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Recurrent pregnancy loss- Evaluation and treatment

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Abstract
This prospective study was conducted at Padmashree Dr. D.Y. Patil Hospital from July 2012 to September 2014. A total of 30 cases were evaluated. This study included all women who presented with a history of two or more consecutive abortions in the 1st trimester or one in 1st trimester and one fetal death in late trimester and its various causes were evaluated. This study concluded that genetic abnormalities, immunological factors, anatomic defects, endocrinal factors, certain thrombophilias and infections are established causes of RPL and specific treatment improves pregnancy outcome.

Keywords: Recurrent pregnancy loss, miscarriage, APLA, office hysteroscopy, karyotyping

Introduction
Recurrent pregnancy loss is an experience which can be very painful for the couple.
Most of the miscarriages occur in the first trimester and affect about 15% of all recognized pregnancies [1].
Recurrent miscarriage or recurrent pregnancy loss (RPL) is defined as three or more consecutive miscarriages [2]. A miscarriage is defined as the spontaneous loss of pregnancy before the fetus reaches viability. This includes all pregnancy losses up to the 24th week of gestation. A first-trimester miscarriage is defined by spontaneous loss of pregnancy before the 12th week of gestation and a second-trimester miscarriage by spontaneous pregnancy loss between the 12th and 24th weeks of pregnancy.
Defining RPL as a clinical entity requires thorough diagnostic testing and therapeutic intervention and rests on the knowledge of elevation of risk for subsequent fetal loss and the probability of finding a treatable etiology for the disorder.
A successful pregnancy is an interplay of multiple factors. Considering this fact, many things can go wrong in a pregnancy and the cause of a pregnancy loss can reside in one's genes, endocrine, immunological factors, anatomical defects, environmental factors and sometimes the cause could not be determined.

Aims and Objectives
- To evaluate the etiopathological factors responsible for recurrent pregnancy loss.
- To give appropriate treatment for the cause and thereby increase the pregnancy outcome.

Materials and Method
The study was conducted in the tertiary care hospital from July 2012 to September 2014. A total of 30 cases were evaluated.

Inclusion Criterion
- All women presenting with a history of two or more consecutive abortions in the 1st trimester or one in 1st trimester and one fetal death in 2nd trimester.
- All women who came between 6 to 24 weeks with two or more consecutive pregnancy losses.

The methodology includes
- Detailed history of the patient including age, weight, body mass index, menstrual history, obstetric history, previous obstetric outcomes, family history.

- Past history of the patient including pregnancy loss, any treatment taken for the sustainment of pregnancy and investigations done for the same.
- General and Systemic examination.
- Laboratory investigations -
- Haemogram
- Blood group
- Blood sugar levels (fasting and post prandial), HbA1c
- Urine microscopy
- Urine routine
- HIV, HbsAg, VDRL
- Special investigations
- Karyotyping
- Antiphospholipid antibody
- Protein C
- Thyroid profile
- Diagnostic tools –

a) Ultrasonography – transabdominal/ transvaginal
b) Office hysteroscopy
c) Diagnostic laparoscopy – in selected cases

Observations

Table 1: Etiological factors in association with RPL

Etiology	Number of cases	Percentage ;
Unknown	12	40
Anatomical defects	7	23.33
Genetic	3	10
Endocrine	3	10
Immunological	2	6.67
Others	3	10
Total	30	100

Table 1; shows the various etiological factors responsible for recurrent pregnancy loss. The identifiable causes accounted for 60% cases, out of which anatomical defects accounted for 23%. However, 40% of cases had no identifiable cause present.

Table 2: Age wise distribution

Age (years)	No of cases (n= 30)	Percentage
20-25	17	56.66
26-30	12	40
31-35	1	3.33
>35	0	0
Total	30	100

Table 2; depicts the age wise distribution, wherein maximum patients were in the age group 20-30 yrs. Increasing maternal age is associated with RPL. However, in our study, 96% patients were in the reproductive age group.

