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Stillbirth Society of India

International Stillbirth Alliance Member

Theme of the Month:
Recurrent Pregnancy Loss

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From the Editor's Desk

Dear Readers,

I am greatly honoured to be entrusted the work of editing the e-newsletter of the Stillbirth Society of India. The theme for this month's e-newsletter is **"Recurrent Pregnancy Loss".**

Recurrent pregnancy loss [RPL] is a distressing disorder which owes its etio-pathogenesis to multiple causes. This remains a highly debated and researched area. We have put in dedicated efforts to compile and bring forth to you important articles illustrating the same.

The first article, **'Genetics and Evaluation of RPL'** serves as a beginners guide to genetic tests for evaluating RPL. The authors have presented an algorithm which will be very helpful in the work up of RPL.

The next article, **'Antiphospholipid Syndrome'** introduces a tricky subject and lucidly walks through the clinical aspects involved. **'Evaluation of RPL- Newer Perspectives'** focuses on the latest guidelines on evaluation along-with basics of genetics in RPL. **'Uterine Anomaly as a cause of RPL'** deals with anatomical abnormalities, classification and diagnosis in evaluation of RPL.

Lastly, we have the Secretary's report which summarises the relevant activities of the SBSI in the month of September.

We wish our readers a happy reading!!!

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Genetics & Evaluation of Recurrent Pregnancy Loss

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What is RPL?

Recurrent pregnancy loss (RPL) also referred to as recurrent spontaneous abortion, is defined as the loss of a clinical pregnancy before 20 completed weeks of gestational age (18 weeks after fertilisation) or, if gestational age is unknown, the loss of an embryo/ foetus of <400 g.

However, the definition is debated:

- According to European Society for Human Reproduction and Embryology (ESHRE) and Royal College of Obstetricians and Gynaecologists (RCOG), RPL is referred as three or more consecutive pregnancy losses, including the non-visualised ones too.
- While as per American Society for Reproductive Medicine (ASRM), RPL is defined as two or more loss of clinical pregnancy which not necessarily needs to be consecutive.

The aetiology behind RPL is unknown in about 50% of cases, despite having a lot of known factors. Genetic causes contribute to 2-5% of aetiology for RPL. There are a variety of genetic factors that may result in failure of a pregnancy to develop. These include aneuploidy (gain or loss of a chromosome), chromosomal imbalances as a result of parentally harboured translocations or inversions, deletions or duplications of genetic information within chromosomes, and single-gene mutations. Broadly, genetic factors may be divided into embryonic errors derived from known parental chromosomal abnormalities and embryonic errors that arise de-novo in apparently chromosomally normal parents.

Identifying the cause of pregnancy loss is important for couples and may be critical for the management of their future pregnancies. A complete diagnostic RPL workup can be instituted after two miscarriages and includes evaluation of:

- Uterine cavity
- Testing for endocrine factors
- Immunological tests for anti-phospholipid antibodies
- Parental genetic karyotypes for structural chromosome rearrangement
- Genetic testing of product of conception (POC)

Current Guidelines for RPL Work up

Screening test	Royal College 2011	ASRM 2012	ESHRE 2017
Parental karyotyping	Not recommended Unless POC reveals unbalanced translocation	Recommended	Conditional recommendation: Only after 'individual risk assessment'[a]
POC cytogenetic analysis	Recommended (after third and subsequent miscarriage)	Not recommended (karyotype analysis of POC only in the setting of ongoing therapy for RPL)	Conditional recommendation: for explanatory purposes (strong recommendation to use CMA when POC genetic analysis is performed)
Uterine anatomy evaluation	Recommended: If Pelvic ultrasound abnormal get Hysteroscopy or 3D ultrasound	Recommended: 3D ultrasound Hystero-salpingogram Hysteroscopy	Strong recommendation: (conditional recommendation: prefer 3D ultrasound)
Antiphospholipid antibodies	Recommended: lupus anticoagulant and anticardiolipin antibodies	Recommended: lupus anticoagulant Anticardiolipin antibodies Antiβ2 glycoprotein I	Strong recommendation: lupus anticoagulant and anticardiolipin antibodies Good clinical practice: antiβ2 glycoprotein I
Thyroid function	Recommended: TSH	Recommended: TSH Not recommended: TPO	Strong recommendation: TSH and TPO antibodies
Prolactin	Not discussed	Recommended	Conditional recommendation: if hyperprolactinemia (oligo- or amenorrhea)
Hemoglobin A1c	Recommended	Recommended to evaluate for diabetes	Not recommended
Hereditary thrombophilia	Not recommended for first trimester (recommended for second trimester loss)	Only recommended if a personal or strong family history of thrombosis or thrombophilia	Conditional recommendation: Only in the context of research or in women with additional risk factors[a]
Sperm DNA fragmentation	Not discussed	Not recommended Controversial data	Conditional recommendation: only for explanatory purposes
PCOS and insulin resistance	Insufficient evidence	Not recommended Controversial data	Not recommended
Luteal insufficiency	Insufficient evidence	Not recommended	Not recommended
Ovarian reserve testing	Not discussed	Not recommended	Not recommended
Vitamin D deficiency	Not discussed	Not discussed	General advice to consider vitamin D supplementation

Fig: Summary of the current guidelines from the Royal College of Obstetricians and Gynaecologists (RCOG), American Society for Reproductive Medicine (ASRM), and European Society of Human Reproduction and Embryology (ESHRE)

Genetic Testing as a Diagnostic Tool

When assessing a new patient with two or more spontaneous losses, it is important to obtain POC karyotype results from past losses, if available, or to obtain the tissues from those losses for subsequent genetic analysis. This allows the practitioner to determine more precisely whether a diagnostic work-up for RPL is indicated. Post demise, genetic analysis of POCs for spontaneous karyotypic abnormalities offers a fiscally and emotionally responsible approach to the management of couples presenting with repeated losses.

Cytogenetic abnormalities in the POC can be detected by:

- Conventional G-band karyotyping
- Fluorescence in situ hybridization (FISH)
- Multiplex ligation dependent probe amplification (MLPA)
- Array comparative genomic hybridization (aCGH)
- Single-nucleotide polymorphism (SNP) microarray
- Chromosomal Microarray [CMA] (Most Recent)

However, the traditional karyotype testing by G-banding requires tissue culture, which is labour intensive and carries a significant failure rate (approximately 30%), especially when the sample is of poor quality.

