joubert syndrome and related disorder (JSRD). Prenatal diagnosis is rare. MRI is usually the first choice diagnostic modality with typical brain images characterized by MTS .

CASE PRESENTATION

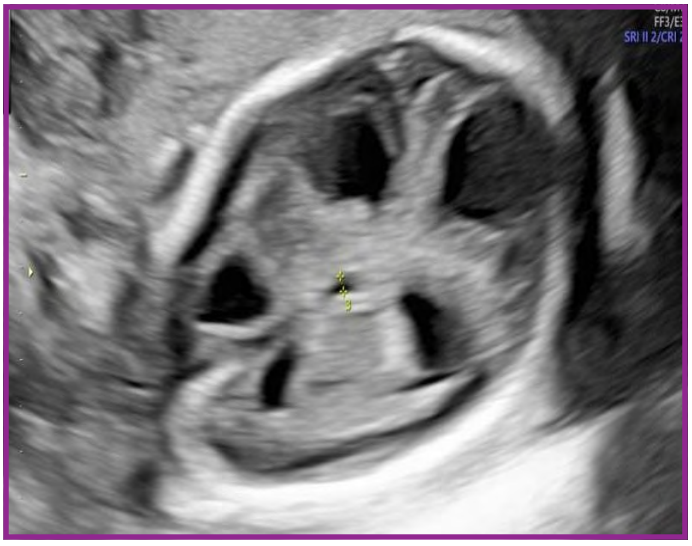
- A 22 Years old G3P0L0A2 of 20 weeks of gestation
- G1- Missed abortion at 3 month of gestation
- G2- Missed abortion around 45 days of gestation
- Married since 3 yrs
- H/o Second degree consanguinity
- No H/o DM/ Hypertension/epilepsy/ Thyroid disorders
- FTS done - Low risk .
- Referred for second opinion for severe oligohydramnios and Hydrocephalus.

USG FINDINGS:

Neurosonogram appears to be ABNORMAL

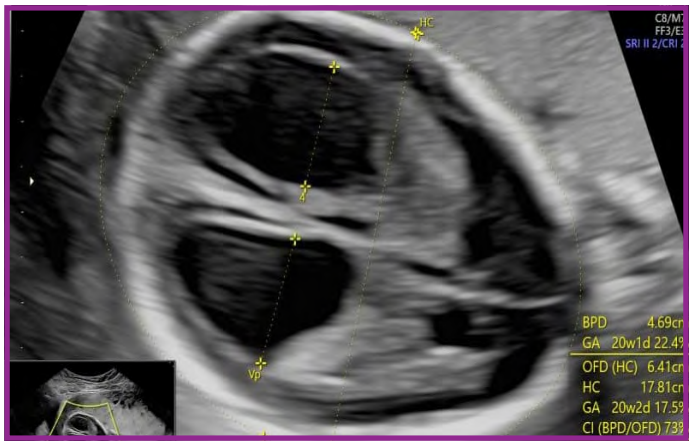
Smooth skull bone and normal head shape.

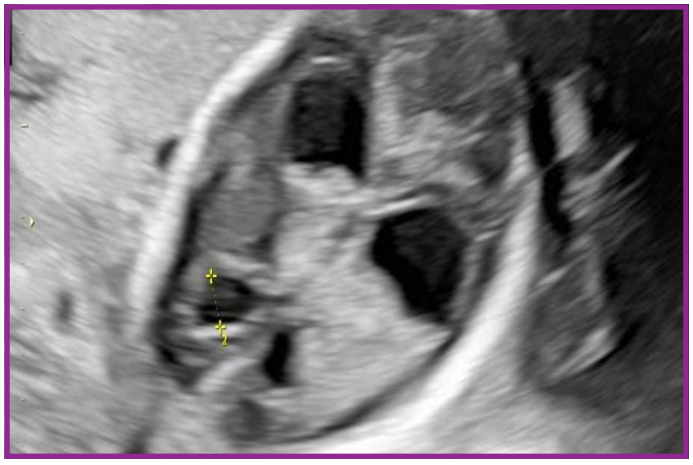
ANTERIOR CRANIAL FOSSA



- Midline falx seen
- Thalami , cavum septum pellucidum appears normal
- Third ventricle is identified without significant dilatation.
- Bilateral gross ventriculomegaly ,measuring 14mm each.
- Corpus callosum not Visualised due to Severe hydrocephalus.

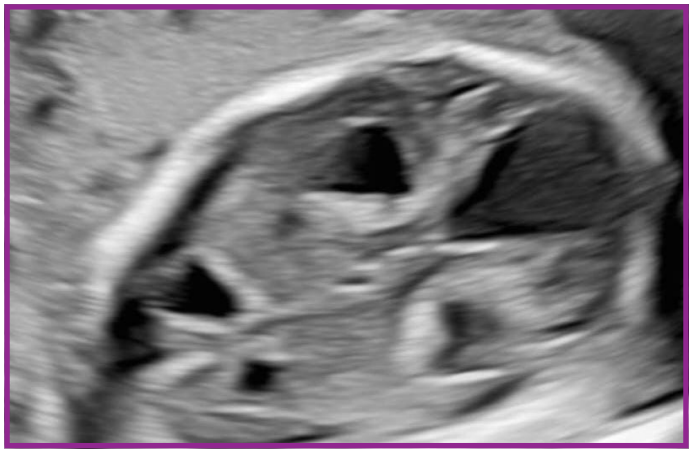
Anterior horn dilated measuring -5.7mm





POSTERIOR CRANIAL FOSSA

- Cisterna magna communicating with fourth ventricle - keyhole appearance seen.
- Fourth ventricle ratio is reduced (0.61)
- Pons - normal

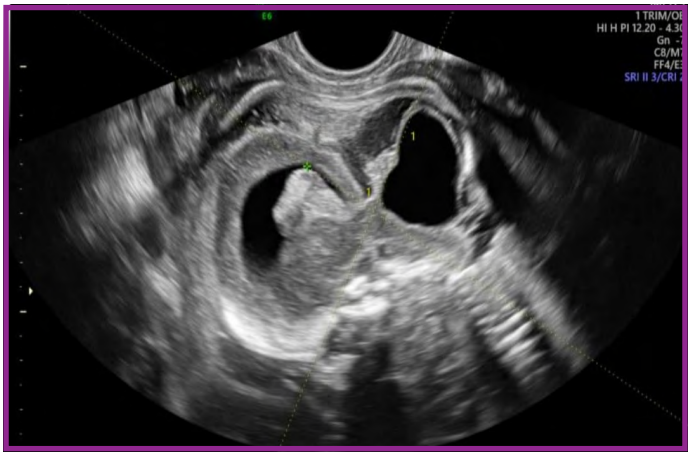


VERMIS

- Appears to be hypoplastic measuring 5.6mm (<5th percentile)
- Fastigial point not identified
- Fissure , lobe of vermis not identified

IN SAGITTAL SECTION

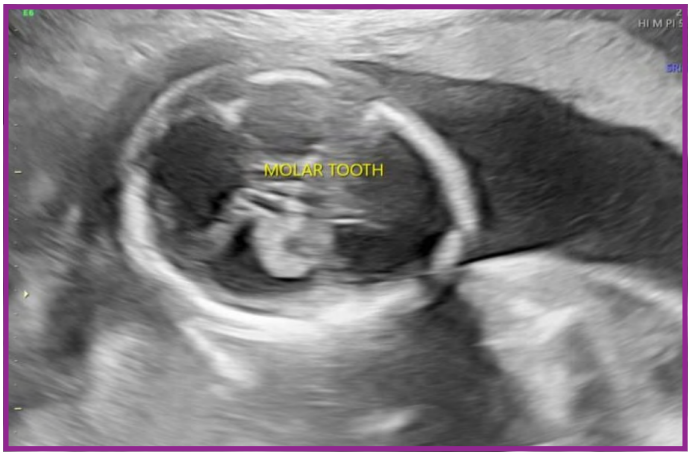
- Corpus callosum not visualised due to severe hydrocephalus .
- Vermis rotated
- Tentorium elevated
- Brainstem vermis angle (77 degree) elevated



- Brainstem tentorium angle (96 degree) elevated

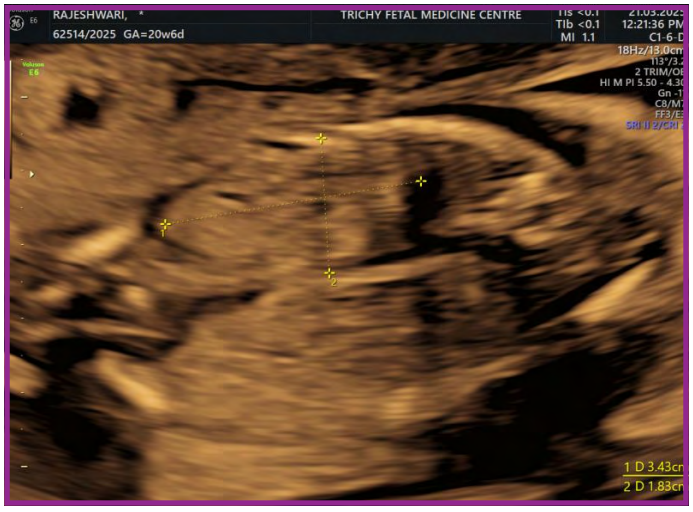
IN TRANSCEREBELLAR VIEW

MOLAR TOOTH SIGN IS SEEN



KIDNEY

- Bilateral echogenic kidneys suggestive autosomal recessive polycystic kidneys
- Right kidney- 39x24mm
- Left kidney- 34x 18mm



CLINICAL DIAGNOSIS :

Joubert syndrome - vermian hypoplasia type with bilateral enlarged and echogenic autosomal recessive polycystic kidneys and severe oilgohydramnios.

COUNSELLING

The couple should be informed about the neurological morbidities above mentioned findings may present with

1. Ataxia
2. Developmental delay
3. Abnormal eye movements
4. Tachypnoea -apnea spells
5. Retinal coloboma
6. Hyperechoic kidneys
7. Polydactyly has been discussed.

The risk of aneuploidies to the extent of 20% has been discussed.

- The couple has been counselled about the risk of increasing ventriculomegaly in ongoing pregnancy and postnatally also has been discussed.
- The likelihood of neurodevelopmental delay is high with increasing ventriculomegaly
- The need for genetic testing to exclude autosomal recessive /inheritance has been discussed.
- In the presence of polycystic kidneys , the risk of recurrence is 25% in every pregnancy has been discussed.
- In view of echogenic kidneys - gene sequencing by fetal DNA storage has been discussed to confirm the presence of single gene disorder.

The risk of IUD has been explained.

- Maternal and paternal kidneys appears to be normal
- Amniocentesis cannot be done due to severe oligohydramnios
- The need for Tissue biopsy for aneuploidy / cordocentesis and fetal DNA storage to prognosticate present and future pregnancies has been discussed.

PROCEDURE DONE

CORDOCENTESIS FOR MICROARRAY AND WHOLE EXOME SEQUENCING has been done in view of Joubert syndrome with bilateral echogenic autosomal recessive polycystic kidneys.

CHROMOSOMAL MICROARRAY

Chromosomal microarray appears to be normal in this case.

LifeCell® Diagnostics

Name	: **F/O. RAJESHWARI SILAMBARASAN**	Lab ID	: KT50300110032	**CRM: 223002076644**
Age	: NA	Sample Collection Date	: 21-03-2025 16:00	
DOB	: **NA**	Sample Receipt Date	: 22-03-2025 13:30	
Gender	: UNKNOWN	Reporting Date	: 28-03-2025 17:29	
Referring Physician	: Dr. MALATHI G PRASAD	Location	: Trichy	
Hospital Name	: Trichy Fetal Medicine And Fertility Centre			

Initial Report	☑	Duplicate Report	☐	Revised Report	☐	Version No	1

CHROMOSOMAL MICROARRAY CYTOSCAN OPTIMA

Sample Type	:	Fetal Cord Blood
Quality of Sample	:	Adequate
Gestational Age	:	20 WEEKS
Clinical Indication	:	To evaluate chromosomal aneuploidy in view of USG scan showed vermian hypoplasia and features suggestive of Dandy walker malformation and bilateral gross ventriculomegaly and bilateral enlarged and echogenic polycystic kidneys.
Test Requested	:	Aneuploidy

Interpretation	:	No clinically significant deletions, duplications or other chromosomal abnormalities were found in the sample submitted for analysis. Note: No significant maternal cell contamination is detected.
Recommendation	:	Clinical correlation is suggested and further genetic counselling is recommended.

EXOME SEQUENCING REPORT

Whole exome sequencing report shows pathogenic variant for Joubert syndrome and microarray appears to be normal .

RESULT SUMMARY

Pathogenic Variant causative of the reported phenotype were identified.
No significant maternal cell contamination (MCC) was detected in this sample

*Correlation with clinical profile and family history is required

Summary of Findings

Variants Potentially Relevant to the Indication for Testing:

The index patient is:

- Homozygous for a Pathogenic variant in the *CEP290* gene associated with MECKEL SYNDROME, TYPE 4; MKS4 JOUBERT SYNDROME 5; JBTS5 .

Carrier Status / Unrelated Findings:

- The index patient is Heterozygous for a Pathogenic variant unrelated to phenotype in the *COL7A1* gene associated with EPIDERMOLYSIS BULLOSA DYSTROPHICA, AUTOSOMAL RECESSIVE; RDEB EPIDERMOLYSIS BULLOSA WITH CONGENITAL LOCALIZED ABSENCE OF SKIN AND DEFORMITY OF NAILS EPIDERMOLYSIS BULLOSA DYSTROPHICA, AUTOSOMAL DOMINANT; DDEB .
- The index patient is a carrier of a Heterozygous Likely Pathogenic variant in the *ARSA* gene associated with METACHROMATIC LEUKODYSTROPHY; MLD .

Secondary Findings (AGMG gene list):

- No Pathogenic or Likely Pathogenic (Class 1/2) variants were detected in the ACMG gene list.

FINDINGS RELATED TO PHENOTYPE

Gene&Transcript	Variant	Location	Zygosity	In silico Parameters**	Disorder(OMIM)	Inheritance	Variant Classification
CEP290 NM_025114.4	c.5445_5448del p.Thr1816fs*3	Exon 40	Homozygous	NA	MECKEL SYNDROME, TYPE 4; MKS4:611134 JOUBERT SYNDROME 5; JBTS5:610188	Autosomal Recessive	Pathogenic

* Genomic Position based on Assembly GRCh37, **Number of applied in silico programs predicting the effect of the variant on the protein outcome (CADD: Combined Annotation Dependent Depletion (v1.6), SIFT, PolyPhen-2, MT: Mutation Taster), N/A: Not Applicable, ***Minor Allele Frequency as described in GnomAD (Controls), ****based on ACMG Guidelines. het=heterozygous, hom=homozygous, hemi=hemizygous.

MOLECULAR DIAGNOSIS

DISCUSSION

JOUBERT SYNDROME AND RELATED DISORDERS

- **Incidence of 1 in 80,000- 1,00,000 live birth.**
- **First diagnosed in 1968 by Dr. Marie joubert**
- These disorders constitute an autosomal recessive group called ciliopathies.
- Joubert syndrome present as ataxia, developmental delay , abnormal eye movements , tachypnea - apnea spells , retinal coloboma , hyperechoic kidneys and polydactyly.

DIAGNOSIS CONFIRMATION

1. Molar tooth sign in MRI/Ultrasound
2. Hypotonia in infancy with later development of ataxia
3. Developmental delays/ intellectual disability .

PRENATAL ULTRASOUND SUSPICION

MOLAR TOOTH SIGN + VERMIAN HYPOPLASIA

ALSO EXTRA CNS MANIFESTATION.

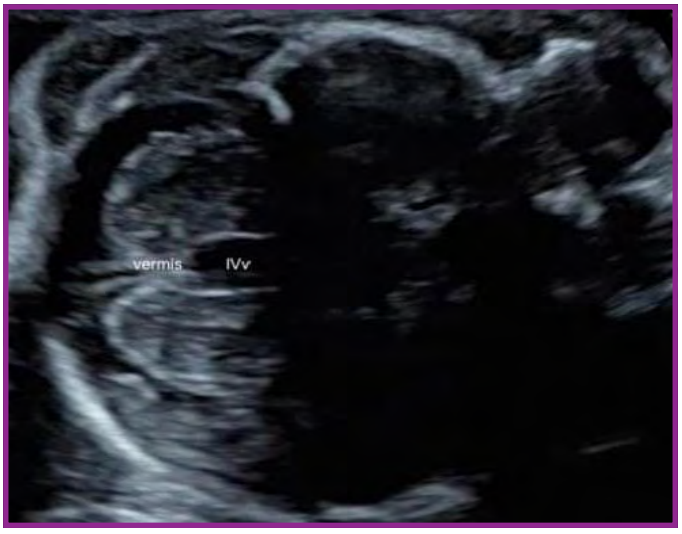
1. COLOBOMA
2. ENCEPHALOCELE

3. KIDNEY ANOMALIES
4. POLYDACTYLY

JOUBERT SYNDROME (MTS AS A GUIDE SIGN)

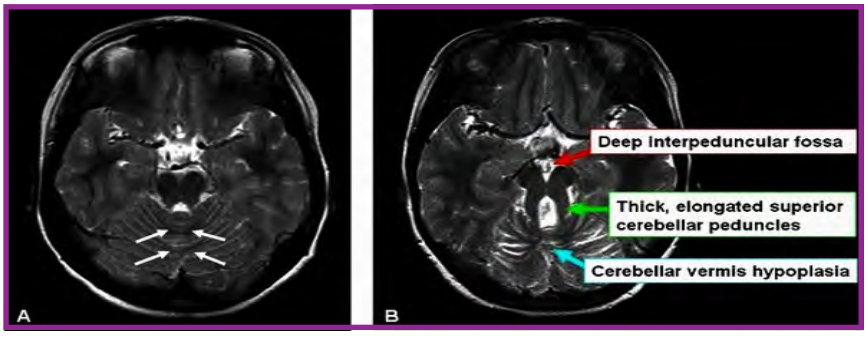
Pathognomonic radiologic sign on axial planes derived from mid-hindbrain malformation .

Molar tooth sign is obligatory for JB diagnosis



MOLAR TOOTH SIGN - ORIGIN

- Abnormally deep interpeduncular fossa
- Horizontal , thickened and elongated superior cerebellar peduncles.



MOLAR TOOTH SIGN IN JB (AXIAL VIEW)

In molar tooth sign, cerebellar peduncles are elongated, thickened , run horizontally do not decussate.

TRANSCEREBELLAR PLANE

Vermis - very thin , ugly, anomalous

VERMIAN DYSPLASIA

The malformation of midbrain in joubert syndrome

1. Cerebellar dysplasia
2. Hypoplastic vermis
3. Totally dysplastic lobulation
4. Cerebellar hemisphere may internally rotated
5. Fourth ventricle anomaly
6. Superior cerebellar peduncle are horizontal not crossed .

ROLE OF PRENATAL MRI IN JB

- SHEPARD CROOK SIGN
- No fiber decussation in superior cerebellar peduncle, pontine fibres and pyramidal tract.

JS - other CNS disorder

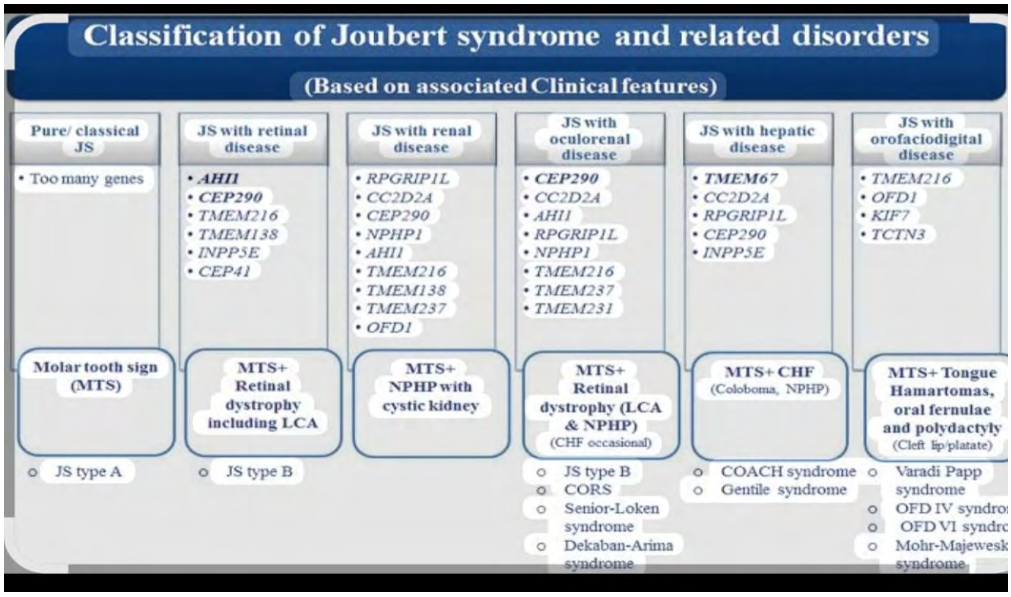
- - 10% enlarged posterior fossa fluid collection
- - 30% other abnormalities of brainstem
- - 30% supra tentorial involvement
- - Callosal dysgenesis, Occipital encephalocele ,polymicrogyria and hamartoma

Extra CNS abnormalities

- Retinal dystrophy
- Retinal coloboma
- Polydactyly
- oral frenulae
- Heart defects
- Tongue hypertrophy
- Liver fibrosis
- Kidney disease
- Scoliosis
- Obesity

Typical facial features

CLASSIFICATION OF JOUBERT SYNDROME AND RELATED DISORDERS



JOUBERT SYNDROME - GENETIC TESTING

'ALWAYS MANDATORY '

- Should offer amniocentesis
- Exome sequencing
- Recessive autosomal inheritance , except OFD1-related JS is inherited in an x-linked manner
- >31 ciliopathy gene have been identified account for 50% JB .

MOLECULAR GENETICS

JS caused by pathogenic mutations in 34 genes

- 33 genes are AR (Predominant)
- One gene X Linked (Heterozygous pathogenic variant)
- Autosomal recessive - Siblings of affected individual 25% of being affected ,50% asymptomatic carrier
- 25 % chance of being not affected and not a carrier.
- Mutations in nine genes have been implicated in Joubert syndrome todate: TMEM67/MKS3, AHI1, CC2D2A, CEP290,RPGRIP1L, ARL13B, NPHP1, INPP5E and TMEM21615

CONCLUSION

Currently, a diagnosis of JS is commonly made after birth. Fewer cases of prenatal diagnosis by USG have been made, and they are more liable to be misdirected because of some non specific features that also manifest in DMW, Cranio cerebellar cardiac syndrome and so on. WES is mandatory in Joubert syndrome to know whether both partners of a couple are carriers or not in JSRD.

REFERENCES

1. 1.Maria BL, Boltshauser, PalmerSC, TranTX.Clinical features and revised diagnostic criteria in Joubert syndrome. J Child Neurol 1999;14:583–590;discussion 90–91.
2. 2. JoubertM, EisenringJJ, RobbJP, AndermannF. Familial agenesis of the cerebellar vermis. A syndrome of hyperpnea,abnormal eye movements,ataxia,and retardation. Neurology 1969;19:813–825
3. 3. Boltshauser E, IslerW. Joubert Syndrome : episodic hyperpnea, abnormal eye movements, retardation and ataxia, associated with dysplasia of the cerebellar vermis. Neuropediatrie 1977;8: 57–66.

4. 4.MariaBL, HoangKB, TusaRJ, MancusoAA, HamedLM, QuislingRG,HoveMT,Fennell EB,Booth-JonesM,Ringdahl DM, Yachnis AT, CreelG, Frerking. "Joubert syndrome" revisited: key ocular motor signs with magnetic resonance imagingcorrelation. JChildNeurol1997;12:423–430.
5. 5.MariaBL, QuislingRG, RosainzLC, Yachnis AT, GittenJ, DedeD, FennellE. Molar tooth sign in Joubert syndrome: clinical, radiologic, andpathologicsignificance.JChildNeurol 1999;14:368–376.
6. 6. Parisi MA. Clinicaland molecular features of Joubert syndrome and related disorders. AmJMedGenetCSeminMedGenet 2009;151C:326–340.
7. 7.GleesonJG, KeelerLC, ParisiMA, MarshSE, ChancePF, IA, GrahamJMJr, MariaBL, BarkovichAJ, DobynsWB. Molar tooth sign of the midbrain–hindbrain junction: occurrencein multiple distinct syndromes. AmJMedGenetA2004; 125A:125–134; discussion17.
8. 8.MariaBL, Bozorgmanesh A, Kimmel KN,TheriaqueD, Quis ling RG.Quantitative assessment of brainstem development in Joubert syndrome and Dandy-Walker syndrome. JChild Neurol 2001;16:751–758.
9. Spamp inato MV,KraasJ, MariaBL,WaltonZJ, Rumboldt Z. Absence of decussation of the superior cerebellar peduncles in patients with Joubert syndrome. AmJMedGenetA2008; 146A:1389–1394.
10. 10.QuislingRG, BarkovichAJ, MariaBL. Magnetic resonance imaging features and classification of central nervous system malformations in Joubert syndrome. JChildNeurol1999;14: 628–635;discussion69–72

OVULATION INDUCTION IN POLYCYSTIC OVARIAN SYNDROME (PCOS)

DR CHARMILA AYYAVOO MD DGO DFP FICOG PGDCR

Vice President FOGSI 2024
Director, Aditi Hospital & Parvathy Ayyavoo Fertility Centre, Trichy

The commonest anovulatory disorder causing infertility is PCOS. It is considered as a functional derangement. There is no peripheral or central defect which is attributed to the disease. PCO develops when a chronic anovulatory state persists for a long period of time.

MANAGEMENT OF INFERTILITY IN PCOS:

Lifestyle interventions like diet and exercise are the primary management of PCOS associated infertility. Pharmacological therapy is initiated in the form of ovulation induction. The drugs used as first line therapy are oral ovulogens. They can be combined with metformin. The second line therapy are with gonadotropins, and laparoscopic ovarian drilling (LOD). Third line therapy for PCOS patients with infertility are in-vitro fertilization (IVF) and in-vitro maturation (IVM). [1]

ORAL OVULOGENS:

The oral drugs for ovulation induction are clomiphene citrate and letrozole.

CLOMIPHENE CITRATE:

Historically, clomiphene citrate was the first orally active agent used for ovulation induction. It is an elective estrogen receptor modulator. It is given at a dose of 50 mg/day from day 2-5. The dose is increased if no ovulation is documented to a maximum of 150 mg per day. If ovulation is documented, 6 cycles of therapy are given (Practice committee of ASRM). Clomiphene is associated with a 60-85% ovulation rate but the pregnancy rate is 40-50%.

LETROZOLE:

In the early 2000s, the aromatase inhibitor, letrozole was introduced as an alternative ovulation-inducing agent. It inhibits the conversion of androgens to estrogens. It had the advantage of not interfering with endometrial development and proved to be more effective in inducing ovulation in obese patients with PCOS. The other advantage was a mono-follicular development. It is now considered as first line therapy. The dose prescribed is 2.5-5 mg/day from D2-D6. [2]

Letrozole is preferred as an ovulation induction drug in PCOS patients because it has a lower resistance, the likelihood of live birth is more, the chance of multiple pregnancies and hot flushes are lesser compared to clomiphene.

The number of days of therapy with oral ovulogens is traditionally fixed as five days. The interval of 5 days was chosen arbitrarily but was found to be effective in most cases and continues to be used to this day.

Clomiphene resistance is defined as failure to ovulate after receiving 150 mg of CC daily for 5 days per cycle, for at least three cycles. It occurs in approximately 15-40% in women with PCOS. Women who respond normally to CC but fail to conceive after 6 cycles of treatment is termed as clomiphene failure.

GONADOTROPINS: [3]

Gonadotropins can be primary treatment for ovulation induction or can be started after failure of other medications to induce ovulation. It is indicated for hypogonadotropic hypogonadism and eugonadotropic eugonadism, also defined as type I and type II amenorrhea by the World Health Organization. Hypergonadotropic hypogonadism or primary ovarian insufficiency (WHO type III amenorrhea) is generally not responsive to exogenous gonadotropins.

ASRM committee opinion on gonadotropins in PCOS: [3]

The recommended approach in the first dose-finding cycle is to begin with a low dose of gonadotropin, typically 37.5–75 IU/day, and increasing in small increments after 7 days or more if no follicle >10 mm has developed. Pen devices allow more finely tuned incremental dosing. In subsequent cycles, treatment generally begins at the threshold of response previously determined. 7–12 total days of treatment is typical but longer durations of treatment may be required. There is no difference between urinary or recombinant gonadotropin. If there is a high risk for ovarian hyperstimulation syndrome (OHSS), a GnRH agonist trigger can be given instead of human chorionic gonadotropin (HCG).

A systematic review of 13 studies found pregnancy rates of 15% per cycle and 41% per patient over an average of 2.7 cycles with the use of gonadotropins. Women who were obese or insulin resistant required higher doses of gonadotropins. Insulin resistance, but not obesity, was associated with a lower pregnancy rate.

Disadvantages of continuous gonadotropin therapy

- High treatment cost,
- Multi follicular development leading to
- multiple pregnancy,
- OHSS and
- frequent shifting of cycle to IVF-ET treatment

There are alternatives to gonadotropin therapy for ovulation induction in patients who do not respond to the traditional doses and days of oral ovulogens. Other regimes of oral drugs have been introduced for ovulation induction (OI) for PCOS patients. They are as follows:

- Extended days regimes
- Increased doses
- Stair step protocols
- Combination protocols
- Sequential regimes

EXTENDED DAYS REGIMES: [4]

Not all patients with PCOS achieve ovulation after 5 days, even with high doses. The concept of extending the duration of therapy was first reported more than 40 years ago. An extended regimen of 8 days for patients who failed to ovulate with 5 days of therapy was found to be effective in more than 50% of cases

Letrozole is better for extended regimes because when clomiphene citrate is used at high doses or for repeated cycles, it can cause multiple follicular development. Its long half-life leads to drug accumulation and high rates of multiple ovulation as well as antiestrogenic effects on the endometrium. Unlike clomiphene, letrozole has a short half-life, which reduces the possibility of drug accumulation and does not have active metabolites.

COMPARISON OF REGIMES: [5]

In a study by Mandelbaum et al, the different regimes of letrozole were compared. A 5 mg dose or an extended 10-day course was better than the conventional dose.

STAIR STEP PROTOCOLS: [6]

Prolonged letrozole therapy can be continued for several weeks. It is very cost-effective because the cost of letrozole is much lower than that of gonadotropins. The time to ovulation is significantly shorter, with the stair-step protocol compared with traditional regimen.

The least dose of OI is started (50 mg CC or 2.5 mg Letrozole) for 5 days beginning on day 3–5. A transvaginal ultrasound is done 1 week (5–7 days) after the last pill. If no response (all follicles < 10 mm) is seen, the patient was given the higher dose and an ultrasound was repeated in 1 week (5–7 days). CC 50 mg can be increased to 150 mg and up to 250 mg as needed and letrozole 2.5 mg can be increased to 5 mg and up to 7.5 mg as needed. When a 18 mm dominant follicle was noted on ultrasound, it was triggered with 10,000 IU HCG. Letrozole stair-step was found to be as efficacious as CC stair-step. The time to ovulation was shorter in the Letrozole protocol.

SEQUENTIAL THERAPY: [7]

Clomiphene citrate (CC) was started at 100 mg/day from D2 for 5 days. 75 iu of gonadotropins (GT) was started from day 5 for alternate days. The follicular study was done from day 10. This regime can be used in CC resistance and CC failure cases.

In the sequential therapy with letrozole, patients received 2.5 mg letrozole on cycle days 3–7 or 2.5 mg letrozole on cycle days 3–7 with a sequential injection of 75 IU HMG on cycle days 8–10 for one treatment cycle. [8]

Sequential letrozole/HMG protocol may be superior in terms of ovulation induction and pregnancy promotion.

COMBINATION PROTOCOLS: [9]

- CC+ Gonadotropins (GT)
- Letrozole+ GT
- CC+ Letrozole
- First group received letrozole 5 mg daily from D_2 to D_6 and injection FSH- 75 IU on D_2, D_5 and D_8 of cycle
- Second group received continuous gonadotropin FSH- 75 IU starting from D_2 of cycle
- No significant difference in ovulation and pregnancy rate between both groups.
- 2.5 mg letrozole alone or the combination of 2.5 mg letrozole and 50 mg CC daily on cycle days 3–7 for one treatment cycle.
- The combination of letrozole and CC was associated with a higher ovulation rate compared with letrozole alone in women with infertility and PCOS. Further studies are needed to evaluate the effect on live birth rate. [10]

PROTOCOLS TO REDUCE LH SURGE: [11]

Clomiphene when given continuously till day of HCG will block estrogen receptors in hypothalamus and pituitary. This mimics a GnRH analog and prevents a LH surge. Low dose GT of 75-150 are added to enhance response.

LUTEAL PHASE SUPPORT: [12]

Supra-physiological hormone levels tend to cause low endogenous LH activity resulting in luteal phase defect. Progesterone support is essential in gonadotropin cycles.

OVARIAN DRILLING: [13]

It is the second line therapy for OI and in CC resistance. It can be first line therapy if laparoscopy is considered for other reasons.

The common indications for LOD are PCOS patients with repeated pregnancy loss, younger women, women with less than 3 years of infertility and having a normal BMI

IVF: [14]

It is the third line of therapy for infertility and is used when there is CC resistance, failure of OI therapy, and other infertility factors.

Urinary and recombinant FSH give similar results during OI. Exogenous recombinant LH should not be used routinely. Antagonist protocol is preferred because of reduced duration of stimulation, reduced usage of gonadotropins, and reduced risk of OHSS.

To prevent OHSS, antagonist protocol is preferred. The trigger is with GnRh agonist and suitable embryos are frozen.

IVM:

This method is the maturation in vitro of immature oocyte cumulus complexes collected from antral follicles in both stimulated and unstimulated cycles. There is a reduced chance of OHSS. The embryo is generated, vitrified, and transferred in the next cycle.

METFORMIN: [15]

Previous nonrandomized trials suggested high ovulatory rates on metformin in PCOS. The treatment with metformin alone or in combination with CC was not superior to CC alone in the RCT.

IUI IN PCOS: [16]

With OI, only 50% of patients conceive. This may be because other mechanisms may contribute to infertility. One potential mechanism is the negative effect of unopposed estrogen at the level of the endometrium and/or cervical mucus. This may be overcome by intrauterine insemination (IUI). At current the mainstay of treatment for PCOS is ovulation induction with timed intercourse. If this is not effective, patients are often offered empiric IUI, or IVF as secondary modalities of treatment. The benefit of IVF has been established; however, it is unknown if IUI adds any clinical benefit in this population. IUI does not improve pregnancy outcomes. It is more expensive and invasive.

IS IVF THE ANSWER IN PCOS? [17]

Modifiable risk factors such as BMI and associated insulin resistance can worsen embryonic development through select biochemical pathways. Therefore, before they undergo IVF treatment, it is reasonable to encourage patients with PCOS to optimize their health status by losing weight and using metformin. Our patients may even increase their chances of conceiving naturally after such interventions, which would be helpful for many reasons: lower costs, fewer interventions, and perhaps in the long run less time before birth.

