VOLUME-6 | ISSUE-1 | JANUARY-2017 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 78.46

"A Study of Etiological Factors of Recurrent Pregnancy Loss Before 20 Weeks of Gestation In A Tertiary Health Care Center."

Medicine

KEYWORDS: recurrent pregnancy loss, aetiological factors.

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ABSTRACT

Objectives: To study the incidence of aetiological factors for recurrent pregnancy loss. To find out any newer aetiological factors in an unexplained recurrent pregnancy loss before 20weeks of gestation and its incidence. Design: An observational study. **Methods:**A sample of 120 cases of recurrent pregnancy loss was investigated at department of obstetrics and gynaecology with inclusion criteria: - women with history of 2 or more weeks consecutive spontaneous abortions below 20weeks of gestation. **Results;**- 42.5% were in the age group of 21 – 30 yrs, 49.17% cases in age group 31-35 yrs and only 8.33% were above 35 yrs. 80% of patients were primary aborters while 20% were secondary aborters. Majority patients had 2 previous miscarriages (65.83%), 25% had 3 previous losses, 6.67% had 4 previous losses and only 2.5% had previous 5 losses. Maximum patients had a miscarriage before 12 weeks of gestation (90). **Conclusion:**Recurrent miscarriage needs extensive work up and may result from genetic, anatomical, endocrine and thrombotic causes. Hyperhomocysteinemia and biotinidase deficiency found to be the newer emerging cause

INTRODUCTION

Recurrent pregnancy loss is defined as occurrence of three or more consecutive spontaneous clinically detectable pregnancy losses prior to the 20th week of gestation from the last menstrual period Edmonds DK et al. (1)

Recurrent Pregnancy Loss complicates 0.5-3% of all pregnancies Daya S et al (2) It is distressing for couples and often to the clinicians who are involved in care of such patients. Aetiology is varied with combination of factors playing a role in such patients. Despite recent advances, large portion remains unexplained. As the technology advances, some of the so called unexplained or idiopathic recurrent pregnancy loss will be reclassified.

The evidence emerging is that prevalence of various aetiological factors in those who have had two or more spontaneous recurrent pregnancy losses is similar to that in who have had three.

Some investigators included two or more miscarriages in their series (Quenby and Farquharson, 1993 et al(3); Stephenson et al, 1998(4); Dubey S et al 2005(5)

In patients with history of two miscarriages, the subsequent risk of pregnancy loss rises to about 25%, whereas three abortions raise the risk of a fourth miscarriage to 33%. Dubey S et al 2005(5)

Various Possible Aetiological Factors Are Genetic (5%) , Anatomical (12-16%), Endocrine (17-20%), Immunological (20-50%), Infections (0.5-1.5%), hrombophilia (5-8%), Maternal Systemic Illness & Unexplained (30-40%)[9]. The unexplained which accounts for 30-40% of etiological factors remains a challenge to solve the mystery of recurrent pregnancy loss. Thus, it becomes a necessity to prepare a proper proforma or a protocol clinically as well as laboratory backed, to find out the exact aetiology of recurrent pregnancy loss.

MATEERIAL AND METHODS.

This observational study of 120 cases of recurrent pregnancy loss before 20 weeks of gestational period was conducted in the department of obstetrics and gynaecology at Govt. Medical College, Akola over a period of two years (01/03/2012 to 28/02/2014).

The permission from head of institution and clearance from ethical committee was obtained before starting the study.

Inclusion Criteria: Women with history of 2 or more consecutive miscarriages before 20 weeks of gestation, among those attending the outpatient department of the hospital.

Exclusion Criteria were: Non-consecutive abortion ,induced abortions and gestation above 20 weeks.

Women were seen in the intercurrent phase between pregnancies and at this visit, a thorough clinical history was recorded and an investigation protocol was followed to exclude known associations with recurrent miscarriage.All patients coming with history of recurrent abortion before 20 weeks of gestational period were investigated on OPD basis, to find out aetiological factors of recurrent pregnancy loss.At the follow up visit, results and plan for the management of subsequent pregnancy were discussed. Clinical evaluation was done as per findings of case history. The data was collected after taking an informed consent ensuring confidentiality and guarantee of anonymity to the individual. The data was coded tabulated and analysed using suitable statistical methods.

RESULTS

In this present study,80% patients were primary aborters and 20% were secondary aborters.

It is seen that majority of the patients belonged to the group with 2

miscarriages (65.83%).Only 2.5 % had >5 miscarriages. Most of the pregnancy losses in this study (90%) occurred before 12 weeks of gestation and 71.67% pregnancy losses occurred between 6-8 weeks of gestation. 42.5% of women were between 21-30 years of age, 49.17% were between 31-35 years and 8.33% of women were more than 35 years.

