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Couple's Battle to Achieve Parenthood

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I. INTRODUCTION

Recurrent Pregnancy Loss (RPL), also referred to as recurrent miscarriage or habitual abortion, affects around 1% of couples.[1] There are several recognized causes for RPL, such as chromosomal abnormalities, structural uterine anomalies, endocrine and metabolic disorders, prothrombotic conditions like antiphospholipid syndrome and environmental factors. However, in about 50% of the couples, there is no obvious underlying pathology. Most often the cause of RPL is multifactorial. Thus, the management of recurrent pregnancy loss should be holistic and should include investigating for the various causes and the appropriate treatment for the same.

II. CASE REPORT

36 Years, G9A8, married for 10 years, presented to the OPD with history of recurrent pregnancy loss and anxiousness to conceive. All the pregnancies were spontaneous conceptions with first trimester abortions, managed medically. Patient was diagnosed with APLA syndrome after 2nd conception and she was started on Aspirin and Heparin, which was given in the subsequent pregnancies. She was diagnosed with type II Diabetes mellitus 6 years back and was started on OHAs. She was on L-thyroxine for hypothyroidism which was diagnosed 5 years back. The couple were Rh incompatible and Anti D was not given after the first two miscarriages but was given after the rest of the miscarriages, as she was ICT negative. Last pregnancy was 2 years back. Karyotyping done for both partners was found to be normal.

On examination, Her BMI was 28 Kg/m^2 and there was no sign of anaemia. Abdomen was soft with no organomegaly. Bimanual examination revealed a bulky uterus with left fornix fullness. USG showed adenomyotic changes in the uterus with left ovarian complex cyst. Diagnostic Hysterolaparoscopy was done, which revealed posterior uterine fixity with omental adhesions, which were released. Right ovary and tube were normal. Left ovary had an endometriotic cyst and cystectomy was done. A left fimbrial endometriotic cyst was also noted and the same was removed.

Hysteroscopy showed multiple endometrial polyps and hence polypectomy with curettage was done. Chromopertubation revealed bilateral tubal blockage.

Figure 1: Laparoscopic view

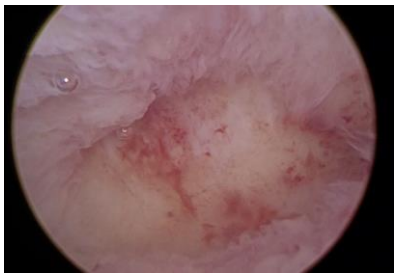

Figure 2: Hysteroscopic view

Histopathological examination of endometrium showed endometrial hyperplasia without atypia and the ovarian cyst was found to be endometriotic cyst. Patient was given 3 doses of GnRH analogues for the management of adenomyosis. The couple were given extensive psychological counselling and support during the follow up period.

HSG was done after 2 months of laparoscopy and tubes were found to be normal. Her AMH was found to be 0.67ng /ml and FSH was also mildly elevated. AFC was low on both ovaries. Ovulation induction was done with letrozole and gonadotropins followed by IUI, as the male partner had mild asthenospermia. Adequate luteal phase support with progesterone was given. The patient conceived during the same cycle. Once pregnancy was confirmed, patient was switched over to insulin for diabetic control. She was started on Aspirin, LMWH and micronized progesterone 600 mg/day. NT scan and quadruple marker test was done and found to be normal. Anomaly scan was done in the second trimester and found to be normal. ICT was negative at 28 weeks of gestation and antenatal Anti-D prophylaxis was given. The patient turned positive for Covid-19 at 34 weeks of gestation. She was treated with home quarantine as she had only mild respiratory symptoms. At 38 weeks gestation, elective LSCS was done and the patient delivered a healthy, male baby of weight 2.9 kg. After delivery, heparin was continued for 2 weeks and insulin was converted again to OHAs. Patient had an uneventful postpartum period with adequate lactation.

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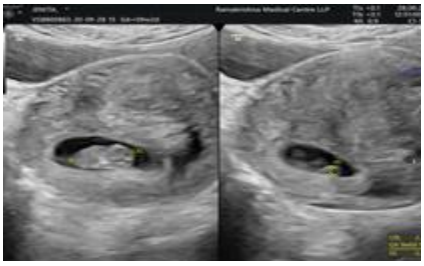