VITAMIN D DEFICIENCY: [18]

Vitamin D deficiency is not associated with a decreased response to letrozole. While supplementation may benefit overall health, OI should not be delayed until vitamin D deficiency has been corrected.

CONCLUSION:

- Letrozole is preferred to clomiphene for OI.
- A starting dose of letrozole 2.5 mg for 5 days may lead to inferior response rates for ovulation induction in some patients. Hence a higher dose or an extended duration should be considered in PCOS.
- If the patient did not respond to the initial letrozole regimen, they can be re-dosed or "stair-stepped".
- Ovulation does not guarantee a pregnancy in PCOS.
- IUI and IVF do not give better results in PCOS.
- OI in IVF patients should be done with care to avoid OHSS. Antagonist protocol with freeze all is preferred.

- Adjuvants like metformin, vitamin D are of doubtful value.

References:

1. Evidence summaries and recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome: assessment and treatment of infertility M F Costell; Human Reproduction Open, Volume 2019, Issue 1, 1 January 2019
1. Elizur, S. and T. Tuland, Drugs in infertility and fetal safety. Fertility & Sterility, 2008. 89: p. 1595– 1602
1. Use of exogenous gonadotropins for ovulation induction in anovulatory women: a committee opinion; Fertility and Sterility; Vol. 113Issue 1p66–70; 2020; Practice Committees of the American Society for Reproductive Medicine and Society for Reproductive Endocrinology and Infertility
1. Lobo R.A. An extended regimen of clomiphene citrate in women unresponsive to standard therapy. Fertil Steril. 1982; 37: 762-766
1. Mandelbaum RS, et al. A comparison of letrozole regimens for ovulation induction in women with polycystic ovary syndrome. F&S Reports. 2024 Mar 28.
1. Thomas S, et al. Ovulation rates in a stair-step protocol with Letrozole vs clomiphene citrate in patients with polycystic ovarian syndrome. Contraception and Reproductive Medicine. 2019 Dec;4:1-6.
1. Abdelazim IA et al. Sequential CC/HMG Vs HMG for OI in CC resistant women. Acta Gynaecol Obstet 2013; 287(3); 591-97.
1. Dai X, et al. Ovulation induction using sequential letrozole/gonadotrophin in infertile women with PCOS: a randomized controlled trial. Reproductive BioMedicine Online. 2023 Feb 1;46(2):352-61.
1. Saha, Suvasmita et al. Fertility and Sterility, Volume 114, Issue 3, e525 2020
1. Rachel B. Mejia; A randomized controlled trial of combination letrozole and clomiphene citrate or letrozole alone for ovulation induction in women with polycystic ovary syndrome; Fertility and Sterility; Vol. 111Issue 3p571–578.e1, 2019
1. Kato K; Minimal OS combined with selective SET policy, Reprod Biol Endocrinol 2012;10;35.
1. Oktem M et al; Effect of luteal phase support after ovulation induction and IUI- Gynecol Endocrinol 2014; 30; 909-12.
1. Shruti Agarwal; Pregnancy rates after laparoscopic ovarian drilling in polycystic ovary syndrome patients following unsuccessful ovulation induction; Fertility and Sterility Vol. 112Issue 3Supplemente414; September, 2019
1. Misso ML, Tassone EC, Costello MF, Dokras A, Laven J, Moran LJ, Teede HJ. Large-Scale Evidence-Based Guideline Development Engaging the International PCOS Community. InSeminars in reproductive medicine 2018 Jan (Vol. 36, No. 01, pp. 028-034). Thieme Medical Publishers.
1. Cooperative Multicenter Reproductive Medicine Network. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med. 2007; 356: 551-566
1. Jasmine Aly; Fertility and Sterility Vol. 113Issue 4Supplemente44–e45; 2020
1. Sajal Gupta; Fertility and SterilityVol. 115Issue 2p330–331; 2021
1. Gigg MC, Mandelbaum RS, Sriprasert I, Brahaney C. THE IMPACT OF VITAMIN D DEFICIENCY ON RESPONSE TO LETROZOLE OVULATION INDUCTION IN PATIENTS WITH PCOS. Fertility and Sterility. 2024 Oct 1;122(4):e424.

SUCCESSFUL PREGNANCY OUTCOME IN A RENAL TRANSPLANT RECIPIENT - A CASE REPORT

PRESENTOR : DR RAKSHITHA M. 2YR MS.,OG PG

GUIDE: DR PUNITHAVATHI MS.,(OBG)

PROFESSOR, DEPARTMENT OF OBG
DHANALAKSHMI SRINIVASAN MEDICAL COLLEGE AND HOSPITAL, PERAMBALUR

INTRODUCTION:

Pregnancy following renal transplantation has become increasingly feasible due to advancements in transplant medicine and immunosuppressive therapies. However, these pregnancies are considered high-risk due to increased risks of graft dysfunction, hypertension, pre-eclampsia, and adverse fetal outcomes. Ovulation induction in women with infertility and renal transplantation adds another layer of complexity due to potential risks of ovarian hyperstimulation and medication interactions.

We present the case of a 28-year-old woman with a history of renal transplantation, who conceived after ovulation induction and delivered successfully by caesarean section following a failed induction of labor. The case underscores the critical role of multidisciplinary coordination in achieving favorable outcomes.

CASE REPORT:

A 28-year-old female with a history of chronic kidney disease underwent renal transplantation five years ago, receiving a donor kidney from her mother. Prior to transplantation, she had been on maintenance hemodialysis. Post-transplant, her renal function remained stable under immunosuppressive therapy with Tab Tacrolimus, Tab Azathioprine, and T-prednisolone (Wysolone).

The patient had a history of two medically induced abortions due to elevated serum creatinine levels during previous pregnancies. She experienced a prolonged period of infertility and underwent ovulation induction therapy, following which she conceived.

ANTENATAL COURSE:

Meticulous Antenatal care was provided with frequent monitoring of renal function and fetal well-being.

At 28 weeks of gestation, she was diagnosed with gestational hypertension and was initiated on oral labetalol. A comprehensive cardiovascular, ophthalmologic, and nephrological evaluation was performed to assess end organ damage and risk stratification.

PRE DELIVERY EVALUATION:

In anticipation of delivery, multidisciplinary evaluations were conducted including CTVS, Nephrology, and Urology. Renal function tests and renal Doppler studies were found to be within normal limits. Induction with prostaglandin E2 gel was done with close monitoring.

MODE OF DELIVERY:

Despite pharmacological induction, there was failure to progress, and the patient was taken up for caesarean section. Intraoperative period was uneventful. An alive term female baby bwt -2.798 kg, APGAR: 8/10, 9/10) was delivered.

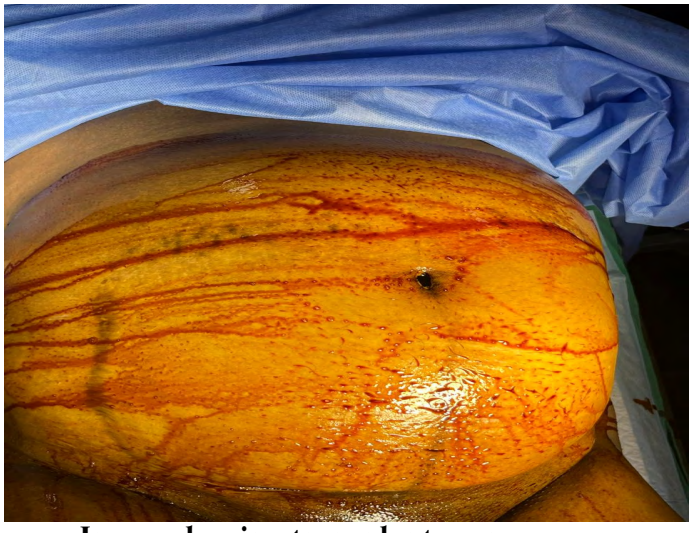
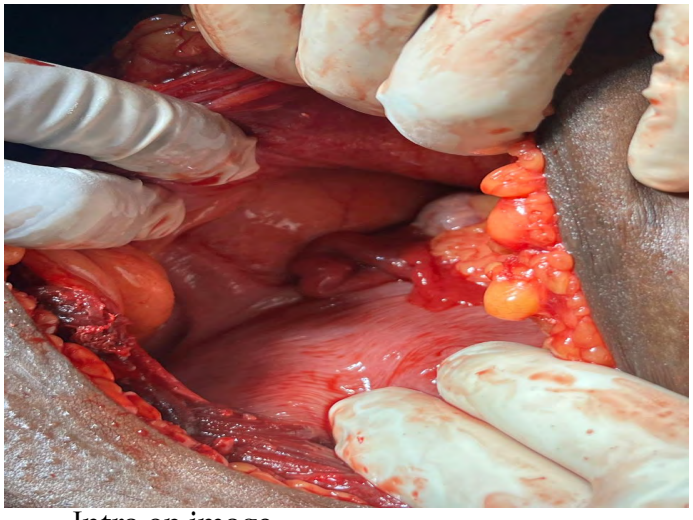
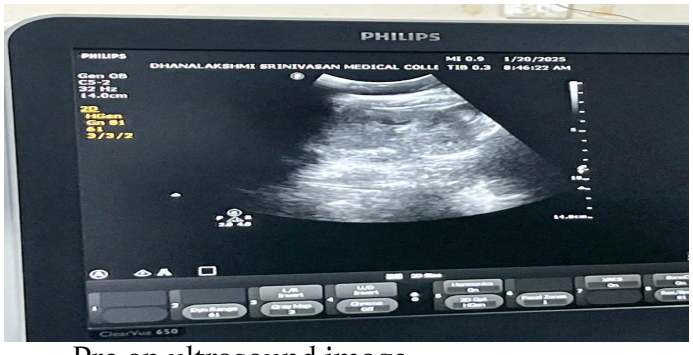


Image showing transplant scar.



Intra op image



Pre op ultrasound image

POST OPERATIVE COURSE:

Post-operative renal function tests and Doppler imaging of transplanted kidney were repeated. Broad-spectrum antibiotic prophylaxis was administered. She was discharged on post-operative day 7 after a final nephrology review confirmed stable graft function.

DISCUSSION:

A pregnant renal transplant recipient remains a complex clinical scenario requiring careful planning and monitoring. Successful outcomes depend on stable pre-conception renal function, appropriate immunosuppression, and multidisciplinary care.

Immunosuppression and pregnancy:

Tacrolimus, Azathioprine, and low-dose corticosteroids are commonly used immunosuppressants deemed relatively safe during pregnancy.

Hypertensive disorders in pregnancy:

Gestational hypertension occurs in 30–50% of pregnant renal transplant recipients. In this case, Tab Labetalol was effective in managing blood pressure in this patient.

Delivery consideration:

Elective caesarean section is commonly chosen in transplant recipients to avoid prolonged labor stress on the graft, especially when associated with infertility or prior obstetric complications.

CONCLUSION:

This case highlights the feasibility of a successful pregnancy in renal transplant recipients with appropriate multidisciplinary care. Preconception counseling, close monitoring during pregnancy, judicious use of immunosuppressants, and individualized delivery planning are pivotal to optimizing maternal and neonatal outcomes.

References

1. J. E. Murray, D. E. Reid, J. H. Harrison, and J. P. Merrill, "Successful pregnancies after human renal transplantation," The New England Journal of Medicine, vol. 269, pp. 341–343, 1963.
2. J. M. Davison and C. W. G. Redman, "Pregnancy posttransplant: the establishment of a UK registry," British Journal of Obstetrics and Gynaecology, vol. 104, no. 10, pp. 1106–1107, 1997.
3. G. Rizzoni, J. H. H. Ehrich, M. Broyer et al., "Successful pregnancies in women on renal replacement therapy: report from the EDTA Registry," Nephrology Dialysis Transplantation, vol. 7, no. 4, pp. 279–287, 1992.
4. L. A. Coscia, S. Constantinescu, M. J. Moritz et al., "Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation," Clinical Transplants, pp. 65–85, 2010.
5. V. Levidiotis, S. Chang, and S. McDonald, "Pregnancy and maternal outcomes among kidney transplant recipients," Journal of the American Society of Nephrology, vol. 20, no. 11, pp. 2433–2440, 2009.
6. J. L. Holley, R. J. Schmidt, F. H. Bender, F. Dumler, and M. Schiff, "Gynecologic and reproductive issues in women on dialysis," American Journal of Kidney Diseases, vol. 29, no. 5, pp. 685–690, 1997.

MULLERIAN ANOMALY IN EARLY PREGNANCY

DR. RAJAILAVARASI MS (OG), DNB (OG), FRM.,
DR. NAGAMANI MD (OG), DGO.,

INTRODUCTION:

The female reproductive tract develops from the mullerian ducts which later differentiate into the fallopian tubes, uterus, cervix and the upper one-third of the vagina. This development is regulated by numerous signaling molecular pathways and gene expressions like the HOXA13, PAX2, EMX2, LIM1 and Wnt[1]. Any disruption in the expression of these genetic factors during embryogenesis can lead to an array of congenital malformations which are termed "MULLERIAN ANOMALIES". These anomalies can be classified into four major categories based on their developmental defects as follows:

- Developmental failure of one or both the ducts - Unicornuate uterus/ Aplasia.
- Failure of the ducts to canalise - Unicornuate uterus with a non-communicating rudimentary horn.
- Failure to fuse or abnormal fusion of the mullerian ducts -
- Horizontal defect: Transverse vaginal septum/ imperforate hymen.
- Vertical defect: Bicornuate uterus/ Uterine didelphys.
- Failure of resorption of midline remnants of the ducts - Septate/ Arcuate uterus[2].

Mullerian anomalies are prevalent in 5.5% of the general population, 8% of the infertile couples, 13.3% of the miscarriage population and 24.5% of people with both infertility and miscarriage[3]. While most of these patients are asymptomatic and are being diagnosed for the first time during an ultrasound (USG) evaluation for infertility or any other indication; some of these people present in their adolescent life with complex genitourinary symptoms or later in life with a miscarriage.

DEVELOPMENT OF MULLERIAN DUCTS:

Around six weeks of embryonic life, two pairs of genital ducts: the mesonephric (wolffian) ducts and the paramesonephric (mullerian) ducts are seen in both, male and female embryos (Fig 1). They are morphologically similar with difference in cellular architecture. In a female fetus, the wolffian ducts degenerate due to the absence of testosterone and anti-mullerian hormone. The mullerian ducts develop as a longitudinal invagination of the coelomic epithelium on the anterolateral aspect of the urogenital ridge. By nine weeks of intra uterine life, the ducts elongate into three main regions: cranial vertical, horizontal and caudal vertical regions.

The cranial parts that open into the primitive peritoneal cavity develop as the fimbrial region of both the fallopian tubes. The horizontal parts form the remaining structure of the fallopian tubes. Both the caudal-vertical regions come in contact with each other in the median plane. After the resorption of the midline septum, they fuse to form a single Y shaped uterovaginal primordium (UVP). The uterine region of the UVP gives rise to the uterus, while the vaginal

region forms the upper one-third of the vagina. At this stage the uterus is still bicornuate and by 12 weeks of intra-uterine life, the fundus completely develops to form the pear-shaped cavity. The lower two-thirds of the vagina develops by canalisation of the vaginal plate arising from the sinovaginal bulb. This entire process gets completed by about 22 weeks of embryonic life, giving rise to a well developed female reproductive system. The development of the gonad is independent of the mullerian ducts development. Hence, women with mullerian anomalies usually have normal ovaries. But, renal anomalies are often associated with the mullerian anomalies because of their common embryonic origin[4].

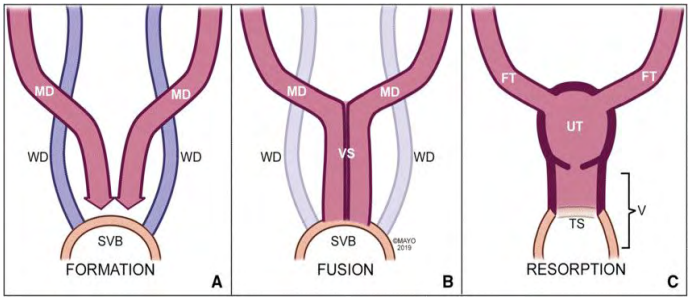


Figure 1- schematic representation of mullerian duct development [5]

[MD - Mullerian Duct; WD - Wolffian Duct; SVB - SinoVaginal Bulb; VS - Vertical Septum; TS - Transverse septum; FT - Fallopian Tube; UT - Uterus; V - Vagina]

CLASSIFICATION OF MULLERIAN ANOMALIES:

As we all know that there are numerous classification systems for mullerian anomalies, in this chapter we will be discussing only about the classification by the American Society of Reproductive Medicine (ASRM) published in 2021 as it has been widely used in all the recent works of literature. The earliest classification attempted to classify mullerian anomalies was done in the 19th century by Cruveilher, Foerster and Von Rokitansky. The AFS classification was developed from the classification of mullerian anomalies published by Buttram and Gibbons in 1979. Unlike the previous classification, the anomalies are identified by their descriptive terminologies and are no longer numbered in the recent 2021 ASRM classification (Table 1) and (Fig 2 & 3)[6].

TABLE 1: ASRM 2021 CLASSIFICATION OF MULLERIAN ANOMALIES

MAIN CLASS	SUB-CLASS
Mullerian agenesis	• Complete Mullerian agenesis • Mullerian agenesis with R/L atrophic uterine remnant with functional endometrium
Cervical agenesis	• Complete Cervical agenesis • Distal Cervical agenesis
Unicornuate uterus	• R/L Unicornuate uterus • R/L Unicornuate with R/L distal atrophic uterine remnant • R/L Unicornuate with R/L distal uterine remnant with functional endometrium • R/L Unicornuate with R/L associated atrophic uterine remnant • R/L Unicornuate with R/L uterine horn communicating at the level of cervix

MAIN CLASS	SUB-CLASS
Uterus Didelphys	• Uterus didelphys and complete longitudinal vaginal septum • Uterus didelphys and +/– longitudinal vaginal septum of variable length • Uterus didelphys and obstructed R/L hemi-vagina
Bicornuate uterus	• Bicornuate uterus (with single cervix) • Bicornuate uterus with R/L communicating tract • -Uterus bicornuate bicollis • -Combined bicornuate septate uterus
Septate uterus	• Partial septate uterus • Normal/arcuate uterus • Robert's uterus (Septate uterus with noncommunicating hemi uterus) • Complete septate uterus with duplicated cervices and longitudinal vaginal septum • Complete septate uterus with septate cervix and longitudinal vaginal septum • Complete septate uterus, duplicated cervices, and obstructed R/L hemi vagina
Transverse vaginal septum	• Midvaginal septum • Distal vaginal agenesis
Longitudinal vaginal septum	• Longitudinal vaginal septum of variable length • Longitudinal vaginal septum of variable length and uterus didelphys • Longitudinal vaginal septum of variable length and complete septate uterus with duplicated cervix • Obstructed R/L hemi vagina and uterus didelphys • Obstructed R/L hemi vagina and complete septate uterus with duplicated cervices
Complex anomalies	• Bicornuate uterus with bilateral obstructed endometrial cavities • Uterus didelphys with communicating hemi uteri and unilateral R/L cervicovaginal atresia • Obstructed R/L hemi vagina, hemi uterus and single cervix with separate contralateral R/L patent hemi uterus, cervix and vagina • Bicornuate uterus with R/L communicating tract and transverse vaginal septum • Uterus isthmus agenesis

MERITS OF ASRM CLASSIFICATION:

The task force has expanded the classification from 1988 to add most of the complex anomalies including the cervical and vaginal anomalies.

The classification has extensively discussed about each class, its variants, similar lesions, their presentation, imaging modality and treatment options.

DEMERITS OF ASRM CLASSIFICATION:

Though, this 2021 classification has included a wide range of complex anomalies, all the anomalies are not included here considering the huge range of possible variations.

There are some anomalies that are categorized into more than one sub-class; especially the vaginal anomalies considering their combination with other uterine and cervical anomalies.

The classification of cervical and vaginal anomalies were more precise and clear in the ESHRE-ESGE classification compared to ASRM 2021 which is more complex.

The normal/arcuate uterus has been classified under the main class of septate uterus instead of providing a separate class for it.

Hypoplastic uterus has not been included in this classification.

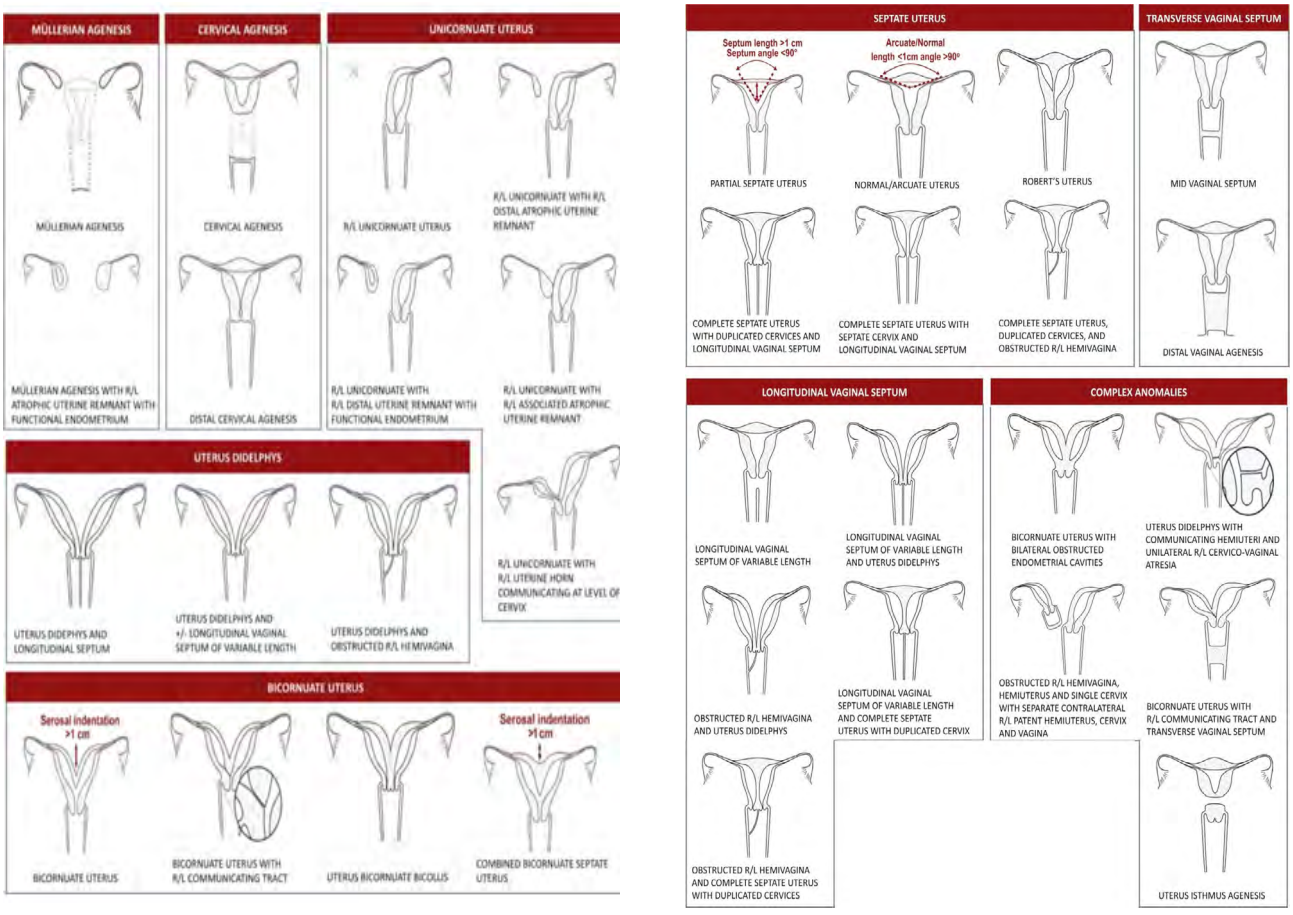


Figure 2 & 3: diagrammatic representation of mullerian anomalies: ASRM 2021[6]

DIAGNOSIS:

Although congenital uterine anomalies (CUA) are present at birth, majority of these women are asymptomatic while some experience painful menstruation. These anomalies have to be diagnosed accurately, as the counselling regarding the management and the prognosis of these cases entirely relies on it. The best method to diagnose these anomalies is a combined laparoscopy and hysteroscopy which is an invasive procedure. Though, non-invasive methods like the two-dimensional (2D) USG, sonohysterography and hysterosalpingography (HSG) are available to diagnose mullerian anomalies, Magnetic Resonance Imaging (MRI) and 3D USG are more accurate in diagnosing them. 3D USG is comparable in efficacy to MRI and widely used clinically as it is a less expensive procedure[7].

HYSTEROSALPHINGOGRAPHY:

While HSG is primarily used as a diagnostic test to assess the patency of both the fallopian tubes, it is also the best screening tool to study the uterine cavity. The detection rate of uterine anomalies with HSG is 35.84%[8].

DEMERITS:

The external fundal contour cannot be delineated by an HSG making it a less efficient diagnostic tool[9].

HSG cannot differentiate a septate and bicornuate uterus.

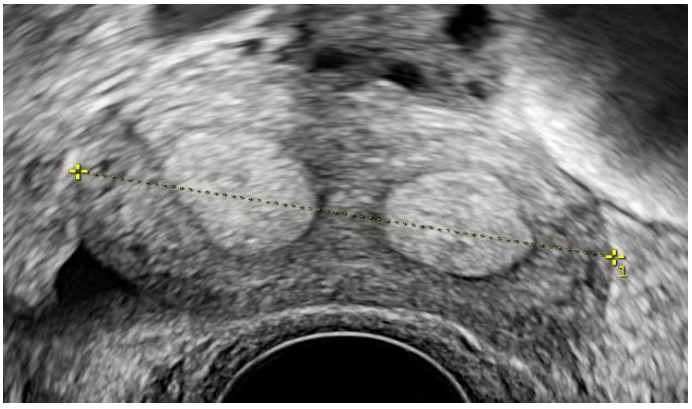
A non-communicating uterine cavity cannot be made out in an HSG.

TWO DIMENSIONAL ULTRASONOGRAPHY:

2D USG is the conventional method of diagnosing uterine anomalies with a detection rate of 72 %. With a good expertise in USG, two separate cavities seen in the transverse plane is diagnostic of a uterine anomaly. Also, when the USG probe is swiped from one lateral fornix to the other in a trans-vaginal scan (TVS), the appearance, disappearance and reappearance of the endometrial contour is diagnostic of an uterine anomaly.

DEMERITS:

- In a 2D USG, as the coronal plane cannot be obtained, the external fundal and endometrial contours cannot be well delineated to diagnose the uterine anomaly accurately.
- Unicornuate uterus cannot be diagnosed in a 2D USG as it cannot be differentiated from a deviated uterus[2,10,11].



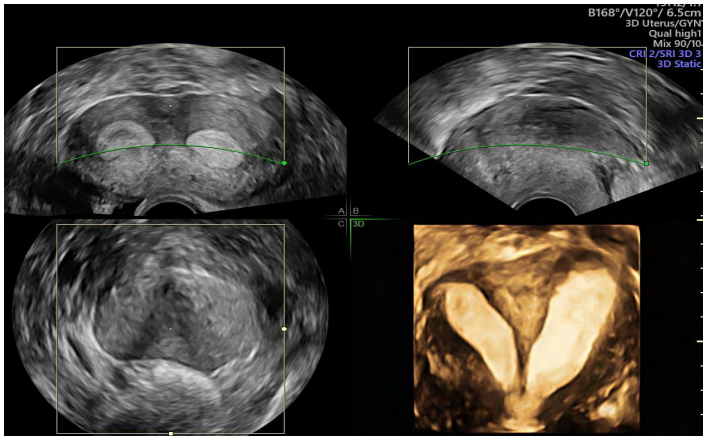
2D IMAGE OF AN UTERINE ANOMALY

THREE DIMENSIONAL (3D) ULTRASOUND:

- As 3D USG is equally efficacious as an MRI in diagnosing uterine anomalies, 3D USG is considered as the least expensive, less invasive gold standard technique compared with hystero-laparoscopy and MRI[12].
- Clear visualization of the external fundal and endometrial contour is possible as the coronal plane of the uterus can also be obtained by 3D USG.
- Transvaginal 3D USG should be done in the secretory phase as the endometrium

is hyperechoic and well grown this period, making the diagnosis more accurate.

- With advances in the 3D USG software like the omniview and HD LIVE render, real time imaging of the uterine anomalies is possible.
- **3D USG based classification system**: The ESHRE/ESGE classification of mullerian anomalies has been proposed by the Thessaloniki consensus group in 2013. It is a very precise and clear classification system with separate classifications for the uterine, cervical and vaginal anomalies. Definite, measurable cut-offs are given to diagnose T-shaped uterus unlike the ASRM classification. But the main disadvantage is the slight over-estimation of septate uterus[13,14].
- 3D USG has a diagnostic accuracy of 97.6%, sensitivity of 98.3% and specificity of 99.4% in diagnosing the mullerian anomalies[15].
- **Limiting factor:** good clinical training in 3D transvaginal USG is required to render the acquired USG volumes so that accurate images of the uterine anomalies are obtained.
- An additional abdominal USG is required if an associated renal anomaly is suspected.



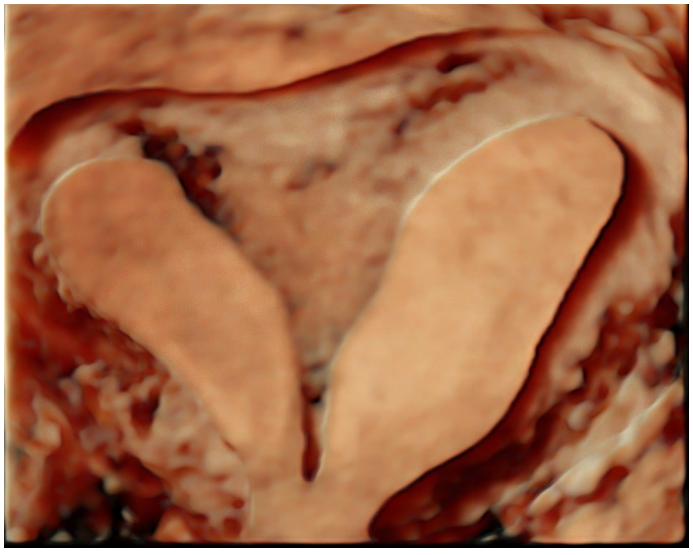
3D IMAGE OF AN UTERINE ANOMALY

MAGNETIC RESONANCE IMAGING:

- MRI is considered in all cases with complex anomalies involving the cervix, vagina and/or the kidneys in addition to the uterine defect if the other diagnostic methods are inconclusive.
- As multi-planar images are obtained with an MRI, soft tissue delineation is at its best in this modality with a wider field of assessment.
- Cases like the unicornuate uterus with a rudimentary horn lying far away in the pelvis and severe mullerian agenesis with an atrophic remnant can be easily diagnosed with a MRI. Thus, MRI is very useful in cases with complex anatomical variations.

IMPACT OF MULLERIAN ANOMALIES IN EARLY PREGNANCY:

Majority of these women are asymptomatic and are diagnosed with a CUA only after their first ultrasound evaluation for a miscarriage. Even though these anomalies can be diagnosed accurately, their obstetric journey is very different with each pregnancy and every anomaly. Mullerian anomalies are associated with infertility and a lot of adverse obstetric outcomes like the recurrent miscarriage, cervical insufficiency & preterm birth, fetal growth restriction and many more. These women are also found to have an increased risk for pre-eclampsia and stillbirth because of the poor placentation[16]. We will be discussing in detail, the obstetric course of every anomaly in early pregnancy.



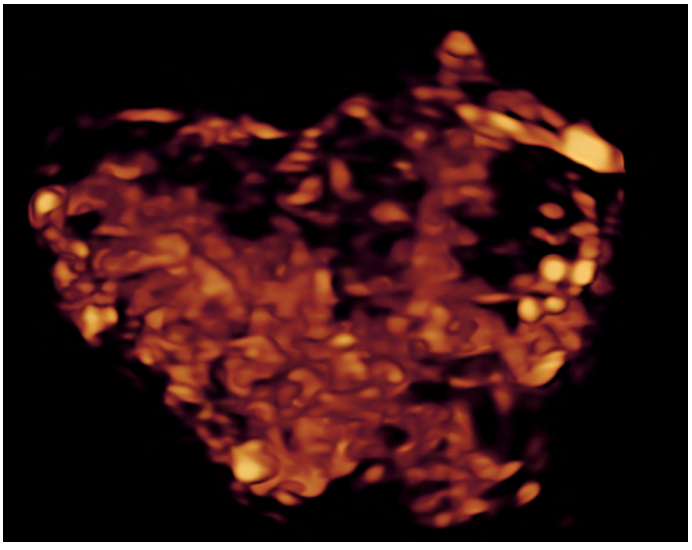
3D IMAGE OF A COMPLETE SEPTATE UTERUS

The prevalence of septate uterus in the general population is 2.3% while in the infertile population it is 3%[3]. Septate uterus is the leading cause of first-trimester miscarriage and recurrent miscarriage (RPL) in a high risk population with uterine anomalies[3,11,15,17]. It has a prevalence of 15.4% in the infertile miscarriage population[3]. A systematic review done with 3805 women with mullerian anomalies reported that those with a septate and partial septate uterus have the poorest reproductive outcome with a reduced conception rate, increased risk of first-trimester miscarriage (OR 2.89; 95% CI 2.02–4.14), preterm birth (OR 2.14; 95% CI 1.48–3.11), fetal growth restriction and fetal malpresentation (RR, 6.24; 95% CI, 4.05–9.62; $P < 0.001$) at delivery compared to a normal women. Also, women with a septate uterus have a poorer pregnancy outcome in all the three trimesters compared to those with a partial septate uterus[18]. The poorest fetal survival rates among all the uterine anomalies are seen in the sub septate and septate subgroups (48.4%)[19].

CAUSES OF MISCARRIAGE:

The septum has more muscle fibres and less connective tissue. The interlacing of the muscle fibres cause the blood vessels in between to get squeezed thereby decreasing the blood supply to the endometrium overlying the septum. This causes poor implantation of embryo and abortion[20].

- There is a reduction in the uterine cavity volume.
- Poor decidualisation happens because of less connective tissue.
- The endometrium overlying the septum is less sensitive to estrogen as the glandular tissue is irregularly distributed[21].
- Incomplete ciliogenesis in the epithelium can also be the cause of infertility.
- 71.2% of septa show vascularity with high impedance: Resistance index (RI) between 0.68 and 1. The vascular pattern is irregular with high resistance in a septum because of the interlacing muscle fibres[22].



