RESEARCH ARTICLE

Etiological Factors for First Single Early Pregnancy Loss: Are They Different from Recurrent Pregnancy Loss?

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Abstract

Aim and objective: The recommendation for investigation of pregnancy loss is to test only after two or more pregnancy losses. But in practice, we find women with single pregnancy loss seeking explanation. The purpose of this study was to determine the identifiable causes and their proportion in women with *first early pregnancy loss* and to compare with that of women with *recurrent pregnancy loss (RPL).*

Materials and methods: This cross-sectional analytical study was undertaken between 2018 and 2019. Group A included 105 women with first single pregnancy loss and group B included 105 women with RPL. The recommended investigations for etiological factors were done in both groups except karyotyping, and thrombophilia screening was done in those with unknown etiology.

Statistical analysis: Etiological factors were expressed as proportions, and comparison between two groups was done by unpaired *t*-test and Mann–Whitney test.

Results: Sociodemographic factors and gestational age were similar in both the groups. Significantly more number of women with first single pregnancy loss (58%) had known etiological factors than women with RPL (43%) ($p = 0.038$). Endocrine causes were commonest in both the groups (first pregnancy loss 36% vs RPL 21%; $p = 0.023$). Out of the women with unknown causes, 18% of women were positive for thrombophilia in each group and more than 50% of them were antiphospholipid antibodies (APLA) positive.

Conclusion: Significant proportion of women with single first 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: Evaluation of women with first pregnancy loss helps the clinician to prevent pregnancy loss in subsequent pregnancies by appropriate management as per the etiology.

Keywords: Endocrine cause, Etiology, First early pregnancy loss, Miscarriage, Recurrent pregnancy loss, Thrombophilia.

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Introduction

Pregnancy loss is a distressing condition for both the patient and obstetrician. It can occur at any gestational period but most commonly during early pregnancy. The etiologies for early pregnancy loss and late pregnancy loss are most often different. 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 12 + 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.

Whenever a woman suffers pregnancy loss, an explanation is sought for the same from the treating obstetrician. Sometimes women approach the clinicians after having suffered pregnancy loss and request for investigations, but the clinical practice recommendations are in place to investigate after two or more pregnancy losses and not for single pregnancy loss.

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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. 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 early 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 was done in the Department of Obstetrics and Gynaecology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, South India, between January 2018 and August 2019. Processing of various samples was done in the department of biochemistry glucose tolerance test and clinical immunology [antiphospholipid antibodies (APLA)], and pathology (protein C and protein S). Two groups of women with 105 subjects in each group were enrolled (group A—first early pregnancy loss; group B—RPL).

Participants

Inclusion Criteria

The inclusion criteria were as follows:

Group A—Pregnant women admitted with first early pregnancy loss (gestational age ≤14 weeks) or 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 were age <18 years and >35 years, prior live birth, known cases of hypertension, diabetes mellitus (DM), hypothyroidism, and autoimmune disorders.

Sample Size Calculation

The sample size was calculated using OpenEpi software version 3.0 using 95% confidence level (CI) and power of 80%. As there were no prior studies on single early pregnancy loss we assumed that the difference in proportion of identifiable causes in two 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 is 50% among women in RPL.[4] The proportion of identifiable causes in group A is 30%, the sample size was 95 in each group, and with 10% dropouts, the final sample size was as follows: group A—105; group B—105. For sampling, purposive sampling technique was used.

Study Procedure

Women fulfilling the inclusion criteria were explained about the protocol of the study and a written informed consent was taken from each participant enrolled in the study. The enrolled participants were divided into two groups: group A—women with first early pregnancy loss and group B—women with two or more than two pregnancy losses (RPL). Demographic data including age, occupation, education, socioeconomic status were collected by interviewing the patient. Clinical profile including gravidity, parity, past obstetric history, family history, and treatment history was documented on a proforma after interviewing the patient and from the medical records. A general physical examination was carried out, and height, weight, and BMI were calculated. A complete systemic examination, including thyroid, breast, respiratory, cardiovascular, abdominal, and gynecological examination, was performed. Parameters noted in this study were age, BMI, socioeconomic status, number of pregnancy losses, clinical assessment to find out the cause of pregnancy loss, thyroid function test, 75 g oral glucose tolerance test, urine culture sensitivity, cervical swab culture sensitivity, ultrasonogram to assess uterine anomalies, fetus assessment, and polycystic ovary syndrome (PCOS). If no cause was found, thrombophilia profile for acquired thrombophilias and congenital thrombophilias (lupus anticoagulant; β2 glycoprotein antibodies; IgM and IgG, anticardiolipin antibodies, IgM and IgG; and protein C and protein S) was done. Investigation for protein C and protein S deficiency was done 6 weeks after pregnancy loss to avoid false negatives during pregnancy.

