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Comparative study of etiological factors of single early pregnancy loss with that of recurrent pregnancy loss

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Abstract
Aim and Objective: Investigating for pregnancy loss is usually recommended only after two or more pregnancy losses. But women with single pregnancy loss seek explanation, in practice. This study is conducted in order to determine the identifiable causes and their proportion in women with single early pregnancy loss and to compare with that of women with recurrent pregnancy loss (RPL).
Materials and Methods: This cross-sectional analytical study is undertaken between January 2021 and January 2022. Group A included 50 women with single early pregnancy loss and Group B included 50 women with RPL. The recommended investigations for etiological factors are done in both groups except karyotyping, and thrombophilia screening is done in those with unknown etiology.
Statistical analysis: Etiological factors are expressed as proportions, and comparison between two groups is done by unpaired *t*-test and Mann–Whitney test.
Results: Socio demographic factors and gestational age are similar in both the groups. Significantly more number of women with single early pregnancy loss (60%) had known etiological factors than women with RPL (48%) ($P = 0.038$). Endocrine causes are commonest in both the groups (single early pregnancy loss 36%, RPL 22%; $P = 0.023$). Out of the women with unknown causes, approximately 25% of women are positive for thrombophilia in each group.
Conclusion: Significant proportion of women with single early pregnancy loss have treatable etiological factors like those of RPL. Hence evaluation should be undertaken to achieve optimum outcomes during the next pregnancy and prevent RPL.
Clinical significance: Assessing the women with first pregnancy loss aids the obstetrician to avert pregnancy loss in further pregnancies by apt management according to etiology.

Keywords: Endocrine cause, etiology, single early pregnancy loss, miscarriage, recurrent pregnancy loss, thrombophilia

Introduction

Pregnancy loss, a distressing condition for both the patient and obstetrician, can occur at any gestational period, however, usually during early pregnancy. The etiologies for early pregnancy loss and recurrent pregnancy loss are most often distinct. Early pregnancy loss is defined as a nonviable intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or fetus without cardiac activity within the first 13 + 6/7 weeks of gestation. In the first trimester, the terms miscarriage, spontaneous abortion, and early pregnancy loss are used interchangeably as there is no consensus on terminology in the literature [1].

Early pregnancy loss occurs in 10% of all clinically recognized pregnancies and approximately 80% of all cases of pregnancy losses occur within the first trimester [2]. Pregnancy loss when occurs repeatedly is termed recurrent pregnancy loss (RPL). According to the European Society of Human Reproduction and Embryology (ESHRE), RPL is a distinct disorder defined by two or more failed clinical pregnancies [3]. Guidelines recommend evaluation only for RPL as a wide variety of etiological factors have been described in the literature and evaluation of RPL revealed causes only in 50%. [4] But there are no recommendations for initiation of investigations after first or single pregnancy loss.

A significant proportion of women (20%) who experience a miscarriage become symptomatic for depression and anxiety [5]. This warrants diagnostic workup and interventions. There are no studies with regard to the initiation of investigations after first early pregnancy loss. The high baseline rate of spontaneous isolated and recurrent pregnancy losses in the general population, the lack of consistent definition for RPL, limited access to tissues allowing study of the disorder,

and the remarkably good prognosis for live birth among patients with RPL combine to aim at diagnostic and therapeutic recommendations. In this context, this study aims to find out the etiological factors in women with first early pregnancy loss and to compare it with women who had two or more than two pregnancy losses (RPL). This study will establish the need, if any, to investigate a woman after one pregnancy loss for possible etiological factors. This will also find out the common causes of early pregnancy loss in this population and ensure adequate timely intervention for treatable causes without waiting for the subsequent pregnancy loss.

Materials and Methods

Study design and settings

This cross-sectional analytical study is done in women attending the Department of Obstetrics and Gynaecology, at Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar, between January 2021 and January 2022. Processing of various samples is done in the department of biochemistry [glucose tolerance test] and clinical immunology [anti-phospholipid antibodies (APLA)], and pathology (protein C and protein S). Two groups of women with 50 subjects in each group are enrolled (group A-single early pregnancy loss; group B-RPL).

Participants

Inclusion criteria

The inclusion criteria are as follows:

Group A

Pregnant women admitted with single early pregnancy loss (gestational age ≤14 weeks)

Nonpregnant women attending outpatient department (OPD) with history of one early pregnancy loss and requesting investigations for pregnancy loss.

Group B

Women with two or more than two early pregnancy losses (RPL).