Chromosomal Microarray (CMA)

- The recent advances in molecular genetic technology now led to an increasingly popular alternative method for cytogenetic analysis is using CMA technology for cytogenetic evaluation of POC. POC CMA performed in conjunction with a regular complete maternal RPL work-up will help to identify the group of truly unexplained RPL
- The 2017 ESHRE Guidelines issued a conditional recommendation against the routine use of POC genetic analysis but issued a strong recommendation in favour of using CMA whenever genetic analysis was performed on POC for explanatory purposes.
- Furthermore, ESHRE recognized that the genetic analysis of pregnancy tissue has the benefit of providing the patient with a reason for the pregnancy loss and may help to determine whether further investigations or treatments are required.

Some investigators suggest that the genetic analysis of POC should be first undertaken using quantitative fluorescence-PCR (QF-PCR) combined with MLPA for chromosomes 13, 15, 16, 18, 21, 22, X and Y. If the result of QF-PCR/MLPA is abnormal (aneuploidy detected for one of the tested chromosomes), the pregnancy loss is therefore explained and no further action is required at this stage.

On the other hand, if the QF-PCR/MLPA result is normal for the tested chromosomes, CMA is warranted to complete the testing of the remaining chromosomes

Limitations of CMA

- CMA is associated with increased cost
- Not easily available in every practice
- May detect deletions or duplications of uncertain prognostic significance
- Cannot detect balanced translocations and mosaicism

But the significant number of details which CMA provides cannot be overlooked. Therefore, recently, Papas RS et al (2020), proposed an updated algorithm for the evaluation and management of RPL, which includes CMA analysis of POC after the second or subsequent loss combined with a modified ASRM evaluation that omits parental karyotypes.

In the event that POC analysis reveals an unbalanced translocation, karyotypes for both parents are warranted and preimplantation genetic testing for structural rearrangements (PGT-SR) or prenatal diagnosis (PND) can be offered for any desired or established pregnancy, respectively.

Proposed Evaluation for Recurrent Pregnancy Loss

[Papas RS et Al (2020)]

AFTER 2nd MISCARIAGE: BOX. 1

For 1st Trimester Loss

WORK-UP includes,
1- Screen for Weight extremes, Alcohol and Smoking
2- Cavity Check (3D U/S recommended modality)
3- Screen for APS (Lupus, Anti-phosphatidylserine and Anti-Cardiolipin IgG & IgM)
4- Endocrine Testing (TSH and TPO, Prolactin and Hemoglobin A1C)

⇨ Manage abnormalities in 1-, 2-, 3- and 4- accordingly
⇨ Consider Prophylactic Vit. D Supplementation for all
⇨ Provide Psychological support

5- POC CMA CYTOGENETIC ANALYSIS

POC ANEUPLOID → **NO FURTHER TESTING Expectant Management**

POC EUPLOID
- → **IF ABNORMAL CAVITY, ENDOCRINE ETIOLOGY and/or APS ADDRESSED** → **NO FURTHER TESTING Expectant Management**
- → **IF NO IDENTIFIED ETIOLOGY SO FAR** → **UNEXPLAINED CASES** BOX. 2

UNBALANCED TRANSLOCATION or INVERSION → **DO PARENTAL KARYOTYPE + GENETIC COUNSELING CONSIDER PGT-SR vs. EXPECTANT MANAGEMENT**

UNEXPLAINED CASES BOX. 2

COMPLETE FULL W/U vs. EXPECTANT MANAGEMENT
1- Consider Hereditary Thrombophilia Testing
ONLY IF: Familial or Personal History of VTE
2- Consider Sperm DNA Fragmentation Testing
3- Consider Parental Karyotyping
4- Consider Luteal Phase Deficiency Testing
5- Consider Chronic Endometritis Testing
6- Consider Hysteroscopy *if History of Uterine Surgery*

⇨ ADDRESS IDENTIFIED ETIOLOGIES

AFTER 3rd MISCARRIAGE: BOX. 3

- If no testing has been done so far: Investigate and Manage according to above algorithm
- If above algorithm has been followed in previous miscarriage: Repeat POC Chromosomal Testing and Complete the full W/U if not already done
- If all possible known etiologies have been addressed and POC aneuploidy is repetitive, consider Expectant management vs. PGT-A

Conclusion

- Therefore, new guidelines for the complete evaluation of RPL should consider adding CMA testing on the miscarriage tissue.
- The combination of a genetic evaluation on miscarriage tissue with an evidence-based evaluation of RPL will provide a probable or definitive explanation for the loss in 90% of couples.
- Providing couples with an explanation for recurrent loss assists them in dealing with the loss and discourages the clinician from instituting unproven therapies.
- Truly unexplained pregnancy loss can be reduced to less than 10% with this new algorithm.
- Incorporation of these strategies will result in significant cost savings to the healthcare system.

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Anti Phospholipid Syndrome

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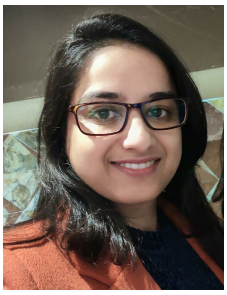

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Anti Phospholipid Syndrome [APS] is a systemic autoimmune disease with vascular and obstetrical manifestations. It is characterised by thrombosis and inflammatory pathogenesis and presence of aPL antibodies. Defined prior as primary or secondary to other autoimmune pathology, the new terminology defines APS with SLE and without SLE. (1) Asymptomatic aPL antibodies are present in 1-5% of healthy individuals. (2) However, it is seen in 5-20% of women with recurrent miscarriages.