Figure 3: Early gestation

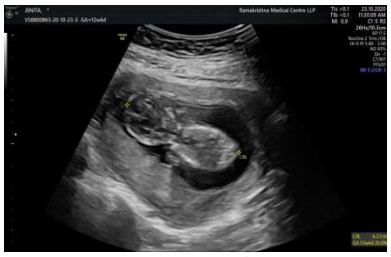

Figure 4: 12 weeks of gestation

III. DISCUSSION

There is lack of consensus regarding the definition of recurrent pregnancy loss (RPL). RCOG defines RPL as 3 or more consecutive pregnancy losses prior to 24 weeks from conception, which includes biochemical pregnancies.[2] However, ASRM and ESHRE define recurrent pregnancy loss (RPL) as two or more failed clinical pregnancies.[3,4] Primary RPL is described as RPL without a previous ongoing pregnancy (viable pregnancy) beyond 24 weeks' gestation, while secondary RPL is defined as an episode of RPL after one or more previous pregnancies progressing beyond 24 weeks' gestation.[3] There are various causes of RPL, which include parental chromosomal abnormalities, untreated hypothyroidism, uncontrolled diabetes mellitus, certain uterine anatomic abnormalities, and anti-phospholipid antibody syndrome (APS). Other probable or possible etiologies include additional endocrine disorders, heritable and/or acquired thrombophilias, immunologic abnormalities, infections and environmental factors. At times, multiple causes are at play for causing RPL in a couple. Hence, the management should include identifying all the possible causes of RPL and their appropriate management.

Anti-phospholipid Antibody syndrome is found in 5–20% of women with RPL and is considered the most important treatable cause.[2] Anti-phospholipid antibodies are thought to impair pregnancy through various mechanisms, including inhibition of trophoblastic function, thrombosis of the utero-placental vasculature and initiation of a local inflammatory response at the maternal-fetal interface.[4] APS treatment includes a daily low- dose aspirin (LDA, commencing prior to pregnancy until 34 weeks of gestation) and Low molecular weight heparin (LMWH) once daily administration until 6 weeks post partum.

Diabetes mellitus is known to be associated with recurrent pregnancy losses. Egerup et al., found significant and consistent association between pregnancy loss and type 2 diabetes, that increased with increasing number of losses.[5] The association between pregnancy loss and type 2 diabetes mellitus could be due to a shared immunological and/or metabolic etiology. Insulin resistance and the resultant hyperinsulinemia that is present in type II diabetes mellitus plays a role in RPL. This is evidenced by the decreased rate of spontaneous pregnancy loss when patients undergo therapy with the insulin sensitizing drug metformin.[6]

The miscarriage rate is increased with overt hypothyroidism. However, association between subclinical hypothyroidism (SCH) and pregnancy loss is less clear, in the absence of thyroid antibodies.[1]A meta analysis done by Dong et al found no association between subclinical hypothyroidism and RPL, when RPL is defined by nonconsecutive pregnancy losses.[7] In contrast, the study by Triggianese et al suggested that there may be an association between subclinical hypothyroidism and consecutive RPL.[8] However, the American Thyroid Association now advises using supplementary thyroxine for TSH >4 mIU/L.[9]

In our patient, during her previous pregnancies, focus was directed only towards the management of diabetes, hypothyroidism and APLA. However, adenomyosis and endometriosis were recognized recently as important causes of RPL and their adequate management before conception became the cornerstone for a healthy pregnancy.[10] Adenomyosis induces inflammatory processes within the eutopic endometrium, which induces cellular and biochemical alterations. Adenomyosis leads to progesterone resistance, dysregulation of uterine contractility and endometrial peristalsis. Recent reports indicate that adenomyosis is associated with decreased HOXA-10 gene expression, dysregulation of endometrial leukemia inhibitory factor, increased IL-1b and corticotrophin releasing hormone, natural killer cells, macrophages and a spectrum of cytokines, which are all associated with impaired implantation and miscarriage.[6]

The impact of endometriosis in recurrent pregnancy loss is due to following factors. The toxic pelvic environment causes an alteration in the oocyte quality, which leads to aneuploidy. Also, the altered endometrial environment leads to immunogenic changes such as the aberrant expression of b-V3 integrin during the window of implantation, which leads to defective placentation.[11] These changes result in pregnancy losses, especially in the first trimester and ultimately RPL. Thus, appropriate management of endometriosis prior to conception is essential for preventing miscarriage and RPL.

Finally, psychological support and counselling is essential for all the couples experiencing miscarriage and RPL. The psychological consequence and implications of repeated miscarriages are well acknowledged.[12] Studies have emphasized on the abortogenic effects of high stress on the hypothalamic–pituitary–adrenal axis, particularly during early gestation. Thus, empathetic support and counselling for the couple during preconception as well as the antenatal period is an integral part in the management of recurrent pregnancy loss and for a healthy pregnancy.

IV. CONCLUSION

Recurrent miscarriage is a complex condition requiring consideration of multiple factors for appropriate workup and management. Proper evaluation of the couple, addressing all

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the potential causes of miscarriage, adequate antenatal monitoring and extensive psychosocial support and counselling are essential for achieving a successful parenthood.

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