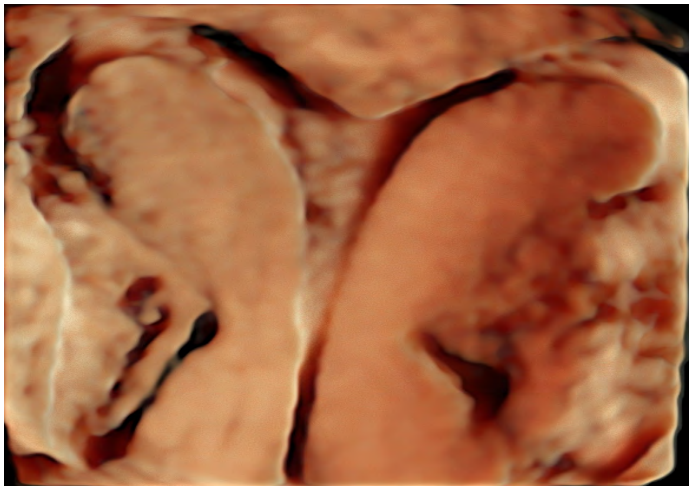
3d power doppler of endometrial cavity with the septum showing the vascular pattern

When to operate a septum:

There is a significant decrease in the preterm birth rate (OR = 0.30; 95% CI, 0.11–0.79) in women with a partial septate uterus who underwent a septal resection, while no difference is observed in the complete septum group. Some works of literature quote an increased risk for preterm birth even after resection of the septum[23,24]. Hence, infertile women with a septum more than 10mm in depth or septum with a depth of 5 to 10mm

associated with unexplained recurrent miscarriage and infertility benefit from a septal resection[25].

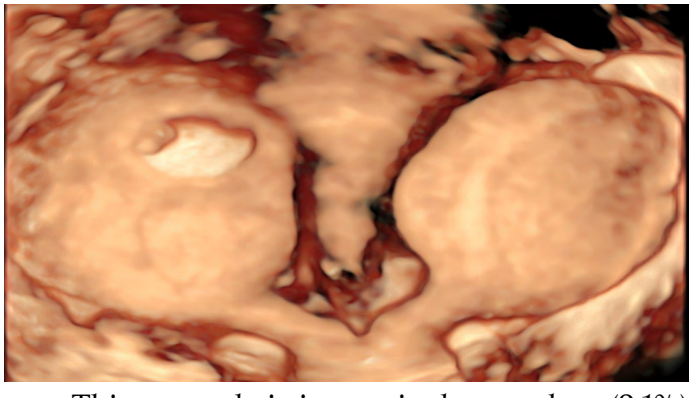
BICORNUATE UTERUS:



3d image of bicornuate bicollis uterus

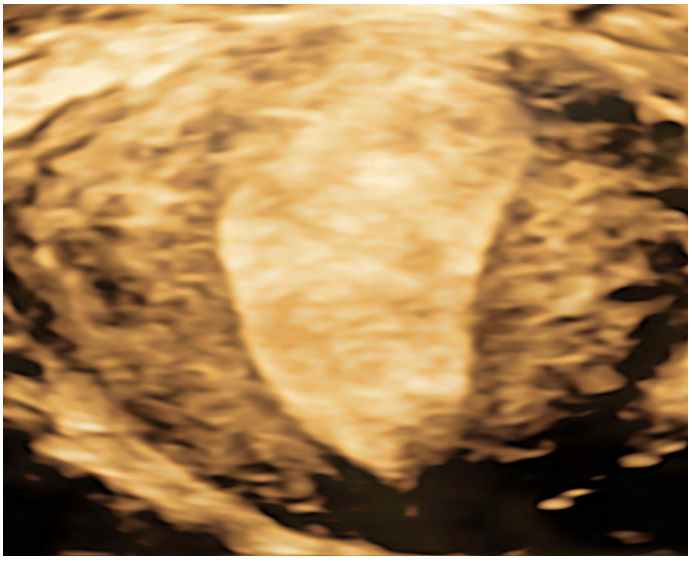
Bicornuate uterus is prevalent in 1.1% of the infertile population and 2.1% of the miscarriage population[3]. While bicornuate uterus does not reduce the fertility potential in the women, the adverse obstetric events like, the first trimester miscarriage (RR: 3.40; 95% CI, 1.18–9.76), preterm birth (RR, 2.97; 95% CI, 2.08–4.23; *P* < 0.001), fetal malpresentation (RR, 3.87; 95% CI, 2.42–6.18; *P* < 0.001) and low birth weight are increased[11,18,19,26]. There is a significant increase in the prevalence of second trimester miscarriages (RR, 2.32; 95% CI, 1.05–5.15; *P* = 0.04) in women with a bicornuate uterus compared to those with a normal uterus[18].

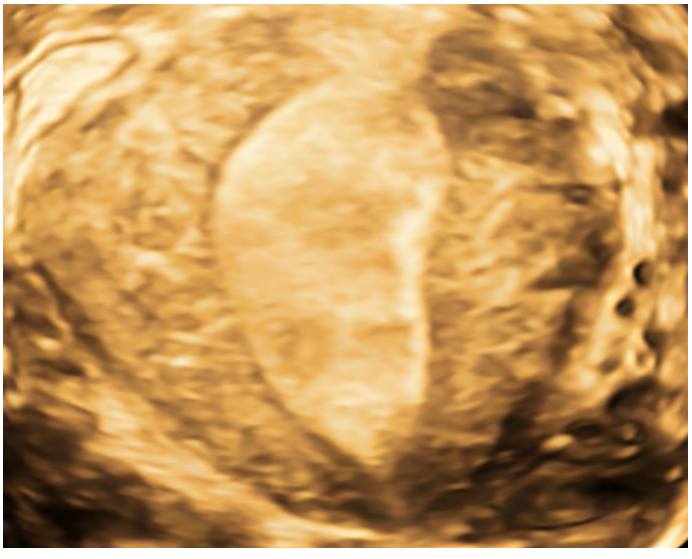
UTERINE DIDELPHYS:



This anomaly is increasingly prevalent (2.1%) in the infertile women with a miscarriage (95% CI, 1.4–3.2, P< 0.001). These women have an increased risk of second trimester miscarriage (RR, 1.39; 95% CI, 0.44–4.41), preterm birth (34.9%), fetal growth restriction (26.1%) and malpresentation at the time of delivery (39.1%)[3,18,19]. Among the uterine anomalies, women with didelphys have the best pregnancy outcome. They have the lowest rate of spontaneous abortions compared to all the other mullerian anomalies[19].

UNICORNUATE UTERUS:





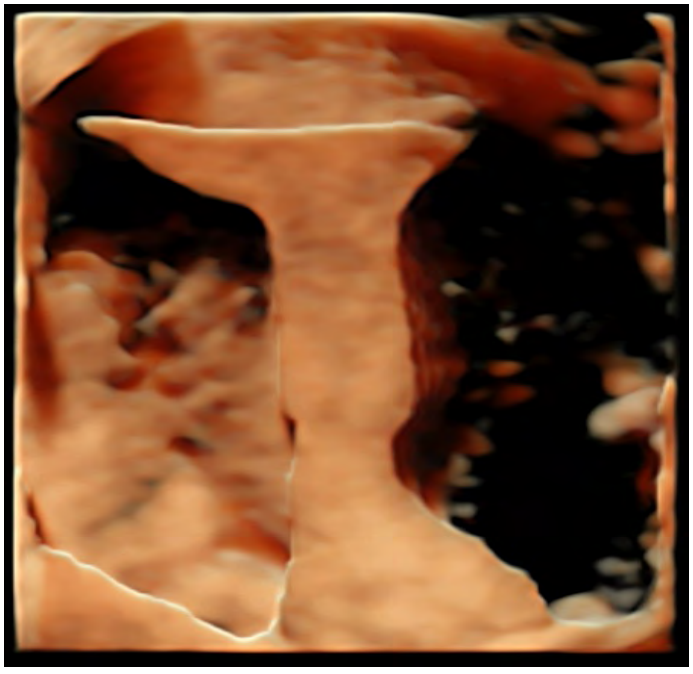
This anomaly is prevalent in 3.1% (95% CI, 2–4.7; P , 0.001) of women with infertility and

miscarriage[3]. They have very low clinical pregnancy rates (OR 0.75; 95% CI 0.58–0.99; $p = 0.04$)[27]. Women with a unicornuate uterus have an increased risk for the first trimester (RR, 2.15; 95% CI, 1.03–4.47; $P = 0.04$) and second trimester miscarriage (RR, 2.22; 95% CI, 0.53–9.19; $P = 0.27$) compared to those with a normal uterus[18,19,26,28]. These women are more prone to have preterm birth (OR 2.83, 95% CI 1.92–4.19; $p < 0.001$) and fetal growth restricted babies (OR 3.5; 95% CI 1.24–9.91; $p = 0.02$)[26]. They also have high rates of malpresentation (RR, 3.87; 95% CI, 2.42–6.18; $P < 0.001$) and cesarean delivery[18,19]. Ectopic pregnancies are more common in women with a communicating horn.

WHEN TO OPERATE IN A UNICORNUATE UTERUS:

Unicornuate uterus needs to be operated only to remove a functional rudimentary horn (non-communicating) presenting with hematometra or rarely an ectopic pregnancy. Usually, pregnancy in the communicating horn does not continue beyond the first trimester and often require a surgical removal[29,30].

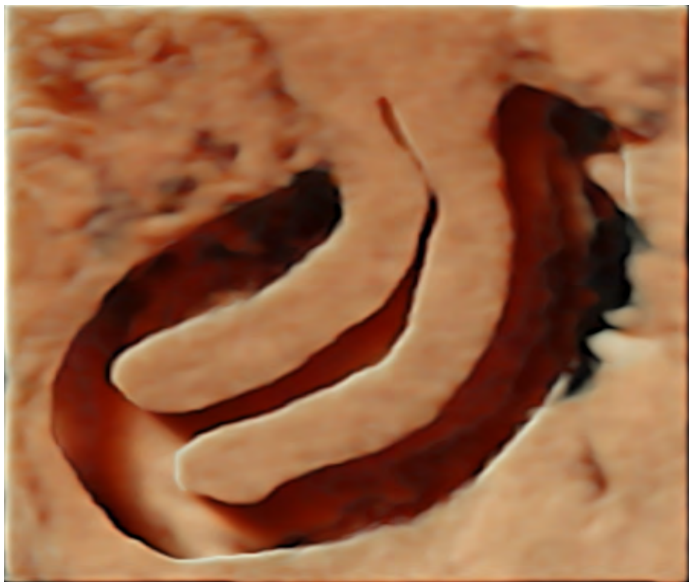
T-SHAPED UTERUS:

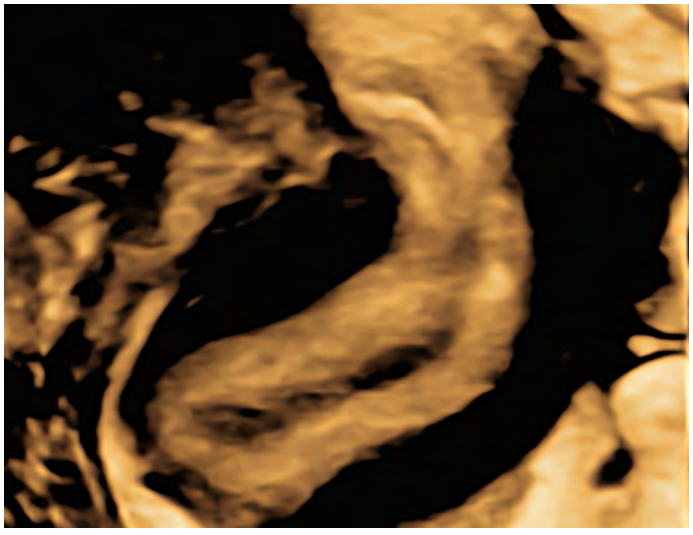


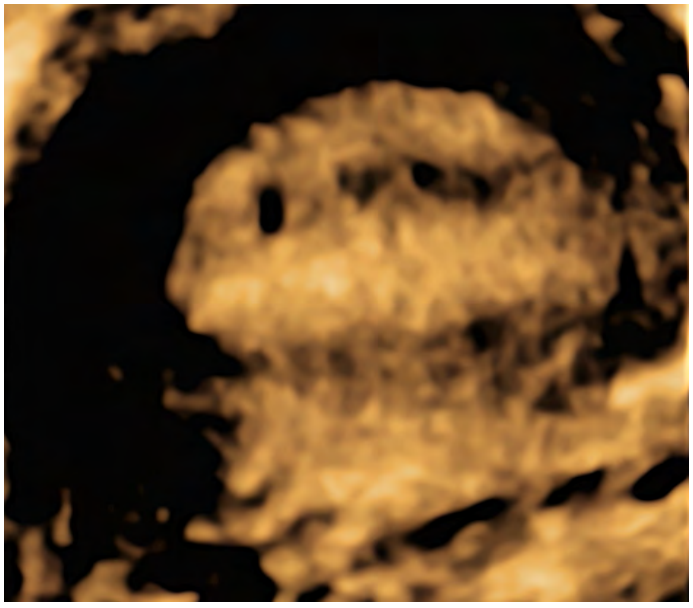
This anomaly has a very low prevalence in the fertile population (0.8%), contributing to the fact that most of them present with infertility. These women present with first and second trimester miscarriages when they are pregnant[31].

OBSTETRIC IMPLICATIONS OF CERVICAL AND VAGINAL ANOMALIES:

- When a septum is seen extending into the cervix, removal of the cervical part is not usually recommended as the risk for cervical incompetence increases in these women[32,33].
- All cases of cervical atresia need a reconstructive surgery to create a patent cervix. When they get pregnant, abdominal encerclage is done with a planned cesarean section.
- Transverse or longitudinal vaginal septum has to be resected prior to pregnancy to avoid obstruction in labour.
- Women with vaginal atresia who have undergone reconstruction with a mucosal graft are prone to vaginal obstruction in labor[33].
- When women with double cervix, transverse/longitudinal vaginal septum or vaginal graft present with a miscarriage, visualization and dilatation of the cervix for evacuation of the products of conception can be difficult. When these anomalies are associated with bicornuate uterus or didelphys, instrumentation into the wrong cavity can happen unless it is done under ultrasound guidance[34].
- Operative hysteroscope can be of help in cases where conventional dilatation under USG guidance is unsuccessful[35].







EVALUATION OF CERVICAL LENGTH IN UTERINE ANOMALY:

All women with a uterine anomaly are at an increased risk for spontaneous preterm birth (SPTB). SPTB has its highest incidence in women with canalisation and unification defects. The risk of preterm birth increases further, when a short cervix (less than 25mm) is present along with the CUA. Measurement of cervical length between 16 and 24 weeks has been instrumental in predicting spontaneous preterm birth in women with resorption defects[36,37]. However, various studies have found that SPTB occurred independently of a short cervix in the majority of the women with a CUA[11,36,37]. Hence, measurement of the cervical length has less predictive value in detecting the chances for an SPTB in women with uterine anomalies.

ROLE OF PROGESTERONE AND ENCERCLAGE:

Various studies have concluded that there is no role for routine prophylactic encerclage in women with CUA. Cerclage should be considered in women with a history of cervical insufficiency, preterm birth or cervical shortening in the current pregnancy[38]. The role of vaginal and intramuscular progesterone has not been extensively studied in this population of women[11,33]. Classic treatment with progesterone and en-cerclage might not prevent preterm birth in this group of women[39,40].

KEY POINTS:

- 3D USG is equally efficacious as an MRI in diagnosing congenital uterine anomalies.
- Complex anomalies involving the additional systems require an MRI for accurate diagnosis.
- Poorest reproductive outcome with early pregnancy losses are most common in the

women with septate/subseptate uterus.

- Septate uterus is associated with poor fertility outcomes while unification defects are associated with poor neonatal outcomes.
- None of these anomalies need to be operated for improving an obstetric outcome except for those cases of RPL, were other causes of miscarriage have been excluded.
- Measurement of the cervical length has less predictive value in detecting the chances for an SPTB in women with uterine anomalies.
- Larger randomized control trials (RCTs) are required to evaluate the role of cerclage and vaginal progesterone in this group of women.

REFERRENCES:

1. Wilson D, Bordoni B. Embryology, mullerian ducts (paramesonephric ducts). InStatPearls [Internet] 2021 Jul 30. StatPearls Publishing.
2. Jayaprakasan K, Ojha K. Diagnosis of Congenital Uterine Abnormalities: Practical Considerations. Journal of Clinical Medicine. 2022 Feb 25;11(5):1251.
3. Chan YY, Jayaprakasan K, Zamora J, Thornton JG, Raine-Fenning N, Coomarasamy A. The prevalence of congenital uterine anomalies in unselected and high-risk populations: a systematic review. Human reproduction update. 2011 Nov 1;17(6):761-71.
4. Sadler TW. Langman's medical embryology. Lippincott Williams & Wilkins; 2018 Sep 6.
5. Pitot MA, Bookwalter CA, Dudiak KM. Müllerian duct anomalies coincident with endometriosis: a review. Abdominal Radiology. 2020 Jun;45:1723-40.
6. Pfeifer SM, Attaran M, Goldstein J, Lindheim SR, Petrozza JC, Rackow BW, Siegelman E, Troiano R, Winter T, Zuckerman A, Ramaiah SD. ASRM müllerian anomalies classification 2021. Fertility and sterility. 2021 Nov 1;116(5):1238-52.
7. Graupera B, Pascual MA, Hereter L, Browne JL, Úbeda B, Rodríguez I, Pedrero C. Accuracy of three-dimensional ultrasound compared with magnetic resonance imaging in diagnosis of Müllerian duct anomalies using ESHRE–ESGE consensus on the classification of congenital anomalies of the female genital tract. Ultrasound in Obstetrics & Gynecology. 2015 Nov;46(5):616-22.
8. Schramm D, Wohlgemuth WA, Wagner S, Knoergen M, Svatko Z, Seliger G. Diagnostic value of hysterosalpingography. J Clin Med Res. 2022;4(5):1-8.
9. Yousif A, Moustafa AS, Abuzeid OM, Corrado JM, Abdullah A, Abuzeid MI. Limitations of imaging screening tests in the detection of incomplete uterine septum or arcuate uterine anomaly. International Journal of Gynecology & Obstetrics. 2022 Mar 22.
10. MA AE, MA EN, ME M, LK AE. Sonohysterography And 3d Transvaginal Ultrasonography Versus Diagnostic Hysteroscopy In Assessment Of Uterine Abnormalities In Female Infertility. Benha Journal of Applied Sciences. 2022 Mar 1;7(3):101-9.

11. Akhtar MA, Saravelos SH, Li TC, Jayaprakasan K, Royal College of Obstetricians and Gynaecologists. Reproductive implications and management of congenital uterine anomalies: scientific impact paper No. 62 November 2019. BJOG: An International Journal of Obstetrics & Gynaecology. 2020 Apr;127(5):e1-3.
12. Wang L, Chen XJ, Liang JH, Zhang ZK, Cao TS, Zhang L. Preliminary Application of Three-Dimensional Printing in Congenital Uterine Anomalies Based on Three-Dimensional Transvaginal Ultrasonographic Data.
13. Gupta U, Tripathi V, Sharma P. Clinical Implications and ESHRE/ESGE Classification of Mullerian Anomalies: A Case Series. Obstet Gynecol Cases Rev. 2021;8:191.
14. Knez J, Saridogan E, Van Den Bosch T, Mavrelos D, Ambler G, Jurkovic D. ESHRE/ESGE female genital tract anomalies classification system—the potential impact of discarding arcuate uterus on clinical practice. Human Reproduction. 2018 Apr 1;33(4):600-6.
15. Grimbizis GF, Di Spiezio Sardo A, Saravelos SH, Gordts S, Exacoustos C, Van Schoubroeck D, Bermejo C, Amso NN, Nargund G, Timmerman D, Athanasiadis A. The Thessaloniki ESHRE/ESGE consensus on diagnosis of female genital anomalies. Human Reproduction. 2016 Jan 1;31(1):2-7.
16. Fox NS, Roman AS, Stern EM, Gerber RS, Saltzman DH, Rebarber A. Type of congenital uterine anomaly and adverse pregnancy outcomes. The journal of maternal-fetal & neonatal medicine. 2014 Jun 1;27(9):949-53.
17. Chester MR, Tirlapur A, Jayaprakasan K. Current management of recurrent pregnancy loss. The Obstetrician & Gynaecologist. 2022 Oct;24(4):260-71.
18. Chan YY, Jayaprakasan K, Tan A, Thornton JG, Coomarasamy A, Raine-Fenning NJ. Reproductive outcomes in women with congenital uterine anomalies: a systematic review. Ultrasound in Obstetrics & Gynecology. 2011 Oct;38(4):371-82.
19. Zlopaša G, Škrablin S, Kalafatić D, Banović V, Lešin J. Uterine anomalies and pregnancy outcome following resectoscope metroplasty. International Journal of Gynecology & Obstetrics. 2007 Aug 1;98(2):129-33.
20. Lekovich J, Stewart J, Anderson S, Niemasik E, Pereira N, Chasen S. Placental malperfusion as a possible mechanism of preterm birth in patients with Müllerian anomalies. Journal of perinatal medicine. 2017 Jan 1;45(1):45-9.
21. Hassan MA, Lavery SA, Trew GH. Congenital uterine anomalies and their impact on fertility. Women's Health. 2010 May;6(3):443-61.
22. Kupesic S. Clinical implications of sonographic detection of uterine anomalies for reproductive outcome. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2001 Oct;18(4):387-400.
23. Carrera M, Millan FP, Alcázar JL, Alonso L, Caballero M, Carugno J, Dominguez JA, Moratalla E. Effect of hysteroscopic metroplasty on reproductive outcomes in women with septate

uterus: systematic review and meta-analysis. Journal of minimally invasive gynecology. 2021 Oct 11.

24. Loddo A, D'Alterio MN, Neri M, Masala F, Cane FL, Melis GB. Pregnancy Complications After Hysteroscopic Metroplasty: A Ten-Year Case-Control Study. Surgical Technology International. 2017 Jul 1;30:205-9.
25. Ouyang Y, Chen H, Gong F, Lin G, Li X. Septum Resection Prior to In Vitro Fertilization-Embryo Transfer: A Retrospective Controlled Study. Journal of Ultrasound in Medicine. 2022 Nov 17.
26. Qiu J, Du T, Chen C, Lyu Q, Mol BW, Zhao M, Kuang Y. Impact of uterine malformations on pregnancy and neonatal outcomes of IVF/ICSI–frozen embryo transfer. Human Reproduction. 2022 Mar;37(3):428-46.
27. Kim MA, Kim HS, Kim YH. Reproductive, Obstetric and Neonatal Outcomes in Women with Congenital Uterine Anomalies: A Systematic Review and Meta-Analysis. Journal of clinical medicine. 2021 Oct 20;10(21):4797.
28. Zhang Y, Zhao YY, Qiao J. Obstetric outcome of women with uterine anomalies in China. Chinese Medical Journal. 2010 Feb 20;123(04):418-22.
29. Troiano RN, McCarthy SM. Mullerian duct anomalies: imaging and clinical issues. Radiology. 2004 Oct;233(1):19-34.
30. Liu Y, Wang S, Hong Y, Wang J, Niu J, Li X, Li H, Wang Y. Pregnancy in the blind hemi-cavity of Robert's uterus: a case report. Radiology Case Reports. 2021 May 1;16(5):1085-8.
31. Seyhan A, Ertas S, Urman B. Prevalence of T-shaped uterus among fertile women based on ESHRE/ESGE and Congenital Uterine Malformation by Experts (CUME) criteria. Reproductive BioMedicine Online. 2021 Sep 1;43(3):515-22.
32. Rikken JF, Kowalik CR, Emanuel MA, Bongers MY, Spinder T, De Kruif JH, Bloemenkamp KW, Jansen FW, Veersema S, Mulders AG, Thurkow AL. The randomised uterine septum transsection trial (TRUST): design and protocol. BMC women's health. 2018 Dec;18(1):1-5.
33. Oelschlager AM. Uterine anomalies in pregnancy. Contemporary OB/GYN Journal. 2022 Dec 7;67(12).
34. Rubin ES, Huttler A, Mainigi M, Roe AH. Surgical uterine evacuation in patients with two cervices: a case series. Contraception. 2022 Apr 1;108:73-7.
35. Ryu S, Baek HW, Lee I, Won YB, Kim H, Lee JH, Yun BH, Park JH, Seo SK, Cho S, Choi YS. Operative hysteroscopy-assisted pregnancy termination after failed surgical abortion in missed abortion of woman with complete septate uterus. Obstetrics & Gynecology Science. 2019 Dec 26;63(1):102-6.
36. Hughes KM, Kane SC, Haines TP, Sheehan PM. Cervical length surveillance for predicting spontaneous preterm birth in women with uterine anomalies: A cohort study. Acta Obstetricia et Gynecologica Scandinavica. 2020 Nov;99(11):1519-26.
37. Ridout AE, Ibeto LA, Ross GN, Cook JR, Sykes L, David AL, Seed PT, Tribe RM, Bennett PR, Terzidou V, Shennan AH. Cervical length and quantitative fetal fibronectin in the prediction of spontaneous preterm birth in

asymptomatic women with congenital uterine anomaly. American Journal of Obstetrics and Gynecology. 2019 Oct 1;221(4):341-e1.

38. Vaz SA, Dotters-Katz SK, Kuller JA. Diagnosis and management of congenital uterine anomalies in pregnancy. Obstetrical & gynecological survey. 2017 Mar 1;72(3):194-201.
39. Romero R, Nicolaides K, Conde-Agudelo A, Tabor A, O'Brien JM, Cetingoz E, Da Fonseca E, Creasy GW, Klein K, Rode L, Soma-Pillay P. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. American journal of obstetrics and gynecology. 2012 Feb 1;206(2):124-e1.
40. Hynes JS, Schwartz AR, Abdalla A, Manuck TA, Dotters-Katz SK. 17-hydroxyprogesterone caproate for women with congenital uterine anomalies: does it impact the risk of recurrent preterm birth?. American journal of obstetrics & gynecology MFM. 2021 Jan;3(1):100278.

ENTER INTO THE MIND THROUGH THE STOMACH !

DR. PARIMALA RANI

I LEARNED ABOUT THIS PHRASE FROM MY MENTOR THE LATE DR BC. WHO GAVE A POWERFUL UNCONVENTIONAL ACUMEN INTO MENTORSHIP.

I remember my teacher always winning over most of his colleagues in my college. Despite being a stout man, he won many hearts . Even though he was revered by his students for his mentorship he was a perfect gourmand.

He never missed an opportunity to offer his delicious homemade food to any of his students. I had always wondered how he was able to implement such a unique virtuous practice in his work. What truly matters is the positive impact of his actions and the inspiration he provides in a more realistic way of life that speaks to the essence of human experience.

Whenever I made this recipe at home, I realised how much he had influenced me, as a protege, in my personal and professional growth.

I fondly remember my post graduate days when a task or duty or an assignment or any undertaking for that matter given to us ,in the so called OG 3 unit , ended with a treat.Though criticised by his colleagues for this attitude of his, he never bothered , because he knew that they longed to be associated with him , to be included in the treats, that happened at the end of any chore.

I learnt how to relish a meal and eat hearty. No need of a flavourful condiment ,but I was taught about the act of enjoying something, that's made out of simple ingredients. It was of course a blended mentoring.

Accompanied by Meena madam, his beloved wife, I immensely enjoyed the food prepared by her which was quite expeditious. The veggies were cut over the pan ,only after it was kept over the stove. Not only I relished the savors from his home ,but also his wit from time to time.

Like how a parent encourages their children, by rewarding them after a desired behaviour, the phrase it's my treat or it's your treat ,gave us a pleasant stimulus and a positive reinforcement

,which tapped our curiosity and inclined us to do beyond what was expected of us to do towards our goals. He was not only a king on a throne dispersing duties ,but a humble teacher who created a feast, often to show appreciation.

Each dish meticulously crafted ,spoke a specific dialect of care and understanding .His comforting warmth of support, nourished our hearts and minds .He fostered trust and ignited in us the courage to grow.

Just on the eve of our postgraduate practical exams, he called us outside our hostel, to deliver us a meal prepared in his home. Amidst those days of proneness and susceptibility ,we were overtaken by fierce loyalty, towards a more profound and realistic way of life.

His leadership reminded me that victory begins not only in the intellect ,but in the shared meal, the nurtured spirit and the unwavering integrity , found in the embrace of a full stomach. My teacher's journey was a testament to the power of diverse learning paths and the innate human capacity for insights and virtues.

I see through my perspective of entering the mind through the stomach, that his influence lingers long enough for his students ,even after their last bite is taken.

PAIN IN WOMEN IN ENDOMETRIOSIS

DR.K. PARIMALA RANI MD(OG)

MISSED MISCARRIAGE

DR. GAYATHRI.N. M.D., DNB, PGDMLE.,

DR. S. CHITRA., M.D., D.G.O., FICOG.

INTRODUCTION

It is indeed a moment of celebration when a couple who is just married, or a woman who is trying to conceive, reports a pregnancy. But, nevertheless, there are many a slip between the cup and the lip. Some of these pregnancies land up in miscarriage. To the treating personals, missed miscarriage is particularly distressing as the mother has no symptoms such as bleeding or pain when she is diagnosed. Hence convincing her, gaining her confidence for further management etc., becomes an ordeal. The acceptance from the patient side is also poor due to the absence of symptoms.

DEFINITION

Miscarriage is defined as the spontaneous end of pregnancy at a time before fetal viability. In some countries it is taken as 20 weeks and in other countries it is taken as 24 weeks. Loss of pregnancy beyond this gestation is stillbirth.

A missed miscarriage, also known as missed abortion or silent miscarriage, occurs when fetus is no longer alive, but the maternal body does not recognise the pregnancy loss or expel the products of conception. In other words, there are no symptoms like bleeding or cramps despite the fetus not being viable.

INCIDENCE

About 20-30% of pregnancies miscarry. The common predisposing factors include – maternal age, obesity, history of previous loss. Lowest risk was at 22 yrs and risk is highest at 48 yrs(as high as 85%). [1]

RISK FACTORS:

There are many proposed risk factors for miscarriage. But the risk of miscarriage may increase in such cases, but it is very difficult to propose a causative relation in those situations.

CHROMOSOMAL ABNORMALITIES IN THE FETUS:

This can happen even in the absence of abnormalities in the parents, de novo. This is nature's way of getting rid of genetically abnormal baby into this world. More than half of all miscarriage have some chromosomal abnormalities. Most common abnormality noted are autosomal trisomies. [2,3]

MATERNAL AND PATERNAL AGE:

It is long known that as maternal age advances, the risk of miscarriage increases. There is an approximate 4-foldincrease in the risk from 20 to 40 yrs of age of the mother. This may also

be secondary to the fact that, as maternal age advances, chance of genetic and chromosomal abnormalities increases. [4,5,6]

Although to a lesser extent, advanced paternal age has also been found to be associated with miscarriage.[7]

PREVIOUS HISTORY OF MISCARRIAGE:

Every miscarriage increases the risk of subsequent miscarriage. The cause may be persistence of risk factors (Ex. Maternal obesity, lifestyle factors, age etc). Surgical management of miscarriage has been further shown to increase risk of subsequent miscarriage. [8]

SUBFERTILITY:

Pregnancy after a period of treatment for subfertility or after a period of subfertility are known to have higher incidence of miscarriage. The cause implicated is the underlying factor causing subfertility (Ex: obesity, PCOS, Age) [9]

SOCIO-ECONOMIC STATUS:

There is an increased risk of miscarriage with lower socio-economic status. The implied reasons include – poor nutritional status, increased incidence of infections, environmental, occupational and behavioral factors.[10, 11]

PREPREGNANCY WEIGHT:

Obesity before, during and after pregnancy has major health issues. BMI >30 kg/m2 has been taken as a cut off. Studies suggest 10% increased risk in overweight mothers and 30% increase in obese mothers. (12). Very low BMI also carries with it an increased risk for miscarriage. [13]

DIET:

Risk was found to be lower in women with good dietary intake of folate (green vegetables, fruits, milk, cheese, fish) [9,14].

CAFFEINE:

Results of studies have been inconclusive. But heavy caffeine intake has found to increase the risk of miscarriage (>300 mg)

SMOKING:

There is a definite increase in risk of miscarriage for women who smoke in pregnancy. There is also a borderline increase in risk for women who are exposed to passive smoking.[15].

ALCOHOL:

A dose related association between alcohol conception and risk of miscarriage has been observed.[16].

PHYSICAL AND PSYCHOLOGICAL STRESS:

Negative life events like stressful life events, stressful job situations and feeling of anxiety and depression have an increased risk of negative pregnancy outcome. It has been suggested that level of maternal cortisol will influence outcome. [17]

THYROID DISORDERS:

Both hypothyroidism and hyperthyroidism have been implicated in miscarriage. Pre-conceptional evaluation and correction is strongly recommended.

METABOLIC DISORDERS:

Of all the metabolic disorders, Diabetes mellitus poses the highest chance of miscarriage, especially if poorly controlled. It not only increases the miscarriage rate, but also significantly increases the rate of anomalies in the offspring. It is, therefore, prudent to keep the HbA1C below 7% at the periconceptional period.

VITAMIN D DEFICIENCY:

Though evidence is inconclusive, a lot of studies suggest that deficiency of vitamin D is implicated in subfertility, early pregnancy loss and a lot of complications of pregnancy.

Modifiable risk factors	Non modifiable risk factors
• Being over weight or obese • High caffeine • Smoking / passive smoking • Alcohol • Diet • Stress- physical / psychological	• Age – both mother and father • Previous history of miscarriage • Surgical management of miscarriage • Subfertility

A knowledge of these risk factors will be very handy when we counsel the couple after miscarriage

DIAGNOSIS [18,19]

Diagnosis of miscarriage is essentially sonographic. When a woman reports with positive urine pregnancy test, she has to be offered an ultrasonogram. Early USG will let us know about the location of the pregnancy and dating of the pregnancy.

The woman should be informed that transvaginal ultrasound is preferable as it is more accurate and precise and is not associated with any negative pregnancy outcome.

Location of the Gestational Sac. The earliest sonographic sign of pregnancy is a gestational sac. It is usually eccentrically placed and regular. If a gestational sac is not seen, serum Beta HCG is asked for. The threshold for seeing a gestational sac in a TVS is 1500 IU/ml. If beta HGC is more than 1500 IU/ml and a gestational sac is not seen, extrauterine pregnancy should be considered. A paired beta HCG sample 48 hrs after the first one can guide us in the diagnosis.

Size of Gestational sac. MSD (Mean Sac Diameter) is the average of the three measured dimensions of the gestational sac. The measurement is taken from the inner margin to the inner margin in all 3 dimensions. If size is more than 25 without a yolk sac or fetal pole, a repeat scan is offered in 1 week to look for growth. If no growth is seen, it may be diagnosed as anembryonic gestation or blighted ovum.

Fetal Pole / CRL: Once a fetal pole is seen it is measured. The longest measurement is taken as the Crown Rump length. If it is >7 mm without a visible cardiac activity, a repeat scan after 1 week is advised. If after 1 week, there is still no demonstrable fetal cardiac activity, it is early embryonic loss.

It is prudent to not diagnose pregnancy loss in the light of a single USG finding. A repeat USG after 1 week may be done to confirm the findings before giving the diagnosis.

INVESTIGATIONS

To clinch the diagnosis: Other than ultrasound, in cases of pregnancy of uncertain viability, we may need serum HCG evaluation and a repeat of the same in 48 hours.

To proceed with treatment: Blood grouping and Rh typing, Hemoglobin, serology for infextious diseases (HIV, HBsAG, HCV, VDRL).