Table 3: Number of consecutive abortions

No. of consecutive abortions	No. of cases (n=30)	Percentage
Two	19	63.33
Three	10	33.33
More than three	1	3.33
Total	30	100

Table 3; shows that 63.33% patients had two consecutive abortions whereas 33.33% patients had three consecutive abortions. The number of consecutive abortions is related to the future obstetric outcome. The risk of an abortion is more than 40% after 3 consecutive abortions.

Table 4: Genetic factors

Genetic factors	No. of cases (n=30)	Percentage
Normal karyotype	27	90
Trisomy 21	2	6.67
Trisomy 18	1	3.33
Total	30	100

Table 4; depicts the incidence of genetic factors responsible for RPL. In our study, 10% patients had abnormal karyotype like Trisomy 21 and 18. All three cases presented as first trimester abortions.

Table 5: Anatomical defects

Anatomical defects	No of cases (n=30)	Percentage
Normal	24	80
Cervical incompetence	4	13.33
Septate uterus	2	6.67
Unicornuate uterus	1	3.33
Total	30	100

Table 5; shows the incidence of anatomical defects responsible for RPL. Cervical incompetence was the foremost anatomical anomaly accounting for 13.33%. It was also observed that amongst the 4 cases of cervical incompetence, 2 cases presented with early second trimester consecutive abortions and 2 with late second trimester consecutive abortions. Whereas septate and unicornuate uterus presented with first trimester abortions.

Table 6: Immunological Factor

Immunological finding	No of cases (n=30)	Percentage
Normal	28	93.33
Antiphospholipid Antibodies (APLA) positive	2	6.67
Total	30	100

Table 6; is showing the incidence of immunological factors which account for 6.67% cases. APLA was positive in 6.67 % cases and both these cases came as late second trimester abortions and also were diagnosed to have early onset pregnancy induced hypertension.

Table 7: Endocrinal factors

Endocrine factors	No of cases(n=30)	Percentage
Normal	27	90
Hypothyroid	2	6.66
Diabetes mellitus	1	3.33
Total	30	100

Table 7 shows that thyroid disorders were the commonest endocrinal factor associated with RPL. Both cases had hypothyroid and accounted for first trimester consecutive abortions. Diabetes mellitus was associated with second trimester consecutive abortions and accounted for 3.33%.

Table 8: Other factors associated with RPL

Other factors	No of cases (n=30)	Percentage
Endometrial TB	3	10

In the evaluation of RPL, hysteroscopy was of great value. Infective causes like endometrial tuberculosis was found in 10% cases wherein 2 cases presented as first trimester consecutive abortions and 1 case as one first trimester abortion and one early second trimester abortion.

