Puzzle Out the Reason behind Habitual Miscarriage

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ABSTRACT

Aims: As no data is available in Pakistan so the aim of current study is to find out the link of multiple risk factors with recurrent pregnancy loss (RPL) in Pakistan.
Study Design: Case control study.
Place and Duration of Study: Study conducted in Obstetrics and Gynecology Clinic of Benazir Bhutto Hospital, Holy Family Hospital Rawalpindi and Polyclinic Hospital Islamabad from November 2018 to April 2019.
Methodology: Subjects were investigated on the basis of an in depth Performa. For data analysis Statistical package for social sciences version-20 was used. Beside this, height in cm, weight in kg and blood pressure in mmHg were recorded. All the statistical calculations were performed by using SPSS 20. For association analysis of qualitative variables Spearman bivariate correlation was calculated while for numerical variables ANOVA was applied. Multinomial logistic regression model was used and the odd ratio and relative risk were calculated.

Results: Among cases 91.34% were having spontaneous miscarriage and majority (64.86%) were during first trimester. Spearman bivariate correlation reported a strong association of recurrent pregnancy loss with the risk factors including family history, smoking, obesity, history of hypertension and history of diabetes, having highly significant p-values, on the hand, significant association of maternal age with the frequency of recurrent pregnancy loss was found but not with the paternal age and parity. The multinomial logistic regression model showed that smokers were19.012 times more prone to develop recurrent pregnancy loss.
Conclusion: The multiple risk factors including maternal age, obesity, smoking, family history, body mass index, hypertension and diabetes have a strong association with the recurrent pregnancy loss. So keeping these risk factors in mind a careful evaluation of each pregnancy is necessary to reduce the risk of recurrent pregnancy loss.

1. INTRODUCTION

Consecutive spontaneous loss of two or more pregnancies occurring before 24 weeks of conception is defined as Habitual abortion or recurrent pregnancy loss (RPL) and it is a condition that is distinct from infertility [1]. The experience of repeated pregnancy loss is physically and emotionally traumatic to women who are trying to have children. In the general population, almost 15-20% of the total pregnancies undergo into miscarriage, among them 5% experience consecutive two or more pregnancy loss while 0.5-2.3% have consecutive three or more pregnancy loss [2,3]. Most of them are spontaneous while a few are induced. Sometimes the women undergo miscarriage without being conversant of the fact that she is being conceived so the exact frequency of miscarriages is still unknown [4,5].

Among all the miscarriages the dominant one are those which involve the chromosomal aberrations [6]. There are many risk factors which are unverified or controversial. Increased age of mother, history of previous miscarriage and obesity are those factors which are well-established, while paternal age, infertility and parity are those risk factors which are complicated and still not evidently understood. It has been reported that some social risk factors and several behavioral factors are increasing the risk of miscarriage, but most of these are still unverified. The main examples are smoking, caffeine intake and alcohol consumption that cause DNA fragmentation [7-9]. There is also a contradiction on the effect of vitamin supplementation, particularly folic acid, on risk of miscarriage, but there are few studies that have accustomed for mystifying support a protective effect [3,10].

Careful review is necessary to determine whether specific evaluation may be appropriate for each pregnancy if the cause of RPL is unknown. As no data is available in Pakistan to give special consideration to the RPL leading risk factors so the aim of current study is to find out the link of multiple risk factors with recurrent pregnancy loss in Pakistan.

2. MATERIALS AND METHODS

In this case control study, two hundred and forty-five (245) women were enrolled. The data was collected from Obstetrics and Gynecology Clinic of Benazir Bhutto Hospital, Holy Family Hospital Rawalpindi and Polyclinic Hospital Islamabad. The study was conducted started in November 2018 and ended in April 2019. The inclusion criteria for cases including women with a history of recurrent miscarriages, who were referred to the Recurrent Miscarriage Clinic, on the other hand, those who had normal pregnancies beyond 24-weeks of gestation and no previous history of miscarriage were recruited as control group. Date of last menstrual period was used for calculating the age of gestation which was later confirmed by using ultrasound. The controls were of the same age group as the cases that was between 15-40 years. The exclusion criteria including if any of the partner was known case of medical illness or having history of induced abortion.