MANAGEMENT [18,19]

Management may be expectant, medical or surgical

EXPECTANT MANAGEMENT:

It is safe to try expectant management for 7 – 14 days following diagnosis of miscarriage awaiting spontaneous expulsion of products of conception. Yet another aspect of expectant management is that, the time can be taken by the patient and her family to psychologically accept the fate of pregnancy and get adjusted to it.

MEDICAL MANAGEMENT:

This is recommended if sac size is less than

9 wks. Since this is a case of missed miscarriage, evidence suggests that Mifepristone- anti progesterone is not required and misoprostol 800 micrograms, vaginal or oral may be given alone. But many doctors still believe, giving a 200 mg dose of mifepristone prior to misoprostol decreases the incidence of failed medical treatment. Analgesics may be given to the patients for cramps.

CONTRAINDICATIONS FOR MEDICAL MANAGEMENT ARE:

- Anaemia – Arbitrary cut off- 110 g/dL
- Coagulopathy/ women on anticoagulant
- Infections
- Mitral stenosis
- Hypertension
- Porphyria

Follow up is very essential in expectant and medical management. A follow up ultrasound to confirm complete abortion may be done 10 to 15 days after perceived expulsion of products of conception.

SURGICAL MANAGEMENT:

The indications of surgical management are

1. Pregnancy >9 weeks duration
2. Failed medical management
3. Adherent retained products
4. Retained products >5 cm
5. Signs of sepsis
6. Follow up not possible.
7. Any contraindications to medical management

Preoperative administration of misoprostol 200 – 400 mics vaginally will prevent cervical trauma during dilatation.

ANAESTHESIA:

Paracervical block/ short GA

Procedure involves manual vacuum aspiration syringe or a suction cannula. Sharp curettage is not preferred for fear of permanent endometrial damage.

Immediate complications are uterine perforation, cervical injury, haemorrhage, infection , anaesthesia complications.

Delayed complications include intrauterine adhesion, Asherman's syndrome, subfertility.

ANTIBIOTICS:

Prophylactic antibiotic is not needed in expectant management and medical management. For surgical management strict asepsis according to WHO guidelines and a single dose of prophylactic antibiotic is recommended as per local protocols.

An antibiotic with broad spectrum to cover gram negative and anaerobes should be preferred. Suggested combinations include-

- Fluroquinolone + metronidazole
- 3rd generation Cephalosporins + metronidazole
- Ampicillin + Gentamicin + Metronidazole.

This can be followed by Doxycycline 100 mg twice a day for 5-7 days or Azithromycin 500mg once a day for 3 days.

ANTI D PROPHYLAXIS:

Rh negative mother has to be offered anti D prophylaxis after surgical management. Those opting for expectant and medical management need not be offered Anti D Prophylaxis.

POST MISSED MISCARRIAGE COUNSELLING

Breaking the bad news and counselling following that are very crucial for the family to understand and wade through the process. After learning the news, the tendency of self-blame is quite high. “Was it something I did or dint do??”

It is the duty of the medical personnel to counsel the patients that it is difficult to pinpoint

the cause of miscarriage in individual cases. But presence of risk factors- especially modifiable risk factors should be discussed and advice to avoid them in future should be emphasised.

Most cases are genetic, and the knowledge of which may not be helpful in avoiding it in the future, as it is barely under control.

CONTRACEPTION

Individual preference as to when she wants to plan her next pregnancy should be considered. The patients coexisting co-morbidities may also be considered.

IUCD: For women who do not want conception for some time after miscarriage, due to social or family reasons.

COCP: for women who request contraception for 1 to few months, women with coexisting PCOS.

INJECTABLES: Injection depo provera is generally not preferred as there may be a delay in return of fertility in a few cases which in turn may lead to undue stress during following conception.

If coexisting endometriosis is diagnosed, a course of Dinegest may be advised, so on and so forth.

PLANNING NEXT PREGNANCY [18,19]

Evidence suggests that a wait for at least one normal period prior to planning the next conception is preferred. The previous belief of having to wait for 3 to 6 periods is not required.

No period of abstinence is required. She may resume her sexual activity as soon as she is ready and may use a barrier method of contraception until she is ready physically and psychologically for her next pregnancy.

A lot of emphasis had to be given to the psychological healing of the woman and appropriate counselling has to be arranged based on the individual ability of each patient to handle the miscarriage.

Once the mother is ready for her next conception, she has to be started on pre-conceptional folic acid and methylcobalamine and advised to continue till pregnancy is achieved.

PRE-PREGNANCY COUNSELLING AND INVESTIGATIONS: [19]

After a pregnancy loss and before she proceeds to try to conceive another time, it is prudent to evaluate and optimize maternal health.

General physical examination, BMI, blood pressure measurement any other co-morbidities, including screening the couple for genital infections to be done and optimal control achieved before embarking on pregnancy.

INVESTIGATIONS INCLUDE:

- CBC
- Blood group and Rh Type
- Viral markers and rubella autoantibodies
- Vit D, B12
- Thyroid function test
- HbA1C

PREVENTION

Most cases of missed miscarriage has a genetic component which cannot be prevented or treated. At the most, we can identify it, if detailed study was done. In a minority of cases, corpus luteal insufficiency, APLA syndrome, inherited thrombophilia may be the cause of the loss.

Though there is insufficient evidence to support, many doctors prefer to put the patient with risk factors for miscarriage including women with previous history of miscarriage on progesterone supplements and low dose aspirin in following pregnancy.

RECURRENCE

The risk of recurrence after one miscarriage is about 20%. It is 28% after 2 miscarriages and the risk further increases to 43% after 3 miscarriages.

About 1% of couple end with recurrent pregnancy loss, which is defined as 3 or more subsequent pregnancy losses. Thorough evaluation to rule out known causes should be undertaken. But, even after thorough evaluation, in more than 50% of the cases, cause cannot be identified. When no cause is identified, the couple should be reassured that the chance of going through the following pregnancy uneventfully is high. Simple tender loving care will suffice.

CONCLUSION

A miscarriage is a catastrophe, especially from the psychological front. A missed miscarriage is more difficult to handle as the family or the couple are not prepared for the news due to absence of any negative symptoms. Thus, empathetic counselling is very very vital in helping the couple overcome.

Diagnosis is sonological. But always repeat an ultrasound 7 – 14 days later before pronouncing the diagnosis.

Take the woman's preference while formulating the treatment for her.

Follow up counselling, USG, pre conceptional care are very important for better future outcome.

Available management and pharmacological prevention options are limited. But, most cases do well in the following pregnancy with simple tender loving care.

References:

1. https://progeny.com
2. Hassold T, Abruzzo M, Adkins K, et al. Human aneuploidy: incidence, origin and etiology. Environ Mol Mutagen. 1996 : 28(3): 167-75.
3. Warburton D, Byrne J, Canki N. Chromosomal anomalies and prenatal development: An Atlas. Oxford Monographs on Medical Genetics, No 21 NewYork, NY: Oxford University Press; 1991
4. Nybo-Anderson A-M, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population-based register linkage study. BMJ. 2000; 320 1708-12.
5. Feodar Nilsson S, Anderson PK, Strandberg-Larsen K, Nybo Anderson AM. Risk factors for miscarriage from a prevention perspective: a nationwide follow-up study. BJOG. 2014;121(11):1375-84.
6. Maconochie N, Doyle P, Prior S, Simmons R. Risk factors for first trimester miscarriage – results from a UK-population-based case-control study. BJOG. 2007; 114(2):170
7. Sharma R, Agarwal A, Rohra VK, Assidi M, Abu-Elmagd M, Turki RF. Effects of increased paternal age on sperm quality, reproductive outcome and associated epigenetic risks to offspring. Reprod Biol Endocrinol. 2015;13:35.
8. Sun Y, Che Y, Goa E, Olsen J, Zhou W. Induced abortion and risk of subsequent miscarriage. Int J Epidemiol. 200332:449-54.
9. Maconochie N, Doyle P, Prior S, Simmons R. Risk factors for first trimester miscarriage – results from a UK-population-based case-control study. BJOG. 2007; 114(2):170
10. Hemminki K, Niemi ML, Saloniemi I, Vainio H, Hemminki E, spontaneous abortions by occupation and social

class in Finland, Int J Epidemiol. 1980;9(2):149-53.

11. Weck RL, Paulose T, Flaws JA. Impact of environmental factors and poverty on pregnancy outcomes. Clin Obstet Gynecol.2008;51(2):349-59.
12. Boots C, Stephenson MD. Does obesity increase the risk of miscarriage in spontaneous conception: a systematic review. Semin Reprod Med. 2011;29(6):507-13.
13. Helgstrand S, Andersen AM. Maternal underweight and the risk of spontaneous abortion. Acta Obstet Gynecol Scand. 2005;84(12):1197-201.
14. 14. Gaskins AJ, Rich-Edwards JW, Hauser R, et al. Maternal prepregnancy folate intake and risk of spontaneous abortion and stillbirth. Obstet Gynecol.2014;124(1):23-31.
15. Pineles BL, Park E, Samet JM, Systematic review and meta-analysis of miscarriage and maternal exposure to tobacco smoke during pregnancy. Am J Epidemiol.2014;179(7):807-23
16. Andersen AM, Andersen PK, Olsen J, Gronback M, Stanberg-Larsen K. Moderate alcohol intake during pregnancy and risk of fetal death. Int J Epidemiol,2012;41(2):405-13.
17. Nepomnaschy PA, Welch KB,McConnell DS, Low BS, Strassmann BI, England BG, Cortisol levels and very early pregnancy loss in humans. Proc Natl Acad Sci USA. 2006; 103(10):3938-42.
18. NICE guidelines on Ectopic Pregnancy and miscarriage: diagnosis and initial management: 17, April 2019.
19. FOGSI – GCPR – Early Pregnancy loss

INTERESTING CASE OF SIRENOMELIA

DR MALATHI G.PRASAD

DR. VASANTHA KARUNYA R,

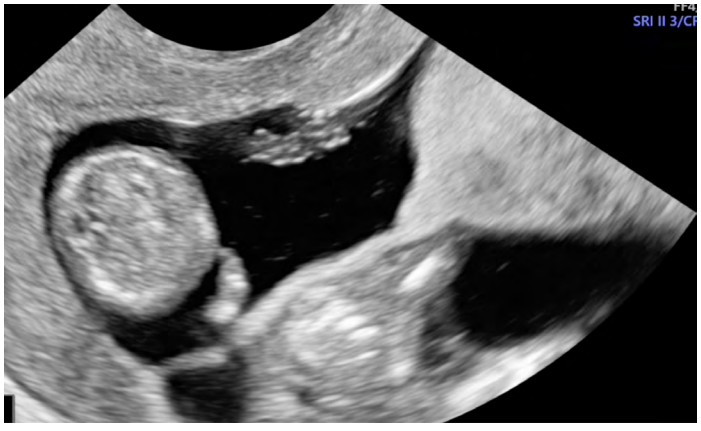
TRICHY FETAL MEDICINE CENTRE

HISTORY:

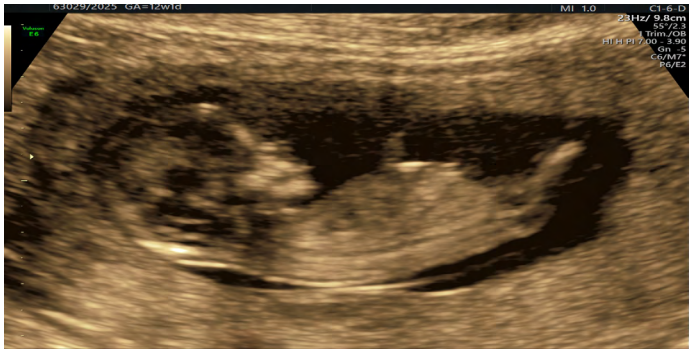
A 22 year old G2P0L0A1 (G1: 3 month amenorrhoea, missed abortion; G2: PP), Hypothyroidism on medication, Non consanguineous marriage came for NT scan. Maternal baseline investigations were normal.

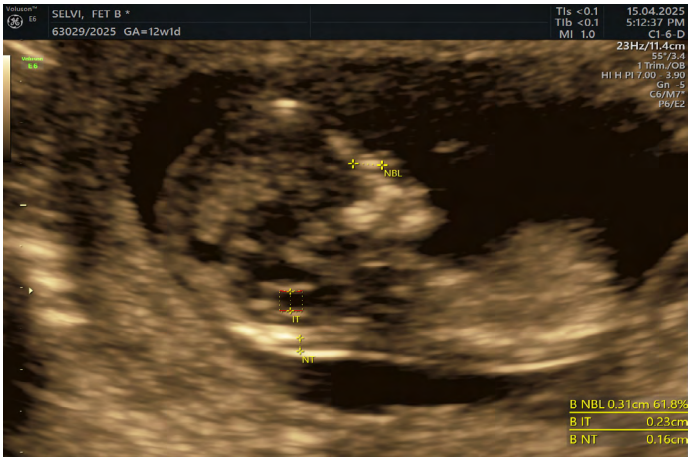
ULTRASOUND FINDINGS:

Lambda/ Twin peak sign seen, indicating it is case of Dichorionic Diamniotic pregnancy.



Fetus- B : Fetal pole and yolk sac seen with CRL of 66.4 mm (12- 13 weeks), Nuchal translucency measuring 1.6 mm and FHR : 165 bpm.

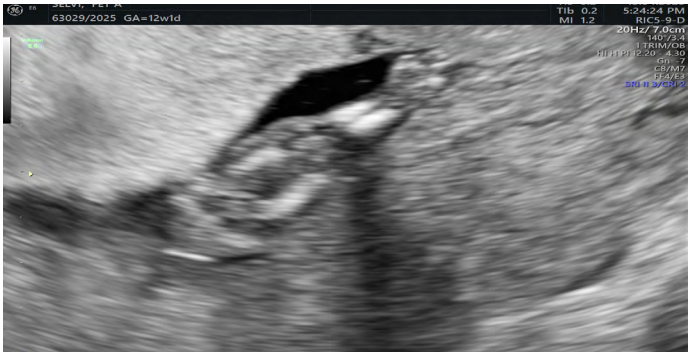


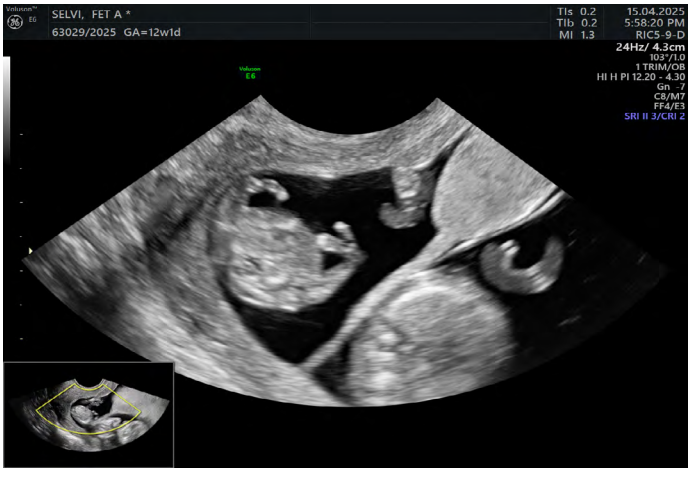


Fetus- A : Fetal pole and yolk sac seen with CRL of 52.8 mm (11- 12 weeks) and FHR : 176 bpm.

Fetus A showed complex anomalies.

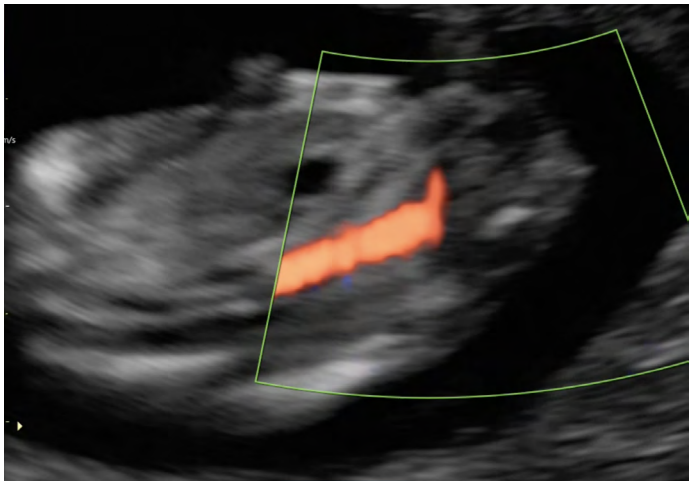
Sirenomelia (fused bilateral lower limb with presence of bilateral femur, tibia and fibula)





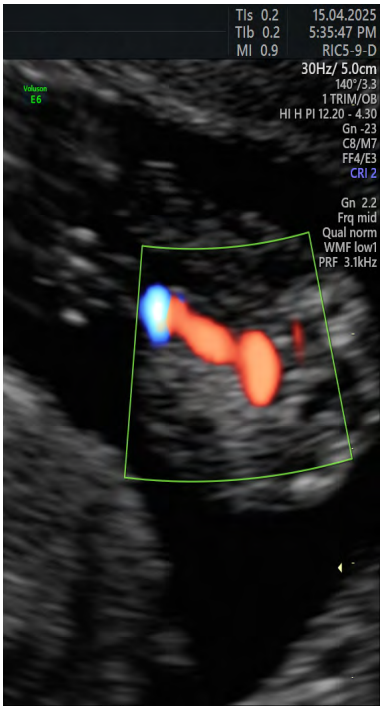
Upper limb phocomelia (Right upper limb - Radius, Ulna not seen, few limb buds seen; Left upper limb - Humerus, radius, Ulna not seen, ending as soft tissue stump).

Features of absent bilateral kidney (non visualization of both kidney in renal fossa/ pelvis & colour doppler showing absent bilateral renal artery)

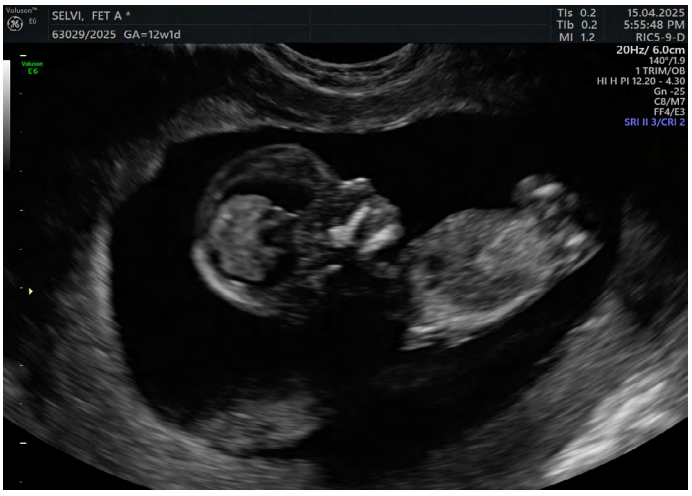


Non visualization of bladder.

Single umbilical artery.



Non visualization of nasal bone.



DIAGNOSIS:

This is a case of DCDA twin with Fetus A shows features of Stocker and Heifetz Type I - Sirenomelia, upper limb phocomelia, absent bilateral kidney, absent bladder and Single umbilical artery.

COUNSELLING

- Sirenomelia is a lethal anomaly and the need for selective feticide has been explained to the couple.
- Bilateral upper limb phocomelia appears to be sporadic in origin and may not be associated with vascular insult. The morbidities of the above condition has been explained . The need for limb prosthesis has been explained.
- Absent nasal bone is a marker of chromosomal abnormalities in particular, Trisomy 21. It is also seen in 5 - 10% of normal babies.
- Bilateral Renal agenesis - Chromosomal abnormality mainly trisomy 18 is seen in 1 -2% of cases. Associated syndromes may be seen in 10% of cases. Unilateral renal agenesis has a good prognosis with a small risk of vesico ureteric reflux.
- Genetic syndrome such as Robert's

syndrome, Grebe syndrome may be seen 30 - 40% of cases which is an autosomal recessive disorder.

RECOMMENDATIONS

- Early risk assessment for chromosomal abnormalities by Double marker test (Beta hCG and PAPP-A).
- Review with double marker test for 1st trimester combined test report.
- Selective feticide of fetus - A.
- Anomaly scan at 18 - 20 weeks and placental localization.

DISCUSSION

- Sirenomelia, also called mermaid syndrome, is a rare lethal multi-system congenital deformity.
- Incidence - 1 in 60,000–70,000 pregnancies
- Sirenomelia is characterized by various kinds of fusions of the lower extremities.
- Associated with dysgenesis or agenesis of the kidneys, ureters, and urinary bladder.
- In most cases, it is also associated with single umbilical arteries.
- The presence of a single umbilical artery derived from the vitelline artery is the main anatomical feature distinguishing sirenomelia from caudal regression syndrome.
- Because of the dysgenesis of the urinary system, sirenomelia is usually complicated by severe oligohydramnios in the second and third trimesters of gestation.
- Due to oligohydramnios it becomes very difficult in diagnosing sirenomelia in 2nd and 3rd trimester.

ETIOLOGY

The exact etiologies are unknown & Two chief pathogenetic hypotheses.

The possible mechanism is failure of separation of extremity bud from the primordial cells is due to a developmental anomaly in the veins feeding the lower extremities and an anomaly in mesodermal cell migration.

Another hypothesis - Abnormal vasculature pattern- Fetuses with sirenomelia exhibit a SUA with an abnormal origin, derived from the vitelline artery.

Below the origin of the SUA, the aorta becomes abnormally narrow and lacks a considerable number of branches that normally supply the kidneys, large intestine, and genitalia.

The blood is shunted away from the absent or hypoplastic arteries into the SUA, which diverts blood flow to the placenta, causing defects in circulation and nutrient supply to the lower limbs, leading to their arrested development.

RISK FACTORS

Maternal DM, teratogenic drugs, Heavy metal exposure, genetic susceptibility, vascular hypoperfusion, cocaine, landfill water, and maternal age < 20 years or > 40 years.

Sirenomelia is more common in monozygotic twins and males.

STOKER & HEIFETZ CLASSIFICATION

	Classification
Type I	All thigh and leg bones are present
Type II	Single fibula
Type III	Absent fibula
Type IV	Partially fused femurs, fused fibulae
Type V	Partially fused femurs
Type VI	Single femur, single tibia
Type VII	Single femur, absent tibia

MANAGEMENT

Sirenomelia is lethal anomaly - termination of pregnancy.

PROGNOSIS:

Guarded prognosis.

ASSOCIATION WITH ANEUPLOIDY/ SYNDROMES.

Caudal dysgenesis (CD) and VACTERL (vertebral defects, anal atresia, cardiac abnormalities, tracheoesophageal fistula with esophageal atresia, renal and limb abnormalities).

CONCLUSION

The roles of maternal diabetes, exposure to heavy metals, and maternal age have been acknowledged in the incidence of sirenomelia and have been described as important environmental risk factors.

Given its sporadic nature in humans, it is possible that sirenomelia occurs due to an autosomal-dominant genetic background; however, it is more likely that a combination of genetic and environmental components are responsible.

Since it is a lethal anomaly with association with other anomalies and syndrome, the guarded prognosis is explained to the couple and option of termination should be given.

REFERENCE

1. Tamene A, Molla M. Sirenomelia: A case report. SAGE Open Medical Case Reports. 2022 Apr;10:2050313X221092560.
2. Yoshida A, Okumura A, Nakao M, Suzuki R. A case of type I sirenomelia complicated by severe oligohydramnios in the first trimester. Case Reports in Obstetrics and Gynecology. 2019;2019(1):4564260.
3. Shojaee A, Ronnasian F, Behnam M, Salehi M. Sirenomelia: two case reports. Journal of medical case reports. 2021 Apr 26;15(1):217.
4. Russo A, Reginelli A, Pignatiello M, Montella M, Toni G, Cappabianca S, Grassi R. Sirenomelia: The role of post-mortem diagnostic imaging. Journal of Pediatric Surgery Case Reports. 2021 Aug 1;71:101921.

TAKING CARE OF ART CONCEPTION IN EARLY PREGNANCY

DR. UMA VELMURUGAN MD,FRCOG (UK), CCT (UK)., FELLOWSHIP IN FERTILITY (BIRMINGHAM, UK)

DR. LAVANYA DGO, DNB (OG), FICOG

LEARNING OBJECTIVES

To understand the maternal complications associated with ART, including ovarian hyperstimulation syndrome, miscarriage, ectopic pregnancy, multiple pregnancies, pregnancy-induced hypertension, pre-eclampsia, gestational diabetes and venous thromboembolism in the first trimester

To understand the fetal complications associated with ART, including genetic and chromosomal disorders, structural abnormalities and their screening in first trimester.

To establish an evidence-based approach to the antenatal management of pregnancies conceived using ART.

INTRODUCTION:

Use of ART to acheive conception is increasing worldwide. 1–5% of the babies born in developed countries have been conceived through IVF.

All pregnancies following IVF are HIGH RISK, especially because of age.

Assisted conceptions are at increased risk of maternal and fetal complications, but it is not clear whether this is a consequence of the ART procedures, or of the innate characteristics of the women who undertake them.

Healthcare professionals involved in the antenatal management of pregnancies conceived using ART must understand the potential risks and how best to manage them.

EARLY PREGNANCY COMPLICATIONS

Gestoses is the fuctional multiorgan systemic complication of pregnancy connected with the development of fertilised ovum.Gestoses is the result of advanced age ,chronic hypertension ,Diabetes and antiphospholipid antibody syndrome,Obesity,multifetal gestation,etc. Gestoses is more commomon in ART conceptions. Miscarriage and ectopic pregnancy are common complications of early pregnancy. Although not unique to assisted conceptions, these diagnoses often come as a shock to women undergoing treatment and her family. Psychological sequelae can therefore be profound.Ovarian hyperstimulation syndrome (OHSS) is unique to fertility treatment. All women, and particularly those at increased risk, should be counselled about this condition both before consent to treatment is given and before treatment is provided or continued.

OVARIAN HYPERSTIMULATION SYNDROME

Following conventional IVF, mild OHSS has been estimated to affect around one-third of cycles, while the combined incidence of moderate or severe OHSS varies from 3.1% to 8.0%. In 2010, data from 25 European countries found the incidence of hospitalisation caused by OHSS to be 0.3%.

There is some evidence to suggest an increased risk of pregnancy-induced hypertension (PIH) and preterm labour (PTL) in pregnancies complicated by severe OHSS. Furthermore, OHSS is also a risk factor for venous thromboembolism (VTE), with the incidence of thrombosis estimated to lie between 0.7% and 10%. Thrombosis in women with OHSS frequently affects upper body sites and/or the arterial system, and women may present with symptoms several weeks after the apparent resolution of OHSS. Thromboprophylaxis is recommended for women with severe OHSS or other risk factors for VTE. If conception occurs, thromboprophylaxis should be continued until at least the end of the first trimester.

MISCARRIAGE

The miscarriage rate among pregnancies following ART is estimated to be approximately 15–20% and, like spontaneous conceptions, increases with increasing age. The specific cause of subfertility may also affect the miscarriage rate: women with, for example, certain congenital uterine anomalies, fibroids and some endocrine disorders, age over 40yrs,poor embryo quality,LPD have higher rates of miscarriage than do those without.Frozen cycle babies have less problems. USG evidence of pregnancy is essential to rule out biochemical pregnancy. The management of women with both sporadic and recurrent miscarriage in the ART population is no different to that of women in the general population.

SUBCLINICAL HYPOTHYROIDISM

Although the relationship between overt hypothyroidism and adverse pregnancy outcomes including miscarriage, pre-eclampsia, gestational diabetes mellitus (GDM), PTL and cognitive delay in children is well established, and the benefit of treatment with levothyroxine for such women is clear, the same is not true for subclinical hypothyroidism (SCH).

A recent meta-analysis incorporating 18 cohort studies found that pregnant women with untreated SCH are at increased risk of miscarriage, placental abruption, premature rupture of the membranes and neonatal death compared with euthyroid women.

Free T3 T4 TSH and TPOab testing should be offered to high risk women.

Current guidelines therefore recommend treatment with levothyroxine in pregnant women with SCH.

ECTOPIC PREGNANCY

This risk of an ectopic pregnancy following ART is approximately 1.4%.

Causes: Tubal factor infertility,use of assisted hatching,ICSI,fresh compared with frozen embryo transfers, multiple embryo transfers(>4 embryos),etc.Incidence is more with multiple transfers.

An early ultrasound scan should be done to confirm pregnancy location and viability. Heterotopic pregnancies are also more common following ART.Careful ultrasound examination of the adnexa is required, even in the presence of an intrauterine pregnancy. Management of ectopic pregnancies includes conservative, medical and surgical approaches.

For a tubal ectopic pregnancy in women with a history of fertility-reducing factors, salpingostomy should usually be considered (because of the

higher subsequent intrauterine pregnancy rates observed). In women who are reliant on ART to conceive, however, the fallopian tubes are redundant. Therefore, a salpingectomy may actually be preferential (depending on the cause of subfertility) because it eliminates the possibility of a subsequent ectopic pregnancy on that side without compromising fertility.

MULTIPLE PREGNANCY

Multiple pregnancy is the most powerful predictive factor for adverse obstetrical outcome. Couples should be thoroughly counselled about the adverse outcomes.Incidence in ART is 1 in 50.IVF increases the risk of monozygous twins by 2 fold compared with natural conception.

Prevention : single embryo or 2 embryo transfer.Multifetal reduction is the option for higher order pregnancies.

HYPEREMESIS GRAVIDARUM

Advanced maternal age,medical disorders like hypothyroidism,supportive medications,psychological anxiety,etc are some of the causes.

Treat it as in any pregnant women.

MATERNAL COMPLICATIONS

Pregnancies resulting from ART may have increased risks for maternal medical complications, especially PIH, pre-eclampsia, GDM and VTE. These risks largely arise owing to the characteristics of those undergoing ART and are most marked in older women (aged >35 years), women with a high body mass index (BMI; >30 kg/m^2) or polycystic ovary syndrome (PCOS) and in multiple pregnancies, as well as pregnancies that are created from oocyte, sperm or embryo donation.

PREGNANCY-INDUCED HYPERTENSION AND PRE-ECLAMPSIA

According to a systematic review and meta-analysis incorporating 15 cohort studies, women who become pregnant as a consequence of ART are more likely to develop PIH and pre-eclampsia than those with a spontaneous conception.Women who become pregnant as a consequence of oocyte donation appear to be at slightly greater risk of PIH than women undergoing ART using autologous oocytes.

Women who become pregnant as a consequence of ART should, like all women, have a risk assessment at booking.(Gestosis scoring) Those considered to be at high risk of PIH or pre-eclampsia should be offered low-dose aspirin (150mg) from 12 weeks of gestation until delivery.

Women considered to be at high risk of pre-eclampsia include those with one major risk factor or more than one moderate risk factor. Major risk factors are hypertensive disease during a previous pregnancy, chronic kidney disease, autoimmune diseases, diabetes and chronic hypertension. Moderate risk factors include first pregnancy, maternal age ≥40 years, pregnancy interval >10 years, BMI >35 kg/m^2, family history of pre-eclampsia and multiple pregnancy.

Women with any of these risk factors, irrespective of whether they meet their criteria for prophylaxis, should also have a plan for closer maternal and fetal surveillance.

GESTATIONAL DIABETES MELLITUS

Due to the advanced age of ART women pre existing Diabetes is common and the need for shiftting from OHAs to Insulin is essential once pregnancy is confirmed.The prevalence of GDM is twice as high among women with PCOS than among women without.

All ART conceptions should be offered GCT or GTT in the first trimester.Patients who were on metformin for PCOS should continue it even with normal sugars until fetal cardiac activity is confirmed.

VENOUS THROMBOEMBOLISM

ART has been shown to double the risk of VTE during pregnancy. The risk is particularly great in the first trimester (when is is approximately four-fold). Unlike PIH, pre-eclampsia and GDM, ART is itself considered to be a risk factor for developing VTE in pregnancy. In the absence of any other risk factors, however, prophylactic anticoagulation with low molecular weight heparin is not required. Prophylaxis is recommended from the first trimester onwards if ther are an additional three risk factors and from 28 weeks of gestation onwards if there are an additional two risk factors. Additional risk factors include BMI >30 kg/m^2, age >35 years, parity ≥3, smoking, gross varicose veins, immobility, family history of unprovoked or estrogen-provoked VTE in a first-degree relative, low-risk thrombophilia and multiple pregnancy. Temporary factors including OHSS, hyperemesis, dehydration, surgery, systemic infection, immobility and long-distance travel also increase the risk of VTE and should prompt initiation of thromboprophylaxis till the risk period is crossed.

FETAL COMPLICATIONS

While some complications are more common in fetuses arising as a consequence of ART, it is not known whether this is because of the ART procedure itself, the underlying subfertility, the increased incidence of multiple pregnancies, advanced maternal age or poor gamete quality.

FETAL GENETIC AND CHROMOSOMAL DISORDERS AND STRUCTURAL ABNORMALITIES

Some studies report a significantly increased rate of structural abnormalities (including anorectal malformations, congenital cardiac lesions, and nervous system and genital structural abnormalities) in the assisted conception.Congenital abnormalities are more common in children conceived following intracytoplasmic sperm injection than standard IVF.

The risk of unrecognized chromosomal abnormalities is higher in those requiring ART than in the general population. In oligozoospermic men, the incidence of autosomal translocations or inversions is 4.6–13.7%_and the incidence of microdeletions of the Y chromosome is 5—15%. Subtle Y chromosomal genetic defects are associated with minor anomalies of the male genitalia, including hypospadias. Women who require ART may be seven times more likely to have reciprocal balanced translocations than are those who do not.Rarely there's excess of fetal imprinting disorders such as Angelman and Beckwith–Weidermann syndromes following ART.

SCREENING TESTS

Women with assisted conceptions should be offered antenatal screening such as the first trimester combined test (nuchal translucency and maternal serum biochemistry). However, numerous studies have demonstrated that ART is associated with changes in biochemical serum screening markers, such as pregnancy-associated plasma protein A and human chorionic gonadotrophin. A few studies (although not the majority) have even shown that nuchal translucency measurements may also be affected by the type of conception. It is also worth remembering that if donor eggs are used, the age of the donor should be used to calculate the a priori age-related risk, not the age of the woman undergoing treatment.Pregnancies conceived using ART have low levels of PAPP-A leading to a high rate of false positive results in 1st trimester screening for Downs syndrome.

Furthermore, screening tests rely on an accurate gestational age to interpret the results of the nuchal translucency and maternal serology. Therefore, it is important that the estimated date of delivery is calculated from the date of oocyte retrieval and not the measured crown–rump length. The use of cell-free fetal DNA (from maternal plasma) as a 'non-invasive prenatal test' to screen pregnancies for trisomies 13, 18 and 21

is becoming increasingly available. This test is extremely accurate.

Prevention : proper genetic counselling, karyotyping of male partners before ICSI for severe oligoasthenozoospermia,cystic fibrosis testing in both partners before ICSI in CAVD,PGD in some patients.

PLACENTAL COMPLICATIONS

A recent systematic review and meta-analysis concluded that singleton pregnancies conceived using ART are associated with a significantly higher risk of placental anomalies, including placenta praevia (OR 3.76, 95% CI 3.09–4.59), morbidly adherent placenta (OR 2.27, 95% CI 1.79–2.87) and placental abruption (OR 1.87, 95% CI 1.70–2.06), compared with spontaneously conceived pregnancies.