Table 1- Distribution of cases according to aetiological Factors of recurrent pregnancy loss.

Aetiological factors	Number	Percentage
Chromosomal	4	3.33%
Anatomical		
a) Intrauterine septum	8	6.67%
b) Submucous fibroid	5	4.17%
c) Cervical incompetence	5	4.17%
d) Asherman's syndrome	2	1.67%
Endocrinological		
a) Thyroid	9	7.5%
b) Diabetes	1	0.83%
c) Hyperprolactinemia	8	6.67%
APLA	16	13.33%
Hyperhomocysteinemia	5	4.17%
Thrombophilia	4	3.33%
Biotinidase deficiency	10	8.33%
Unexplained	43	35.83%
Total	120	100%

Table no. 1 shows that 43 (35.83%) patients had unexplained recurrent pregnancy loss. In 20 (16.68%) patients anatomical and in 18 (15%) patients endocrinological, in 16 patients (13.33%) APLA contributed as an aetiological factor for recurrent miscarriage.

Table 2-Aetiological Factors Noted In Cases With At least One Successful Pregnancy Outcome

Aetiological factors	Number	Percentage
Chromosomal	0	0%
Anatomical		
a) Intrauterine septum	0	0%
b) Submucous fibroid	0	0%
c) Cervical incompetence	2	8.33%
d) Asherman's syndrome	0	0%
Endocrinological		
a) Thyroid	3	12.5%
b) Diabetes	0	0%
c) Hyperprolactinemia	0	0%
APLA	3	12.5%
Hyperhomocysteinemia	3	12.5%
Thrombophilia	0	0%
Biotinidase deficiency	1	4.17%
Unexplained	12	50%
Total	24	100%

Table no. 2 shows that in 50% of women, the aetiology could not be ascertained. APLA, hypothyroidism and hyperhomocysteinemia each contributing 12.5% as an aetiological factor for recurrent miscarriage.

In this study, it is seen that anatomical, endocrinological and APLA were the most significant aetiological factors in cases with recurrent miscarriage with no previous successful outcome. The majority of patients were in the unexplained category. It is seen that after appropriate treatment of patients with anatomical factor as a cause of recurrent miscarriage, 25 % were having ongoing pregnancies in third trimester and 40 % were delivered successfully at term. With low dose ASA started preconceptionally , low dose ASA and LMWH after fetal heart is seen on ultrasound,25 % patients with APLA were having ongoing pregnancies in third trimester and 43.75% patients delivered successfully at term. With low dose aspirin and LMWH,50 % patients with Factor V Leiden mutation were having ongoing pregnancies in third trimester and 25% patients delivered successfully at term. In patients with hyperhomocysteinemia ,with folic acid and Vitamin B 12 supplementation,80 % patients were having ongoing pregnancies in third trimester and 20 % patients delivered successfully at term. After appropriate treatment of patients with Endocrinological factor as a cause of recurrent miscarriage, 33.34% were having ongoing pregnancies in third trimester and 44.44 % were delivered successfully at term.

In present study, it is seen that patients with biotinidase deficiency with biotin supplementation and dietary modification started preconceptionally, 20 % patients were having ongoing pregnancies in third trimester and 30% patients delivered successfully at term With proper psychological support, 27.91% patients with un-explained recurrent miscarriage were having ongoing pregnancies in third trimester and 25.58% patients delivered successfully at term. Among 75 cases who conceived during the study period, one had a spontaneous miscarriage,39 patients had delivered and remaining 35 were ongoing pregnancies in the third trimester.

DISCUSSION

Among 120 cases, 96 (80%) had no previous successful pregnancy outcome and 24 cases (20%) had at least one previous successful outcome. This percentage may be higher in the present study because it includes all patients with 2 or more losses instead of 3 or more losses.

The present study shows that 90% (108) of miscarriages took place before 12weeks of gestation and only 10 % (12) were beyond 12weeks of gestation. The present study suggests that 71.67 % (86) losses occur between 6-8 weeks of gestation. Similar results were obtained by S A Brigham, R.G.Farquharson in 1999(7).They suggested that most perilous time for women with recurrent pregnancy losses is between 6-8 weeks of gestation, between which 78 % of losses occurred.

In this study, 42.5% (51) of cases belonged to the age group 21-30 years , 49.17%(59) of cases belonged to age group 31-35 yrs and 8.33%(10) were >35years.

A study conducted in 1996 Smith K.E.(12) showed that a woman's chance of miscarriage increases with her age. It not only becomes more difficult for a woman to get pregnant but to stay pregnant as well.

In the present study out of 120 cases, 4 of them (3.33%) had chromosomal anomalies as an etiological factor for recurrent miscarriages. A similar incidence (4.67%) has been reported by Schust DJ ,Hill JA (5%)(6), Dubey et al in 2005 (4%)(3).