Primary outcome measures were proportion of women with identifiable causes for first early pregnancy loss and RPL.

Secondary outcome measures were proportion of women with various etiological factors.

Statistical Analysis

Data were collected and entered into statistical software SPSS version 15. Continuous variables like height, weight, age, BMI, and hormonal levels were expressed as mean (standard deviation) or median (interquartile range) as per 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 were described as frequency and proportions and compared between groups by Chi-square test. A *p* value <0.05 was considered as significant.

Results

One hundred and five patients were recruited in group A (pregnant women admitted with first early pregnancy loss or nonpregnant women attending OPD with history of one pregnancy loss) and 105 patients were recruited in group B with RPL. Four women in group A (first pregnancy loss) and two women in group B (RPL) were in nonpregnant state, rest of the women were recruited immediately after pregnancy loss as inpatients.

The demographic profile of subjects is shown in Table 1. The mean age of women with first early pregnancy loss (group A) was 25 ± 4.2 years and mean BMI was 22 kg/m^2. Seventy-three percent of women with first pregnancy loss had normal weight, 21% were pre-obese, and only one woman was obese (class I). Majority of patients belonged to class III and IV Kuppuswamy socioeconomic status classification (34 and 67%, respectively). The mean gestational age at pregnancy loss in group A was 10 weeks. There was no statistically significant difference of age, BMI, socioeconomic status, and gestational age at pregnancy loss between women in both the groups.

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 was 58% as compared to 43% in group B (women with RPL) and the *difference was statistically significant*. Endocrine causes were the commonest in both the groups, and the proportion of endocrine causes *in first pregnancy loss (36%) was significantly more* than RPL group (21%) with $p = 0.023$. Combined etiology was the second commonest (group A 15.23% vs group B 19%; $p = 0.46$). The percentage of anatomical, infectious, and combined causes was similar between both the groups.

Thrombophilia evaluation was done for unknown causes (103) in both the groups (group A—44 and group B—59). Eighteen percent of women in each group were positive for thrombophilia with *p* value of 0.47. Thus, the proportion of thrombophilia-positive women in both the groups was similar (Table 3). Of the acquired

Table 1: Comparison of sociodemographic and clinical profile

Sl. No	*Parameter*	*Group A N (%)*	*Group B N (%)*	*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)	4 (3.8%)	4 (3.8%)	
	Normal weight (18.5–24.9)	77 (73.3%)	75 (71.4%)	
	Pre-obesity (25–29.9)	23 (21.9%)	22 (21%)	
	Obesity class I (30–34.9)	1 (1%)	4 (3.8%)	
4	Socioeconomic status (Kuppuswamy classification)			0.226
	Class I	—	—	
	Class II	3 (3.5%)	4 (3.8%)	
	Class III	29 (34.5%)	40 (38.1%)	
	Class IV	73 (67%)	61 (58.1%)	
5	Mean gestational age at pregnancy loss (weeks) ± SD	10.3 ± 1.9	10.23 ± 2.1	0.49

[*] *p* value was 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

Sl. No	*Etiological factors*	*Group A N (%)*	*Group B N (%)*	*p value*[*]
1	Unknown	44 (41.90%)	59 (56.19%)	**0.038**
2	Known	61 (58.09%)	46 (43.80%)	
A	**Anatomical factors**	**5 (4.76%)**	**2 (1.90%)**	0.249
	Uterine anomaly	3 (2.9%)	1 (0.95%)	
	Fibroid	2 (1.9%)	0	
	Cervical incompetence	—	1 (0.95%)	
B	Fetal anomaly	0		
C	**Endocrine**	**38 (36.19%)**	**23 (21.90%)**	**0.023**
	Hypothyroidism	9 (8.6%)	5 (4.8%)	
	Type 2 diabetes mellitus (T2DM)	8 (7.6%)	5 (4.8%)	
	Polycystic ovary syndrome (PCOS)	6 (5.7%)	1 (0.95%)	
	Gestational diabetes mellitus (GDM)	15 (14.28%)	12 (11.42%)	
D	**Infections**	**2 (1.9%)**	**1 (0.95%)**	0.48
E	**Combined etiology**	**16 (15.23%)**	**20 (19.04%)**	0.464
	GDM + PCOS	0	1 (%)	
	GDM + hypothyroidism	3 (2.9%)	7 (6.7%)	
	GDM + PCOS + hypothyroidism	0	1 (0.95%)	
	GDM + cervicovaginal infections	4 (3.80%)	3 (2.9%)	
	T2DM + hypothyroidism	5 (4.8%)	3 (2.9%)	
	T2DM + PCOS	3 (2.9%)	0	
	Uterine anomalies + hypothyroid	1 (1%)	1 (0.95%)	
	Uterine anomalies + PCOS	0	1 (0.95%)	
	Cervical incompetence + GDM	0	1 (0.95%)	
	Cervical incompetence + hypothyroid + PCOS	0	1 (0.95%)	
	Lupus anticoagulant + hypothyroid	0	1 (0.95%)	