Discussion

- In our study we accounted various etiological factors responsible for recurrent pregnancy loss. The identifiable causes accounted for 60% cases (as shown in Table 1), out of which anatomical defects were the commonest etiology. However, 40% of cases had no identifiable cause present. A similar study conducted by Samina Mohyiddin and Syed Tousif Ahmed in 2014 revealed unidentified causes accounting for 46%. Amongst the identifiable causes endocrinal factors accounted for 17%, anatomical defect for 10–15% and chromosomal abnormalities accounting for 12% [3].
- Our study depicted that 96% of patients were in reproductive age group (as shown in Table 2). In a similar study conducted by E C van Niekerk *et al.* in 2013 and de la Rochebrochard E *et al.* in 2002 found that majority of patients were beyond 35 years of age [4]. This discrepancy in age related factor is because of early marriage practice in developing country like India.
- In our study genetic factors like Trisomy 21 and 18 accounts for 10% of RPL which presented as first trimester abortions (as shown in Table 4). Patients who come with very early first trimester abortions especially early missed abortions always point to the possibility of a genetic factor and therefore they need to undergo a parental karyotyping as well as karyotyping of the abortus. Thus, genetic counselling of the couple is of utmost importance. A study conducted by Goncalves R O *et al.* in 2014 on 151 women out of which 7.3% cases presented with chromosomal abnormalities [5]. Tunc E *et al.* in 2007 conducted a study of 41 patients showed trisomies accounting for 8.7% patients with RPL [6].
- Present study shows cervical incompetence is the most common anatomical defect factor accounting for 13.33% of RPL (as shown in Table 5). It was also observed that amongst the 4 cases of cervical incompetence, 2 cases presented with early second trimester abortions and 2 with late second trimester abortions. Cervical encerclage was beneficial in these patients. The uterine anomalies (septate and unicornuate uterus) accounted for 10% of cases and presented as first trimester abortions. Hysteroscopic metroplasty was performed and proved to be beneficial in patients with septate uterus. Drakeley AJ *et al.* in 2003 found that cervical insufficiency was diagnosed in 4.6 per 1000 women, and it is estimated to occur in 8% of women with recurrent mid-trimester losses [7]. K. K. Roy *et al.* in 2011 concluded that Hysteroscopic septal resection for women with history of recurrent abortions, preterm deliveries and in women with infertility is a safe and effective method of choice for improving the obstetric outcome [8].
- Immunological factors accounted for 6.67% cases in present study (as shown in Table 6). APLA was positive in 6.67 % cases and both these cases came as late second trimester abortions and also had features of early onset pregnancy induced hypertension. In a study conducted by Luis S. Noble *et al.* in 2005 found that 16% of cases of RPL were APLA positive. These patients were provided with low molecular weight heparin which resulted in 80% viable deliveries of APLA positive cases [9].
- In our study 6.66% patients had a thyroid disorder (as shown in Table 7). Hypothyroidism was detected and accounted for first trimester abortions. Diabetes mellitus was associated with second trimester abortion and accounted for 3.33%. Shakila Thangaratinam *et al.* in 2011 stated that the miscarriage rates ranged from 2.4% to 42.9% [10]. Studies conducted by E C van Niekerk *et al.* in 2013 have linked high glycosylated haemoglobin (HbA1C) values (>8%) early in pregnancy to an increase in early pregnancy loss and congenital malformations. There is no increased risk of miscarriage in women with well-controlled diabetes mellitus.
- In the evaluation of RPL, office hysteroscopy played a pivotal role. Infective causes like endometrial tuberculosis was found in 10% cases which presented as first trimester abortions or early second trimester abortions. All these 3 cases underwent office hysteroscopy which revealed periosteal hyperaemia and micropolyps pointing towards tuberculosis. The endometrial biopsy was taken by hysteroscopy and was sent for histopathological evaluation by TB-PCR. The report confirmed the presence of mycobacterium tuberculosis which clinched the diagnosis. In our country, tuberculosis is a highly prevalent infection which is known to cause infertility and RPL. In a study conducted by E C van Niekerk *et al.* in 2013 concluded that no infectious agent has been proven to cause RPL. Genital tuberculosis may cause implantation failure or early embryonic rejection, leading to RPL and ectopic pregnancy [11].

Conclusion

- Genetic abnormalities, immunological factors, anatomic defects, endocrinal factors, certain thrombophilias and infections are established causes of RPL and specific treatment improves pregnancy outcome.
- Women with unexplained pregnancy loss represented a heterogenous group of patients and accounted for 40% of the cases in our study.
- Karyotyping of parents to detect chromosomal anomalies and karyotyping of tissue when a couple with RPL experiences a subsequent consecutive abortion must be done.
- Office hysteroscopy has emerged as a novel tool to diagnose uterine anomalies especially septet uterus as well as endometrial defects like infections, ashermann's syndrome. Other anomalies can also be diagnosed with a concomitant laparoscopy in selected cases.

Summary

- A specific guideline for evaluation of RPL should be formulated which should include karyotyping, assessment of uterine anomaly, evaluation of endocrinal factors and selected cases of thrombophilic disorders.
- Evaluation of RPL must be considered after two consecutive clinical pregnancy losses.
- Psychological counselling and support must be included

as a part of treatment modality.

- Unexplained losses still account for a large proportion of patients and further research is still warrantied.

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