Exclusion criteria

The exclusion criteria are:

- Age <18 years and >35 years
- Prior live birth

Sample size calculation

The sample size is calculated using OpenEpi software version 3.0 using 95% confidence level (CI) and power of 80%. As there are no prior studies on single early pregnancy loss, it is presumed that the difference in proportion of identifiable causes in both groups, that is women with two or more than two pregnancy losses (RPL) and women with first early pregnancy loss to be 20%. The proportion of identifiable causes in group A is 30% and those in RPL is 50% [4].

Study procedure

Women fulfilling the inclusion criteria are explained about the protocol of the study and a written informed consent is taken from each participant enrolled in the study. The enrolled participants are divided into two groups: group A-women with single early pregnancy loss and group B-women with two or more than two pregnancy losses (RPL). Demographic data including age, occupation, education, socioeconomic status are collected by interviewing the patient. Clinical profile including gravidity, parity, past obstetric history, family history, and treatment history is documented on a proforma after interviewing the patient and from the medical records. A general physical examination is carried out, and height, weight, and BMI are calculated. A complete systemic examination, including thyroid, breast, respiratory, cardiovascular, abdominal, and gynaecological examination, is performed. Parameters noted in this study are age, BMI, socioeconomic status, number of pregnancy losses, clinical assessment to find out the cause of pregnancy loss, thyroid function test, 75 gm oral glucose tolerance test, urine culture sensitivity, cervical swab culture sensitivity, ultra sonogram to assess uterine anomalies, fetus assessment, and polycystic ovary syndrome (PCOS). If no cause is found, thrombophilia profile is done. Investigation for protein C and protein S deficiency is done 6 weeks after pregnancy loss to avoid false negatives during pregnancy.

Primary outcome

Measures are proportion of women with identifiable causes for single early pregnancy loss and recurrent pregnancy loss.

Secondary outcome

Measures are proportion of women with various etiological factors.

Statistical analysis

Data is collected and entered into statistical software SPSS version 15. Continuous variables like height, weight, age, BMI, and hormonal levels are demonstrated as mean (standard deviation) or median (interquartile range) according to distribution of data and compared across two groups using unpaired *t*-test (normal/parametric distribution) or Mann–Whitney test (nonparametric distribution). Categorical variables (outcome) like proportion of women with endocrine causes and other nonendocrine causes are described as frequency and proportions and compared between groups by Chi-square test. A p value <0.05 is considered as significant.

Results

Fifty patients are recruited in group A (pregnant women admitted with single early pregnancy loss or non-pregnant women attending OPD with history of one pregnancy loss) and 50 patients are recruited in group B with RPL. Eight women in group a (first pregnancy loss) and four women in group B (RPL) are in non-pregnant state, rest of the women are recruited immediately after pregnancy loss as inpatients.

Table 1 shows sociodemographic profile of the subjects. The mean age of women with single early pregnancy loss (group A) is 25.1 $\pm$ 4.2 years and mean BMI is 22 kg/m2. Seventy two percent of women with first pregnancy loss had normal weight, 22% are pre-obese, and only one woman is obese (class I). Majority of patients belonged to class III and IV Kuppuswamy socioeconomic status classification (32 and 66%, respectively). The mean gestational age at pregnancy loss in group A is 10 weeks. There is no statistically significant difference of age, BMI, socioeconomic status and gestational age at pregnancy loss between women in both the groups.

Table 1: Comparison of sociodemographic and clinical profile

SI. No	Parameter	Group AN N (%)	Group BN (%)	p value
1	Mean age (years) ± SD	25.1±4.26	25.9±4.21	0.17
2	Mean BMI (kg/m^2) ± SD	22.74±2.84	23±3.16	0.68
3	BMI (kg/m^2)			0.584
	Underweight (<18.5)	2 (4%)	2 (4%)	
	Normal weight (18.5–24.9)	36 (72%)	35 (70%)	
	Pre-obesity (25–29.9)	11 (22%)	11 (22%)	
	Obesity class I (30–34.9)	1 (2%)	2 (4%)	
4	Socioeconomic status (Kuppuswamy classification)			0.226
	Class I	—	—	
	Class II	1 (2%)	2 (4%)	
	Class III	16 (32%)	19 (38%)	
	Class IV	32 (66%)	29 (58%)	
5	Mean gestational age at pregnancy loss (weeks) ± SD	10.3±1.9	10.23±2.1	0.49

*p value is calculated using independent Student t-test for age, BMI, and gestational age and Chi-square test for BMI classification and socioeconomic status

Table 2: Comparison of etiological factors: first early pregnancy loss vs recurrent pregnancy loss