Sampling technique used was random. Subjects were investigated on the basis of an in depth Performa. This Performa include all the relevant clinical and family history of the patient along with the personal details. Beside this, height in cm, weight in kg and blood pressure in mmHg were recorded.

All the statistical calculations were performed by using Statistical Package for Social Sciences

version- 20. For qualitative variables frequency and percentages were calculated while for quantitative variables mean and standard deviations were calculated. For association analysis of qualitative variables Spearman bivariate correlation was calculated while for numerical variables ANOVA with post Hoc-Tukey's test was applied. For the application of ANOVA, the maternal and paternal age was classified into 5 groups as 15-20 years, 21-15 years, 26-30 years, 31-35 years and ≥36 years while parity and BMI were classified into 3 groups including 0, 1, ≥2 and 18-25, 26-30 and ≥31 respectively. Multinomial logistic regression model was used to find the strength of association of risk factors with RPL and the odd ratio and relative risk were calculated.

3. RESULTS

Total of about 245 participants, out of which 81 cases and 164 cases were enrolled in the study. Among cases 74 (91.34%) were having spontaneous miscarriage while on further elaborating it was found out that majority (64.86%) were during first trimester. The baseline data for cases and controls groups are mentioned in Table 1. The same maternal and paternal age groups were taken for both cases and controls as the mean maternal ages were 28.86 ± 4.45 years and 28.21 ± 4.22 years while mean paternal ages were 31.67 ± 4.67 years and 31.22 ± 5.04 years for cases and controls respectively. The cases were having more weight and BMI as compared to controls.

Spearman bivariate correlation reported a strong association of RPL with the risk factors including family history, smoking, obesity, history of hypertension and history of diabetes, having highly significant p-values, as mentioned in Table 2. On the other hand, effect of numerical variables over the RPL was calculated by using ANOVA which showed significant association of maternal age with the frequency of RPL but not with the paternal age. Likewise, parity had nothing to do with RPL as p-value was non-

significant. The ANOVA was further confirmed by applying Post Hoc-Tukey's test. As in Table 2 the bivariate correlation of obesity manifested strong association with RPL and this was further confirmed when ANOVA reported significant association of body mass index (BMI) with RPL as shown in Table 3.

Table 4 reported strength of association of risk factors with RPL in the multinomial logistic regression model. Based on the analysis of results, smokers have highest risk of developing RPL as non-smokers, i.e. approximately 19.012 times more prone to develop RPL. After smoking second most important risk factor was positive family history followed by history of hypertension or diabetes and lastly the obesity.

4. DISCUSSION

RPL is a heterogeneous condition and it is unlikely that only a single factor is attributed to it. Current literature suggests that the cause of RPL is only identifiable in up to 40%-50% of cases. The remaining RPL cases are referred to as idiopathic. This merits further research to look for other possible underlying causes of RPL. The current study is helpful in identifying some of the risk factors that might be the probable cause behind RPL [11].

It is well recognized that female fertility declines with advancing age, which manifests increase rate of RPL along with trisomy 21 and monosomy X of the fetus [12]. It has been reported that maternal age is an independent risk factor for RPL. After the age of 35 years, the risk of RPL increases rapidly and reaches up to 75% in women with age over 45 years, while this risk is as low as 9% in women between aged from 20 to 24 years [13]. Further clarified by the studies that increase in probability of chromosomal abnormalities in the fetus is linked with maternal age [14]. The current study also reported that maternal age is positively associated with the frequency of RPL and the number of RPL cases increases after crossing the age of 30 years.