Historically, Nilsson first reported the association of spontaneous abortion and circulating anticoagulant, LA in 1975. (3) The Sapparo's criteria were first defined in Japan in 1999 and these were modified in Sydney 2006. (4)

The Sydney modification required the laboratory criteria to include lupus anticoagulant, aCL or b2- glycoprotein to be positive at two or more occasions 12 weeks apart (4). Vascular thrombosis included ≥1 validated clinical episode of arterial, venous or small vessel thrombosis, in any tissue or organ. Pregnancy morbidity included (a) ≥3 unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded ; (b) ≥1 unexplained deaths of morphologically normal foetus at or beyond the 10th week of gestation, or ; (c) ≥1 premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe pre-eclampsia, or recognised features of placental insufficiency. Time between clinical manifestation and aPL test positivity should be between 12 weeks to 5 years. Triple aPL positivity or LA positivity are speculated to be stronger predictors for pregnancy morbidity. (5)

APA- associated cardiac valve disease, APA-associated lupus reticularis, APA-associated nephropathy, APA- associated thrombocytopenia, other skin manifestations like ulcerations, digital gangrene, superficial phlebitis and subungual splinter haemorrhages and neurological manifestations like chorea, headache, multiple sclerosis, transverse myelopathy and epilepsy are associated but not independent criteria of APS. (4)

Pregnancy outcomes in women with APS include pregnancy induced hypertension, fetal loss, placental abruption, abortion, thrombosis, preterm delivery and pulmonary embolism, among others. Adverse fetal outcomes include neonatal morbidity, small for gestational age, prematurity and admission to neonatal ICU. (6)

Mainstay of treatment include Aspirin and Heparin which are shown to improve the pregnancy outcomes to 70%. The importance of Fetal surveillance cannot be overemphasised. Pre-conceptional counselling should include assessment and discussion of risk factors- high risk aPL profile, SLE, h/o thrombosis, BOH, need for blood pressure monitoring, use of medications i.e. pre-conceptional aspirin and heparin in pregnancy. The risk of adverse outcome should be discussed, including the risk of special education services for offsprings, as shown by Marder et al. Close surveillance of foetus should include early scan and uterine artery Doppler at 20 weeks gestation. Third trimester surveillance includes regular fetal growth monitoring and dopplers along with NST and biophysical profile. The treatment of Hydroxychloroquine is required in patients with SLE. Calcium and Vitamin D supplementation may be given with long term heparin in pregnancy. (6)

Aspirin and Heparin

APS WITHOUT PRIOR THROMBOSIS

Recurrent early miscarriage

- Unfractionated heparin-5000-7500 U subcutaneously, 12 hourly
- LMWH- Enoxaparin 40 mg SC, OD or 30 mg SC, BD
- Dalteparin, 5000 U SC, OD or BD

Fetal death beyond >10 weeks or prior preterm delivery at less than 34 weeks due to uteroplacental Insufficiency or pre-eclampsia

- Unfractionated heparin-7500-10000 U subcutaneously, 12 hourly in first trimester and 10000 U subcutaneously, 12 hourly in second and third trimester
- LMWH- Enoxaparin 30 mg SC, BD
- Dalteparin, 5000 U, SC, BD

APS WITH THROMBOSIS

- Unfractionated heparin- 8-12 hourly, adjusted to maintain aPTT in therapeutic range
- LMW- Enoxaparin 1 mg/kg SC, BD or Dalteparin, 200 U/kg, SC, BD with monitoring of anti X-a activity
-

European League Against Rheumatism (EULAR) recommendations (7)

Category	Recommended treatment
No history of thrombosis or pregnancy complications	Treatment with LDA during pregnancy
Thrombotic APS	LDA and heparin at therapeutic dose during pregnancy
History of obstetric APS only	LDA and prophylactic dose of heparin
Obstetric APS with RPL despite treatment	Therapeutic dose of heparin Addition of HCQ or low dose prednisolone in first trimester may be considered IVIG may be considered in selected cases

Peri-partum guideline for anticoagulation

Anticoagulant should stop for labor pain, CS or bleeding and resume- 6 hours of delivery or 6-12 hours of CS. Regional anesthesia should be avoided at least 12 hours after prophylactic dose, 24 hours of therapeutic dose and No LMWH should be administered for 4 hrs of SA/ epidural catheter removal.

Thromboprophylaxis needs to be given for at least 6 months or longer as per the thromboprophylaxis risk assessment as per RCOG guidelines. As these women have a higher risk of thrombotic complications in later life, they should be followed up with a haematologist (8).

As for contraception, combined oral contraceptive are contraindicated. Progesterone only- pill, DMPA can be used- carefully weighed against thrombosis risk. Intrauterine device may also be used with caution for risk of heavier bleeding especially with anticoagulants.

Catastrophic/ Refractory Obstetric APS:

For cases with recurrent APOs despite LDA and heparin, evidence for effective management is lacking. However, various therapies have been suggested including corticosteroids (10mg/day in Trimester 1), IVIG (2g/kg/month), Hydroxychloroquine (400mg OD), Statins (Pravastatin-20mg/day) and TNF inhibitor-etanercept (9).

Catastrophic APLA is a rare (1% of APS) but accelerated form of APS with high morbidity & mortality, multiple organ failures. The diagnostic criteria include 1. evidence of involvement of 3 or more organs, systems and/or tissues; 2. development of manifestations simultaneously or in less than a week; 3. confirmation by histopathology of small- vessel occlusion and 4. laboratory confirmation of the presence of antiphospholipid antibodies. High index of suspicion is needed as in 50% patients- CAPS as the first manifestation of APS. Albeit there are no prospective studies, recommendations are based on expert opinion & retrospective data and include treatment with triple therapy (anticoagulation, corticosteroids, and plasma exchange/IVIG) and concurrent treatment of precipitating cause eg. Infections, gangrene, malignancy (9).

Carry Home Message:

- Every obstetrician must have a high index of suspicion in patient with RPL.
- Pre-conceptional LDA should be considered in such patients.
- Close maternal and fetal surveillance should be done and adequate treatment to be provided with LDA and heparin.
- Postpartum thromboprophylaxis is strongly recommended in patients with APS.