SI. No	Etiological factors	Group- A (%)	Group- B (%)	P value
1	Unknown	20 (40%)	26 (52%)	**0.038**
2	Known	30 (60%)	24 (48%)	
A	Anatomical factors	3 (6%)	2 (4%)	0.249
	Uterine anomaly	1 (2%)	1 (2%)	
	Fibroid	2 (4%)	0	
	Cervical incompetence	-	1 (2%)	
B	Fetal anomaly	0	0	
C	Endocrine	18 (36%)	11 (22%)	0.023
	Hypothyroidism	4 (8%)	2 (4%)	
	Type 2 diabetes mellitus (T2DM)	4 (8%)	2 (4%)	
	Polycystic ovary syndrome (PCOS)	3 (6%)	1 (2%)	
	Gestational diabetes mellitus (GDM)	7 (14%)	6 (12%)	
D	Infections	1 (2%)	1 (2%)	0.48
E	Combined etiology	8 (16%)	10 (20%)	0.464
1	GDM + PCOS	0	1 (2%)	
2	GDM + hypothyroidism	1 (2%)	2 (4%)	
3	GDM + PCOS + hypothyroidism	0	1 (2%)	
4	GDM + cervicovaginal infections	2 (4%)	1 (2%)	
5	T2DM + hypothyroidism	3 (6%)	1 (2%)	
6	T2DM + PCOS	1 (2%)	0	
7	Uterine anomalies + hypothyroid	1 (2%)	1 (2%)	
8	Cervical incompetence + GDM	0	1 (2%)	
9	Cervical incompetence + hypothyroid + PCOS	0	1 (2%)	
10	Lupus anticoagulant + hypothyroid	0	1 (2%)	

*P value is calculated using Chi-square test for known, endocrine, infections, and combined causes and Fischer exact test for anatomical causes.

Table 2 shows the comparison of causes of first pregnancy loss with that of RPL. The proportion of known causes in group a women with single pregnancy loss is 60% when compared to 48% in group B (Women with RPL) and the difference is statistically significant. Endocrine causes are the commonest in both the groups, and the proportion of endocrine causes in first pregnancy loss (36%) is significantly more than RPL group (22%) with $p = 0.023$. Combined etiology is the second commonest (group A 16% vs group B 20%; $p = 0.46$). The percentage of anatomical, infectious, and combined causes is similar between both the groups.

Table 3: Comparison of thrombophilia evaluation

Sl. No	Thrombophilia evaluation	Group A n (%) N = 20	Group B n (%) N = 26	P value
1	Thrombophilia negative	15 (75%)	19 (73%)	
2	Thrombophilia positive	5 (25%)	7 (27%)	0.47
A	APLA positive	2 (40%)	4 (57%)	NS
	Primary	2	3	
	Secondary	-	1	
B	Protein C deficiency	-	0	
C	Protein S deficiency	2 (40%)	2 (28.6%)	
D	APLA positive + protein S deficiency	1 (20%)	1 (14.3%)	

P value is calculated using Chi-square test; APLA, anti-phospholipid antibodies.

Thrombophilia evaluation is done for unknown causes (46) in both the groups (group A-20 and group B-26). Approximately twenty five percent of women in each group are positive for thrombophilia with *p* value of 0.47. Thus, the proportion of thrombophilia-positive women in both the groups is almost similar, as shown in table 3.

Table 4: Proportion of etiological factors with addition of thrombophilia evaluation

Parameter studied		Group A N = 50 (%)	Group B N = 50 (%)	p value
Excluding thrombophilia evaluation	Known etiology	30 (60%)	24 (48%)	0.038
	Unknown etiology	20 (40%)	26 (52%)	
Including thrombophilia evaluation	Known etiology	35 (70%)	30 (60%)	0.09
	Unknown etiology	15 (30%)	20 (40%)	

*P value is calculated using Chi-square test

When thrombophilia evaluation is considered to be a known cause for pregnancy loss, for women with single early pregnancy loss, the proportion of known causes increased from 60 to 70% and 48 to 60% in the RPL group. The proportions of identifiable causes in both the groups after addition of thrombophilia evaluation are: group A - 70% and group B - 60%; (p = 0.09) as shown in table 4.

Discussion

The present study is a descriptive, analytical study to know the etiology of single early pregnancy loss and to compare the proportion of identifiable causes between single early pregnancy loss and recurrent pregnancy loss. The study included 50 women in group a (single early pregnancy loss) and another 50 women in group B (recurrent pregnancy loss). We found that the proportion of identifiable causes in single early pregnancy loss is similar to that of RPL (P = 0.09). In 70% (N = 35) of women in group A and 60% (N = 30) women in group B, various etiological factors are identified.

