

Frequency of Recurrent Miscarriages in Kashmiri Population (A High Incidence Zone)

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ABSTRACT

Introduction: Recurrent miscarriages (RM) can be defined as the spontaneous loss of two or more consecutive pregnancies before twenty weeks of gestation. The aim of the study was to analyse the incidence of RM in our region.

Method: The study screened retrospectively for all patients who had experienced the miscarriages between 2015 and 2019.

Results: Among RM cases, 80 (26.9%) were observed in consanguineous marriage group as against 217(73.06%) cases in non-consanguineous group. Of all cases 43(16.04%) were found with known family history for RM. The frequency of RM was observed as comparable to be 50.6% (163) in cases that belonged to the age group of <30 years to that of the 49.37% (159) cases seen in ≥30 years.

Conclusion: The frequency of RM is very high in our region and interestingly apart from consanguinity; the pattern of these events observed was with a very less difference in both age groups.

Key words: Miscarriages, Family History, Gestation, Consanguineous marriage.

INTRODUCTION

The term miscarriage (or abortion) is used to explain a pregnancy that fails to progress, resulting in death and expulsion of the fetus or embryo. The most widespread complication of pregnancy is spontaneous abortion, which is vague to occur in 10-15 % of pregnancies and about 80 % of these abortion occur within 2 to 3 months of gestation. Complete abortion is defined as the expulsion of products of conception before the 20th week of gestation [1]. Of the pregnancies that are lost, ~70-75% are caused by failures of implantation or early placentation and are therefore not clinically recognized as pregnancies. As a consequence, only about half of all conceptions advance into the second trimester of pregnancy. Recurrent

Miscarriage is one of the least understood pathological process. The classic definition of Recurrent Miscarriage is the loss of 3 or more clinically recognized pregnancies spontaneously during early gestation [2,3]. The repetitive miscarriages in some couples suggest that certain women are at particular risk of losing their pregnancy and that there must be an underlying explanation for this. Even though much work has been done to identify these underlying mechanisms, the aetiology of miscarriage is still unknown in many cases. Additionally, on an individual level the exact reason for a particular miscarriage is rarely defined. In many prospective studies of RM, patients show remarkable consistency in finding an increasing risk of miscarriage as the number of previous miscarriages increases. The

possibility of miscarriage ranges from 22 to 57% at < 6 weeks of gestation, it declines to 15% at 6-10 weeks and 2-3% after 10 weeks of gestation [2,4,5]. Recurrent Spontaneous Abortion is a complex multifactorial problem associated with autoimmune disorders, endocrine dysfunction, advanced paternal and maternal age, environmental toxins, infectious processes and congenital or uterine anomalies apart from genetic aberration reflected by inherited disorders and endometriosis [6, 7]. It is assessed that <5% of women will experience two consecutive miscarriages, and only 1% experience 3 or more [8, 3]. In many studies influence of maternal characteristics especially risk of fetal death with increased maternal age has also been reported. It seems that the impact of age on miscarriage rate in such patients is somewhat understood until age 40, but beyond this age it is the strongest prognostic factor [9-14]. To a certain extent, few studies have explored the occurrence of Recurrent Miscarriages and sporadic miscarriage in families of women with RM with normal parental karyotypes [15-19]. Relevant published studies [16,17] have found in their results, significantly increased RM rates in first degree relatives of RM women

As per the hospital based observational study in our tertiary care hospital Sher-I-Kashmir Institute of Medical Sciences (SKIMS), nearly 350 to 400 cases of pregnancy losses due to recurrent miscarriages are managed in the Department of Obstetrics and Gynaecology, SKIMS. These women belong to varied age groups and different regions of the valley. Keeping in view the nature of the strong ethnic nature and high incidence of RM, we initiated a cohort study in patients with 2 or more miscarriages and evaluated its various risk factors (like maternal age, prevalence of consanguineous marriage, family history).