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Evaluation of Recurrent Pregnancy Loss - Newer Perspectives

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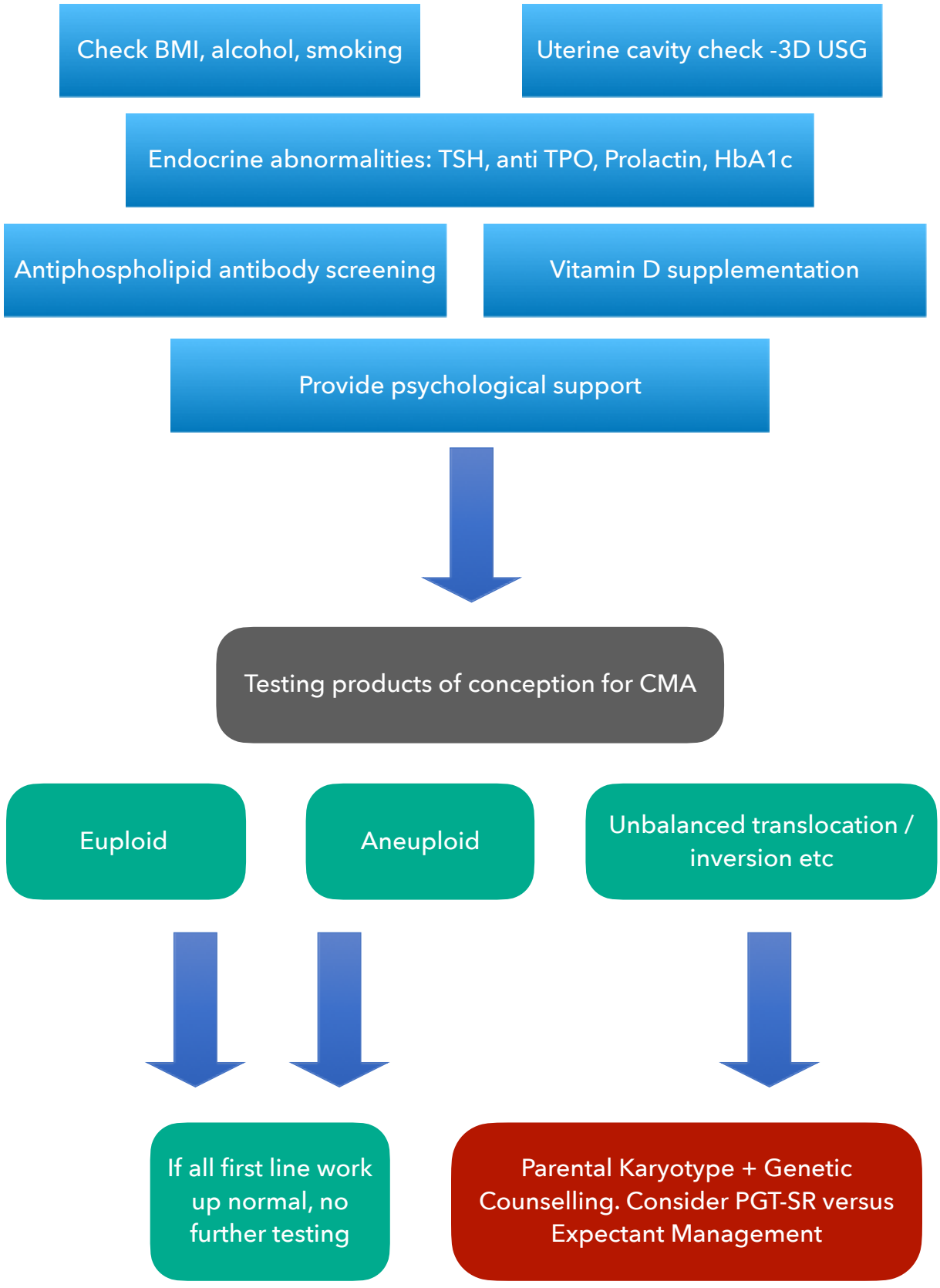
Recurrent pregnancy loss [RPL] /recurrent miscarriage is quite a devastating event for a couple mentally, physically and financially.

The definition of RPL varies, which makes studying the phenomenon, and determining which couples to counsel or treat, more challenging.

Different organisations give varying definitions- which can be:

- Two or more failed clinical pregnancies as documented by ultrasonography or histopathologic examination [1,2]
- Three consecutive pregnancy losses, which are not required to be intrauterine [3,4]

Suggested Algorithm for Evaluation of RPL



- Amongst the various etiologies causing RPL, only a few are well supported by evidence. Literature shows that for most proposed etiologies, there is no one consensus but the once backed with good quality evidence should be advocated for, and the once for which there aren't enough studies should be advised after explaining so and after considering the cost-effectiveness.
- As a part of work up , one of the most well studied cause of RPL is Antiphospholipid Antibody (APLA) syndrome, which includes testing for antibodies - lupus anticoagulant, anti cardiolipin antibodies IgG, IgM, Anti B2Gp-1 IgG, IgM ; to be positive on 2 occasions 6- 8wks apart. For anti cardiolipin and anti B2 GP-1 only medium to high titres are diagnostic, low positive antiphospholipid immunoassay should not be considered.
- Testing for inherited thrombophillias is not routinely recommended unless there is a suggestive history especially rare cases of recurrent losses after 9 weeks associated with evidence of placental ischemia and infarction with maternal vessel thrombosis..
- Evaluation for anatomic abnormalities should be done. Ultrasound (3D) being the most suitable primary investigation, other modalities like saline infusion sono-salpingography, hystero-salpingography, magnetic resonance imaging [MRI] can be considered but no consensus is yet reached as to what is the best second line investigation modality.

- There is no compelling evidence seen as to screen for "microbiological factors"; some studies are against screening for infections including TORCH.
- Endometrial biopsies to rule out chronic endometritis are not yet recommended.
- Luteal phase progesterone levels is also not recommended as studies show no benefit of luteal phase progesterone supplementation in women with RPL.
- Screening for immunological factors is also not advisable currently as it is yet not supported by good quality evidence. HLA analysis, peripheral /uterine NK cell analysis, T helper type 1 and 2 measurements are all experimental yet and even if considered no treatment available.
- Evaluation for structural chromosomal abnormalities i.e. screening for "genetic factor" is recommended. Preferred test nowadays over karyotype is chromosomal microarray analysis (CMA) as we can gather more information from the latter. More so to be considered with maternal age, number of prior losses, history of still birth or anomalous baby or history of positive results of genetic testing of prior losses. It is advisable after proper discussion of cost and practical approach of such evaluation.