[*] *p* value was calculated using Chi-square test for known, endocrine, infections, and combined causes and Fischer exact test for anatomical causes

thrombophilias, more than 50% were APLA positive in both the groups.

When thrombophilia evaluation was considered to be a known cause for pregnancy loss, in women with first pregnancy loss, the proportion of known causes increased from 58 to 65% and 43 to 54% in the RPL group. The proportion of identifiable causes in both the groups was similar after addition of thrombophilia evaluation (group A 65% vs group B 54%; $p = 0.09$) (Table 4A).

Antiphospholipid antibodies examination was done for all the women with unknown causes (44 in group A and 59 in group B). Beta-2 glycoprotein was positive only in one woman in group B, and anticardiolipin antibodies were positive in three women in group A and four women in group B. Lupus anticoagulant was positive in three women in group A and six women in group B. As congenital thrombophilia screening being costly and because of limited funds, it was performed for 23 women with first pregnancy loss and 27 women

with RPL. Protein S deficiency was present in four women in group A and five in group B (Table 4B). There was no significant difference between both groups.

Discussion

The present study was a descriptive, analytical study to know the etiology of first early pregnancy loss and to compare the proportion of identifiable causes between first early pregnancy loss and RPL. The study included 105 women in group A (first early pregnancy loss) and another 105 in group B (RPL). We found that the proportion of identifiable causes in first early pregnancy loss was similar to that of RPL ($p = 0.09$). In 65% ($n = 69$) of women in group A and 54% ($n = 57$) women in group B, various etiological factors were identified.

There are no studies in the literature that evaluated causes for first early pregnancy loss. In the present study, about 40% of pregnancy loss both in first pregnancy loss and RPL group was 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 was 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 (71%) and 21% women were pre-obese, which was comparable to previous studies, but only 3.8% women were obese, which was 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 (21.9%) were commonest among RPL women which was comparable to previous study.[13] DM, hypothyroidism, and PCOS comprised 16.2%, 4.8% and 0.95% 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 was found to

Table 3: Comparison of thrombophilia evaluation

Sl. No	*Thrombophilia evaluation*	*Group A n (%) N = 44*	*Group B n (%) N = 59*	*p value**
1	Thrombophilia negative	36 (81.81%)	48 (81.35%)	
2	Thrombophilia positive	8 (18.18%)	11 (18.64%)	0.47
A	APLA positive	4 (50%)	6 (54.5%)	NS
	Primary	4	5	
	Secondary	—	1	
B	Protein C deficiency	—	0	
C	Protein S deficiency	3 (37.5%)	4 (36.3%)	
D	APLA positive + protein S deficiency	1 (12.5%)	1 (9.09%)	

**p* value was calculated using Chi-square test; APLA, antiphospholipid antibodies

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

Parameter studied		*Group A N = 105 (%)*	*Group B N = 105 (%)*	*p value**
Excluding thrombophilia evaluation	Known etiology	61 (58.09%)	46 (43.80%)	0.038
	Unknown etiology	44 (41.90%)	59 (56.19%)	
Including thrombophilia evaluation	Known etiology	69 (65.17%)	57 (54.28%)	0.09
	Unknown etiology	36 (34.28%)	48 (45.71%)	

**p* value was calculated using Chi-square test

Table 4B: Subgroup analysis: thrombophilia

		Group A		*Group B*		
Sl. No	*Type of thrombophilia*	*Number screened*	*Thrombophilia positive N (%)*	*Number screened*	*Thrombophilia positive N (%)*	*p value*
A	Acquired thrombophilia	44	6	59	8	
1	Beta-2 glycoprotein antibody	44	0	59	1 (1.51%)	1.00
2	Anticardiolipin antibody (ACLA)	44	3* (6.81%)	59	3** (6.06%)	1.00
3	Lupus anticoagulant (LAC)	44	3 (6.81%)	59	4 (9.09%)	0.736
B	Congenital thrombophilia	23	4	27	5	
1	Protein C deficiency	23	0	27	0	—
2	Protein S deficiency	23	4 (17.39%)	27	5 (18.51%)	1.00