Compared with spontaneous conceptions, there is a higher incidence of placenta praevia in assisted conceptions,particularly those that have involved the transfer of a blastocyst rather than cleavage stage embryo. Placenta previa could also be a consequence of an underlying maternal structural complication such as Asherman's syndrome,adenomyosis,hysterotomy,myomectomy and repeated abortions. Assisted conceptions occurring following transfer of a fresh embryo rather than cryopreserved embryo are more likely to be complicated by placenta praevia.

PHARMACOLOGICAL TREATMENTS

Folic acid 5mg once a day just like all normal pregnancies.

Metformin should be continued in the PCOS patients.

Aspirin should be given to patients with Hypertension and Antiphospholipid antibody syndromes.Its given as a prophylactic drug to prevent preeclampsia in high risk patients.

Progesterone should be continued in ART conceptions with Luteal phase defect,agonist protocols,etc.It can be given as vaginal capsules or oranl tablets(dydrogetrone) or intramuscular injections.

Antiemetics as necessary.

PSYCHOSOCIAL CARE AND COUNSELLING

A guideline from ESHRE provided information for all clinic staff(eg.,doctors,nurses,counsellors,etc) on when they should refer patients for additional psychosocial care after a successful pregnancy with ART treatment.

The levels of anxiety and depression ,which are both key indicators of psychological health,were highest during the first trimester.The couple are worried about the complications in pregnancy to the fetus and mother.Individualised care is essential to support the pregnant women and their partner.They should be allowed to discuss their worries.

Tender loving care & reassurance are crucial from the health care workers.

CONCLUSION

While most assisted conceptions have a normal course, not all do. The elective transfer of a single embryo reduces many risks, but even singleton pregnancies resulting from ART are at increased risk of some maternal and fetal complications. An awareness of these risks is mostly all that is required, and assisted conceptions should be managed in the same way as spontaneous pregnancies. A thorough risk assessment immediately after conception is imperative, since many women undergoing ART have additional risk factors that necessitate increased monitoring.

UTI IN PREGNANCY

DR.AKILA.V M.D(OG).,

DR.S.CHITRA MD,DGO.,

Urinary tract infection (UTI) is very common among women due to the anatomy of the reproductive system. It is the most common bacterial infection during pregnancy. About 15% of women will have at least one episode of UTI in their life time[1].The incidence of UTI in pregnancy is about 8%[1,2]. UTI is defined (classified) "as either lower tract (acute cystitis) or upper tract (pyelonephritis) infection." When there is growth of organism >10^5 then it is UTI." It is grouped into 2 categories as asymptomatic and symptomatic bacteriuria[3,4].

PATHOPHYSIOLOGY:

During pregnancy, urinary tract changes predispose women to infection. Urethral dilation is seen due to compression of the ureter by the gravid uterus. Hormonal effects of progesterone also may cause smooth muscle relaxation leading to urethral dilation and urinary stasis, and vesicoureteral reflux increases. Decreased bladder capacity commonly results in urinary frequency. All these factors predispose to UTI. Pregnancy is a state of relative immune compromise, this might be another cause for the increased frequency of UTIs seen in pregnancy.

EPIDEMIOLOGY:

E.COLI is the commonest bacteria associated in UTI it contributes to about 90% of the cases[1]. Other organisms like proteus mirabilis, Klebsiella pneumoniae, Gram positive organisms, Group B streptococcus, staphylococcus is also seen.[1,5]

Risk factors for UTI during pregnancy are low socio-economic status, sexually active, multiparity, anatomical tract abnormalities sickle cell anaemia and diabetes are some of them. History of pre-pregnancy UTI is a strong predictor of pyelonephritis after 20 weeks of gestation.

SCREENING:

All pregnant women should be screened for UTI. Urine c/s is sent at their first Antenatal Check-up. Mid stream urine should be collected after proper washing of the urethral meatus and labia should be separated. In early routine mid stream urine culture to screen for ASB is grade A recommendation by RCOG. Follow up cultures are recommended.

ASYMPTOMATIC BACTERIURIA (ASB):

When there is a "significant bacteriuria (10^5 colony forming unit) in urine culture without any symptoms, it is known as asymptomatic bacteriuria[1,2"]. It can be present even before pregnancy. The incidence of ASB in non-pregnant women is 5%-6%. Asymptomatic bacteriuria is prevalent in about 10% of pregnant patients. If untreated it can lead to both maternal and foetal complications. Maternal complication are Hypertension, Pre-eclampsia, Anaemia, Cystitis and Pyelonephritis. foetal complications are foetal growth restriction, low birth weight and premature rupture of membranes PROM[3,5,6].

TABLE 1:

COMPLICATIONS ASSOCIATED WITH UTI IN PREGNANCY

MATERNAL	FETAL
Anemia	FGR
Pre-Eclampsia	Low Birth Weight
Hyper Tension	Pre-Maturity
Cystitis	PPROM
Pyelonephritis	IUD

ACUTE CYSTITIS:

Usually present with symptoms like dysuria, urgency and increased frequency of micturition without any systemic illness. About 30% of untreated asymptomatic bacteriuria patient develop acute cystitis.

PYELONEPHRITIS:

Incidence is about 2%. They usual present with signs and symptoms like fever, chills, nausea, vomiting and flank pain. Parenteral antibiotic is required. Pyelonephritis is the commonest non obstetric cause of hospitalisation.[3]

Group B Streptococcus infection

About 5% of UTI patients are infected with GBS. It is associated with premature rupture of membranes, preterm labour, neonatal sepsis and congenital pneumonia.

TREATMENT:

Asymptomatic Bacteriuria / cystitis

Treated with oral antibiotics. Long course is more effective than a single dose of Fosfomycin. First line of choices are 1.Nitrofurantoin 100mg bd for 5-7 days (Avoided at term because it has a potential risk of haemolysis if the foetus has G6PD -Deficiency), Cephalexin 500 bd for 5-7 days. Second line of drugs are cefuroxime 250-500mg bd for 5 -7 days, Trimethoprim Sulfamethoxazole 160mg 5-7 days(to be avoided in early pregnancy and at term)[7].

PYELONEPHRITIS

Intravenous antibiotic is usually given till patient becomes afebrile for 48 hrs.

Choice of drug is ceftriaxone 2g iv, cefepime 1g, gentamycin and ampicillin can be given for 10 to 14 days[8].

Group B Streptococcus infection

Usually treated with IV.Antibiotic.Amoxicillin 500 (Tid) or penicillin VK 500 (Qid) can be given orally.

TABLE 2:

TREATMENT FOR UTI IN PREGNANCY

ASYMPTOMATIC BACTERIURIA AND CYSTITIS

FIRST LINE	NITROFURANTOIN 100MG PO BID FOR 5-7 DAYS (TO BE AVOID NEAR TERM)	CEPHALEXIN 500MG PO QID FOR 5 TO 7 DAYS.
SECOND LINE:	CEFUROXIME 250-500MG PO BID FOR 5 TO 7 DAYS	TRIMETOPRIN SULPHA METHAZOLE 1 DS PO (BID) x 5 - 7 DAYS (AVOID IN THE 1ST & 3RD TRIMESTER)
Pyelonephritis	IV THERAPY IS REQUIRED TILL AFEBRILE	
Mild Cases	Ceftriaxone 1-2g every 6 hrs Cefepime 1g every 12 hrs Ampicillin 1-2 g every 6hrs Gentamycin 1.5mg/kg every 8 hrs	

UTI in pregnancy can be devastating, it can cause both maternal and neonatal complication. About 30% of untreated asymptomatic bacteriuria patient develop cystitis and 50% leads to pyelonephritis. All pregnant mothers should be screened for UTI and treated. If untreated it can lead to Foetal growth restriction, pre term labour low birth weight, gestational hypertension and anaemia.

References:

1. Delzell JE, Lefevre ML. Urinary tract infections during pregnancy. Delzell JE, Lefevre ML. Urinary tract infections during pregnancy. A.M Fam Physician. 2000;61(3):713-21
2. Orenstein R, Wong ES, Urinary tract infection in adults.AM Fam physician. 1999;59(5):1225-37.
3. Schnarr J, Smaill F. Asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. Eur J Clin Invest.2008;38 Suppl2;50-7
4. Alemu A , Moges F, Shiferaw Y, Tafees K, Kassu A, Anagaw B,et al.bacterial profile and drug susceptibility pattern of urinary tract infection in pregnant women at university of Gondar teaching hospital, northwest Ethiopia. BMC Rec notes 2012;5:197.
5. Fitzgerald MA, Urinary tract infection: providing the best care. Medscape 2002.
6. Romero R, Oyarzun E, Mazor M, et al. M eta analysis of relationship between asymptomatic bacteriuria and preterm delivery/low birth weight. Obstet. Gynecol.1989;73(4);576-82.
7. Antimicrobial Stewardship Program, Jul.3, 2019.
8. FOGSI FOCUS 2017
   - 1.Delzell JE, Lefevre ML. Urinary tract infections during pregnancy.
   - 8.Bachman JW, Heise RH, Naessens JM, et al. A study of various
   - tests to detect asymptomatic urinary tract infections in an obstetric
   - population. JAMA. 1993;270(16):1971-4 [PubMed]
   - 9.McGladdery SL, Aparicio S, Verrier-Jones K, Roberts R. Outcome
   - of pregnancy in an Oxford-Cardiff cohort of women with previous
   - bacteriuria. QJM. 1992;83(303):533-9 [PubMed]
   - 10.Uncu Y, Uncu G, Esmer A, Bilgel N. Should asymptomatic
   - bacteriuria be screened in pregnancy? Clin Exp Obstet Gynecol.
   - 2002;29(4):281-5 [PubMed]

MTP IN FIRST TRIMESTER

DR.SHILPA GANDHI. M.S (OG),

DR.ABIRAMI KARPAGAM M.D(OG)

INTRODUCTION:

First trimester pregnancy loss is most commonly defined as the loss of a pregnancy within 14 weeks of gestation. Globally 30 percent[1] of all pregnancies end in abortion out of which majority occur even before they are recognized. Global estimates demonstrate that 45% of all abortions are unsafe. In India it accounts to 8% of MMR[2]. Abortion using medication or a simple outpatient surgical procedure is a safe health-care intervention when carried out with a method appropriate to the gestational age and by someone with the necessary skills. Having a clear understanding of the national laws and regulations relating to abortion is crucial to maintain quality abortion services.

Medical abortion has revolutionized the access to quality of abortion care globally as compared with uterine aspiration due to improved access to medical abortion methods with eventually minimal complications. It can be safely and effectively self - administered outside a medical facility (e.g. at home) by a trained health worker in the first 12 weeks of gestation. It improves privacy, convenience and acceptability without compromising safety and effectiveness.

MTP ACT AMENDMENTS 2021 (INDIA):

Act expands access to safe and legal abortion services on therapeutic, eugenic, humanitarian and social grounds to ensure universal access to comprehensive care.

Abortion to be available on the request of the woman without the authorization of any other individual, body or institution irrespective of marital status [1].

Gestational age limit is up to 24 weeks for rape survivors and beyond 24 weeks for fetal abnormalities.

One registered medical practitioner (RMP) opinion is sufficient up to 20 weeks, two RMP's for 20-24 weeks and medical board approval after 24 weeks. For rape survivors beyond 24 weeks the only recourse remains through a WRIT petition.

Any hospital established or maintained by government or a place approved for this act can perform MTP.

MTP census registers to be maintained and reported monthly to the government health authorities.

Women's confidentiality to be maintained. If breached, can be subjected to fine or imprisonment for 1 year. Confidentiality meaning the identity document (name, address) to be maintained confidentially by the hospital, not to be disclosed in any records like case sheets, censor register or MTP registers. Can be revealed only to authorized persons in any law that is currently in force.

COUNSELLING AND CONSENT:

Maintaining confidentiality, encouraging women contemplating abortion to seek care as early as possible, by supporting women to deal with non-medical aspects such as decision making, relationships with family, possible social consequences and psychological aspects

encourages women to have quality abortion care.

Proper counseling should be done on pre abortion assessment, approved medical and surgical methods of termination, the risks and probable complications, follow up and contraception.

Informed consent is documented, including consent for uterine aspiration in the setting of continued pregnancy or symptomatic retained tissue following administration of the medication abortion.

Patients should be counseled on failure rates following medical abortion which increases as gestational age approaches 10 weeks.

CLINICAL ASPECTS:

Clinical assessment is critical to avoid complications while providing abortion services. The assessment helps to identify the woman who needs referral for the procedure at a higher level of facility, which is better equipped and can handle complications, if any.

past and present medical and surgical conditions, contraceptive history, status of tetanus immunization, if any sexual or domestic violence, previous female genital mutilation.

Psychosocial assessment to be done to assess family support.

Clinical condition should be assessed by general physical examination. Bimanual pelvic examination should be done to assess the uterine size, adnexal masses and tenderness that may indicate ectopic pregnancy or rupture. Speculum examination can be diagnostic if the products of conception are visible in the cervical os or vaginal vault.

LABORATORY TESTING[15]:

NOT A PREREQUISITE FOR ABORTION.

- A pregnancy test is required if the pregnancy is uncertain.
- Hematocrit.
- ABO-Rh testing is recommended in patients with unknown Rh status.
- HIV test, other tests for sexually transmitted infections or tests related to specific individual health problems may be needed.
- Cervical cultures to be taken as per local protocols, or if signs of vaginal / cervical infection are present.
- Screening for cervical cancer can be done if facilities exist.
- An ultrasound may be helpful for accurate dating when there is a discrepancy in the size of the uterus by LMP and bimanual examination. It is not a mandatory requirement. It can also be used to detect ectopic pregnancies along with quantitative βHCG measurements[2].

MEDICAL ABORTION:

INDICATED UP TO 9 WEEKS[2] OF GESTATION BEYOND WHICH MAY RESULT IN LOWER EFFICACY AND MORE SIGNIFICANT BLEEDING AND CRAMPING.

The medical abortion regimen supported by major medical organizations nationally and internationally includes two medications mifepristone and misoprostol.

MECHANISM OF ACTION:

Mifepristone is a derivative of norethindrone with antiprogestin action. It binds to progesterone receptors in the endometrium resulting in decidual necrosis and detachment of the products of conception. It also softens the cervix, causes mild uterine contractions and sensitizes the uterus to the effect of prostaglandin.

Misoprostol is a prostaglandin E1 analogue

which causes strong myometrial contractions, cervical softening and dilatation. This leads to the expulsion of conceptus from the uterus. It is stable at room temperature and well absorbed from the gastro- intestinal tract and vaginal mucosa. Being selective for PGE1 receptors, there are no significant effects on bronchi and blood vessels, minimising its side-effects, as compared to other prostaglandins. Sublingual route is the most recommended route as it has the fastest onset of action and prolonged action. Buccal, vaginal and oral route can also be used out of which oral route is least recommended as its lesser duration of action,

SAFETY AND EFFICACY:

The combination of mifepristone and misoprostol have higher rates of successful abortion (> 96%) than misoprostol alone. Factors associated with decreased efficacy include increased gestational age, increased parity, and prior abortion [8].

TERATOGENECITY:

No evidence exists to date on teratogenic effect of mifepristone. However, misoprostol can result in congenital anomalies such as limb defects with or with - out Mobius' syndrome (ie, facial paralysis) when used during the first trimester

CONDITIONS IN WHICH MEDICAL ABORTION IS PREFERRED OVER SURGICAL ABORTION:

- Uterine fibroids that significantly distort the cervical canal or uterine cavity and uterine malformations.
- Previous cervical surgery, Introital scarring related to infibulation.
- Patients with asthma are candidates for medication abortion because misoprostol does not cause bronchoconstriction and actually acts as a weak bronchodilator.

CONTRAINDICATIONS:

Known allergy to mifepristone, misoprostol or other prostaglandins.

Mifepristone is a glucocorticoid receptor antagonist and is therefore contraindicated in patients with chronic adrenal failure or who are on concurrent long-term corticosteroid therapy and is also contraindicated in patients with porphyria's as it is porphyrinogen [3].

Anemia or anticoagulation therapy: Due to risk of heavy bleeding at home, patients with known anemia (typically with hemoglobin levels below 8.0 g/dL)[2], bleeding diathesis or on anticoagulant therapy may be directed toward uterine aspiration, particularly at a gestational age later in the first trimester.

Confirmed or suspected ectopic pregnancy and undiagnosed adnexal mass.

Also contraindicated in patients with glaucoma.

Precautions:

Patients with significant comorbidities may still have a medical abortion with close monitoring during the process depending on the stability of the conditions.

If intrauterine device in place it has to be removed before administering mifepristone.

Pregnancy Women with symptomatic large fibroids encroaching on endometrial cavity can have heavy bleeding and fibroids may interfere with the uterine contractility

Use of anti-tubercular drugs may decrease the efficacy of drugs.

PROTOCOLS FOR MIFEPRISTONE AND MISOPROSTOL[1]:

COMBINATION REGIMEN [1]

Mifepristone – 200 mg orally, followed by 800

µg misoprostol 24 to 48 hrs later buccally, vaginally or sublingually.

MISOPROSTOL ONLY REGIMEN:

800 µg misoprostol administered buccally, vaginally or sublingually.

Rarely, patients will experience bleeding or cramping during the 24 to 48 hours after taking mifepristone but before the misoprostol dose. In such cases the patient should still take the misoprostol since mifepristone alone is not highly effective unless expulsion is confirmed.

ADDITIONAL DOSE INDICATIONS:

For patients at 9+0 to 11+0 weeks dose repeated 3 to 6 hours after the first dose to decrease the risk of ongoing pregnancy [5].

If the woman vomits within half-an-hour of the intake of oral misoprostol.

If there is no vaginal bleeding even after 24 hours of misoprostol administration or if excessive bleeding during the abortion process.

ADJUNCT MEDICATIONS:

PROPHYLACTIC ANTIBIOTICS:

The routine use of prophylactic antibiotics is not recommended[1].While fever is common, the incidence of infection is low (0.9 %) as medication abortion does not involve instrumentation of the uterus [9].except in cases of Women with vaginal infections ..

Antibiotics recommended in patients with vaginal infection are Doxycycline 100mg, twice a day for seven days for non-lactating women, and Azithromycin 500mg once a day for three days or Ampicillin 500mg TDS for five days for lactating women.

ABDOMINAL PAIN AND ANALGESICS:

Abdominal pain is experienced by nearly all patients undergoing medication abortion... The pain is usually self-limited and typically is most severe shortly after misoprostol is taken until the expulsion of the pregnancy. If pain is unrelieved with analgesics or if there is increase in severity after the bleeding has subsided, warrants evaluation for other causes, such as ectopic pregnancy, infection or incomplete abortion.

The commonly used drug for pain management is Ibuprofen 400mg. Paracetamol is not effective. for pain relief during the process of medical abortion.

SIDE EFFECTS:

The side-effects are related to the abortion process and the effects of drugs used.

Nausea, vomiting, diarrhoea. Pre-abortion counselling helps. Routine use of antiemetic / antidiarrheal is not necessary.

Fever or chills are usually short-lived and resolve spontaneously. If the temperature exceeds 100.4°F (38°C) or persists for several hours despite antipyretics, infection should be ruled out.

Headache, dizziness and fatigue are manged with non-narcotic analgesics and mild dizziness of is managed by hydration.

ALTERNATE REGIMEN:

Letrozole - a third-generation selective aromatase inhibitor 10 mg orally each day for 3 days followed by misoprostol 800 µg sublingually on the fourth day plus mifepristone or misoprostol alone regimens. However, there is no high-quality evidence supporting this regimen [1].

COMPLICATIONS AND MANAGEMENT:

First-trimester medication abortion is a safe procedure and major adverse events are uncommon with emergency department treatment or hospital admission in 0.1 and 0.06 percent of patients, respectively [10].

VAGINAL BLEEDING:

Is moderate to heavy when compared to regular menses within first few hours and days after misoprostol administration and with the expulsion of pregnancy tissues. Persistent Bleeding after passing of pregnancy tissue, soaking more than two maxi pads per hour for two consecutive hours or bleeding for more than two weeks have to be reported.

INCOMPLETE OR FAILED ABORTION:

This may be suspected if the patient has persistent abdominal pain or vaginal bleeding. Patient is stabilized and treated with Misoprostol 400mcg sublingual or 600mcg orally and if there is no decrease in the vaginal bleeding, uterus should be evacuated under antibiotic coverage[2].

DELAY IN ONSET OF NEXT MENSES:

There might be a delay in the following menstrual period. It can occur from 3-6 weeks after the abortion and is usually normal.

SURGICAL ABORTION:

INDICATIONS:

- Women's preference.
- Gestational age upto 12 weeks.
- Hydatidiform mole upto 12 weeks GA.
- Contraindications to medical abortion.

CONTRAINDICATIONS:

- Presence of acute cervical, vaginal or pelvic infection.
- Suspicion of uterine perforation.
- Suspicion of ectopic pregnancy.

PAIN MANAGEMENT:

At any gestational age pain control should be offered routinely. The routine use of general anesthesia is not required [1]. Available options are,

Oral: NSAIDS are preferred. Paracetamol (500-1000 mg), Ibuprofen (400-800 mg) can be given. Anxiolytics - Diazepam 5-10 mg orally.

Paracervical block: Lidocaine 1% without epinephrine, limited to 3.5 mg/kg body weight and to a maximum level of 20 ml.

IV analgesia: Fentanyl 0.05-0.06 mg plus midazolam 0.5-1 mg.

CERVICAL PRIMING:

Cervical priming makes aspiration or curettage easier and quicker and reducing the risk of cervical laceration and to a lesser degree the risk of uterine perforation. It is recommended when gestational age is beyond 12 to 14 weeks. Routine cervical priming remains controversial. Cervical priming can be done using medication, osmotic dilators or a combination of both.

RECOMMENDED REGIMENS [1]:

Mifepristone 200 mg orally 24-48 hrs. before the procedure or Misoprostol 400 mcg sublingual / vaginal / buccal dose 2-3 hrs. prior to the procedure.

OSMOTIC HYDROPHILIC DILATORS:

Laminaria tents are introduced into the cervical canal and the duration of the placement and the procedure should not be beyond two days. The sizes of the tents vary depending upon the gestational age.5-6 mm for 5-6 weeks,7 mm for 7-8 weeks, 7 - 10 mm for 9-10 weeks , 9-12 mm for 10-12 weeks.

METHODS OF SURGICAL ABORTION:

VACUUM ASPIRATION:

Vacuum aspiration is a very safe and effective procedure up to 12 weeks and can be extended till 14 weeks. The incidence of hemorrhage, pelvic infection, cervical injury and uterine perforation is lower than with dilatation and curettage with less dilatation needed. The costs of the procedure, the staff time and resources needed are lower. No operating theatre or general anesthesia is needed.

MANUAL VACUUM ASPIRATION:

This is used in primary health care facilities with no stable source for electricity.

This technique requires a single or double valve syringe: the vacuum (at least 55 mmhg) is generated by a 60 ml hand-held syringe which accommodates flexible plastic cannulas ranging from 4mm to at least 12 mm in diameter.

ELECTRIC VACUUM ASPIRATION:

This technique requires an electric pump. The technique is fundamentally the same as with manual vacuum aspiration.

DILATATION AND CURETTAGE:

It is less safe and more painful than aspiration.

The procedure involves dilating the cervix and scraping away the endometrium and the products of conception. Dilatation and curettage should never be performed forcefully. It must be performed under paracervical block or if needed with moderate sedation.

Post operative care:

Place the patient on bed rest until fully conscious. Monitor vital signs every 30 minutes or more often if needed. Observation is necessary over 45-90 minutes.

IMMEDIATE COMPLICATIONS:

HAEMORRHAGE:

To rule out Cervical trauma, retained products of conception or AV malformations (rare and can necessitate hysterectomy). To suspect uterine or cervical perforation if hemorrhage occurs after the evacuation is complete.

UTERINE PERFORATION:

Suspected if there is Sudden loss of resistance with the instrument in utero, Fat / omentum / bowel seen in the cannula or at the cervix, presence of signs of shock, Severe abdominal pain, Abdominal rigidity and distension. In such circumstance procedure is stopped and managed accordingly after stabilising the patient.

SHOCK.

In extreme cases patients may end up in hypovolaemic and septic shock as both immediate and delayed complication. Such cases warrant intensive care and management.

DELAYED COMPLICATION:

INFECTION:

Should be suspected in patients with persistent fever, chills, body aches, excessive or prolonged vaginal bleeding, persistent moderate to severe pelvic pain after expulsion of the pregnancy or a purulent vaginal discharge. Infection may include post abortal endometritis, Clostridial sepsis (rare). Treatment includes surgical debridement, removal of infected organs (e.g., hysterectomy) and broad spectrum antibiotics (Ampicillin/azithromycin 1g and metronidazole 400 gm to be started)[2].

INCOMPLETE ABORTION:

Suspected if there is Pallor, Excessive or prolonged vaginal bleeding ,fever or abdominal pain. Patient is stabilised and treated with tablet misoprostol 400mcg sublingual/or 600mcg orally and observed for decrease in the vaginal bleeding or uterus is evacuated by vacuum aspiration under antibiotic cover.

PLAN FOR CONTRACEPTION:

As ovulation can occur soon after medical abortion, contraception counselling to be done prior to the medication abortion procedure.

For those who choose to use barrier methods they are advised to use as soon as sexual activity is resumed.

For women choosing hormonal contraception it can be started on day 3 with the dose of misoprostol or within day 15 after confirmation of

a completed medical abortion. Following complete surgical abortion hormonal contraceptives to be started Immediately or within 7 days[2].

For those who choose to have an IUD inserted, IUD placement is suggested after success of the abortion procedure is determined.

Women desiring concurrent tubal ligation should be counselled for surgical abortion so that the two procedures can be combined. Alternatively, tubal ligation can be done after the next cycle following medical abortion if the woman so desires. Can be performed after a surgical abortion in the absence of any infection or severe blood loss, concurrently or up to seven days (both minilap and laparoscopic sterilization can be done)

Fertility-awareness-based (FAB) methods should only be started after abortion with caution. The use of calendar-based methods should be delayed.

IMPLICATIONS FOR FUTURE PREGNANCY:

First-trimester medical termination of pregnancy does not appear to be associated with an increased risk of adverse outcomes in subsequent pregnancies.

ANTI -D IMMUNOGLOBULIN:

For both medical and surgical abortion at < 12 weeks in Rh negative women 50- g of Rh-immunoglobulin is administered not later than 72 hours after the abortion[15]. This is not necessary before six weeks after last menstrual period. (WHO recommends against anti-D immunoglobulin administration for gestational age less than 12 weeks[1]).

FOLLOW UP:

Following uncomplicated surgical abortion or medical abortion there is no need for a routine follow-up visit. If medically indicated or preferred by the patient, follow-up evaluation can be performed by medical history, clinical examination, serum human chorionic gonadotropin (HCG) testing or ultrasonography.

If an ultrasound examination is performed, the sole purpose is to determine whether the gestational sac is present or absent. The measurement of endometrial thickness or other findings do not predict the need for subsequent uterine aspiration [13].

Pregnant women should be adequately informed about symptoms of ongoing pregnancy and other medical reasons to return for follow-up, such as prolonged heavy bleeding, absence of bleeding following medical abortion, if pain not relieved by medication or fever.

Follow up is advised in the absence of contraceptive counselling.

REFERENCES:

1. Who - abortion care guidelines 2022.
2. Comprehensive abortion care, training and service guidelines 2018, National health mission,
3. Cable EE, Pepe JA Donohue SE, et al. Effects of mifepristone (RU-486) on heme metabolism and cytochromes P-450 in cultured chick embryo liver cells, possible implications for acute porphyria. Eur J Biochem 1994;225:651.
4. Mifeprex (mifeprestone) information.US Food and drug administration.
5. Coyagi K, Krishna U, Ambardekar S, et al. Are two doses of misoprostol after mifepristone for early abortion better than one? BJOG 2007; 114:271
6. Bartley J, Brown A, Elton R, Baird DT. Double-blind randomized trial of mifepristone in combination with vaginal gemeprost or misoprostol for

induction of abortion up to 63 days gestation. Hum Reprod 2001; 16:2098

7. Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion: A Systematic Review. Obstet Gynecol 2015; 126:12.
8. Spitz IM, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. N Engl J Med 1998; 338:1241.
9. Shannon C, Brothers LP, Philip NM, Winikoff B. Infection after medical abortion: a review of the literature. Contraception 2004; 70:183.
10. Cleland K, Creinin MD, Nucatola D, et al. Significant adverse events and outcomes after medical abortion. Obstet Gynecol 2013; 121:166
11. Suhonen S, Tikka M, Kivinen S, Kauppila T. Pain during medical abortion: predicting factors from gynecologic history and medical staff evaluation of severity. Contraception 2011; 83:357.
12. Fischer M, Bhatnagar J, Guarner J, et al. Fatal toxic shock syndrome associated with Clostridium sordellii after medical abortion. N Engl J Med 2005; 353:2352
13. Bar-Hava I, Aschkenazi S, Orvieto R, et al. Spectrum of normal intrauterine cavity sonographic findings after first-trimester abortion. J Ultrasound Med 2001; 20:1277.
14. Schonberg D, Wang LF, Bennett AH, et al. The accuracy of using last menstrual period to determine gestational age for first trimester medication abortion: a systematic review. Contraception 2014; 90:480.

A CLINICAL RARITY: CASE REPORT OF UTERINE PECOMA

DR.C.LAVANYA D.G.O.,DNB.,FICOG.,

DR.A.PRIYA AARTHY M.S (OBG).,DNB.,

MALAR SPECIALITY HOSPITAL, BEEMA NAGAR, TIRUCHIRAPALLI

ABSTRACT

Perivascular epithelioid cell tumors (PEComas) are rare mesenchymal tumors that originate from perivascular epithelioid cells. After the peritoneum, the uterus is the second most commonly affected organ. These tumors demonstrate a female predominance and are genetically associated with mutations in the tuberous sclerosis complex (TSC) genes—TSC1 and TSC2. Most PEComas are benign, with patients typically having a favorable prognosis. Currently, surgery is the primary treatment, while adjuvant chemotherapy is reserved for malignant cases. Due to the rarity of this neoplasm, optimal diagnostic and management strategies are still evolving.

KEYWORDS:

Perivascular epithelioid cell tumors, uterus, malignant, rare case

INTRODUCTION

The World Health Organization (WHO) defines PEComas as "mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular epithelioid cells" [1]. These cells, known as PECs, were first described in 1943 by Apitz [2] as "abnormal myoblasts" in renal angiomyolipomas (AMLs). PECs co-express myogenic and melanocytic markers, such as HMB-45 and actin. Recent studies have identified recurrent chromosomal alterations in PECs. PEComas are often associated with tuberous sclerosis complex (TSC), an autosomal dominant disorder involving mutations in TSC1 (9q34) or TSC2 (16p13.3), which regulate the Rheb/mTOR/p70S6K signaling pathway [3].Histologically, PECs exhibit an epithelioid appearance with clear to granular cytoplasm, round to oval centrally located nuclei, and inconspicuous nucleoli. They typically have mild or absent atypia and are found in perivascular locations. Immunohistochemically, they express melanocytic (HMB45, HMSA-1, Melan-A/Mart1,MiTF) and myogenic (actin,desmin) markers, though vimentin expression is usually inconspicuous [4–6].Ultrastructural analysis reveals microfilament bundles with electron-dense condensations, numerous mitochondria, and membrane-bound dense granules.The first uterine PEComa was described by Pea et al. [7] as a polypoid neoplasm in the endometrium, showing features similar to clear cell sugar tumors (CCST) of the lung. PEComas associated with TSC tend to be more aggressive.

CASE PRESENTATION

A 37-year-old woman (P3L3, all vaginal deliveries) presented with menorrhagia for the past two cycles. She had no comorbidities, and her vital signs were stable. A routine pelvic ultrasound revealed a 5 cm fundal fibroid indenting the

endometrial cavity. As initial medical management for two months was unsuccessful, she underwent laparoscopic myomectomy with tubal sterilization. Postoperative recovery was uneventful, and she was discharged on day 3.

Histopathology revealed a lesion suspicious for PEComa: predominantly epithelioid cells in a collagenized stroma, with irregular vesicular nuclei and indistinct nucleoli (Figure 1). Tumor cells were seen surrounding vascular channels (Figure 2), with infiltrative margins.

Immunohistochemistry showed tumor cells positive for desmin, SMA, cathepsin K, focal HMB-45, and TFE3, and negative for CK (AE1/AE3).A contrast-enhanced CT of the abdomen showed an umbilical hernia, with no evidence of lymphadenopathy or metastasis. An oncological opinion was sought, and she underwent total abdominal hysterectomy with bilateral salpingectomy. Final histopathology showed no residual PEComa, with multiple small leiomyomas in the uterus and normal cervix and tubes. The postoperative course was uneventful, and the oncologist recommended quarterly follow-ups for the first year.

DISCUSSION

Uterine PEComas can be diagnosed based on histological and immunohistochemical features, although preoperative diagnosis remains challenging. Clinical symptoms are non-specific and include abnormal uterine bleeding, pelvic pain, mass, and presumed fibroids [8]. Rarely, presentations may involve uterine rupture or hemoperitoneum, especially during pregnancy. In a series of six uterine PEComas reported by Folpe et al. [9], two patients had metastases, and one died of the disease. Fadare et al. [10] described a case of uterine PEComa with intra-abdominal "PEComatosis" in a patient with TSC.

Surgical resection is the mainstay of treatment. Prognosis depends on tumor behavior and early diagnosis. Malignant uterine PEComas are rare and often confused with other mesenchymal tumors such as endometrial stromal sarcoma and leiomyosarcoma. Symptoms can include abnormal bleeding, abdominal pain, and palpable mass [11].

Malignant uterine PEComas can metastasize to the ovary (46.2%), pelvic lymph nodes (46.2%), lungs (30.8%), vagina (23.1%), and intestines (15.4%) [11].The role of hormones in PEComa pathogenesis remains unclear.

Folpe et al. [1] proposed the following classification for uterine PEComas:

Classification	Criteria
Benign	No worrisome features (Size<5 cm, noninfiltrative, non–high nuclear grade and cellularity, mitotic rate ≤1/ 50 HPF, no necrosis, no vascular invasion)
Uncertain malignant	1. Nuclear pleomorphism/ multinucleated giant cells only or 2. Size>5cm only
Potential malignant	Two or more worrisome features 1. Size>5 cm 2. Infiltrative 3. High nuclear grade and cellularity 4. Mitotic rate ≥1/50HPF 5. Necrosis 6. Vascular invasion

CONCLUSION

Preoperative diagnosis of PEComa remains difficult and must be differentiated from leiomyoma or leiomyosarcoma. Final diagnosis relies on histopathological and immune histochemical evaluation post-surgery. Surgery remains the cornerstone of treatment, with adjuvant therapy considered for high-risk cases. Due to the rarity of PEComa, conducting large therapeutic trials is challenging, underscoring the importance of case reports in guiding management.

FIGURE LEGENDS

FIGURE 1:

EPITHELIOID CELLS WITH CLEAR CYTOPLASM AND IRREGULAR VESICULAR NUCLEI.