Among 120 cases, 8 cases (6.67%) had intrauterine septum with recurrent spontaneous miscarriages. In view of the uterine anomaly a septoplasty was done. At present,3 cases (37.5%) are currently continuing their pregnancy beyond 28 weeks of gestation,2 cases (25%) delivered successfully at term and 3 cases(37.5%) belonging to the intercurrent group, has not yet conceived.

Grimbizis GF et al(8), in their paper on clinical implications of uterine malformations and hysteroscopic treatment results, reported that the prevalence of uterine anomalies in recurrent miscarriage population ranges between 1.8% and 37.6 16 out of 120

VOLUME-6 | ISSUE-1 | JANUARY-2017 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 78.46

cases (13.33%) were diagnosed as APLA positive. 4 cases were LA positive,6 cases were ACA positive,4 cases were LA and ACA positive and 2 cases were diagnosed as ANA positive, in whom one patient is ACA positive and one patient is LA positive. One patient with ANA and LA positive status delivered successfully at term by caesarean section treated with ASA and Low molecular weight Heparin. One patient with ANA and ACA positive status is having ongoing pregnancy beyond 28 weeks of gestation Out of remaining 14 cases of APLA, 3 cases is having ongoing pregnancies beyond 30 weeks of gestation,6 patients delivered successfully at term, and remaining 5 cases are now trying for conception. Ongoing pregnancies are being treated with low dose aspirin and low molecular weight heparin.

In our study, only 4 patients had thrombophilic defects (3.33%).All were having Facor V Leiden mutation. Out of them, 2 cases (50%) are having ongoing pregnancies beyond 28 weeks of gestation and are taking low dose aspirin along with low molecular weight heparin. One patient (25%) delivered successfully at term after being treated with low dose aspirin along with low molecular weight heparin and one patient belongs to intercurrent group.

In the present study, it was estimated that approximately 15% of all pregnancy losses were the result of endocrine factors which were found to be similar to the study conducted by Arrendondo F, Noble LS(9) (8-12%).

The percentage of diabetes as a possible etiological factor is 0.83 % in the present study.

In the present study, out of 120 cases 1 had diabetes. The patient was treated with insulin and was well controlled before conception. The patient underwent caesarean section. Thus, if diabetes is well controlled the chance of having a miscarriage is minimized..

In our study among 120 cases, 9 cases (7.5%) were hypothyroid and were treated for the same with thyroxin. Regular monitoring of TSH and free T4 levels was done and dosage adjusted. 3 (33.33%) cases had a normal vaginal delivery and 5 (55.56%) have ongoing pregnancies beyond 28 weeks of gestation. This is similar to study done by Rao VR et al in 2008, 10 who concluded that hypothyroidism was found in 4.12 % women with recurrent pregnancy loss and treatment of hypothyroidism could help couples with recurrent pregnancy loss to have successful outcome in subsequent pregnancy In present study, out of 120 cases,8 patients (6.67 %) were hyperprolactinemic.They were treated with cabergoline..

Biotin is an important vitamin for cellular function and growth and, therefore, essential for fetal development. The fetus is exclusively dependent on maternal biotin supply Mantagos S et al (11).

In our study, out of 120 cases,10 cases(8.33%) were having marginal/partial biotinidase deficiency. Biotinidase deficiency uniformly responds to moderate biotin supplementation.

In 43 out of 120 cases (35.83%) no cause was found that could explain their recurrent miscarriages. Among these 43 cases, 24 were pregnant during the study period and 19 cases are in intercurrent phase. Out of the 24 pregnant women, 12 (27.91%) have ongoing pregnancies beyond 28 weeks gestation, 11 (25.58%) had delivered successfully at term, and one had a repeat miscarriage at 10 weeks gestation.

CONCLUSION

- Recurrent pregnancy loss needs extensive work up to find out the causes.
- Recurrent miscarriage is a heterogeneous condition and may result from several underlying factors, such as genetic, anatomical, endocrine, and thrombotic causes.
- No explanation was found in as many as 35% of couples with recurrent miscarriage.
- Hyperhomocysteinemia & Biotinidase deficiency were found to be new emerging cause for recurrent pregnancy loss.
- Inj. Low molecular weight heparin and low dose aspirin is seen to work well in immunological causes-APLA, SLE, and Thrombophilias.
- Empirical treatment should be avoided as its benefits are doubtful. There are still many grey areas in the treatment of couples with recurrent miscarriage.
- Psychological support in the form of frequent visits, sympathetic counselling and ready access to emergency care should be part of the management of couples with recurrent miscarriage.
- Counselling does play a scientifically proven adjuvant role to all forms of therapy that may be instituted in cases of recurrent pregnancy loss.
- Supplementation of Biotin in patients of biotinidase deficiency needs to be studied on large scale.

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