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Editorial

Recurrent Miscarriage. A Clinical Dilemma Revisited

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Recurrent miscarriage as also known as recurrent pregnancy loss is defined as 3 or more consecutive clinically recognized pregnancy loss prior to 20 weeks of gestation. Now American society of reproductive medicine has redefined RPL as 2 or more pregnancy losses. Approximately 15% of all clinically recognised pregnancies fail to develop. Where clinically recognised is the one which is visualised on sonography or pregnancy tissue is seen in the histopathology report. In general, less than 5% of all women will experience 2 consecutive miscarriages and 1% will experience 3 or more pregnancy losses [1] spontaneous pregnancy loss seems to be a common occurrence.

Sporadic isolated cases of pregnancy loss before 10 weeks of gestation can be attributed to chromosomal anomalies as trisomy, monosomy or polyploidy but the spontaneous occurrence of 2 or more pregnancy loss makes it a clinically distinct entity. As it is psychologically and emotionally very disturbing for patients and their families. It is been observed that women with recurrent miscarriage tend to loose genetically normal pregnancies as compared to sporadic cases. Risk of sporadic miscarriages between 6 weeks to 12 weeks of gestation is between 9 - 12% in women younger than 35 years of age and this risk is increased in women over 35 years of age due to increased incidence of trisomic pregnancies and in women more than 40 years miscarriage rate approaches 50% [2].

The recurrent miscarriage can occur and in approximately 50% of cases no cause can be identified [3] following causes most commonly found in patients of recurrent miscarriages as:

1. Genetic factors (2% to 5%)
2. Anatomic factors (10 - 15%)
3. Endocrine factors (17 - 20%)
4. Autoimmune (20%)
5. Infections
6. Thrombotic causes, non aps, thrombophilias
7. Environmental and lifestyle factors
8. Unexplained causes (~ 50%)

For prognostic purposes recurrent pregnancy loss can be defined as primary or secondary. In primary RPL women has no prior successful pregnancy and in secondary RPL pregnancy losses occur following successful live birth.

RPL due to parental chromosomal defect involves reciprocal or robertsonian translocation in 2 - 4% of patients in some small genetic studies it has been observed in 36 - 39% of couples with recurrent loss is associated with unbalanced structural chromosomal rearrangements [4] karyotyping and genetic counselling is and important aspect of management as likelihood of future healthy pregnancy depend on chromosome involved and type of rearrangement.

Anatomic abnormalities can cause RPL in 10 - 15% of patients by disrupting blood supply to endometrium or by causing poor placentation. Most relevant anomalies that are often detected includes but not limited to unicornuate uterus, bicornuate, septate, didelphic or arcuate uterus but uterine septum is most common abnormality linked to RPL as is found in some studies uterine septum is having as much as 76% risk of spontaneous pregnancy loss among patients with diagnosed uterine septum [5] and correction of septal defect at hysteroscopy has a beneficial effect. There are no significant surgical corrective options for unicornuate or didelphid uterus. Surgical management of uterine synechiae may be beneficial as synechiae leading to asherman's syndrome may impact placental implantation and cause pregnancy loss.

Surgical management of any submucous fibroid and intramural fibroid more than 5 cm in size also has beneficial effect. These common uterine abnormalities can be diagnosed by clinical examination, ultrasonography, 3d or 4d scan and if needed by MRI scan. Hysterosalpingography or sonosalpingography can identify the cavity and tubal status also.

Endocrine disorders are found in 17 - 20% of couples with RPL [6]. It includes thyroid diseases, PCOD, luteal phase defects and uncontrolled diabetes mellitus. Luteal phase defect (LPD) is a term used to describe decrease in amount or duration of progesterone secretion from corpus luteum or lack of response to ovarian steroids. LPD is diagnosed by morphological examination of timed luteal phase endometrium sample according to noye's criteria [7] as persistent lag of more than 2 days in histologic development of endometrium compared with menstrual cycle day, but now a days endometrial biopsy to diagnose LPD is rarely used.

Nearly 40% of patients with RPL shows some evidence of PCOS as evident by elevation of luteinizing hormone and androgen and insulin resistance causing hyperinsulinemia as seen in type 2 DM.

Poorly controlled type 1 diabetes is more the casual factor in RPL. Hyperinsulemia can cause RPL by altering HPO axis, impairing folliculogenesis and oocyte maturation and also by causing short luteal phase. As for hyperprolactinemia, untreated hypothyroidism can also cause RPL, but the RPL of antithyroid antibodies in euthyroid patients is debatable.

Anti-phospholipid syndrome constitutes an important cause of RPL as between 5 - 20% of patients will test positive for antiphospholipid antibodies (APLS). These antibodies are diverse and variable from patient to patient and specific for verity of specific cellular phospholipid and phospholipid binding proteins, they have variety of effects on trophoblast including inhibition of villous cytotrophoblast differentiation, induction of syncytiotrophoblast apoptosis, inhibition of extravillous cytotrophoblast invasion into decidua also it initiates maternal inflammatory pathways on syncytiotrophoblast surface [8] antiphospholipid syndrome is diagnosed if 1 clinical and 1 laboratory criteria is met from following.

Clinical criteria

- 1 or more confirmed vascular thrombosis episodes (venous, arterial, small capillaries).
- Pregnancy complications including either 3 or more consecutive pregnancy losses at < 10 weeks of gestation, 1 or more foetal death at > 10 weeks of gestation or at least 1 preterm birth (< 34 weeks) due to severe preeclampsia or placental insufficiency.

Laboratory criteria (repeated at least 2 times and > 12 weeks apart):

- Positive plasma levels of anticardiolipin antibodies (IgG/IgM) at medium to high level.
- Positive plasma levels of lupus anticoagulants.

Recommended treatment for diagnosed case of APS is low dose aspirin plus low molecular weight heparin as it confers significant benefit in antiphospholipid syndrome and unexplained pregnancy loss. Administration of prednisolone does not improve pregnancy outcome but it may be associated with increased risk of GDM and gestational hypertension [9]. In some couples with personal history of venous thromboembolism or having first degree relatives with known or suspected thrombophilia screening for heritable thrombophilia

is to be carried out as it is commonly linked to RPL. Common causes include hyperhomocysteinemia, protein c and protein s deficiency, factor v leiden mutation and antithrombin mutation. Appropriate therapy for such cases includes supplemental folic acid and prophylactic or therapeutic anticoagulation as the case may be.

Some infections are found more commonly in women with RPL includes *Ureaplasma urealyticum*, *Mycoplasma hominis, Chlamydia, Toxoplasma*, rubella cmv, and herpes virus.

Psychological factors are also implicated in the etiology of RPL along with some lifestyle factors as cigarette smoking more commonly associated to RPL due to nicotine vasoconstrictor effect also positive link is found between alcohol consumption (> 3 - 5 drinks/wk) and caffeine consumption (> 3 cups/day).

Inspite of large scale studies and research into the subject no apparent cause can be found in about 50% of cases of RPL.

The treatment recommendations should be based on underlying cause of RPL. Most effective therapy for RPL due to unexplained causes is antenatal counselling and psychological support, making them feel positive and emphasising patient about chance of successful future pregnancy as is evident by studies is highland can exceed 50 - 60% depending on maternal age and parity, so to conclude correction of endocrine disorder, anti-phospholipid syndrome and surgical correction of uterine anomalies has highest successful pregnancy outcome and in cases of unexplained RPL progesterone has been shown to be beneficial in decreasing miscarriage rate in women who had experienced at least 3 losses.

Karyotypic analysis of products of conception may be useful in the setting of ongoing treatment of recurrent miscarriages [10].

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