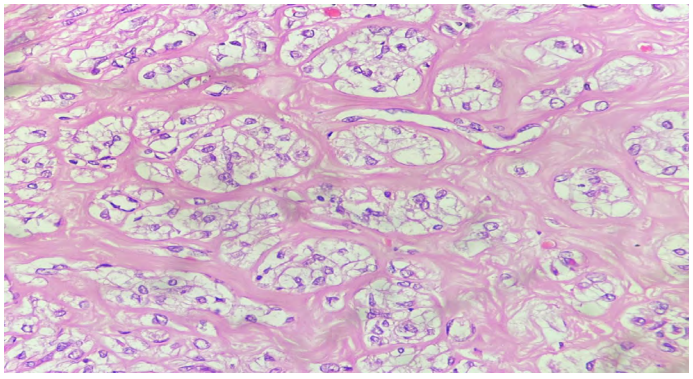
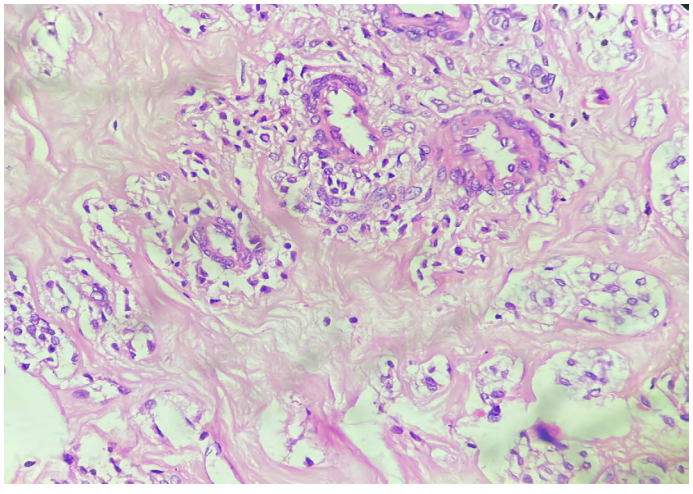


FIGURE 2:

TUMOR CELLS ARRANGED AROUND CAPILLARY VESSELS.



Reference:

1. Folpe AL (2002) Neoplasms with perivascular epithelioid celldifferentiation (PEComas). In: Fletcher CDM, Unni KK, EpsteinJ, Mertens F (eds) Pathology and genetics of tumours of soft tissue and bone. Series: WHO Classification of tumours. IARCPress, Lyon, pp 221–222
2. Apitz K (1943) Die Geschwülste und Gewebsmissbildungen derNierenrinde. II Midteilung. Die mesenchymalen Neubildungen.Virchows Arch 311:306–327
3. PEComas: the past, the present and the futureGuido Martignoni & Maurizio Pea & Daniela Reghellin &Giuseppe Zamboni & Franco BonettiReceived: 7 August 2007 / Accepted: 6 September 2007 / Published online: 14 December 2007# Springer-Verlag 2007 Virchows Arch (2008) 452:119–132DOI 10.1007/s00428-007-0509-1
4. Bonetti F, Pea M, Martignoni G, Zamboni G, Manfrin E,Colombari R, Mariuzzi GM (1997) The Perivascular EpithelioidCell and related lesions. Adv Anat Pathol 4:343–358
5. Jungbluth AA, Busam KJ, Gerald WL et al (1998) A103: ananti-melan-a monoclonal antibody for the detection of malignantmelanoma in paraffin-embedded tissues. Am J Surg Pathol22:595–602
6. Zavala-Pompa A, Folpe AL, Jimenez RE, Lim SD, Cohen C, EbleJN, Amin MB (2001) Immunohistochemical study of microophtalmiatranscription factor and tyrosinase in angiomyolipomaof the kidney, renal cell carcinoma, and renal and retroperitonealsarcomas:

comparative evaluation with traditional diagnosticmarkers. Am J Surg Pathol 25:65–70

7. Pea M, Bonetti F, Zamboni G, Martignoni G, Riva M, et al. Melanocyte-marker-HMB-45 is regularly expressed in angiomyolipoma of the kidney. Patho-logy. 1991;23(3):185-.
8. Bennett JA, Braga AC, Pinto A, et al. Uterine PEComas: a morphologic, immunohistochemical, and molecular analysis of 32 tumors. Am J Surg Pathol. 2018;42(10):1370–1383. doi:10.1097/pas.0000000000001119
9. Folpe AL, Mentzel T, Lehr HA, Fisher C, Balzer BL, Weiss SW(2005) Perivascular epitheliod cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases andreview of the literature. Am J Surg Pathol 29:1558–1575
10. Fadare O, Parkash V, Yilmaz Y, Mariappan MR, Ma L, HileetoD, Qumsiyeh MB, Hui P (2004) Perivascular epithelioid celltumor (PEComa) of the uterine cervix associated with intraabdominal'PEComatosis': a clinicopathological study withcomparative genomic hybridization analysis. World J Surg Oncol2:35
11. A Case Report of Malignant Perivascular Epithelioid Cell Tumors of the Uterus and Literature Review Daifeng Hu1,*, Mengyue Miao1,*, Hui Zhou1, Xia Gu1,2, Xuedan Wang3, Alexander Tobias Teichmann1, Qin Wang 1, Youzhe Yang1 International Journal of Women's Health 2024:16

UNRUPTURED ECTOPIC PREGNANCY

PROF. DR. T. RAMANIDEVI, MD., DGO., FICS., FICOG., PH.D.,
Vice President FOGSI 2020
President TNFOG 2024
Director Ramakrishna Medical Centre LLP
Director Janani Fertility centre, Trichy & Patukkottai

DR. M. SUDHA SHANTHI, DNB (OG).,
Consultant at Maa Kauvery Hospital Trichy

INTRODUCTION

Ectopic pregnancy is the result of a flaw in human reproductive physiology that allows the conceptus to implant and mature outside the endometrial cavity, which ultimately ends in the death of the fetus and time causes maternal death. Without timely diagnosis and treatment, ectopic pregnancy can become a life-threatening situation.[1] Most common site of ectopic pregnancy is fallopian tubes (approximately 97.7%). Of tubal pregnancies, the ampulla is the most common site of implantation (80%), followed by the isthmus (12%), fimbria (5%), cornua (2%), and interstitia (2 - 3%). Incidence of ectopic pregnancy is approximately 11/1000 pregnancies.[2] The contribution of ectopic pregnancy to the maternal mortality rates in developing countries including India is not precisely known, with data from few studies indicating 3.5% -7.1% maternal deaths due to ectopic pregnancy.[3]

Heterotrophic pregnancy is1:30000 to 1:4000. Cervical pregnancies are rare, accounting for less than 1% of all ectopic gestation.[4] The prevalence of caesarean scar pregnancy is estimated to be approximately1 in 2000 pregnancies.[5]

Interstitial pregnancy occurs when the ectopic pregnancy implants in the interstitial part of the fallopian tube. The reported incidence varies between 1.0% and 6.3% of ectopic pregnancies.[6-8]

Cornual pregnancy is the rarest form of ectopic pregnancy with a reported incidence of 1 in 76000 pregnancies.[9]

RISK FACTORS

THE RISK FACTORS FOR ECTOPIC PREGNANCY INCLUDE THE FOLLOWING,[10 - 17]

- Previous ectopic pregnancy
- Prior fallopian tube surgery
- Previous pelvic or abdominal surgery
- Certain sexually transmitted infections (STIs)
- Pelvic inflammatory disease
- Endometriosis

OTHER FACTORS THAT MAY INCREASE A WOMAN'S RISK OF ECTOPIC PREGNANCY INCLUDE:

- Cigarette smoking
- Age older than 35 years
- History of infertility
- Use of assisted reproductive technology, such as in vitro fertilization (IVF)[18]
- IUCD users if failure occurs, 53% of them

chances of ectopic[18]

About one half of all women who have an ectopic pregnancy do not have known risk factors. Sexually active women should be alert to changes in their bodies, especially if they experience symptoms of an ectopic pregnancy.

SYMPTOMS AND SIGNS

THE CLASSIC CLINICAL TRIAD OF ECTOPIC PREGNANCY IS AS FOLLOWS:

- Abdominal pain
- Amenorrhea
- Vaginal bleeding

Unfortunately, only about 50% of patients present with all three symptoms. Atypical presentation like breast tenderness, gastrointestinal symptoms, dizziness, fainting or syncope, shoulder tip pain, urinary symptoms, passage of tissue, rectal pressure or pain on defecation for ectopic pregnancy is common.

THE PRESENCE OF THE FOLLOWING SIGNS SUGGESTS A SURGICAL EMERGENCY[19]

- Abdominal rigidity
- Involuntary guarding
- Severe tenderness
- Evidence of hypovolemic shock (eg, orthostatic blood pressure changes, tachycardia)

FINDINGS ON PELVIC EXAMINATION MAY INCLUDE THE FOLLOWING[20]

- The uterus may be slightly enlarged and soft
- Uterine or cervical motion tenderness may suggest peritoneal inflammation
- An adnexal mass may be palpated but is usually difficult to differentiate from the ipsilateral ovary
- Uterine contents may be present in the vagina, due to shedding of endometrial lining stimulated by an ectopic pregnancy

DIAGNOSIS

TUBAL ECTOPIC PREGNANCY

Trans vaginal ultrasound is the diagnostic tool of choice for tubal ectopic pregnancy with reported sensitivities of 87.0 – 99.0% and specificities of 94.0–99.9% for the diagnosis of ectopic pregnancy.[21,22-25] The majority of ectopic pregnancies will be visualized on the initial ultrasound examination.[26] The remainder will initially be classified as a Pregnancy of Unknown Location. A meta-analysis[27] has confirmed that a single β -hCG level cannot be used in isolation to predict an ectopic pregnancy, in modern practice many ectopic pregnancies have a β -hCG value below (1000iu/l).[28] The initial serum β-hCG level is a key prognostic indicator for the success of conservative management (expectant and medical) in cases of ultrasound visualised tubal ectopic pregnancies.[29]

CERVICAL PREGNANCY

The following ultrasound criteria have been described in the diagnosis of cervical ectopic pregnancy.[30,31]

- Empty uterine cavity
- A barrel-shaped cervix
- A gestational sac present below the level of the internal cervical os
- The absence of the 'sliding sign'
- Blood flow around the gestational sac using colour doppler

A single serum β -hCG carried out at the time of ultrasound diagnosis is useful in deciding management options. A serum β-hCG level greater than 10000IU/L is associated with a decreased chance of successful methotrexate treatment.[32]

CAESAREAN SCAR PREGNANCY

The diagnostic criteria described for diagnosing caesarean scar implantation on trans vaginal ultrasound include,[33]

- Empty uterine cavity
- Gestational sac or solid mass of trophoblast located anteriorly at the level of the internal os embedded at the site of the previous lower uterine segment caesarean section scar.[34]
- Thin or absent layer of myometrium between the gestational sac and the bladder.[33,35]
- Evidence of prominent trophoblastic/ placental circulation on doppler examination.[36]
- Empty endo cervical canal

A serum β-hCG level may be useful as a baseline prior to monitoring if conservative treatment is contemplated, but it does not have a role in the diagnosis of caesarean scar pregnancy.

INTERSTITIAL PREGNANCY

ULTRASOUND CRITERIA HAVE BEEN DESCRIBED FOR THE DIAGNOSIS OF INTERSTITIAL PREGNANCY.[37] THESE INCLUDE,

- Empty uterine cavity
- Products of conception/gestational sac located laterally in the interstitial (intramural) part of the tube and surrounded by less than 5mm of myometrium in all imaging planes.
- The 'interstitial line sign', which is a thin echogenic line extending from the central uterine cavity echo to the periphery of the interstitial sac. The 'interstitial line sign' has been shown to have a sensitivity of 80% and a specificity of 98% for the diagnosis of interstitial ectopic pregnancy.[38]
- A single serum β -hCG should be carried out at diagnosis to help with management. In some cases, a repeat serum β -hCG in 48 hours may be useful in deciding further management.

CORNUAL PREGNANCY

The following ultrasound scan criteria described in the literature can be used for the diagnosis of cornual pregnancy.[39]

- Visualisation of a single interstitial portion of fallopian tube in the main uterine body
- Gestational sac/products of conception seen mobile and separate from the uterus and completely surrounded by myometrium
- A vascular pedicle adjoining the gestational sac to the unicornuate uterus

A single serum β-hCG should be carried out at diagnosis to help with management. In some cases, a repeat serum β-hCG in 48 hours may be useful in deciding further management.

ABDOMINAL PREGNANCY

THE FOLLOWING ULTRASOUND CRITERIA HAVE BEEN SUGGESTED BY GERLI ET AL., 2004[40] AS BEING DIAGNOSTIC OF AN EARLY ABDOMINAL PREGNANCY,

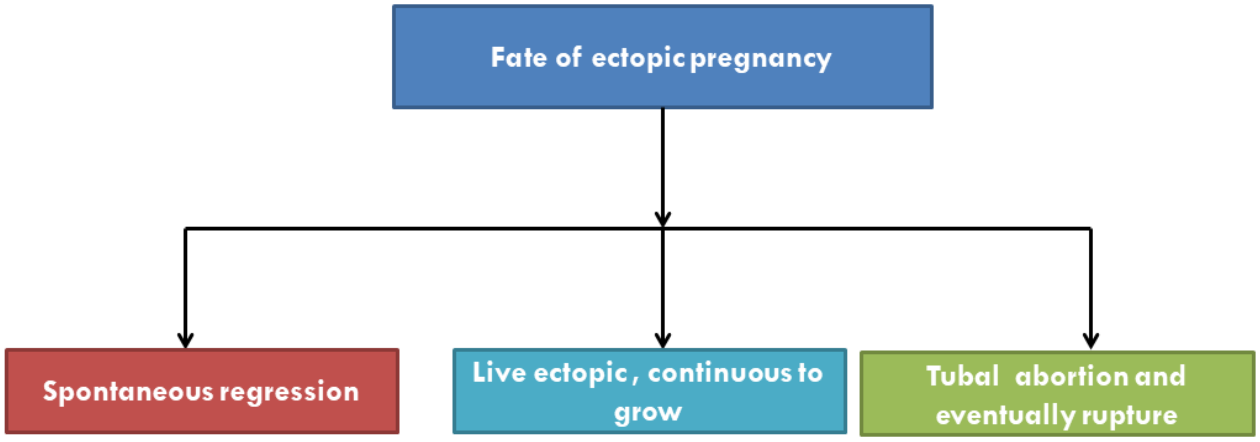
- Absence of an intrauterine gestational sac
- Absence of both an evident dilated tube and a complex adnexal mass
- A gestational cavity surrounded by loops of bowel and separated from them by peritoneum
- A wide mobility similar to fluctuation of the sac, particularly evident with pressure of the trans vaginal probe toward the posterior cul-de-sac

MRI can be a useful diagnostic adjunct in advanced abdominal pregnancy and can help to plan the surgical approach. A high index of suspicion is based upon an elevated serum β-hCG level in combination with ultrasound findings.

HETEROTOPIC PREGNANCY

A heterotopic pregnancy is diagnosed when the ultrasound findings demonstrate an

intra uterine pregnancy and a coexisting ectopic pregnancy. A serum β-hCG level is of limited value in diagnosing heterotopic pregnancy.



TREATMENT OF TUBAL ECTOPIC PREGNANCY

- Expectant management
- Medical management
- Surgical management

EXPECTANT MANAGEMENT

CRITERIA FOR EXPECTANT MANAGEMENT: (NICE GUIDELINES)

- When β-hCG < 1500miu/ ml
- Patient is willing for follow up
- Pain free
- Low/declining hCG done weekly twice
- TV USG showing ectopic pregnancy measuring less than 35 mm with no heart beat

FOLLOW UP OF EXPECTANT MANAGEMENT

REPEAT HCG LEVELS ON DAY 2, 4, AND 7 AFTER THE ORIGINAL TEST

- If hCG levels drop by 15% or more from the previous value on days 2, 4 and 7,then repeat weekly until a negative result (less than 20 IU/L) is obtained or
- If hCG levels do not fall by 15%, stay the same or rise from the previous value review the woman's clinical condition and seek senior advice to help decide further treatment like medical management or rarely surgical management

Reported success rate 57- 100%.[41] Success rates are inversely proportional to serum β-hCG levels.[42]

MEDICAL MANAGEMENT

CANDIDATES FOR MEDICAL MANAGEMENT (NICE GUIDELINE) [43]

- Have no significant pain
- Have an un ruptured ectopic pregnancy with an adnexal mass smaller than 35 mm with no visible heartbeat
- Have a serum β- hCG less than 5000 IU/L
- USG confirmed no intrauterine pregnancy
- Able to follow up

Systemic methotrexate is the most commonly used drug for the pharmacological treatment of tubal ectopic pregnancy.

METHOTREXATE TREATMENT PROTOCOLS

SINGLE-DOSE REGIMEN

- Single dose of Methotrexate at a dose of 50mg/m2 IM on day 1

MEASURE HCG LEVEL ON POST-TREATMENT DAY 4 AND DAY 7

- If the decrease is > 15%, measure hCG levels weekly until reaching non-pregnant level
- If decrease is <15%, re administer MTX at a dose of 50 mg/m2 IM and repeat hCG level
- If hCG does not decrease after two doses, consider surgical management
- If hCG levels plateau or increase during follow up, consider administering methotrexate for treatment of a persistent ectopic pregnancy.

Overall, success rates of single-dose methotrexate for tubal ectopic pregnancy range from 65–95%, with 3–27% of women requiring a second dose.[45]

TWO-DOSE REGIMEN[45]

METHOTREXATE AT A DOSE OF 50MG/M2 IM ON DAY 1 AND 4

- **Measure hCG level on post-treatment day 4 and day 7**
  - If the decrease is >15%, measure hCG levels weekly until reaching non-pregnant level
  - If decrease is <15%, re administer of Methotrexate 50 mg/m2 IM on day 7 and check hCG levels on day 11
  - If hCG levels decrease 15% between day 7 and day 11, continue to monitor weekly until reaching non pregnant levels.
  - If the decrease is <15% between day 7 and day 11, repeat Methotrexate on day 11 and check hCG levels on day 14
  - If hCG does not decrease after 4 doses, consider surgical management
  - If hCG levels plateau or increase during follow up, re administer Methotrexate for treatment of a persistent ectopic pregnancy.

Two dose protocol is significantly superior to the single dose protocol in terms of odds of treatment success and treatment failure. These findings hold true in patients thought to be at a lower likelihood of responding to medical management, such as those with higher hCGs and large adnexal mass. [46]

FIXED MULTIPLE-DOSE REGIMEN

- Administer Methotrexate 1 mg/kg IM on day 1,3,5,7; alternate with folinic acid 0.1 mg/kg intramuscularly on days 2,4,6,8.
- Measure hCG levels on Methotrexate dose days and continue until hCG has decreased by 15% from its previous measurement.

- If the decrease is greater than 15%, discontinue administration of Methotrexate and measure hCG levels weekly until reaching non pregnant levels (May ultimately need one, two, three or four doses)
- If hCG does not decrease after four doses, consider surgical management.
- If hCG levels plateau or increase during follow up, consider administering Methotrexate for treatment of a persistent ectopic pregnancy

PRECAUTIONS TO BE TAKEN BEFORE METHOTREXATE ADMINISTRATION

- Check CBC, LFT, RFT
- Rule out intr
- No alcohol
- No folate supplementation
- Avoid sexual activity
- Maintain plenty of fluid intake

ADVERSE EFFECTS

- Marrow suppression
- Pulmonary fibrosis
- Nonspecific pneumonitis
- Liver failure
- Renal failure
- Gastric ulceration

CANDIDATES FOR METHOTREXATE

- Hemo dynamic stability without pain
- B-hCG > 1500 up to 5000 MIU/ML
- No Fetal heart rate
- Mass size 35 mm or less
- No Intra uterine pregnancy
- Willingness for follow up
- No sensitivity to Methotrexate

CONTRAINDICATIONS FOR MEDICAL MANAGEMENT

- High HCG levels >5000MIU/ML
- Mass size greater than 35mm
- Established FH
- Patient not willing for follow up
- Sensitivity to Methotrexate
- Liver/renal compromise
- Clinically unstable patient

COUNSELLING

- Treatment modalities should be explained
- Talk to them about each method
- Allow them to choose the method
- Explain to them regarding the success rate of each method of treatment
- Recurrent ectopic pregnancy 18%
- Support group should be there
- What is the impact of Methotrexate on future fertility?
- Methotrexate does not affect future ovarian reserve Wait for 3 months after Methotrexate to plan for next pregnancy

SURGICAL MANAGEMENT

- Laparoscopic excision of ectopic sac in stable patient Salpingectomy Vs Salpingotomy.
- Laparotomy is indicated in hemodynamically unstable patient Salpingotomy when? Salpingotomy is indicated in previous ectopic pregnancy.
- Contra lateral tubal damage.
- Post salpingotomy follow up the patient with increasing hCG to rule out

persistent ectopic which is about 8% Vs 1% in salpingectomy

- More so in laparoscopic salpingotomy than laparotomy
- Methotrexate is given if the level of HCG raises or it can be given prophylactically

SALPINGECTOMY - WHEN?

- Salpingectomy is indicated if contra lateral tube is healthy
- After Salpingectomy 56.2% women conceive a successful intra uterine pregnancy

ANTI-D IMMUNOGLOBULIN IN ECTOPIC PREGNANCY

In Rh incompatible, non-immunized women confirmed or suspected ectopic pregnancy Anti-D immunoglobulin 250IU should be given (RCOG guidelines no: 22)

CERVICAL PREGNANCY

Medical management with methotrexate can be considered for cervical pregnancy. Surgical methods of management are associated with a high failure rate and should be reserved for those women suffering life-threatening bleeding.

CAESAREAN SCAR PREGNANCY

Medical and surgical interventions with or without additional haemostatic measures should be considered in women with first trimester caesarean scar pregnancy. There is insufficient evidence to recommend any one specific intervention over another for caesarean scar pregnancy, but the current literature supports a surgical rather than medical approach as the most effective.

INTERSTITIAL PREGNANCY

Nonsurgical management is an acceptable option for stable interstitial pregnancies. Expectant management is only suitable for women with low or significantly falling β - hCG levels in whom the addition of methotrexate may not improve the outcome A pharmacological approach using methotrexate has been shown to be effective, although, there is insufficient evidence to recommend local or systemic approach.

Surgical management by laparoscopic cornual resection or salpingotomy is an effective option. Alternative surgical techniques could include hysteroscopic resection under laparoscopic or ultrasound guidance. There is insufficient evidence on safety and complications in future pregnancies to recommend other nonsurgical methods.

OVARIAN PREGNANCY

Definitive surgical treatment is preferred if laparoscopy is required to make the diagnosis of ovarian ectopic pregnancy. Systemic methotrexate can be used to treat ovarian ectopic pregnancy when the risk of surgery is high, or postoperatively in the presence of persistent residual trophoblast or persistently raised β -hCG levels.

CORNUAL PREGNANCY

Early cornual pregnancy can be managed medically when beta hCG is < 5000 units, single or multiple dose can be used.

If cornual pregnancy is advanced with beta hCG > 5000 and with live fetus, ideal is surgical management.

ABDOMINAL PREGNANCY

Laparoscopic removal is an option for treatment of early abdominal pregnancy.

Possible alternative treatment methods would be systemic methotrexate with ltrasoundguided fetocide. D Advanced abdominal pregnancy should be managed by laparotomy.

HETEROTOPIC PREGNANCY

The intrauterine pregnancy must be considered in the management plan. Methotrexate should only be considered if the intrauterine pregnancy is nonviable or if the woman does not wish to continue with the pregnancy. Local injection of potassium chloride or hyperosmolar glucose with aspiration of the sac contents is an option for clinically stable women.

Surgical removal of the ectopic pregnancy is the method of choice for haemodynamically unstable women and is also an option for haemodynamically stable women. Expectant management is an option in heterotopic pregnancies where the ultrasound findings are of a nonviable pregnancy.

References

1. Farquhar CM. Risk factors. Lancet. 2005;366:583-91.
2. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, Harper A, Hulbert D, Lucas S, McClure J, Millward-Sadler H. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006-2008. The eighth report of the confidential enquiries into maternal deaths in the United Kingdom. BJOG: an international journal of obstetrics and gynaecology. 2011;118:1-203.
3. Shah P, Shah S, Kutty RV, Modi D. Changing epidemiology of maternal mortality in rural India: time to reset strategies for MDG-5. Tropical Medicine & International Health. 2014 May;19(5):568-75.
4. Ushakov FB, Elchalal U, Aceman PJ, Schenker JG. Cervical pregnancy: past and future. Obstetrical & gynecological survey. 1997 Jan 1;52(1):45-59.
5. Rotas MA, Haberman S, Levgur M. Cesarean scar ectopic pregnancies: etiology, diagnosis, and management. Obstetrics & Gynecology. 2006 Jun 1;107(6):1373-81.
6. Felmus LB, Pedowitz P. Interstitial pregnancy: a survey of 45 cases. American Journal of Obstetrics & Gynecology. 1953 Dec 1;66(6):1271-9.
7. Eddy CA, Pauerstein CJ. Anatomy and physiology of the fallopian tube. Clinical obstetrics and gynecology. 1980 Dec 1;23(4):1177-94.
8. Al-Sunaidi M, Tulandi T. Surgical treatment of ectopic pregnancy. InSeminars in reproductive medicine 2007 Mar (Vol. 25, No. 02, pp. 117-122). Copyright© 2007 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
9. Nahum GG. Rudimentary uterine horn pregnancy. The 20th-century worldwide experience of 588 cases. The Journal of reproductive medicine. 2002 Feb 1;47(2):151-63.
10. Yuk JS, Kim YJ, Hur JY, Shin JH. Association between socioeconomic status and ectopic pregnancy rate in the Republic of Korea. International Journal of Gynecology & Obstetrics. 2013 Aug 1;122(2):104-7.
11. Job-Spira N, Collet P, Coste J, Bremond A, Laumon B. Facteurs de risque de la grossesse extra-utérine: résultats d'une enquête cas-témoins dans la région Rhône-Alpes. Contraception, fertilité, sexualité (1991). 1993;21(4):307-12.
12. Bouyer J, Coste J, Shojaei T, Pouly JL, Fernandez H, Gerbaud L, Job-Spira N. Risk factors for ectopic pregnancy:

a comprehensive analysis based on a large case-control, population-based study in France. American journal of epidemiology. 2003 Feb 1;157(3):185-94.

13. Ozel S, Alkan M, Tokmak A, Oksuzoglu A, Kaya M, Aktulay A, Engin-Ustun Y. Relationship between polycystic ovarian morphology and ectopic pregnancy. Journal of Reproduction & Infertility. 2021 Jan;22(1):32.
14. Moini A, Hosseini R, Jahangiri N, Shiva M, Akhoond MR. Risk factors for ectopic pregnancy: A case–control study. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2014 Sep;19(9):844.
15. Ankum WM, Mol BW, Van der Veen F, Bossuyt PM. Risk factors for ectopic pregnancy: a meta-analysis. Fertility and sterility. 1996 Jun 1;65(6):1093-9.
16. Kamwendo F, Forslin L, Bodin L, Danielsson D. Epidemiology of ectopic pregnancy during a 28 year period and the role of pelvic inflammatory disease. Sexually transmitted infections. 2000 Feb 1;76(1):28-32.
17. Barnhar KT. Samme MDl, Gracia CR, Chittams J, Hummel AC, Shaunik A. Risk factors for ectopic pregnancy in women with symptomatic first-trimester pregnancies. Fertil Steril. 2006;86:36-42.
18. Li C, Meng CX, Zhao WH, Lu HQ, Shi W, Zhang J. Risk factors for ectopic pregnancy in women with planned pregnancy: a case–control study. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2014 Oct 1;181:176-82.
19. Abbott J, Emmans LS, Lowenstein SR. Ectopic pregnancy: ten common pitfalls in diagnosis. The American journal of emergency medicine. 1990 Nov 1;8(6):515-22.
20. Dart RG, Kaplan B, Varaklis K. Predictive value of history and physical examination in patients with suspected ectopic pregnancy. Annals of emergency medicine. 1999 Mar 1;33(3):283-90.
21. Kirk E, Papageorghiou AT, Condous G, Tan L, Bora S, Bourne T. The diagnostic effectiveness of an initial transvaginal scan in detecting ectopic pregnancy. Human reproduction. 2007 Nov 1;22(11):2824-8.
22. Condous G, Okaro E, Khalid A, Lu C, Van Huffel S, Timmerman D, Bourne T. The accuracy of transvaginal ultrasonography for the diagnosis of ectopic pregnancy prior to surgery. Human reproduction. 2005 May 1;20(5):1404-9.
23. Atri M, Valenti DA, Bret PM, Gillett P. Effect of transvaginal sonography on the use of invasive procedures for evaluating patients with a clinical diagnosis of ectopic pregnancy. Journal of clinical ultrasound. 2003 Jan;31(1):1-8.
24. Braffman BH, Coleman BG, Ramchandani P, Arger PH, Nodine CF, Dinsmore BJ, Louie A, Betsch SE. Emergency department screening for ectopic pregnancy: a prospective US study. Radiology. 1994 Mar;190(3):797-802.
25. Shalev E, Yarom I, Bustan M, Weiner E, Ben-Shlomo I. Transvaginal sonography as the ultimate diagnostic tool for the management of ectopic pregnancy: experience with 840 cases. Fertility and sterility. 1998 Jan 1;69(1):62-5.

26. Hahlin M, Thorburn J, Bryman I. Pregnancy: The expectant management of early pregnancies of uncertain site. Human reproduction. 1995 May 1;10(5):1223-7.
27. Van Mello NM, Mol F, Opmeer BC, Ankum WM, Barnhart K, Coomarasamy A, Mol BW, van der Veen F, Hajenius PJ. Diagnostic value of serum hCG on the outcome of pregnancy of unknown location: a systematic review and meta-analysis. Human reproduction update. 2012 Nov 1;18(6):603-17.
28. Condous G, Kirk E, Lu C, Van Huffel S, Gevaert O, De Moor B, De Smet F, Timmerman D, Bourne T. Diagnostic accuracy of varying discriminatory zones for the prediction of ectopic pregnancy in women with a pregnancy of unknown location. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2005 Dec;26(7):770-5.
29. Potter MB, Lepine LA, Jamieson DJ. Predictors of success with methotrexate treatment of tubal ectopic pregnancy at Grady Memorial Hospital. American journal of obstetrics and gynecology. 2003 May 1;188(5):1192-4.
30. Jwkovic D, Hacket E, Campbell S. Diagnosis and treatment of early cervical pregnancy: a review and a report of two cases treated conservatively. Ultrasound in Obstetrics & Gynecology. 1996;8(6):373-80.
31. Timor-Tritsch IE, Monteagudo A, Mandeville EO, Peisner DB, Anaya GP, Pirrone EC. Successful management of viable cervical pregnancy by local injection of methotrexate guided by transvaginal ultrasonography. American journal of obstetrics and gynecology. 1994 Mar 1;170(3):737-9.
32. Hung TH, Shau WY, Hsieh TT, Hsu JJ, Soong YK, Jeng CJ. Prognostic factors for an unsatisfactory primary methotrexate treatment of cervical pregnancy: a quantitative review. Human Reproduction (Oxford, England). 1998 Sep 1;13(9):2636-42.
33. Godin PA, Bassil S, Donnez J. An ectopic pregnancy developing in a previous caesarian section scar. Fertility and sterility. 1997 Feb 1;67(2):398-400.
34. Jurkovic D, Hillaby K, Woelfer B, Lawrence A, Salim R, Elson CJ. Cesarean scar pregnancy. Ultrasound in Obstetrics and Gynecology. 2003 Mar 1;21(3):310-.
35. Timor-Tritsch IE, Monteagudo A, Santos R, Tsymbal T, Pineda G, Arslan AA. The diagnosis, treatment, and follow-up of cesarean scar pregnancy. American journal of obstetrics and gynecology. 2012 Jul 1;207(1):44-e1.
36. Seow KM, Hwang JL, Tsai YL. Ultrasound diagnosis of a pregnancy in a Cesarean section scar. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2001 Nov;18(5):547-9.
37. Lin EP, Bhatt S, Dogra VS. Diagnostic clues to ectopic pregnancy. Radiographics. 2008 Oct;28(6):1661-71.
38. Ackerman TE, Levi CS, Dashefsky SM, Holt SC, Lindsay DJ. Interstitial line: sonographic finding in interstitial (cornual) ectopic pregnancy. Radiology. 1993 Oct;189(1):83-7.
39. McLeod L, Chitayat D, Thomas M,

Johnson JM. P054: The impact of first trimester screening on trends in termination for chromosome abnormalities. Ultrasound in Obstetrics and Gynecology. 2003 Jan 1;22(1):85-.

40. Gerli S, Rossetti D, Baiocchi G, Clerici G, Unfer V, Di Renzo GC. Early ultrasonographic diagnosis and laparoscopic treatment of abdominal pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2004 Mar 15;113(1):103-5.
41. Craig LB, Khan S. Expectant management of ectopic pregnancy. Clinical Obstetrics and Gynecology. 2012 Jun 1;55(2):461-70.
42. Elson J, Tailor A, Banerjee S, Salim R, Hillaby K, Jurkovic D. Expectant management of tubal ectopic pregnancy: prediction of successful outcome using decision tree analysis. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2004 Jun;23(6):552-6.
43. National Collaborating Centre for Women's and Children's Health (UK. Ectopic pregnancy and miscarriage: diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage.
44. Stovall TG, Ling FW, Gray LA. Single-dose methotrexate for treatment of ectopic pregnancy. Obstetrics and gynecology. 1991 May 1;77(5):754-7.
45. Barnhart K, Hummel AC, Sammel MD, Menon S, Jain J, Chakhtoura N. Use of "2-dose" regimen of methotrexate to treat ectopic pregnancy. Fertility and sterility. 2007 Feb 1;87(2):250-6.
46. Alur-Gupta S, Cooney LG, Senapati S, Sammel MD, Barnhart KT. Two-dose versus single-dose methotrexate for treatment of ectopic pregnancy: a meta-analysis. American journal of obstetrics and gynecology. 2019 Aug 1;221(2):95-108.

COVID -19 IN PREGNANCY

DR.VICTORIA JOHNSTON MD (O&G) FICOG

ABSTRACT

The data pertaining to the COVID-19 pandemic has been rapidly evolving since the first confirmed case in December 2019. This article aims to study COVID-19 and its effect on pregnant women in early pregnancy, including symptoms, disease severity and the risk of vertical transmission. We also review briefly the recommended management of pregnant women with suspected or confirmed COVID-19 and the various pharmacological agents that are being investigated in the first trimester and may have a role in the treatment of this disease. At present, it does not appear that pregnant women are at increased risk of severe infection than the general population, although there are vulnerable groups within both the pregnant and non-pregnant populations, and clinicians should be cognizant of these high-risk groups and manage them accordingly. Approximately 85% of women will experience mild disease, 10% more severe disease and 5% critical disease. The most common reported symptoms are fever, cough, shortness of breath and diarrhoea. Neither vaginal delivery nor caesarean section confers additional risks, and there is minimal risk of vertical transmission to the neonate from either mode of delivery. The true effect of the virus on both maternal and fetal morbidity and mortality will only be evident over time with more studies.