Table 1. Baseline data of study participants

	Cases	Control
Maternal age	28.86 ± 4.45	28.21 ± 4.22
Paternal age	31.67 ± 4.67	31.22 ± 5.04
Parity	1.88 ± 1.49	2.82 ± 1.13
Weight	62.94 ± 8.66	59.88 ± 8.16
Height	5.08 ± 0.146	5.11 ± 0.137
BMI	26.2 ± 3.39	24.7 ± 3.06

Table 2. Risk factors associated with RPL (Spearman Bivariate correlation)

	n	%	p-value
Family history	19	11.2	0.000
Smoking	25	14.7	0.001
Obesity	36	21.2	0.000
History of hypertension	34	20.0	0.000
History of diabetes	34	20.0	0.000

Table 3. Association of numerical variables with RPL (ANOVA)

		Sum of Squares	df	Mean Square	p-value
Maternal age	Between Groups	254.244	4	63.561	0.009
	Within Groups	1331.262	76	17.517	
	Total	1585.506	80		
Paternal age	Between Groups	185.543	4	46.386	0.070
	Within Groups	1558.457	76	20.506	
	Total	1744.000	80		
Parity	Between Groups	7.144	4	1.786	0.535
	Within Groups	171.622	76	2.258	
	Total	178.765	80		
BMI	Between Groups	27.958	4	6.989	0.006
	Within Groups	895.842	76	11.787	
	Total	923.799	80		

Table 4. Multinomial logistic regression

	OR	RR	95% CI	
			Lower	Upper
Obesity	4.742	2.736	2.684	8.378
Smoking	19.012	3.929	3.133	4.925
Family history	14.151	3.645	2.949	4.506
History of hypertension	10.062	3.215	4.732	21.394
History of diabetes	10.062	3.215	4.732	21.394

Few of the studies reported positive association of paternal age with the incidence of RPL, as increasing paternal age leads to decrease in volume of semen and sperm abnormalities in the form of morphology, motility and concentration [15,16]. But the current study did not find any significant correlation between paternal age and the occurrence of RPL. The reason behind this contradictory finding might be the fact that current study enrolled pregnant women between age of 15 years to 40 years while in the reported literature effect of maternal age was eliminated by taking women between age of 20 years to 35 years which is the ideal reproductive age of a women [6,17], so in the current study the effect of paternal age is overwhelmed by the increasing maternal age.

The consequences of earlier pregnancies are autonomous forecaster of upcoming pregnancy outcomes. The rate of RPL is as low as 5% for young women who have never experienced pregnancy loss. In a woman with previous live-born infant, the risk is approximately 30% but this risk increases up to 50% for women who don't have even a single live-born infant. It indicates that number of earlier pregnancy loss increase the risk of future RPL because sporadic fetal loss is linked with an abnormal fetal karyotype [9]. But the current study reported that parity had non-significant association with the RPL while history of previous RPL showed significant association. The reason for this variation might be the superimposing effect of other risk factors.

Smoking has been implicated in increasing the risk of pregnancy loss. It has been postulated that nicotine causes formation of reactive oxygen species which in turn leads to defective DNA replication and repairing mechanism, resulting in DNA fragmentation [7]. Current study reported

smoking as one of the major contributing factor for developing RPL, as the risk of RPL increased 19.012 times more among smokers than non-smokers. Smoking showed a strong positive association with the frequency of RPL.

There is a big role of obesity in fertility and miscarriages. The relationship between BMI and the risk of miscarriages among women in the general population is not well-established, few studies reported significant association of obesity with the increase risk of RPL but no association has been established for underweight [18,19]. Current study manifested that obese women had 4.742 times more risk of developing RPL as non-obese on the other hand, BMI confirmed this finding by showing a strong significant association with RPL.

Increased risk of pregnancy loss also shows association with comorbidity including diabetes and hypertension. Studies reported three times higher level of insulin resistance which causes increase in androgen level, resulting in RPL [20,21]. On the other hand, history of hypertension increases the risk of pre-eclampsia but its association is not well-established [22]. The current study manifested a very significant association of both diabetes and hypertension with RPL. There is a need of study to do on large scale that can address the association of risk factors with RPL more clearly so that minimize the risk of RPL.

5. CONCLUSION

It can be concluded that the multiple risk factors including maternal age, obesity, smoking, family history, BMI, hypertension and diabetes have a strong association with the RPL. So keeping these risk factors in mind a careful evaluation of each pregnancy is necessary to reduce the risk of RPL.

CONSENT AND ETHICAL APPROVAL

Ethical approval for the recruitment of participants was obtained by Ethics committee of PMAS–AAUR (No. PMAS-AAUR/DAS/459). Written informed consent form was also presented to attain acceptance from subjects.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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