MATERIALS AND METHOD

This prospective study was conducted in Advanced Centre for Human Genetics (ACHG) and Department of

Gynaecology and Obstetrics in Sher-i-Kashmir Institute of Medical Sciences (SKIMS). The records were screened retrospectively for all patients who had experienced the miscarriages in the past and the study was conducted between 2015 and 2019. Patients from outside the valley of Kashmir were excluded from the study. Emphasis was laid to determine the various factors responsible for the miscarriages which primarily included age, number of miscarriages, consanguinity, and family history, hormonal and immunological parameters. The patient's history was evaluated thoroughly and a written informed consent was obtained from each recruited subject, and the study was approved by the local Institutional Ethical Committee (SKIMS). The admission records available were scrutinised and reviewed for detailed history. An in-house developed proforma was used to collect information on demographic data and risk factors.

RESULT

In our study we included a total of 322 Kashmiri women who had gone through at least 2 to 5 consecutive abortions (>5 in some cases) from the Department of Gynaecology and Obstetrics of SKIMS hospital of Kashmir Valley. Various parameters were taken into study like age, consanguinity, family history etc which are seen to be the risk factors of RM.

Consanguinity as a factor in RM was included in our study, wherein 80 (26.9%) cases of consanguineous marriage group were observed in comparison to 217(73.06%) cases that belonged to the non-consanguineous marriage group (table 1). Among 217 cases of non-consanguineous marriage group, 105 (49.2%) cases experienced 2 miscarriages, 74 (34.74%) cases 3 miscarriages and the remaining 24 (11.2%), 7 (3.2%) and 3 (1.4%) cases experienced 4,5 and >5 miscarriages respectively. On the other hand in consanguineous marriage group, 40 (53.3%) cases experienced 2 miscarriages, 19 (25.3%) cases had 3 miscarriages, 10

(13.3%) cases with 4 events and remaining 5 (6.6%) and 1(1.3%) cases were seen with 5 and >5 miscarriages respectively (table 2). 43 (16.04%) patients were found with known family history for RM whereas rest 225 (83.9%) cases did not have any previous family history (table 1).

Among 322 cases of RM, 156 (51.31%) patients suffered two miscarriages, 97 (31.90%) had 3, 34 (1.18%) had 4, 12 (3.9%) with 5 events, 5(1.64%) cases had gone through >5 miscarriages. With RM cases, the frequency of miscarriages was observed with 50.6% (163) in cases that belonged to the age group of <30 years with the comparable results as seen in ≥30years of age 49.37% (159) showed in table1. Moreover, in <30 years of age group cases , 56.4% cases experience 2 miscarriages and rest 30.6%, 8.16% ,4.08% and 0.68% of cases experience 3,4,5 and >5 miscarriages respectively (table 2). In contrast, the cases of age group ≥30years, the highest percentage of 46.7% and 33.11% of cases experienced 2 and 3 miscarriages respectively while as the rest 20% of cases had 4, 5 and >5 events of miscarriages respectively (table 2).

We examined the clinical investigations of patients as well where among 250 patients, two had tested positive for TORCH and rest showed negative result. Among 100 patients, all showed negative result for VDRL. Out of 200 patients, 158 were reported normal for TSH, rest 17 and 25 showed hypo and hyperthyroidism respectively. For APLA 8 out of 200 cases were found positive while as rest were negative. Ultra sonography findings of 60 available patients revealed 36 as normal, 9 patients showed fibroid and 15 had uterine cyst (table 1).

Among the couple, paternal parameters aiding risk for RM to their spouses were also taken into consideration and their details are enlisted in table 2.

Table 1: Clinico-pathological features of patients with recurrent miscarriages

Clinico-pathological features		N(%)
Age Group	<30y	163 (50.6%)
	≥30y	159 (49.37%)
Family History	Yes	43 (16.04%)
	No	225 (83.9%)
Consanguinity	CM	80 (26.9%)
	NCM	217 (73.06%)
No. of Miscarriages	2	156 (51.31%)
	3	97 (31.90%)
	4	34 (1.18%)
	5	12 (3.9%)
	>5	5 (1.64%)
TORCH	Positive	2 (0.8%)
	Negative	248 (99.02%)
APLA	Positive	8 (4%)
	Negative	192 (96%)
VDRL	Positive	0 (0%)
	Negative	100 (100%)
TSH	Hypo	17 (8.5%)
	Normal	158 (79%)
	Hyper	25 (12.5%)
USG Impression	Normal Findings	36 (60%)
	Fibroid	9 (15%)
	Uterine Cyst	15 (25%)