I. BACKGROUND

A cluster of four cases of pneumonia of unknown etiology in Wuhan, China, were reported to the World Health Organization (WHO) on 31 December, 2019. Since then, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2) has spread rapidly across the world. On March 12, 2020 the WHO defined the outbreak as a pandemic. As pregnant women are at greater risk of complications and severe disease from infection with other coronaviruses, they were identified as a vulnerable group and were advised to take additional precautions as the COVID-19 pandemic unfolded. To reduce transmission risks for both pregnant women and health care workers, the International Federation of Gynecology and Obstetrics (FIGO) recommended the suspension of routine antenatal care and replacement with video or telephone consultations whenever possible. We will examine the physiological adaptations to pregnancy and the implications for COVID-19, as well as COVID-19's impact on pregnancy outcomes.

II.PHYSIOLOGICAL ADAPTATIONS TO PREGNANCY AND THE IMPLICATIONS FOR COVID-19

A. IMMUNOLOGICAL RESPONSE

COVID-19 is a capsulated single-stranded RNA virus. The immunological response to COVID-19, like other viruses, relies on a working immune system. COVID-19 infection can result in mild disease, in which the virus is cleared effectively by the immune system or severe disease with high mortality rates. The position for pregnant women on this spectrum is unclear. The immune system adapts during pregnancy to allow for the growth of a semi-allogenic fetus, resulting in an altered immune response to infections during pregnancy.

To understand the COVID-19 phenotype during pregnancy, it is important to understand the pathophysiology and molecular mechanisms of COVID-19 and examine these in the context of the modulated maternal immune response.

SARS-CoV-2, is transmitted by respiratory droplets, direct contact with fomites, close person-to-person contact and possibly by aerosols generated, enters the body via the nasal passage and infects pulmonary cells. Infection with SARS-CoV-2 is followed by viral replication and release of the virus, leading to excessive inflammation and damage of the integrity of the lung, resulting in infection with other (host) microbes. The inflammation caused by SARS-CoV-2 may also result in a "cytokine storm" that can lead to multisystem organ failure. This excessive inflammation is thought to be the cause of severe COVID-19 and is associated with high morbidity and mortality.

B. RESPIRATORY RESPONSE

COVID has an impact on lung function, anatomical changes also are present in the respiratory system. Physiological alterations to the chest shape and elevation of the diaphragm due to diaphragmatic splinting by the gravid uterus cause changes to the respiratory function. Although there is a 30–40% increase in tidal volume, the reduction in chest volume leads to a decrease in functional residual capacity, end-expiratory volumes, and residual volumes from early in pregnancy. The reduction in total lung capacity and inability to clear secretions can make pregnant women more susceptible to severe respiratory infections.

C. COAGULATION RESPONSE

In the general population, COVID-19 is associated with high rates of thromboembolic complications. This is due to activation of coagulation pathways and potential progression to disseminated vascular coagulopathy (DIC) and fibrinolysis with resultant dynamic hypercoagulation occurring alongside thrombocytopenia.

Pregnancy is a hypercoagulable state with increased thrombin production and an increase in intravascular inflammation. During pregnancy, there are higher levels of circulating coagulation and fibrinolytic factors, such as plasmin, and these may be implicated in the pathogenesis of SARS-CoV-2 infection. Pregnant women are at increased risk of thromboembolic events with associated mortality. Therefore, pregnant women with COVID-19 may have additive or synergistic risk factors for thrombosis. Current guidelines recommend that all pregnant women with confirmed COVID-19 should have thromboprophylaxis until 10 days postnatal and that their clinicians have a low threshold for investigation of possible thromboembolism.

D. ENDOTHELIAL CELL FUNCTION

Mortality in COVID-19 is predominantly due to acute respiratory distress syndrome (ARDS). Emerging evidence suggests that pulmonary endothelial cell dysfunction has an important role in the onset and progression of ARDS. Risk factors for COVID-19 (increasing age, obesity, diabetes mellitus, and cardiovascular disease) are all associated with endothelial cell dysfunction.

E. PLACENTAL RESPONSES AND MECHANISMS OF VERTICAL TRANSMISSION

The role of the placenta in SARS-CoV-2 infection is currently poorly understood. Although it appears vertical transmission can occur, the mechanisms underlying this type of transmission are uncertain.

PHYSIOLOGY OF THE PLACENTA AND VIRAL INTERACTION

The placenta is usually an effective barrier that prevents maternal infection spreading to the fetus (vertical transmission). Experience of viral

infections in pregnancy has led to three other key observations regarding congenital infection, in general. First, the presence of the virus on the placental surface does not necessarily indicate placental infection—vertical transmission of viruses depends on some kind of breach of the placental barrier. Second, viral infection of placental cells does not necessarily mean that there is transmission to the fetus. Third, even when fetal infection occurs, responses are heterogeneous; thus, fetal infection does not always mean fetal damage.

VERTICAL TRANSMISSION OF SARS-COV-2

Viral infection of placental cells does not necessarily mean fetal infection or fetal harm. So far, 15 reports include neonatal test results for SARS-CoV-2 with positive cases occurring only in the minority. Significant neonatal respiratory diseases appear to be rare, even in the presence of SARS-CoV-2 positivity. It is unclear from reports of PCR-based SARS-CoV-2 testing whether infection occurs in utero or during the labor or birth; or whether transmission occurs from the infected mother or asymptomatic hospital staff in the immediate newborn period.

COVID-19 AND IT'S IMPACT ON PREGNANCY

PREGNANCY RESPONSE TO OTHER VIRAL EXPOSURE

A number of viruses have established effects on the mother and the fetus during pregnancy and may provide information on the potential impact and mechanism of COVID-19 in pregnancy.

VIRUSES AND THE FETUS

Viral illness during pregnancy increases the risk of a range of adverse outcomes for the child. Viruses can have long-lasting detrimental impacts on the fetus. High levels of maternal inflammation in response to viral infection can impact several aspects of fetal brain development, leading to wide-ranging neurological sequelae.

SARS-COV-2 AND EARLY PREGNANCY

There is little evidence about the possible impact of COVID in early pregnancy (up to 12 wk gestation). Seasonal influenza has been associated with higher rates of miscarriage and population level monitoring and upscale of community testing will be needed to ascertain whether this is also the case with COVID-19.

An intense inflammatory response has been reported as one of the key features of severe COVID-19, and as there is relative immunosuppression in pregnancy this may partly explain why many pregnant women do not develop severe respiratory symptoms.

Specific comorbidities to assess women for include the following: hypertension, diabetes, asthma, HIV, chronic heart disease, chronic liver disease, chronic lung disease, chronic kidney disease, blood dyscrasia, those with solid organ transplants, malignancies and people on immunosuppressive medication. These women may be at high risk for severe disease.

EFFECTS ON FOETUS

There are currently no data suggesting an increased risk of miscarriage or early pregnancy loss in relation to COVID-19.

There is no evidence currently that the virus is teratogenic. Long term data is awaited.

COVID-19 infection is currently not an indication for Medical Termination of Pregnancy. ICMR, NIRRH

DIAGNOSIS AND TREATMENT

A real-time reverse transcriptase-polymerase chain reaction assay is the current

gold standard for detecting SARS-CoV-2 from respiratory specimens in patients with suspected COVID-19 with a sensitivity of approximately, 70%. Clinicians should consider re-testing if clinical suspicion for COVID-19 remains with an initial negative swab, and chest imaging may aid confirmation of infection. When CT is required, for further investigation, this should not be delayed in pregnant women. There are significant challenges when treating pregnant women with COVID-19 in severe and critical groups. The adoption of the prone position can help overcome some of these issues. Prone ventilation has been found to significantly improve oxygenation in the setting of ARDS, and it's feasibility and safety in pregnancy have been documented. It must be remembered that the health of the mother should be prioritized in the treatment of severe COVID-19 cases. In these critical cases, this can lead to difficult decisions, which in the maternal interest may be to terminate the pregnancy for pre-viable gestations or result in an iatrogenic preterm delivery, which in turn can result in significant neonatal morbidity and mortality.

ANTENATAL CARE

It is recommended that all pregnant women observe social distancing and follow self-isolation guidance to prevent exposure to COVID-19 and practice good hand hygiene. FIGO currently recommends that during the course of the pandemic, the general principle should be to minimize in-person office visits and if practical and appropriate, consider appointments via telephone or videoconferencing. Women with symptoms of COVID-19 should be tested and appointments delayed if possible, during the period of self-quarantine. If symptoms persist, they should call and make an appointment for testing and/or hospitalization.

However, it is not yet clear how SARS-CoV-2 may influence pregnancy and the risk factors it presents to the mother and unborn child. More precisely, due to the novelty of the virus and relatively recent spread, there are extremely scarce data on maternal and perinatal outcomes when the infection is contracted in the first or second trimester of pregnancy.

SYMPTOMS

Despite a majority of women not reporting any symptoms, the most frequently observed symptoms and clinical signs were fever (39%) and cough (33%). To a smaller extent, dyspnea (24%), nausea and vomiting 12%), and loss of taste or smell (26%) were observed.

LABORATORY AND RADIOLOGICAL FINDINGS

Radiological findings of 24 pregnant women in 12 studies were reported. Pneumonia and ground glass appearance were the first (50%) and second (21%) most common observed radiological findings respectively. Elevated C-reactive protein as well as lymphocytopenia were observed in women (19%), and high levels of hepatic markers (AST/ALT) were recorded in patients (43%).

Elevated body temperature during pregnancy is associated with disruption of cell migration, damage to the vascular systems and death of neuroblast cells. Hence, this is a potential concern during the organogenesis period during the 1st trimester of pregnancy.

Placental inflammation such as villitis/ intervillitis and perivillous fibrin deposition. The literature defines villitis as a damaging inflammation that is characterized by maternal T-cell invasion into chorionic villi. Furthermore, an increase in proinflammatory markers such as tumor necrosis factor (TNF--) and interleukin (IL)-6 is characteristic of COVID-19 infection and has been associated with endothelial activation and apoptosis of the trophoblastic cells.

PHARMACOLOGICAL AGENTS

1. Chloroquine and Hydroxychloroquine
2. Azithromycin
3. Remdesivir
4. Lopinavir/ritonavir

Therapeutic treatments for the COVID-19 infected pregnant women, azithromycin (42%) and hydroxychloroquine (42%) were the most common, followed by lopinavir-ritonavir (33%) and oseltamivir (33%). The inconsistency in the administration of drugs underlies the lack of sufficient data for therapeutic efficacy against the novel coronavirus. A study concerning the safety of hydroxychloroquine in 1st trimester pregnancies reported no notable changes in the nervous/cardiac system formation, prematurity or birth weight of the infants. Despite some data indicating the efficacy of hydroxychloroquine against SARS-CoV-2, consistent clinical results are yet to be presented. Furthermore, lopinavir and ritonavir have also shown an inconsequential effect on pregnancy, and in their study of 955 pregnant women, Roberts *et al.* observed that the incidence of birth defects in children with prenatal exposure to lopinavir/ritonavir did not differ substantially from the control.

THROMBOPROPHYLAXIS

There are emerging reports of an increased incidence of both venous and arterial thromboembolism in patients diagnosed with COVID-19 due to excessive inflammation, hypoxia, immobilization and diffuse intravascular coagulation. Studies observed that anticoagulant treatment with low molecular weight heparin (LMWH) has been associated with improved prognosis in patients with severe COVID-19 infection, stratified by the sepsis-induced coagulopathy score or D-dimer results. Given that normal pregnant women have evidence of the increased generation of thrombin and a prothrombotic state, as well as increased intravascular inflammation, which is exaggerated in the context of infection, such patients may be at an increased risk for thrombosis when affected by COVID-19. International guidelines to date recommend thromboprophylaxis on an individualized basis, particularly women with mild symptoms who are self-isolating. Venous thromboembolism (VTE) risk assessment should be carried out on all women who are admitted with COVID-19, and VTE prophylaxis is recommended if they are unwell. The RCOG recommends that all pregnant women admitted with COVID-19 infection (or suspected COVID-19 infection) should receive prophylactic LMWH unless birth is expected within 12 h. High-risk patients may need prolonged treatment with LMWH or increased doses, in line with local hospital guidelines and on consultation with local hematology services.

COVID VACCINATION IN EARLY PREGNANCY

COVID-19 infection during pregnancy may result in rapid deterioration of health of pregnant woman and could also affect the fetus. Experts are of the view that the benefits of vaccination to the pregnant women outweigh its potential risks. Based on the recommendations from National Technical Advisory Group on immunization (NTAGI), MoHFW has approved vaccination of pregnant women against COVID- 19 with the condition that the pregnant women may be informed about the risks of exposure to COVID-19 infection along with the risks and benefits associated with the COVID-19 vaccines available in the country. Based on the information provided, a pregnant woman will have the choice to take the vaccination.

Pregnant women who develop COVID-19 are more likely to require intensive care than their non-pregnant counterparts. Experts have suggested that the COVID-19 vaccine may be offered to the pregnant women if, no contraindications exist.

The intent is to weigh risk versus benefit on individualized basis, so that a pregnant woman can take an informed decision.

In India, at present three vaccines have received approval for restricted use in emergency situation. One of them is an inactivated vaccine (Covaxin) and other two are based on non-replicating viral vector platform (Covidshield and Sputnik V)

A pregnant women who opts for vaccination, could be vaccinated in any trimester of the pregnancy. To help pregnant women make an informed decision to be vaccinated, they should be provided with information about the risks of COVID-19 infection in pregnancy, the benefits of vaccination, along with the likely side effects of vaccination.

CONCLUSION

The evidence on this novel infection is changing almost on a daily basis. It is hard to determine the true impact it will have on both maternal and fetal well-being. In the interim, our primary responsibility is to ensure all women have access to safe maternity services. This includes remaining up to date with the evidence for the treatment of COVID-19 in the pregnant population and also ensures strict infection control measures to stem the spread of disease within our own units. Second, we must be aware of those that are potentially vulnerable during this time, both patients and colleagues, and we must ensure adequate supports are available to them during these uncertain times. Due to the novelty of the subject, long term follow-up of COVID-19 positive first and second trimester mothers and their newborns is insufficient. Such limitations restrict the assessment of complication development, outcomes (both maternal and neonatal), and course of pregnancies. Very few trials include pregnant women, hence researchers should be urged to include them in trials to create a balanced and informed evidence base with data.

References

1. Guidance for Management of Pregnancy Women in COVID-19 Pandemic ICMR – National Institute for Research in Reproductive Health Jehangir Merwanji Street, Parel, Mumbai-400012.
2. Physiological Reviews Pregnancy and Covid-19 Authors: Elizabeth A.N. Wastnedge, Rebecca M. Reynolds, Sara R. Van Boeckel, Sarah J. Stock, Fiona C. Dension, Jacquline A. Maybin, Hilary O. D. Critchley.
3. SARS-CoV-2/COVID-19 Contracting COVID-19 in the first and second trimester of pregnancy: What we know – a concise qualitative systematic review Jasmine Abu-Amara, Dawid Szpecht, Salwan R. Al-Saad, Lukaxz M. Karbowski.
4. SARS-CoV-2 infection in the first trimester and the risk of early miscarriage: a UK population-based prospective cohort study of 304 I pregnancies conceived during the pandemic Neerujah Balachandram, Melanie C.Davies, Jennifer A. Hall.
5. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis Shu Qin Wei MD PhD, Marianne Bilodeau-Bertrand MSc, Shiliang Liu MB PhD, Nathalie Auger MD MSc Cite as:CMAJ 2021 April 19;193:E540-8. Doi: 10.1503/cmaj.202604;early-released March 19, 2021.
6. COVID-19 and cause of pregnancy loss during the pandemic: A systematic review Seyyedeh Neda Kazemi, Bahareh

Hajikhani, Hamidreza Didar, Sarah Sadat Hosseini, Sara Haddadi, Farima Khalili, Mehdi Mirsaeidi, Mohammad Javad Nasiri.

7. WHO . Rolling updates on coronavirus disease (COVID-19). 2020. Available from URL: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen
8. 8. WHO . Coronavirus disease (COVID-19) outbreak situation. 2020.
9. 9. FIGO . Safe motherhood and COVID. 2020. Available from URL: https://www.figo.org/safe-motherhood-and-covid-19.
10. 10. RCOG . Coronavirus (COVID-19) infection in pregnancy.2020
11. 11. ACOG . Novel coronavirus 2019 (COVID-19). 2020.
12. 12. The Journal of Obstertrics and Gynaecology Research Clinical update on COVID-19 in pregnancy: A review article Gillian A. Ryan, Nikhil C. Purandare, Fionnuala M. McAuliffe, Moshe Hod and Chittaranjan N. Purandare.

OVULATION TRIGGER IN IVF PAST, PRESENT AND FUTURE

PROF. DR. T. RAMANIDEVI, MD., DGO., FICS., FICOG., PH.D.,

Vice President FOGSI 2020
President TNFOG 2024
Director Ramakrishna Medical Centre LLP
Director Janani Fertility centre, Trichy & Patukkottai

One of the key factors for success in ART is the ovulation trigger (OT). The aim of OT in IVF/ICSI cycles is to obtain an optimal output of mature oocytes, mimicking the final oocyte maturation during natural cycle which is induced by the mid-cycle surge of gonadotropins. There are important differences in stimulated IVF cycles compared to the natural cycle, including supraphysiological follicular and luteal phase steroid levels due to multi-follicular development. Altered hypothalamic response due to the use of GnRH analogues leads to low levels of endogenous gonadotropins during the luteal phase. In order to optimize the OT strategy in IVF cycles three main issues should be considered. Ovulation trigger agent, timing of pick up and pre-ovulatory follicle to mature oocyte ratio.

Clinical decision-making should be based on clinical characteristics such as maternal age, endocrinological conditions (hypogonadotropic hypogonadism, PCOS, obesity, etc.), response to ovarian stimulation (hyper-response, poor response, suboptimal response) and response to a previous trigger (previous cycles). ET strategy should be e.g. fresh ET followed by subsequent LPS or eFET in case of high risk of OHSS or in doing an eFET for other indications. A successful OT should result in an optimal LH activity surge and a subsequent P rise and end up with more than 75% mature oocytes without increasing the risk of OHSS development. Lack of response could eventually end up in an Empty follicle syndrome (EFS) condition, and, on the other hand, an excessive response might result in OHSS.

HCG TRIGGER

In comparison with GnRHa triggered IVF cycles, the HCG triggered cycles have been reported to have equal or slightly lower number of mature oocytes retrieved and thus, a lower number of good quality embryos for ET. Both urinary and recombinant HCG are used in doses ranging from 5000 to 10000 IU for OT.

COS in IVF cycles triggered with HCG is characterized by supra-physiological steroid levels during the early luteal phase. This condition is the basis of a negative feedback on the endogenous LH secretion by the pituitary, which results in a severe reduction in circulating LH and, thus, a severely hampered luteal phase, demanding exogenous LPS to achieve ongoing pregnancy.

Although not statistically significant, the hCG group seemed to perform better and the lowest rLH dose was suboptimal when compared with the higher dose. Troubling information regarding reduced clinical pregnancy rates in the rLH group further restricts the use of this medication for ovulation triggering.

GNRH ANALOGUES FOR TRIGGER

GnRHa is a synthetic peptide modelled after the hypothalamic GnRH that interacts with the GnRH receptor to elicit its biological response, *i.e.* the release of LH and FSH. However, following the initial "flare" of gonadotropins, continued stimulation with GnRHa causes GnRH receptor down-regulation and thus, pituitary desensitization. GnRHa for OT will only be possible in GnRH antagonist IVF/ICSI cycles or in cycles in which no GnRH analogue was used during stimulation. GnRH agonists most commonly used for OT are: leuprorelin, buserelin, nafarelin, and triptorelin which can be administered either nasally or subcutaneously. The GnRHa induced circulating LH level is insufficient to support sufficient CL function which leads to implantation failure and early pregnancy loss after fresh embryo transfer cycles, although a standard LPS is used. One suggested protocol is to administer intensive exogenous steroid support (P + E).

OVULATION TRIGGER WITH KISSPEPTIN

Kisspeptin (Kp), albeit not used in daily clinical practice, is a peptide hormone which influences the human neuroendocrine regulation.

It is released in the hypothalamic infundibular nucleus and acts through the Kp receptor (KISS 1R) directly at the level of GnRH neurons as a key regulator of GnRH-secretion, impacted by circulating E and P levels.

In humans, exogenously administered subcutaneous Kp 53 (1.6 to 12.8) nmol/kg) induces a dose-dependent secretion of endogenous LH and to a lesser extent FSH. However, the luteal phase after Kp trigger was seen to be even more impaired as compared to the luteal phase after GnRHa trigger as the LH surge elicited by Kp is of a lower amplitude and significantly shorter than that induced by GnRHa. This is contrasted by the long duration (6-10 days) of LH activity induced by an hCG trigger. Thus, the future role of Kp as an OT agent needs to be further investigated, including the potential benefit of using additional Kp boluses.

DUAL /DOUBLE TRIGGER

A bolus of GnRHa was administered concomitantly with a bolus of HCG in a dose range from 1000 IU to 2500 IU, depending on the body weight of the patient as well as the risk of OHSS.53% ongoing pregnancy rate was reported by the authors, without any OHSS cases.

Double trigger consists of the coadministration of GnRHa and hCG for OT at 40 h and 34 h, respectively, prior to oocyte retrieval. Double trigger has been suggested to improve IVF outcome in patients with a low proportion of mature oocytes retrieved in a previous cycle.

EMPTY FOLLICLE SYNDROME

EFS is defined as the absence of oocytes after follicular aspiration despite an adequate ovarian ultrasonographic response and increase in serum estradiol levels during stimulation, followed by careful follicular aspiration. EFS is classified as either "genuine" or "false." The "genuine" type is defined as a failure to obtain oocytes despite optimal serum HCG levels on the day of the oocyte retrieval. The "false" type has been defined as a failure to obtain oocytes in the presence of low serum HCG (<40 IU/L) on the day of retrieval due to failure of administration or reduction in the bioavailability of HCG, of which the latter seems to be the more frequent type. Dual trigger concept has been proposed to prevent the "genuine" EFS and has been shown to be an applicable OT strategy to yield a larger number of mature oocytes.

Dual trigger combines the advantages of both agents (GnRHa and HCG): the direct intrafollicular LH activity mediated by HCG, the simultaneous

induction of an endogenous FSH surge mediated by GnRHa, and the support of the early luteal phase LH activity mediated by hCG.

The time interval between administration of the OT agent and the oocyte retrieval has been shown to be a key factor for success when planning the OT.

Thus, it has been suggested that in some patients, follicles may need a longer exposure time to the OT agent (either HCG or GnRHa) to allow cumulus expansion and detachment of the COC. Hence, prolonging the interval between HCG/ GnRHa priming and follicular aspiration may be useful in some cases to prevent recurrence of EFS and/or to increase the number of mature oocytes retrieved.

CONCLUSION

- Success rates in ART are increasing due to optimization of ovarian stimulation protocols and advances in laboratory techniques.
- While the stimulation protocol remains crucial, the OT strategy will inevitably impact not only oocyte retrieval and oocyte maturity rates, but also the early luteal phase and, thereby, implantation and ongoing pregnancy rates.
- Hence, individualization in OT strategy is an important clinical tool to optimize the live birth.
- Until now HCG and GnRHa have proven their efficacy when used for ovulation trigger in different clinical scenarios, whereas more trials are needed to reveal the possible future role of dual trigger, double trigger and Kisspeptin as ovulation trigger in IVF cycles in future.

References

1. Dosouto C, Haahr T, Humaidan P. Advances in ovulation trigger strategies. Panminerva medica. 2019 Mar;61(1):42-51.
1. Haahr T, Esteves SC, Humaidan P. Individualized controlled ovarian stimulation in expected poor-responders: an update. Reproductive Biology and Endocrinology. 2018 Dec;16:1-9.
1. Pierce JG, Parsons TF. Glycoprotein hormones: structure and function. Annual review of biochemistry. 1981 Jul;50(1):465-95.
1. Humaidan P, Papanikolaou EG, Kyrou D, Alsbjerg B, Polyzos NP, Devroey P, Fatemi HM. The luteal phase after GnRH-agonist triggering of ovulation: present and future perspectives. Reproductive biomedicine online. 2012 Feb 1;24(2):134-41.
1. Youssef MA, Abou-Setta AM, Lam WS. Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles. Cochrane Database of Systematic Reviews. 2016(4).
1. Gonen YA, Balakier H, Powell W, Casper RF. Use of gonadotropin-releasing hormone agonist to trigger follicular maturation for in vitro fertilization. The Journal of Clinical Endocrinology & Metabolism. 1990 Oct 1;71(4):918-22.
1. Engmann L, Benadiva C, Humaidan P. GnRH agonist trigger for the induction of oocyte maturation in GnRH antagonist IVF cycles: a SWOT analysis. Reproductive biomedicine online. 2016 Mar 1;32(3):274-85.
1. Dosouto C, Haahr T, Humaidan P. Advances in ovulation trigger strategies. Panminerva medica. 2019 Mar;61(1):42-51.
1. Castillo JC, Humaidan P, Bernabéu R. Pharmaceutical options for triggering of final oocyte maturation in ART. BioMed research international. 2014;2014(1):580171.
1. 10. Jayasena CN, Abbara A, Comninos AN, Nijher GM, Christopoulos G, Narayanaswamy S, Izzi-Engbeaya C, Sridharan M, Mason AJ, Warwick J, Ashby D. Kisspeptin-54 triggers egg maturation in women undergoing in vitro fertilization. The Journal of clinical investigation. 2014 Aug 1;124(8):3667-77.

A CASE STUDY ON ALIVE CAESAREAN SCAR ECTOPIC PREGNANCY

DR. G. SUJATHA. MBBS.,DGO.,FMAS.,
DECCA HOSPITAL ,TRICHY.

INTRODUCTION:

Cesarean scar pregnancy is the rarest form of Ectopic pregnancy occurring approximately in 1 in 2000. It has become more common with increasing number of cesarean sections worldwide. It accounts for around 6% of pregnancy related deaths, so early diagnosis of caesarean scar ectopic pregnancy and prompt treatment makes us to avoid life threatening complications like hemorrhage,uterine rupture, placenta accreta spectrum (PAS) and loss of future fertility .

CASE REPORT:

A 32 year old G3 P2 L2 A0 mother with a history of previous 2 LSCS, last LSCS done 5 years back admitted with C/O 45 day'samenorrhea, lower abdominal pain for 10 days and continuous bleeding P/V for 1 week.She gave a history of abortion pill intake 1 week back without prior scan. Here Basic blood investigations done. Her serum BHCG level is 31336 mIU/mL. Ultrasound showed single viable gestational sac in the lower uterine segment scar area with presence of yolk sac, fetal pole corresponding to 6 weeks GA and fetal heart rate of 119 b/mt.MRI confirmed cesarean scar pregnancy of size 30X18 mm with surrounding decidual reaction. Hence a diagnosis of alive caesarean scar pregnancy confirmed and patient was taken up for emergency laparotomy and scar ectopic excision in view of continuous bleeding P/V and lower abdominal pain. Per operatively uterus enlarged to 6 – 8 weeks size, scar ectopic mass of size 3 X 3 cm seen in the lower uterine segment. Prior to scar excision anterior branch of internal iliac artery hooked and kept with stay sutures on both sides prophylactically. Then 30 ml of diluted inj. vasopressin injected into the myometrium around the scar area carefully. Finally scar site incised fetal sac with products pooped out followed by uterine cavity thorough suctioning. Uterine wall closed in continuous layer followed by Bilateral tubectomy. One unit of packed cell blood transfusion done. She had an uneventful post-operative period and was discharged in good condition.

DISCUSSION:

Cesarean scar ectopic pregnancy is defined as implantation of gestational sac into the myometrial defect in the previous uterine incisions like cesarean section, hysterotomy, myomectomy etc. It could be a viable pregnancy (or)miscarriage.

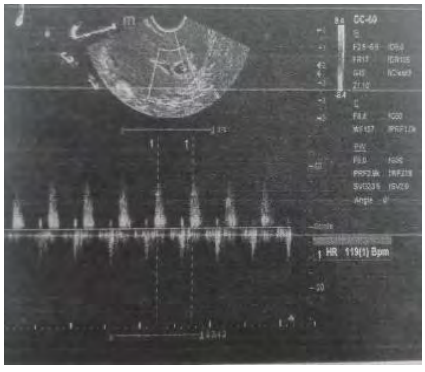
THERE ARE 2 TYPES:

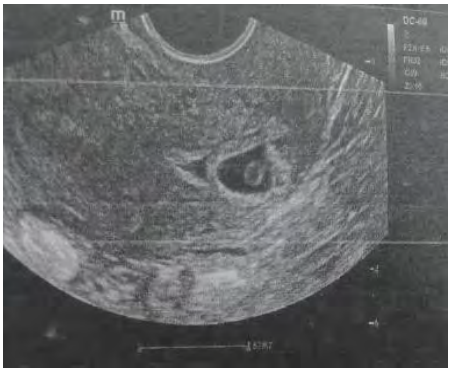
- Cesarean scar pregnancy Type I / Endogenous - sac that grows towards the uterine cavity associated with risk of placenta accreta and obstetric hemorrhage.
- Cesarean scar pregnancy Type II / Exogenous – which grows towards the bladder associated with risk of scar rupture and intra-abdominal bleeding.

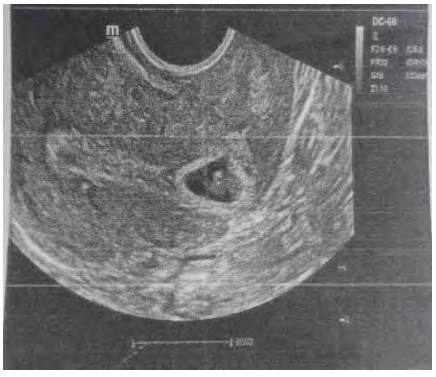
NEW CLINICAL CLASSIFICATION OF CESAREAN SCAR ECTOPIC PREGNANCY

CLINICAL CLASSIFICATION	ANTERIOR MYOMETRIUM THICKNESS (mm)	AVERAGE DIAMETER OF THE GESTATIONAL SAC OR MASS (mm)
Type I	Greater than 3	
Type II	1 – 3	IIa:30 mm or less
		IIb: greater than 30 mm
Type III	1 or less	IIIa: 50 mm or less
		IIIb: greater than 50 mm or with UAVF (uterine arteriovenous fistula)

Patient symptoms includes pelvic pain and vaginal bleeding in the first trimester .Diagnosis made by ultrasound both Transvaginal and Trans abdominal with color Doppler , MRI for confirmation and serum BHCG levels.







Above Ultrasound pictures of the patient shows a gestational sac with yolk sac, fetal pole with fetal heart beat in the lower segment uterine scar area.

ULTRASOUND CRITERIA FOR DIAGNOSIS AS PER RCOG GREENTOP GUIDELINES ARE :

- Empty uterine cavity
- A gestational sac (or) a solid mass embedded within the lower uterine segment scar area.
- Thin (or) absent myometrial layer between the sac and the bladder.
- Prominent vascular flow around the sac.
- Empty cervical canal and closed internal os helps to rule out cervical pregnancy, threatened / incomplete abortion.
- Negative sliding sign.

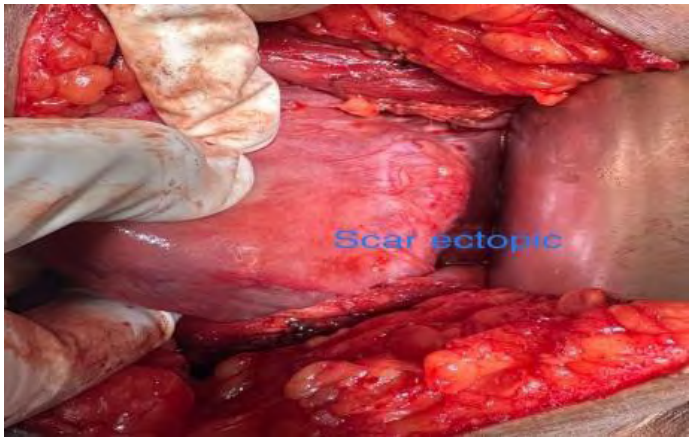


Fig 1shows : Sacr ectopic mass in the previous lower uterine segment scar area

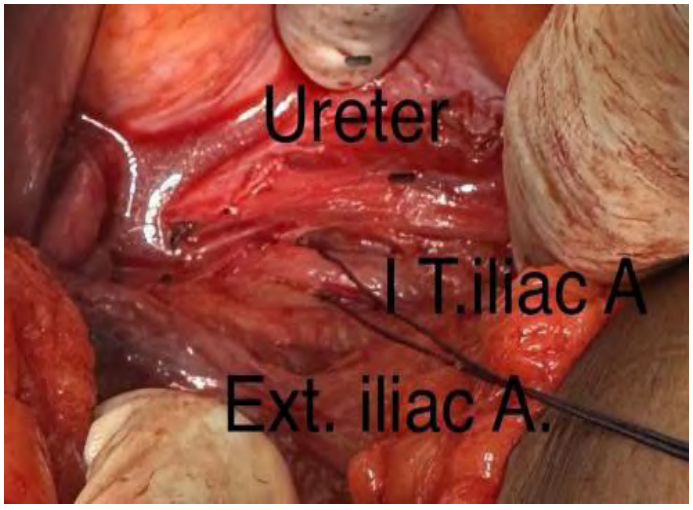


Fig 2 shows: Stay suture in anterior branch of internal illiac artery prior to scar excision

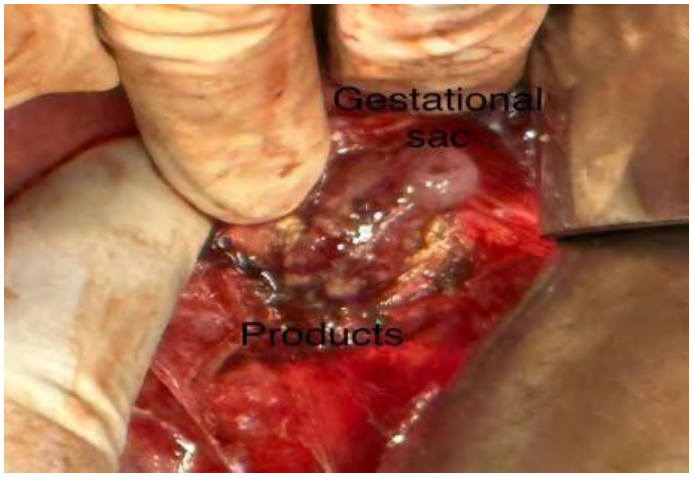


Fig 3 shows : gestational sac with products

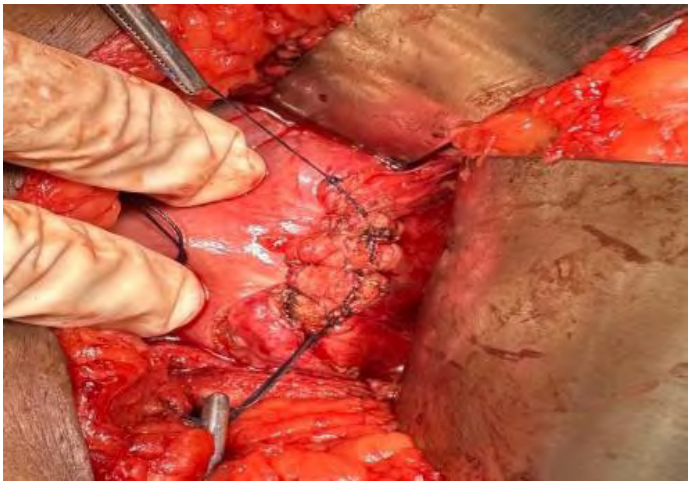


Fig 4 shows : Final closure of the uterine wall after excision.