Though no clear consensus for testing for "metabolic and endocrinologic factors", as they are common, testing and correction is advisable. These include TSH, anti-TPO [if TSH is abnormal], prolactin, and diabetes.

Hematologic assessment includes full blood count, electrolytes, liver function test.

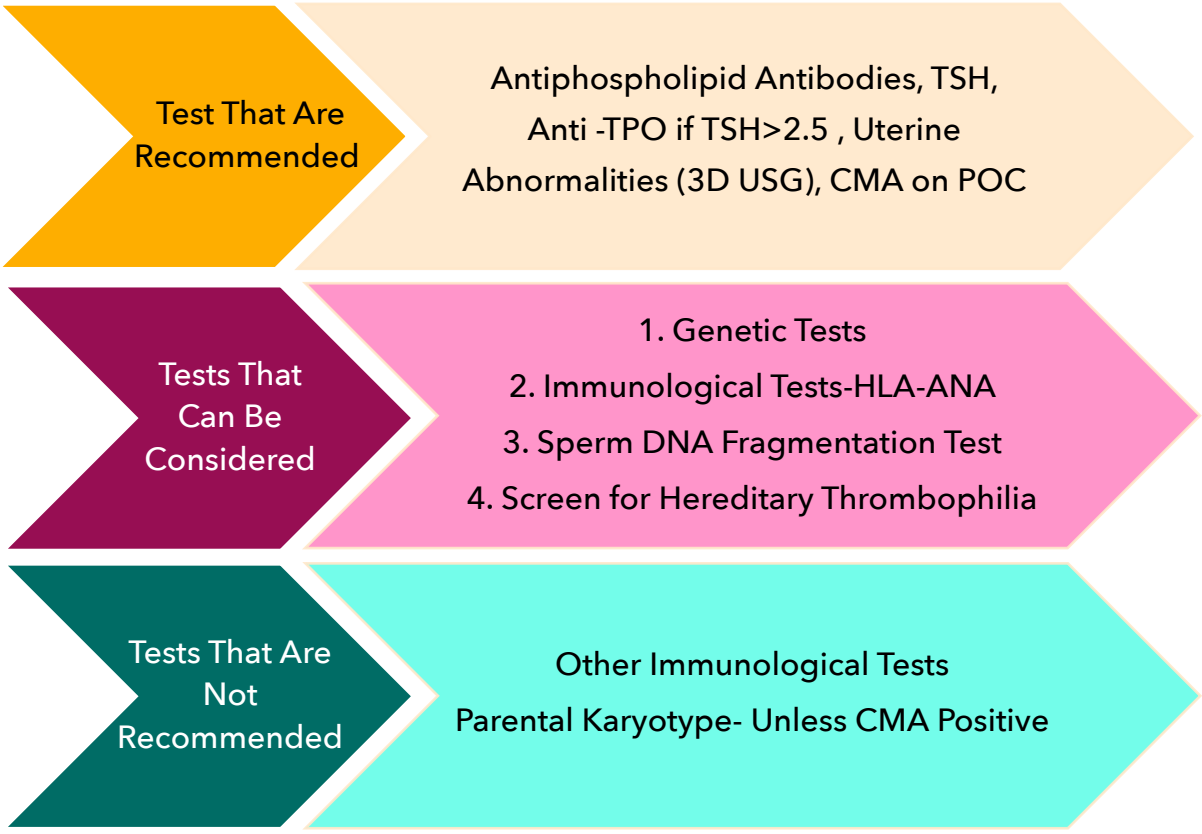
Evaluation and correction of "life style variables" should be done- obesity, drug abuse, cigarette smoking, heavy caffeine consumption all should be counselled against.

Until recently, in cases of RPL possible "male factor" has not been assessed satisfactorily. There is a moderate body of evidence indicating associations between RPL and poor quality sperm, particular sperm with elevated DNA fragmentation index. Clearly ,sperm DNA damage is caused by unhealthy lifestyles, clinicians should make couple aware of it. It is suggested to assess lifestyle factors for male partner also- smoking , alcohol consumption, occupational exposure, body weight, exercise pattern .

As for now, not all societies support testing male partner. Better and more powered studies and needed to reinforce the findings. ESHRE guideline for 2017 is only guideline to suggest Vitamin D supplementation.

Therefore, it is the responsibility of the health care provider to give the bereaved couple a comprehensive and scientific information about the work up required, not to forget, with an empathetic approach.

Proposed testing protocol:



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Uterine Anomaly as a Cause of Recurrent Pregnancy Loss

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Recurrent pregnancy loss has a significant negative impact on the life of couple. WHO defines abortion as spontaneous loss of pregnancy upto 24 weeks period of gestation or fetal weight of up to 500gm before the period of viability. (1) Recurrent abortion is defined as the loss of three or more consecutive pregnancy (2) and it is also defined as two or more failed clinical pregnancy (3) Incidence of RPL is 1-3% and in 50% cases cause is idiopathic (4). Multiple etiologies have been identified such as anatomical, endocrine, chromosomal, genetic, infections and hyper-coagulable disorder. Exact contribution of uterine anomalies causing recurrent abortion is unknown but there is increased incidence of uterine anomaly in the female with recurrent pregnancy loss from 3-25% (5).

A retrospective review of reproductive outcome in women with untreated uterine anomalies has have found high rates of miscarriage and preterm delivery, with a term delivery rate of only 50% (6). Uterine abnormality has high abortion rate in foetus with normal karyotype (7).

Uterine abnormality can be

1. Congenital : Congenital abnormality of uterus can arise any time during abnormal mullerian development and is seen in 10-15%of women with RPL (8)
2. Acquired: It includes polyp, myoma, intrauterine adhesions and cervical incompetence.

Normal Uterine Development:

At 6 weeks mullerian duct elongate and cross the metanephric duct medially to meet midline. At 7 week urorectal septum separates rectum from urogenital sinus. At 12 weeks caudal part of mullerian duct fuse to form utero-vaginal canal which insert at dorsal wall of urogenital sinus at muller's tubercle and at 20 weeks internal canalisation of each duct produces two channel divided by septum which is later absorbed. Cranial unfused portion develop into fimbria and fallopian tubes, caudal fused portion form uterus and upper vagina.