There are no studies in the literature that evaluated causes for single early pregnancy loss. In the present study, about 40% of pregnancy loss both in first pregnancy loss and RPL group is found to be among the age group of 21–25 years. A previous study by Nybo Anderson *et al*. showed that as the age increased, the percentage of RPL increased [6]. We did not find a similar trend in the present study. The incidence of RPL in their study in the age-group of 40–44 years is 51% as compared to 11% in 21–25 years. We did not recruit women >35 years in our study because pregnancy loss occurs more commonly in this group and the number of pregnant women would be less for analysis. The most common age-group of antenatal women in our population is 21–25 years, which might be the reason for finding the maximum incidence of RPL in this age-group.

Bhandari *et al*., in their study on obese women with RPL found that majority of women (48.6%) had normal weight, 31% were pre-obese, and 19% were obese [7]. Matjila *et al*., in their study on medical conditions in RPL found that majority of the women were obese (42%) [8].

Cavalcante *et al*. performed a meta-analysis on obesity and recurrent miscarriage and reported 47% of women with RPL in normal weight category, while 29% were pre-obese and 22% were class I obese [9]. In our study also, similar to Bhandari *et al*. [7] and meta-analysis by Cavalcante *et al*., [9] majority of women had normal weight (70%) and 22% women were pre-obese, which is comparable to previous studies, but only 4% women were obese, which is less as comparable to previous studies. The difference in the findings may be due to different population characteristics. Bhandari *et al*. performed their study in the UK and Matjila *et al*. on South African women. The incidence of obesity as such in India is less as compared to the west.

Based on previous studies, endocrine causes were the commonest among known causes of RPL. DM was found in 26% of women, [10] hypothyroidism in 9–12%, [10, 11] and PCOS in 7.8% of women with RPL. [12] In the present study also, we found that endocrine causes (22%) were commonest among RPL women which was comparable to previous study. [13] DM, hypothyroidism, and PCOS comprised 4%, 4% and 2% respectively, in women with RPL in our study. The prevalence of hypothyroidism and diabetes was found to be higher in previous studies than the present study. The incidence of PCOS in RPL women is found to be 2% in our study. PCOS in RPL varied widely between 4.8 and 80% as described in the literature, so more studies are required to come to a consensus [14].

Salim *et al*. found uterine anomalies in 5% of women with RPL, whereas in our study, it was only 2%. [15] Infections as an etiological factor are found to be less (2%), which is comparable to previous studies in the literature [16]. In the present study, 20% of women had combined etiology and only one study in the literature by Lee *et al*. has reported combined etiology (48%) contributing to RPL, but the authors did not clarify causes included in the combined etiology [11].

Similar to the previous studies, in 52% of women with RPL, the cause of RPL was unknown [4].

There are no studies to find out the etiology of single early pregnancy loss. In our study, it is found that the endocrine causes are significantly higher in first pregnancy loss than RPL. The proportion of other causes is similar to RPL and that of identifiable causes in first early pregnancy loss is more than that of RPL, which is an unanticipated finding as there are no studies or recommendations for evaluation of first pregnancy loss in the literature so far.

Previous study by Vora *et al*. showed that in women with unknown causes of RPL, 75% were thrombophilia positive and that by Patil *et al*. in women with unexplained RPL showed that 40% of RPL women were positive for thrombophilias [17, 18]. In the present study, we found that approximately 25% of RPL women are positive for thrombophilias. We could investigate only 46 women of unknown RPL and single early pregnancy loss, whereas Vora *et al*. tested 381 women only with RPL.

The proportion of women with single pregnancy loss positive for thrombophilia is comparable to women with RPL. There are no previous studies in the literature for thrombophilia evaluation after one miscarriage.

As per ESHRE guidelines, [3] screening for thrombophilia in RPL can be considered, while RCOG [19] and ASRM [20] recommend screening for thrombophilia in RPL women.

Conclusion

A significant proportion of women (70%) with single early pregnancy loss had various etiological factors and endocrine factors are the most common causes. Among the identifiable causes for single early pregnancy loss, anatomical factors are found in 6%, endocrine in 36%, thrombophilia in 25%, and

combined etiology in 16%.

Statistically, significantly more women with single early pregnancy loss are found to have known etiological factors when compared to women with RPL. The thrombophilia positivity is found to be almost similar in both the groups. Hence, it is recommended that evaluation should be undertaken for women with single early pregnancy loss, so that further pregnancy loss can be prevented to achieve optimum pregnancy outcomes. Thrombophilia screening may be undertaken for women when the endocrine causes and anatomical causes are normal.

Limitations of the Study

Thrombophilia evaluation is done only in women with unknown causes in both the groups. Congenital thrombophilia screening could not be done for all women with unknown causes because of high cost and limited funds.

Clinical Significance

Evaluation of women with first pregnancy loss helps the clinician to prevent pregnancy loss in subsequent pregnancies by appropriate management as per the etiology

Conflict of Interest

Not available

Financial Support

Not available

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