*Group A—one woman was both LAC and ACLA positive; One woman was LAC positive and also had protein S deficiency; **Group B—one woman was both LAC and ACLA positive; One woman was ACLA positive and also had protein S deficiency

be 0.95% 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 0.95%.[15] Infections as an etiological factor were found to be less (0.95%), which was comparable to previous studies in the literature.[16] In the present study, 19% 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 56% of women with RPL, the cause of RPL was unknown.[4]

There are no studies to find out the etiology of first early pregnancy loss. The various etiological factors found in the present study for first early pregnancy loss are shown in Figure 1. Endocrine causes were significantly higher in first pregnancy loss than RPL. The proportion of other causes was similar to RPL. We found that the proportion of identifiable causes in first early pregnancy loss was more than that of RPL, which was 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. Forty-six percent were positive for acquired thrombophilia and 37% were positive for congenital thrombophilia (Table 5). They screened for lupus anticoagulant, anticardiolipin antibodies, ß2 glycoprotein 1 antibody, annexin V, protein C, protein S, antithrombin III, factor V Leiden, PT gene G20210A, MTHFR C677T, EPCR 23 bp insertion, and

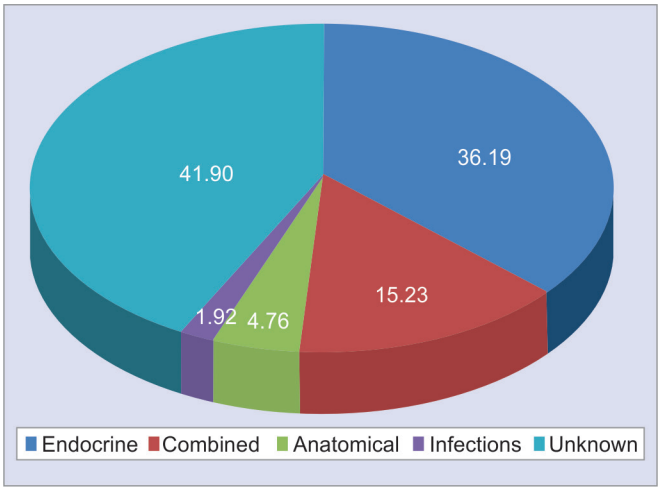

Fig. 1: Etiology of first early pregnancy loss

Table 5: Thrombophilia evaluation for unknown causes in RPL

Sl. No	*Study*	*Thrombophilia*	*Percentage of RPL women positive (%)*
1	Vora et al.[17]	Acquired	46
		Inherited	37
2	Patil et al.[18]	Acquired	24
		Inherited	16
3	Present study (2019)	Acquired	10.1
		Inherited	6.7
		Combined	1.69

PAI 4G/3G polymorphisms.[17] Previous study by Patil et al. in women with unexplained RPL showed that 40% of RPL women were positive for thrombophilias.[18] In the present study, we found that 18% of RPL women were positive for thrombophilias. We could investigate only 103 women of unknown RPL and first pregnancy loss, whereas Vora et al. tested 381 women only with RPL. To come to conclusion regarding the necessity of testing for thrombophilias number needed to test would be 281 with 95% CI when 24% positivity of thrombophilias as reported by Patil et al. in 2015.[18]

Acquired thrombophilia constituted 10% and congenital thrombophilia constituted 6.7%, and one woman had both congenital and acquired thrombophilias. The difference in the results might be because we screened only for APLA, protein C, and protein S as compared to previous studies that screened for more causes of congenital thrombophilias, thus explaining the incidence of thrombophilia being less in the present study. The proportion of women with first pregnancy loss positive for thrombophilia was 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 (65%) with first early pregnancy loss had various etiological factors and endocrine factors were the most common causes. Among the identifiable causes for first early pregnancy loss, anatomical factors were found in 4.76%, endocrine in 36%, thrombophilia in 18%, and combined etiology in 15%.

Statistically, significantly more women with first pregnancy loss were found to have known etiological factors when compared to women with RPL. The thrombophilia positivity was found to be similar in both the groups.

Evaluation should be undertaken for women with first 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 was 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.

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Authors' Roles

Papa Dasari conceived the idea and gave the concept for design of the study after reviewing the literature and edited

the manuscript. Sonal Garg performed the data collection, data analysis, review of the literature, and drafted the manuscript. Rakhee Kar helped in processing the investigations and in their interpretation. Chitra Thyagaraju helped in the recruitment of subjects and reviewed the data. All authors agreed with the contents of the manuscript.

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