Mechanism of abnormal uterine development

Agenesis or hypoplasia	Lateral fusion defect	Vertical fusion defect
Mullerian agenesis with congenital absence of vagina is termed as Mayers Rokintansky- kuster-Hauser syndrome. (MRKH) uterus can have only uterine horn (unicornuate uterus)	Failure of resorption of longitudinal vaginal septum, failure of duct migration leads to symmetric or asymmetric and obstructed or non obstructed development (bicornuate/ uterine didelphys)	Leads to transverse vaginal septum, segmental vaginal agenesis and cervical agenesis or dysgenesis.

Classification

I. The American Society for Reproductive Medicine classification (9) of Mullerian anomalies as depicted in Figure 1.

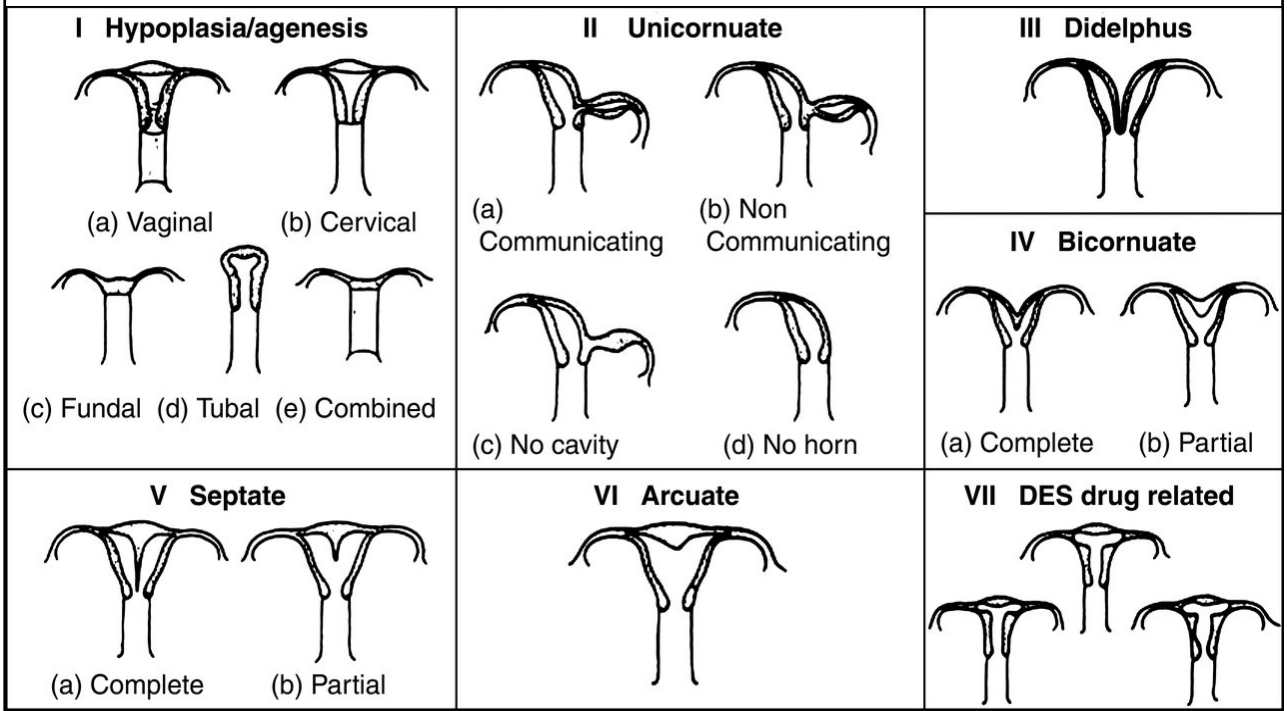

Figure 1

II. ESHRE/ESGE (2013) Working Group classified uterine anomalies into the following main classes (10)

U0: Normal uterus.

U1: Dysmorphic uterus (infantile and T-shaped mainly).

U2: Septate uterus- uterine cavity is partitioned by a fibromuscular septum, but has normal external contour/ shape.

U3: Bicorporeal uterus (partial and complete – bicornuate and uterus didelphys based on AFS) – uterus present as two separate uterine horns, double uterus with/without two separate cervices and rarely a double vagina. Each horn is linked to one fallopian tube and ovary.

U4: Hemi-uterus (unicornuate) – One horn of uterus is present; linked to one fallopian tube and ovary. Other horn of uterus absent/rudimentary.

U5: Aplastic uterus (absent uterus).

U6: Unclassified cases.

III. Uterine septum ARSM (2016) classification (11)

Normal/arcuate – depth from interstitial to apex of indentation less than 1 cm and angle of indentation more than 90°.

Septate – depth of interstitial line to apex more than 1.5 cm and angle of indentation less than 90°.

Bicornuate – external fundal indentation more than 1 cm

Diagnosis

2D ultrasound and HSG is non invasive and widely available but have low sensitivity and accuracy. HSG cannot diagnose between septate and bicornuate uterus. Hysteroscopy and laparoscopy are gold standard for diagnosing uterine anomalies but are invasive tests. (12) 3d ultrasound is noninvasive and has high sensitivity and specificity to diagnose uterine anomaly.(13) MRI is not recommended as first line investigation for uterine malformation. (14)

Pregnancy Outcome and Management Options in Uterine Anomalies

Congenital Uterine Defect

Unicornuate uterus: Pregnancy outcome is very poor with spontaneous abortion rate of 51%, premature birth rate 15% and associated renal anomalies are 40%. (15) Unicornuate uterus can present with rudimentary horn with or without cavity which is further categorised into communicating or non -communicating. Reason for pregnancy loss could be reduced intraluminal volume or altered blood supply to fetus and placenta.