TREATMENT CAN BE MEDICAL (OR) SURGICAL DEPENDING UPON THE SIZE OF PREGNANCY, FETAL VIABILITY, HEMODYNAMIC STABILITY AND NEED FOR FUTURE FERTILITY.

- Medical management includes methotrexate injection, can be given as intrasac along with KCL injection under ULTRASOUND guidance, systemic (or) Intramuscular (or) a combination of both. Systemic methotrexate includes single dose regimen of 50 mg / m2 (or) multi dose regimen of 50mg /m2 on day 1,3,5 and 7 along with alternate folinic acid 0.1mg/kg.Close follow up of the patient with serial BHCG levels and ultrasound is mandatory .It may need surgical approach if medical treatment fails or heavy bleeding occurs.
- Surgical treatment successful in 96% that helps to remove the sac completely and to repair the uterine defect and a chance for future fertility. It includes hysterescopic suction evacuation, excision of scar via Laparotomy, laparoscopy and hysteroscopy. If anterior myometrial wall thickness is < 3mm on ultrasound,

dissection of bladder from the lower uterine segment is needed to decrease the risk of bladder injury which can be done either by laparotomy (or) a combined laparoscopic and hysteroscopy procedure.

- Many methods have been tried before and during procedure to minimize the risk of bleeding that includes uterine artery embolization prior to hysteroscopy but it may cause inadvertent ovarian embolization ,so patients plan for future fertility should be considered, double balloon catheter tamponade, uterine artery ligation, internal illac artery temporary occlusion and vasopressin injection. Newer modality like HIFU(High intensity focused ultrasound)have also been tried which creates thermal effect in pregnancy tissues thereby reducing its blood supply.
- Hysterectomy is reserved for patients with uterine rupture, heavy bleeding and hemodynamic instability.

CONCLUSION:

- Ectopic pregnancies which includes CESAREAN SCAR ECTOPIC PREGNANCYis the leading cause of morbidity and mortality in fertile women .Early diagnosis and prompt treatment is needed, which can be individualized according to the patient's condition and need for future fertility.70% of women are able to conceive in future with 18% of recurrent CESAREAN SCAR PREGNANCY. So follow up in subsequent pregnancies is mandatory to avoid futurecomplications like miscarriage ,pre term birth ,placenta accreta and uterine rupture.

REFERENCES

1. An Unusual Case of Live Caesarean Scar Ectopic Pregnancy: A Common Entity in an Uncommon Location Sayali D Joshi 1,A,B,C,D,E,F,✉, Shenaz A Momin 1,A,C,D,E,F, DevShetty 1,C,D,F. PMCID: PMC5466375 PMID: 28638494
2. Cesarean Scar Ectopic Pregnancy: A Diagnostic and Management Challenge KoulshanJameel 1, Gul-e-rana Abdul Mannan 1, RabiyaNiaz 1, Durr-e-shahwar Hayat 2,.PMCID: PMC8118189 PMID: 33996323
3. Cesarean section scar ectopic pregnancy - a management conundrum: a case report ,RumbidzaiMajangara, ,Mugove Gerald Madziyire,CladiousVerenga &Marshall Manase Article number: 137 (2019)
4. Application of laparoscopic internal iliac artery temporary occlusion and uterine repair combined with hysteroscopy aspiration in type III cesarean scar pregnancy -Xianghui Su 1, MinerYang 1, ZhaoNa 1, CanliangWen 1, Meiling Liu 1, ChunfangCai 1, ZhuohuiZhong 1, Bingqian Zhou 1, Xiang Tang 1.PMCID: PMC8991161 PMID: 35422906
5. Reproductive outcome after cesarean scar pregnancy Author links open overlay panelMaddalena Morlando, Anna Conte, Antonio SchiattarellaDepartment of Woman, Child and General and Specialized Surgery, Obstetrics and Gynecology Unit, University of Campania "Luigi Vanvitelli", 80138, Naples, Italy
6. Diagnosis and management of ectopic pregnancy green top guidelines (GTG) of royal college of obstetrics and gynecology .
7. Cesarean Scar Ectopic Pregnancy Clinical Classification System With Recommended Surgical Strategy-Yanli Ban 1, Jia Shen 1, Xia Wang 1, Teng Zhang 1, Xuxu Lu 1, Wenjie Qu 1, Yiping Hao 1, Zhonghao Mao 1, Shizhen Li 1, Guowei Tao 1, Fang Wang 1, Ying Zhao 1, Xiaolei Zhang 1, Yuan Zhang 1, Guiyu Zhang 1, Baoxia Cui 1 - PMCID: PMC10108840 PMID: 37023450

VACCINATION DURING PREGNANCY

DR. THAMILSELVI M MD, DGO, DNB (OG),FICOG.,

DR. UMA VAIDHIYANATHAN DGO, DNB (OG),FICOG.,

INTRODUCTION:

As altered immune response occurs during pregnancy, pregnant women are more susceptible to infectious diseases. Pregnant women, fetus and new-born are at increased risk of some infections and severe outcomes of certain infections. Infection sequelae in new-born can result in life long disability. The centre for disease control suggests that vaccination is an integral part of pregnancy care as pregnant women and her baby are vulnerable population. Vaccination during pregnancy can guard the mother against the vaccine preventable infections and protect the new-born baby by transferring antibodies to the fetus.

VACCINATION DURING PREGNANCY:

There are vaccines which can be given safely during pregnancy. Inactivated vaccines, bacterial vaccines and toxoids are safe for pregnant women. Live attenuated Vaccines are contraindicated during pregnancy. Let us see about the individual vaccines.

1. TETATUS TOXOID

This is to protect the mother and new-born from tetanus. Tetanus is a life threatening bacterial disease caused by clostridium tetani

Tetatus toxoid vaccine is given as 2 doses at least 28 days apart, intramuscular injection. First dose is given as soon as the pregnancy is detected.

Usually 2 doses of TT vaccine is recommended during pregnancy. If the previous vaccinated pregnancy is less than 3 years, then one single booster dose of TT vaccine is sufficient.

Adverse effects are very rare and few. They are soreness, redness or swelling at the site of injection, fever, headache, body ache, fatigue, nausea, vomiting, diarrhoea.

2. TD VACCINE:

Td vaccine is a combination of tetanus toxoid and lower concentration of diphtheria antigen.

Ministry of health and family welfare has recommended the replacement of TT vaccine with Td vaccine in India's immunisation programme.

Diphtheria caused by coryne bacterium diphtheriae, has been a feared infection disease globally and it causes devastating epidemics.

2 doses of Td vaccine is recommended during pregnancy. First dose is given during early pregnancy and second dose is given 4 weeks after the first dose and at least 2 weeks before the due date.

Td booster is given as a single dose if pregnancy occurs within 3 years of last Td vaccinated pregnancy.

Storage of the vaccine is between 2^0 -8^0 c. Do not freeze. common side- effects are pain & erythema at the injection site, body ache , fatigue, fever.

3. INFLUENZA VACCINE:

Pregnant women have had a higher rate of hospital admission than the general population

from seasonal influenza and they are at higher risk of acute respiratory distress syndrome. Fetuses are at increased risk of preterm birth and low birth weight and also fetal death.

ACOF, WHO, CDC strongly recommends influenza vaccine during pregnancy. This is an inactivated vaccine and is safe during pregnancy. It is mainly recommended during second and third trimester of pregnancy, but it can also be given during first trimester. It is given as intramuscular injection.

Nasal spray influenza vaccine is contraindicated during pregnancy as it is a live attenuated vaccine.

Common side effects from IM injections are pain and erythema at injection site, fatigue, fever, headache & vomiting.

4. COVID 19 VACCINE:

Covid 19 infections during pregnancy may result in serious consequences and rapid deterioration of health and may affect the fetus also. There is increased risk of preterm birth, preeclampsia like illness and increased neonatal morbidity.

WHO recommends vaccination in pregnant women. Covid 19 vaccines available are safe during pregnancy and can be given at any time of pregnancy.

Experts believe that covid 19 vaccines are unlikely to pose a risk to the pregnant women or the fetus[1]

Contraindication for covid 19 vaccinations are:

Anaphylactic / allergic reaction to the previous dose of covid 19 vaccine or other vaccines

Active covid 19 infection

Covid 19 infection treated with anti covid 19 monoclonal antibodies orconvalescent plasma.

WHO does not recommend pregnancy testing prior to vaccination and delaying pregnancy or terminating pregnancy because of vaccination.

RCOG states that pregnant women should be offered the vaccine as the general population[2].

Common side effects following covid 19 vaccine are usually mild like fever, pain on injection site or feel unwell for 1-3 days.

Very rarely symptoms like shortness of breath, chest pain, pain in limbs, petechiae, abdominal pain, vomiting and persistent headaches can occur within 20 days of receiving the covid 19 vaccine.

If the pregnant women is diagnosed with covid 19 infection, vaccination isdeferred for 12 weeks.

5. HEPATITIS B VACCINE:

Hepatitis B vaccine is an inactivated virus vaccine and is composed of non- infectious Hepatitis B surface antigen particles.

Globally many studies confirmed that there are no adverse pregnancy outcomes after Hepatitis B vaccination during pregnancy[3].

Even though Hepatitis B vaccination is not contraindicated during pregnancy, it is offered only for pregnant women who are at high risk of acquiring Hepatitis B infections during pregnancy like doctors, lab technician etc.

Hepatitis B vaccination with an ongoing pregnancy is safe and does not warrant termination.

6. HEPATITIS A VACCINE:

Safety of this vaccine during pregnancy has not been determined. It is an inactivated virus vaccine and hence the risk to the developing fetus is low. So risks should be weighed against benefits of vaccinating the pregnant women whoare at risk of exposure to the infection.

7. RABIES VACCINE:

Rabies has a 100% mortality rate following exposure to rabies like dog bite. Proper wound care,

immunization with rabies vaccine and injection of antirabies immunoglobulin reduces the risk of contracting rabies maximally.

Human rabies vaccine available are purified chick embryo cell vaccine and purified vero cell rabies vaccine.

Both vaccines are safe during pregnancy. Vaccines can be given even in the first trimester. These vaccines did not interfere with the development of fetusor infants[4].

Side-effects are mild pain at injection site, fever, headache and fatigue.

8. YELLOW FEVER VACCINE:

Yellow fever is endemic in rural areas of sub Saharan Africa and tropical regions of South America. It is a mosquito born-viral infection. Yellow fever vaccine is a live attenuated vaccine. So it is contraindicated during pregnancy. Unvaccinated women are advised to avoid travelling to these endemic areas.

Where travel or contact is unavoidable, vaccination in pregnancy should be considered, weighing the possible fetal risk of vaccination against the risk to both mother and the fetus from yellow fever infection which has significant morbidity and mortality.

The data with 690 cases of intrauterine exposure to the vaccine do not currently demonstrate an increase in risk of adverse pregnancy outcomes or congenital infection.

In one study of 74 cases who are vaccinated with yellow fever vaccine during early pregnancy, there were 7 spontaneous abortions, 3 newborns had minor anomalies and 2 had major defects. This sample is too small to rule out a moderate increased risk of adverse effect of yellow fever vaccine.

So we should reassure pregnant women who are inadvertently vaccinated[5].

VACCINES TO BE AVOIDED DURING PREGNANCY:

- Mumps, measles, rubella vaccine
- Small pox vaccine
- Yellow fever vaccine
- Typhoid vaccine
- Oral polio vaccine
- Live influenza vaccine(nasal)
- Japanese encephalitis vaccine
- Chicken pox vaccine
- Human papilloma virus (HPV) vaccine.

VACCINE	GENERAL RECOMMENDATION FOR USE IN PREGNANT WOMEN
Covid 19	Recommended
Hepatitis A	Base decision on risk vs benefit
Hepatitis B	Recommended in some circumstances
HPV	Not Recommended
Influenza(Inactivated)	Recommended
Influenza(nasal)	Contraindicated
MMR	Contraindicated

VACCINE	GENERAL RECOMMENDATION FOR USE IN PREGNANT WOMEN
Meningococcal(ACWY)	May be used if otherwise indicated
Meningococcal(B)	Base decision on risk vs benefits
PCV 13	Not Recommended
Polio (Inactivated)	May be used if needed
Oral Polio	Not Recommended
Td	Recommended
T dap	Recommended
Varicella(Chicken pox)	Contraindicated

TRAVEL AND OTHER VACCINES:	
Anthrax	Not Recommended
BCG	Contraindicated
Japanese encephalitis	Contraindicated
Rabies	May be used if otherwise indicated
Typhoid	Give Vi polysaccharide if needed
Yellow fever	May be used if benefits outweigh risks

CONCLUSION:

FOGSI recommends vaccination counselling as a part of pre pregnancy counselling. Rubella, Hepatitis B and varicella vaccination should be given preferably during post menstrual period. Pregnancy should be deferred for 3 months in case of rubella vaccine.

Vaccination during pregnancy is essential. Vaccination of pregnant women protect the new-born for the first few months of life until the baby gets his own vaccination. Inactivated vaccines and toxoids are safe during pregnancy. Live attenuated vaccine are generally contraindicated during pregnancy.

Vaccination during pregnancy is one of the crucial steps for a healthy pregnancy. Pregnancy vaccination protects both mother and the fetus and is a cost effective strategy to improve pregnancy outcome.

References:

9. Interim clinical consideration for use of covid 19 vaccines currently authorised in theUnited States; centre for disease control andpreventions;https://www.CDC.gov/vaccines/covid19/info.by.product/clinical consideration html # pregnant:
10. Royal college of obstetrician and gynaecologist(RCOG)covid 19 vaccines, pregnancyand breast feeding .[Online] 16 April 2021.https://www.rcog.org.uk/en/guidelines-researchservices/coronavirus-Covid-19-pregnancy-and-womens-health/

Covid-19- vaccines-and-pregnancy/ Covid-19-vaccines-pregnancy-and-breastfeeding/;Accessed:16 May April 2021.

11. Reddy PA, Gupta I, Ganguly NK. Hepatitis-B vaccination in pregnancy: Safety and immunogenic response in mothers and antibody transfer to neonates. Asia Oceania J Obstet Gynaecol 1994;20(4);361-5: PMID:7832667;http://dx.doi.org/10.1111/j.1447- 0756.1994.tb00482.
12. Grosheide PM, Schalm SW, Van Os HC, Fetter WP, Heijtink RA, Immune response to hepatitis B vaccine in pregnant women receiving post-exposure prophylaxis.Eur J Obstet Gynecol Reprod Biol 1993; 50[1]:3-8;PMID:8365536; http://dx.doi.org/10.1016/0028-2243(93)90164-8
13. Safety of post exposures rabies prophylaxis during pregnancy . A follow up study fromGuangzhou, china Humvaccine Immunother 2013 Jan 1; 9 (1): 177-183. Published online 2013 Jan 1
14. Exposure to yellow fever vaccine in early pregnancy E Robert, T Vial,C Schaefer; J Arnon M Reuvers. Vaccine 1999 Jan 21 ; 17(3):283-5

ADNEXAL MASSES IN EARLY PREGNANCY

DR. ARULMOZHI RAMARAJAN, MD, DGO, PGDMLE, FICOG.,

T. RAMANIDEVI, MD, DGO, FICS, FICOG.,

Vice President FOGSI 2020
Senior ConsultantRamakrishna Medical Centre LLP &
Janani Fertility Centre, Trichy

DR. SWATI NETHAJI, MS(OG).,

Fellowship in Endogynaecology.,

INCIDENCE:

Adnexal masses are discovered in 1 per 76 to 1 per 2328 deliveries.([1] Aggarwal).

Most of the cysts are asymptomatic and are diagnosed incidentally during dating scan.

The main concerns of adnexal mass in pregnancy includes complications related to the adnexal mass like torsion, rupture, infection and labor obstruction. Another dreaded concern is malignancy although the over-all incidence of malignancy noted is 1-8%. Timely management of these cases is essential, without jeopardizing the health of the fetus.

CLASSIFICATION

Adnexal masses identified in early pregnancy can be classified in different ways:

1. Asymptomatic (Incidental finding on clinical / ultrasound examination)
2. Symptomatic

OR

1. Functional cysts – Corpus Luteal cyst, lutein cysts, ovarian hyper stimulation syndrome (OHSS)
2. Non-functional cysts – Fimbrial cysts, ovarian cysts, dermoid cyst, endometriotic cyst

OR

1. Benign lesions – Chronic ectopic, sub serous fibroid, peritoneal inclusion cyst,cornual fibroid, accessary horn, heterotopic pregnancy, non-pregnant horn of bicornuate uterus
2. Malignant neoplasms

FUNCTIONAL CYSTS

Follicular cysts are the most commonly found functional cysts and are usually <10cm appearing as a simple cyst. It occurs when a follicle doesn't rupture and they regress spontaneously. Corpus luteal cysts constitute 13-17% of cystic masses in pregnancy and appear as 'ring of fire' on doppler. The corpus luteum which forms after ovulation produces progesterone until the placenta takes over. Failure of corpus luteum to regress after 9 weeks leads to the formation of such cysts. Hemorrhagic cysts appear as a fishnet on USG with fine interdigitating lines and has no flow on doppler.

HYPERSTIMULATED OVARIES

Ovarian hyper stimulation syndrome is an iatrogenic complication of ovulation induction and severe forms occur in 3-8% of IVF cycles. It leads to enlarged ovaries with multiple cysts and vascular hyper permeability with subsequent hypovolemia and hemoconcentration. They usually regress in 90% of cases and the rest may need active interventions.

THECA LUTEIN CYSTS

Also called as hyperreactio luteinalis, they are bilateral functional cysts filled with clear fluid. They occur due to elevated levels of beta hCG and are associated with molar pregnancies, choriocarcinoma, hyperthyroidism and multiple pregnancies. They are also seen in PCOD patients due to increased sensitivity of ovarian stroma to beta hCG. It is mostly seen in the third trimester.

LUTEOMA

It is a rare benign tumor of pregnancy where normal ovarian parenchyma is replaced by proliferating luteinised stromal cells. These tumors secrete androgens leading to maternal hirsutism and virilisation of female fetus resulting in clitoral enlargement and ambiguous genitalia.

ENDOMETRIOTIC CYSTS

Ovarian endometriotic cysts comprise 4-5% of ovarian cysts diagnosed in early pregnancy. Despite their rarity they account for approximately a quarter of surgical interventions for ovarian cysts in pregnancy. They have a typical 'ground glass feature' on USG. High progesterone levels in pregnancy cause decidualisation of ectopic endometrium, and may cause extensive intraluminal papillary projections with increased vascular flow and may appear similar to malignant ovarian tumors. Majority of the cysts regress in size during pregnancy due to high progesterone levels, temporary cessation of menstruation and apoptosis.

DERMOID CYST

They are the most common ovarian germ cell tumor in pregnancy and are commonly diagnosed in second trimester. Dermoid cysts are generally benign with <2% malignant transformation rate into invasive squamous carcinoma. They present with Rokitansky nodule which is a hyper echoic nodule with acoustic shadowing. They exhibit 'tip of iceberg' phenomenon with a highly echogenic cyst having contents of sebum, tooth and hair which causes posterior attenuation of sound. An appearance of 'dermoid mesh' can also be seen on USG with multiple interdigitating lines and dots which are noted due to the floatation of hair in sebum. The chances of torsion is higher with dermoid cysts owing to the weight of the dermoid and its rupture can lead to chemical peritonitis.

CYSTADENOMA

They account for 40-50% of benign epithelial neoplasm. They can be serous or mucinous with serous type being the most common. Serous cyst adenomas often present as large (5-20cm), multiloculated cysts and are bilateral in 20% of cases. They are not sensitive to hormones and usually persist after the second trimester.

NON-OVARIAN MASSES

Non ovarian masses include pedunculated fibroids, accessory horn, non -pregnant horn of bicornuate uterus, chronic ectopic and hydrosalpinx. Fibroids appear as heterogeneous solid masses which are not attached to the ovary whereas hydrosalpinx presents as a tubular shaped structure with incomplete septae. Chronic ectopic pregnancy occurs as a result of small, rupture of tubal pregnancy, which leads to a hematocoele formation. Hematocoele leads to an inflammatory reaction and formation of pelvic adhesions mimicking a complex mass. Beta hCG is usually low or negative in these cases causing diagnostic confusion. Paraovarian cysts are embryological remnants of mesonephric or paramesonephric

ducts. They typically occur in mesosalpinx and are not significant. Peritoneal inclusion cysts are usually asymptomatic and doesn't require intervention.

INFLAMMATORY MASS

Tubo-ovarian abscess, appendicitis and diverticulitis might present as adnexal masses.

CLINICAL FEATURES

Adnexal masses are usually asymptomatic. They might get symptomatic based on their location, size, consistency, mobility or compression of adjacent organs. Symptoms are similar to non-pregnant women like pain, nausea, vomiting and fever. Ectopic pregnancy should always be ruled out in a symptomatic pregnant woman presenting in early pregnancy.

PREGNANCY ASSOCIATED CHANGES OF OVARIAN MASS

RUPTURE

The chances of ovarian cyst rupture during pregnancy is 1%. Pain occurs as a result of capsular stretching or leakage of cyst contents causing peritoneal irritation. Rupture of mucinous cyst might lead to pseudomyxoma peritonei.

TORSION

Torsion of the ovarian cyst might occur in pregnancy resulting in sudden onset of pain. It has a characteristic loin to pelvis pain which occurs as a result of stretching of infundibulo-pelvic ligament. It is reported that pregnant women have one percent increased risk of ovarian torsion when compared to non-pregnant women. The risk of torsion decreases in later stages of pregnancy due to the enlarging uterus which limits the mobility of ovaries. On USG ovaries might appear oedematous and congested with multiple small cysts located at the periphery resulting in 'whirlpool sign'. Absence of blood flow on doppler might occur inlater stages.

OBSTETRIC OUTCOME

Large adnexal masses are linked with poor obstetric outcome like increased risk of miscarriage and preterm delivery. Due to the mechanical effect, they can predispose to labor dystocia especially if the mass is in near the lower uterine segment. They can also compress the lower digestive tract and urinary tract leading to hydroureteronephrosis. A prolapsed mass in the POD can cause urinary symptoms, including retention. Such a situation can be managed conservatively with bladder drainage and rest until the uterus grows out of the pelvis. Other maternal complications such as placental abruption, postpartum haemorrhage did not show any significant difference when compared to normal population. In terms of fetal outcomes, there was no significant increase in risk of IUGR or intra uterine death.

MALIGNANCY

The incidence of malignancy in ovarian masses in pregnancy is noted to be around 5%. Dysgerminoma is the commonly encountered malignancy in pregnancy. Around 10% of ovarian cancers are metastatic with breast, gastric and intestinal cancers being the primary origin of tumors. Hence breast examination must be performed in all cases presenting with an ovarian mass. Though there is no cut off for the size of lesion, a growth rate greater than 0.35cm/week is ominous. In contrast to non-pregnant women, the majority of ovarian malignancies in pregnancy are diagnosed in early stages (80% in stage 1 of FIGO).

DIAGNOSIS

HISTORY

Ovarian stimulation / hyper stimulation / IUI; earlier scan reports if any to identify pre-existing adnexal pathology.

TUMOR MARKERS

Tumor markers have a low validity during pregnancy. CA125, alpha feta protein, lactate dehydrogenase and hCG are physiologically elevated during first trimester of pregnancy and hence have limited value for characterising ovarian lesions. The main need of tumor markers is to monitor the therapeutic response and the risk of relapse.

IMAGING

USG is used as the first modality to assess adnexal masses in pregnancy. It has 97% accuracy in diagnosing dermoid cysts, 80% accuracy for endometrioma and 71% accuracy for simple cysts. USG is the first choice of method not only for diagnosing adnexal mass, but also for distinguishing benign and malignant masses. USG characteristics suggestive of malignancy include thick septations(>2-3mm), increased wall thickness, free pelvic fluid, solid components and papillary components. The incidence of malignancy in unilocular cyst is around 0.3% whereas in multilocular cyst it is around 73%. Doppler is a useful tool to assess malignancy as malignant tumors generally have lower blood flow impedance and higher blood flow velocity. International ovarian tumor analysis (IOTA) has10 simple rules for evaluation of adnexal lesions and has a sensitivity of 91% and specificityof 87%.

- Low risk masses: anechoic, unilocular fluid-filled cysts with thin walls.
- High risk masses: show solid areas, nodularity and thick septations.
- Intermediate risk masses: Not anechoic, not unilocular, but do not have features of malignancy.

MRI

It is estimated that up to 20% of adnexal masses cannot be adequately visualized by proper evaluation on ultrasound. MRI can assist sonographic assessment of adnexal masses in pregnancy by showing uterine origin and distinguishing neoplastic lesions. It has an accuracyof 93% in distinguishing between benign and malignant etiologies. MRI is generally safe in pregnancy, and no reports document adverse effects of its use on the mother or the fetus.

However, contrast materials containing gadolinium increase the risk of skeletal defects and malformations in animal studies and are therefore classified under drug category C in pregnancy.

MANAGEMENT

The major concern when an adnexal mass is discovered during pregnancy is: What is the nature of the mass? Will this mass adversely affect pregnancy? Is there a possibility for the mass to regress? And lastly what is the likelihood of malignancy?

Management varies widely depending upon the pathology, from doing nothing to emergency surgery. Small (<5cms), asymptomatic non-malignant lesions are unlikely to have an adverse effect on the pregnancy. 71% of benign ovarian masses will either decrease in size or resolve spontaneously. As no intervention is required, treatment related morbidity is also averted. However, these need to be monitored for increase in size, torsion, and rupture.

Cysts measuring more than 10cm need to be resected due to increased chances of rupture, torsion or malignancy. Any adnexal mass persisting after 16 weeks of pregnancy areless likely to resolve spontaneously and are more likely to result in complications like torsion, rupture or obstruction of labor. Up to 10% of persistent complex ovarian masses willultimately be diagnosed as malignancy. If ovarian malignancy occurs during pregnancy, it is of early stage and has favorable outcome. Management of ovarian malignancy is same as in non-pregnant woman depending on stage,

gestational age and grade of the tumor.

Management of cysts between 5cm and 10cm remains controversial. If it has suspicious features like thick septa, nodules, papillary excrescences or solid components,then resection is recommended.

When acute complication occurs, surgery is indicated in any trimester. The best time to operate a non-urgent adnexal mass is in the second trimester (16-20 weeks) to avoid risks of miscarriage if performed earlier or preterm delivery if performed later. Also access to the adnexa is much easier when compared to third trimester and anesthesia complications to fetus is less. Any ovarian mass operated before this period should be given progesterone supplement.

Laparotomy or laparoscopy can be performed for adnexal masses needing surgical intervention. Laparoscopy has added advantage with significantly lesser operative time, lesser preoperative morbidity, reduced length of hospital stay and decreased post-operative pain resulting in faster post-operative ambulation and return to regular activity which is very crucial in pregnancy because of the increased thrombotic events. Laparoscopy if performed is preferred in non-urgent cases around 16-20 weeks and trocars should be placed at least 6cm above the fundus or left upper quadrant. Establishment of pneumo peritoneum should be gradual with careful monitoring of hemodynamic status and intra-abdominal pressure between 8 and 12mm Hg is preferred.

References

1. Aggarwal P, Kehoe S. Ovarian tumours in pregnancy: a literature review. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2011 Apr 1;155(2):119-24.
2. Khan M, Zubair M. Evaluation of Adnexal Masses with Gray Scale Ultrasonography and Color Doppler Flow Imaging in the First Trimester of Pregnancy. Journal La Multiapp. 2020 Jun 21;1(2):1-6.
3. Muto MG, Sharp HT, Goff B, Falk SJ. Management of an adnexal mass. UpToDate, Waltham, MA.(Accessed on May 24, 2016.), editor. 2014.
4. Adusumilli S, Hussain HK, Caoili EM, Weadock WJ, Murray JP, Johnson TD, Chen Q, Desjardins B. MRI of sonographically indeterminate adnexal masses. American journal of roentgenology. 2006 Sep;187(3):732-40.
5. van Nagell Jr JR, Hoff JT. Transvaginal ultrasonography in ovarian cancer screening: currentperspectives. International journal of women's health. 2014;6:25.
6. Montoriol PF, Hordonneau C, Boudinaud C, Molnar I, Abrial C, Kossai M. Benign Brennertumour of the ovary: CT and MRI features. Clinical Radiology. 2021 Aug 1;76(8):593-8.
7. Togashi K. Ovarian cancer: the clinical role of US, CT, and MRI. European radiology. 2003Dec;13(6):L87-104.
8. Hoover K, Jenkins TR. Evaluation and management of adnexal mass in pregnancy. Americanjournal of obstetrics and gynecology. 2011 Aug 1;205(2):97-102.
9. Yacobozzi M, Nguyen D, Rakita D. Adnexal masses in pregnancy. InSeminars in Ultrasound, CT and MRI 2012 Feb 1 (Vol. 33, No. 1, pp. 55-64). WB Saunders.

HETEROTOPIC PREGNANCY (HP)

DR. THAMILSELVI M MD., DGO., DNB (OG)

DR. UMA VELMURUGAN MD,FRCOG (UK), CCT (UK).

FELLOWSHIP IN FERTILITY (BIRMINGHAM, UK)

Heterotopic pregnancy is defined as the co-existence of one intrauterine pregnancy and the other outside the uterus, commonly in the fallopian tube and uncommonly in the cervix or ovary. Is a very rare condition, with incidence of 1/30,000 (1) . Pregnancies, and is a potentially fatal condition. It was first reported in 1708 as an autopsy finding (2).

HP occurring in natural conception is rare and HP as a consequence of assistant reproductive technique is more common. The prevalence of HP is having an increasing trend in last decade due to the increased use of ovulation induction (3). Added to this patient who require ART treatment mostly present with tubal pathology which may be a reason for extra uterine pregnancy.

RISK FACTORS:

Risk factors for heterotophic pregnancy is similar to that of ectopic pregnancy. PID, endometriosis, history of ectopic pregnancy, STD infection mainly chlamydia, fertility treatment, fallopian tube surgeries (3) etc.

DIAGNOSIS:

Diagnosis of heterotopic pregnancy is not easy, as the intrauterine pregnancy masks the effect of ectopic pregnancy. Four common presenting signs & symptoms – abdominal pain, adenexal mass, adenexal tenderness, peritoneal irritation and an enlarged uterus (4).

The recent advances in transvaginal sonography (TVS) is a diagnostic tool which helps in early diagnosis of heterotophic pregnancy. In the TVS the typical image will be the presence of I.U gestation with an ectopic gestation in the adenexa (5). Literature review of ultrasound images showed that a tubal ring **(**an adenexal mass with concentric echogenic rim of tissue, a gestational sac, surrounding a hypo echogenic empty center**)** (6) . Sometimes even with TVS, the adenexal mass can be mistaken for haemorrhagic corpus luteum or ovarian cyst, especially in hyper stimulated ovaries (7).

If the B.HCG levels are higher for the period of gestation with an I.U pregnancy, we should be suspicious of coexistent ectopic pregnancy. Presentation of acute abdominal pain with and I.U pregnancy also raises the possibility of concurrent ectopic pregnancy. In majority of cases signs and symptoms of peritonism, shock from internal bleeding secondary to ruptured ectopic pregnancy is the common presenting feature. Ultrasound findings of haemoperitoneum along with I.U pregnancy may be feature which raises the suspicion of heterotrophic pregnancy. If there is uncertainity after performing ultrasound, laparoscopic intervention may be needed to facilitate diagnosis and future treatment (8).

Definitive diagnosis is given by the histopathological examination, as presence of chorionic villi in the wall of the tube, confirming the presence of an ectopic gestation. It may also describe inflammation and distortion of plicae, and modifications consistent with chronic salpingitis (9).

The treatment of heterotopic pregnancy consists of surgical intervention in order to remove the extra uterine pregnancy. A laparoscopic approach is usually desirable, in the absence of contraindications. The intrauterine pregnancy is preserved and may advance with normal surveillance and with no additional complications (10).

In situation where the ectopic pregnancy was detected early and was un ruptured treatment options of expectant management with aspiration and installation of potassium chloride or prostaglandin into the gestational sac (11) was tried Systematic methotrexate (MTX) or local injection of MTX cannot be used in a heterotrophic pregnancy owning to its toxicity (12). Laparoscopy and removal of the ectopic pregnancy is best mode of treatment without disrupting the course of an I.U pregnancy.

REFERENCES

1. Michal,M.; Marian, M.; Marek,M.; Ewa, W.-O. Heterotopic pregnancy in the absence of risk factors-Diagnostics difficulties. Ginekol. Pol. 2011, 82, 866-868. (PubMed)
2. Marcus, S.F.; Macnamee,M.; Brinsden, P. Pregnancy: Heteroptopic pregnancies after in-vitro fertilization and embryo transfer. Hum. Reprod. 1995, 10, 1232-1236. (CrossRef)
3. Ectopic Pregnancy: MedlinePlus Medical Encyclopedia. Available online: https://medlineplus.gov/ency/article/000895.htm (accessed on26 November 2019).
4. Reece EA, Petrie RH,Sirmans MF, Finster M, Todd WD. Cobined intrauterine and extrauterine gestations: a review. Am J Obstet Gynecol. 1983;146:323-30. (PudMed) (Google Scholar)
5. Poujade O, Ducarme G, Luton Cornual heterotopic pregnancy: a case report. J Med Case Reports. 2009;3:7233. (PMC free article) (PudMed) (Google Scholar)
6. Fleischer AC, Pennell RG, McKee MS, Worrell JA, Keefe B, Herbert CM, et al, Ectopic pregnancy: features at transvaginal sonography. Radiology. 1990;174:375-8. (PudMed) (Google Scholar)
7. Cellen PW. Ultrasonography in obstetrics and gynecology. In: Levine D, editor. Ectopic pregnancy.5th ed. Philadelphia: Saunders Elsevier; pp. 1020-47. (Google Scholar)
8. Rezai, S.; Giovane, R.A.; Minton, H.; Bardawil, E.; Zhang, Y.; Patil, N.; Henderson, C.E.; Guan, X. Laparoendoscopic Single-Site Surgery for Management of Heterotopic Pregnancy: A Case Report and Review of Literature. Case Rep. Obstet. Gynecol. 2018,2018, 1-6. (CrossRef) (PubMed)
9. Ravindra, S.; Prasad, S.; Suguna, B.V. Histomorphology of fallopian tubes in ectopic pregnancy. Arch. Med. Health Sci. 2016, 4, 201. (CrossRef)
10. Chen, L.; Wen, H.; Xu, D.; Chen, L.Q.; He, J. Management and pregnancy outcomes of heterotopic pregnancy. Zhonghua Fu Chan Ke Za Zhi 2018, 53, 768-775. (PubMed)
11. Lialios GA, Kallitsaris A, Kabisios T, Messinis IE. Ruptured heterotopic interstitial pregnancy: rare cade of acute abdomen in a Jehovah's witness patient. Fertill Sterl. 2008;90(1200):e15-7. (PubMed)(Googlem sholar)
12. Oyawoyea S, chander B, Pavlovic Hunter J, Gandir AA. Heeotopic pregnancy: sucheesful management which aspiration of corneal/ intersutioal gestational sac and installation of small dose of methotrexate. Fetal diagn ther.2003; 18:1-4. (PubMed) (google Scholar)