Uterine didelphys: Incidence is very less that is 5-7% of mullerian defect. (16) Reproductive outcome is slightly better than unicornuate uterus due increased blood supply. Spontaneous abortion rate is estimated to be 43% and premature birth rate is 38%.(17)

Surgical technique recommended for unification of uterus is method of Strassman, involves unification of both the uterine cavity vertically but benefit is unclear. (18)

Bicornuate uterus: Incidence is 10% of all mullerian defects. Externally there is sagital groove at the fundus and it can extend upto cervix depending upon the incomplete fusion of ducts. Spontaneous abortion rate is 32% and premature birth rate is 21%. (19) Surgical technique for correction is strassman metroplasty but benefit has not been evaluated in the clinical trial. (18)

Septate uterus: Develops due to incomplete resorption of uterovaginal septum following fusion of mullerian duct. It is most common congenital anomaly with incidence of 55%. (16) Septum consists of poorly vascularised fibromuscular tissue arising from fundus can extends upto cervix. It has poorest reproductive outcome with spontaneous abortion rate of 65% and premature birth rate of 21%. (20) As septum is avascular it compromise decidual and placental growth and further fetal loss occurs due to distorted and reduced endometrial cavity. Women with history of pregnancy losses should be considered for surgical treatment. Laproscopy guided hysteroscopic septal resection is the preferred method for treatment of septate uterus. (21) De Cherney et al reported that hysteroscopic resection in women with recurrent pregnancy loss resulted in an 86% successful delivery. (22)

DES exposure: It is the orally active synthetic estrogen which was introduced in 1940 to reduce RPL. In utero exposure of DES leads to uterine abnormality most common being T shaped uterine cavity. Other abnormality includes small uterus, intrauterine fiiling defect constriction rings, hypoplastic cervix, pseudopolyp and cervical ring. It is associated with adverse pregnancy outcome, including a two-fold increased risk of spontaneous abortion and a nine-fold increase in ectopic pregnancy rates. (23)

All congenital malformation of uterus is associated with cervical incompetence but there are no studies to evaluate the empirical use of cerclage in these women.

Acquired Uterine Defect:

Intrauterine adhesion/ Asherman's syndrome: Develops due to vigorous curettage or postabortal endometritis. Reproductive outcome is very poor with 40% spontaneous abortion and 23% preterm deliveries. Adhesion ranges from minimal to complete ablation of uterine cavity that further reduces the volume of cavity and causes defective placentation. Hysteroscopoic excision of adhesions will reduces subsequent pregnancy losses and is superior to blind curettage. (24)

Intracavitary lesion: Includes myoma's and polyp. Association of myoma and polyp with recurrent pregnancy loss depends upon size, number and location. It causes RPL by obliterating and altering the contour of cavity, poor vascularisation of endometrium, compromise placental development and subclinical endometritis.[24] There is insufficent evidence supporting hysteroscopic removal of submucosal fibroid and polyp in RPL.

Cervical incompetence: It is associated with painless cervical dilation and expulsion of fetus in second trimester. Causes are DES exposure, cervical trauma, cone biopsy or loop electrocautry excision procedure. Cervical cerclage is done in women with three or more second trimester loss and women with one or more midtrimester loss with short cervical length.

Conclusion

The uterine anomalies present very differently ranging from asymptomatic to very complex reproductive pathology. Woman can presents with subfertility, infertility and recurrent pregnancy loss. The task of managing and counseling about the reproductive impact of uterine anomalies is challenging as there are several classification in the literature with significant heterogeneity. There is not even a single randomised controlled trial (RCT) to address the surgical management of uterine anomalies, the resection of the uterine septum, which is the most amenable.

Women with uterine anomalies both congenital and acquired have increased risk of RPL than general population. All women with uterine anomalies and treated with hysteroscopic resection of uterine septum should be managed as high risk pregnancies .In addition to routine antenatal care, measures to identify and manage preterm labour should be taken care. Such women should be managed in the facility where services of cervical cerclage and neonatal intensive care are available.

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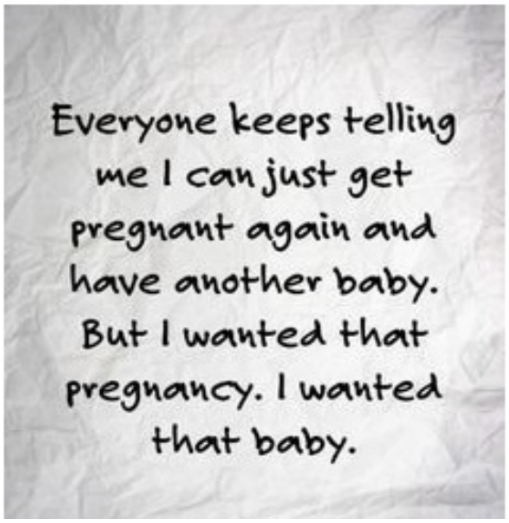
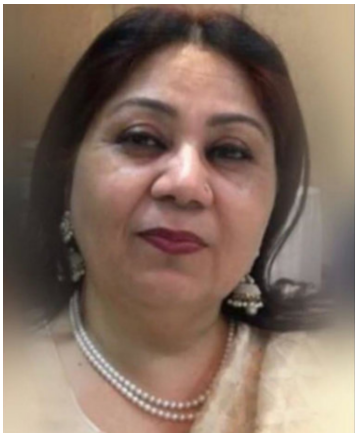
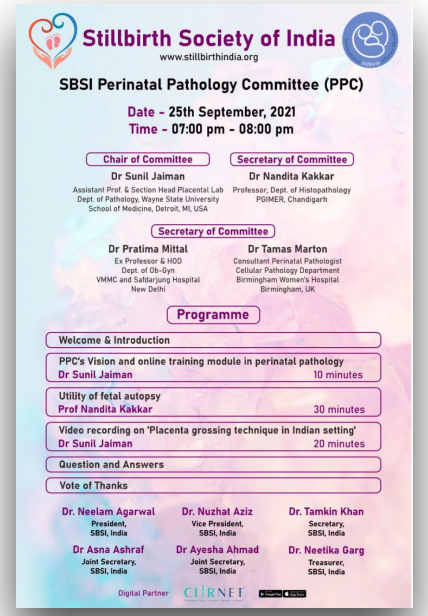


Secretary's Report



Dr. Tamkin Khan

Professor ObGyn, JNMCH
Founder Secretary
Stillbirth Society of India



An online meeting of the Perinatal Pathology Committee [PPC] of the Stillbirth Society of India was held on 25th September, 2021. The meeting started with the President SBSI, Dr. Neelam Aggarwal welcoming all guests. She emphasized the importance of placental pathology in diagnosing the cause of stillbirths. Dr. Tamkin introduced Dr Sunil Jaiman, Chairperson PPC and Dr. Nandita, Secretary, PPC

Dr. Sunil Jaiman presented the PPC's vision and discussed the lack of trained Perinatal Pathologists in India. He discussed the future plans of launching an online training module for perinatal pathology. Dr. Pratima Mittal, Patron SBSI and Dr. Tamas Marton, Consultant Perinatal Pathologist, Cellular Pathology Department, Birmingham Women's Hospital, Birmingham were the Chairpersons for the first session.

Prof Nandita Kakkar, Secretary PPC, SBSI gave a detailed talk on the utility of fetal autopsy in diagnosing and evaluating the cause of stillbirth. The presentation consisted of amazing images from her vast personal collection. This was followed by Dr Sunil Jaiman's 'engrossing' video presentation on 'Placental Grossing Technique in the Indian Setting'. This gave us a glimpse of what academic treat we can expect once the online training module is released. During the question & answer session many important challenges in getting parental consent for autopsy were raised. During the discussion with the experts the following points emerged:

1. Any center who offers autopsy should establish its credibility that it will be able to provide answers in most cases so that parents agree to give consent.
2. Parents can be convinced provided they receive proper counseling which emphasizes that it is being done to find answers for this pregnancy and will help in management of next pregnancy.
3. There is no right way or ideal way of counseling. Discussion, experience sharing and training can help us evolve the right way of counseling.
4. Minimally invasive autopsy can be offered to some parents and may help find some answers for them.

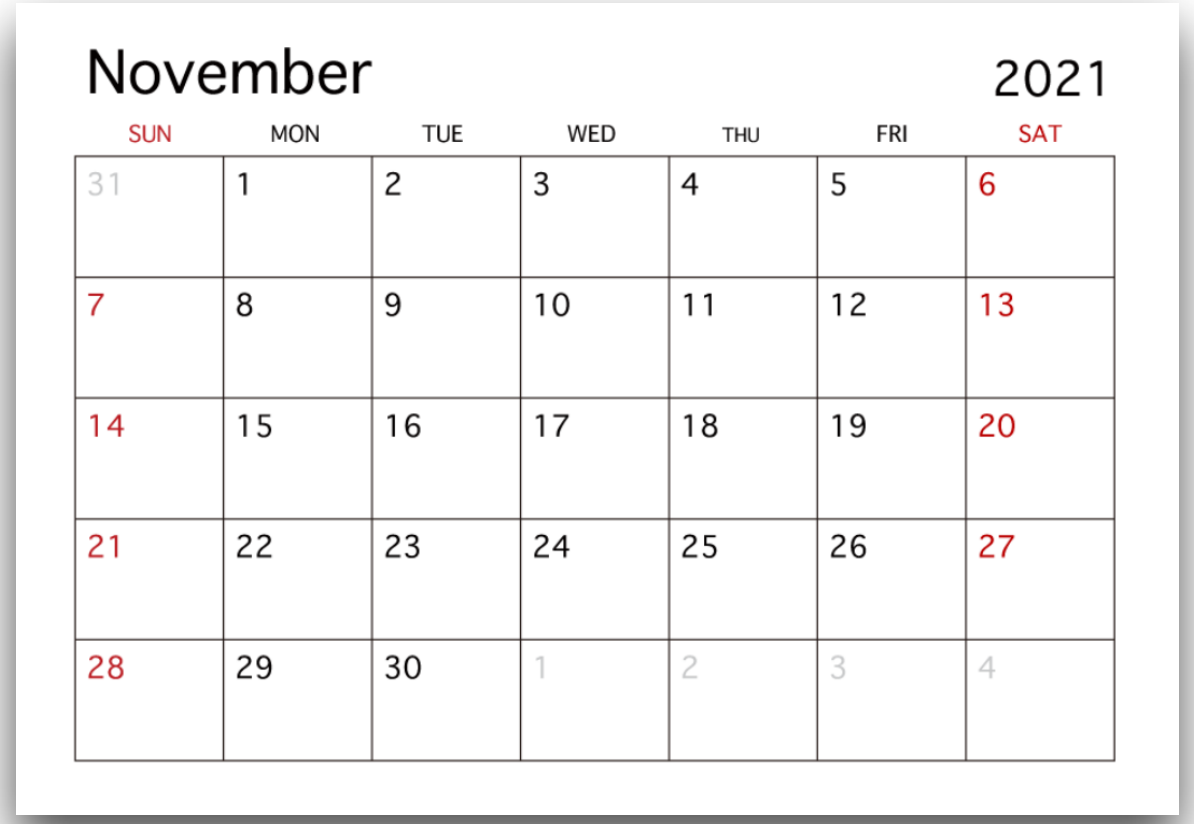
5. A good history by a fetal medicine expert, clinical geneticist and a trained perinatal pathologist can find the cause in most cases.
6. Autopsy is required even in cases of obvious congenital abnormalities as it maybe a part of a genetic syndrome which will affect the next pregnancy.

Dr Tamas Marton gave expert comments and Dr Pratima Mittal gave the concluding remarks. Dr Asna Ashraf, Joint Secretary, SBSI thanked Dr Neelam Aggarwal, President SBSI and Dr Nuzhat Aziz, vice president, SBSI for being the guiding force behind SBSI.

We thank Dr Tamas and Dr Pratima for sharing their knowledge and expertise on the subject. We congratulate Dr Sunil Jaiman for the wonderful planning and execution of the scientific session and for bringing us international experts on the subject. SBSI wants to put on record the heartfelt thanks to him and to Dr Nandita Kakkar for accepting the responsibility of PPC, SBSI in spite of being extremely busy.

November 2021 Calendar

Theme of the Month: Stillbirths in Gestational Diabetes Mellitus



November 2021

SUN	MON	TUE	WED	THU	FRI	SAT
31	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	1	2	3	4