Table 2: Maternal and Paternal characteristics with recurrent miscarriages

Parameters	Miscarriages	Maternal Events	Paternal Events
Age Group			
<30y Nf=147 Nm=78	2	83 (56.4%)	48 (61.5%)
	3	45 (30.6%)	18(23.07%)
	4	12 (8.16%)	6 (7.69%)
	5	6 (4.08%)	3 (3.8%)
	>5	1 (0.68%)	1 (1.2%)
≥30y N f =154 Nm= 205	2	72 (46.7%)	94 (45.8%)
	3	51 33.11%	73 (35.6%)
	4	22 14.28%	26(12.6%)
	5	6 (3.8%)	9 (4.39%)
	>5	3 1.94%	3 (1.46%)
Consanguinity			
Yes N=75	2	40 (53.3%)	
	3	19 (25.3%)	
	4	10 (13.3%)	
	5	5 (6.6%)	
	>5	1 (1.3%)	
No N=213	2	105 (49.2%)	
	3	74 (34.74%)	
	4	24 (11.2%)	
	5	7 (3.2%)	
	>5	3 (1.4%)	

DISCUSSION

Miscarriages are the most frequent complication of pregnancy and occur in 10 to 15% of all pregnancies, of which 1-2% are recurrent [20]. RM can be defined as the spontaneous loss of two or more consecutive pregnancies before twenty weeks of gestation [21]. Etiology of RM is among the most studied, yet unresolved issue in modern gynaecology. Among the

various proposed etiological factors, genetic and cytogenetic alterations, antiphospholipid syndrome and uterine anatomic abnormalities were reported in about 50% of the patients; however, in remaining 50%, the cause is unknown^[22]. The main aim of the study was to observe the frequency of Recurrent Miscarriages in our population particularly in the back drop of consanguineous marriage. Further we determined the risk factors considered to be associated with RM.

Our study revealed that, out of total patients who experienced RM, 50.6% (163) cases belonged to the age group of <30 years while as 49.37% (159) were ≥30 years. Our results point slightly different trend of RM wherein incidence was found to be nearly same in both age groups. Moreover, in both age groups we found highest percentage of RM cases experiencing 2 to 3 miscarriages.

It has been observed through a number of reports that the risk of RM increases with advanced maternal age in a given population^[23, 24]. It is presumed that the influence of advanced age on RM is variable until age 40, and shows the increasing strongest prognostic predictive trend in miscarriages above age 40. In our population this prognostic trend of advanced age seems equally incompatible and is in sharp contrast with previous studies^[25-27].

One more report gives evidence for increasing risk for RM with advanced maternal age^[28]. Contrary to our observation where advancing maternal age group did not show an increasing trend in rate of abortions, the other reports show that RM incidences increases from 12% in women with age 20–24 years and further rises to 26% in the group above 40 years of age. In our region the different scenario needs to be evaluated despite the fact that conception rates decline with increasing rates of abortion by the age of above 40 to 44 years. Age of males as a factor for recurrent miscarriages in our report seems relevant with respect to advanced age. We

observed an increasing trend of abortions as the paternal age advances where in 28% cases of RM were experienced in the spouses whose male partners were below 30 years of age whereas around 72% cases were seen in above 30 years of age. Studies have confirmed that male factors may impact early miscarriages in which the occupational hazards have been shown to deteriorate spermatozoa which cause the embryo loss^[29-31]. Among the various proposed etiologies, genetic factors appear to be highly associated with reproductive loss^[32, 33]. Chromosome abnormalities are the cause for pregnancy loss in 50 to 80 per cent of cases, depending on maternal age and gestational age at time of the loss.

We analysed that among RM cases, 73.06% (217) belong to the non-consanguineous marriage group as against 26.9% (80) of consanguineous marriage group. Moreover, in both groups, the highest percentage of RM cases experience 2-3 miscarriages. There was an appreciable frequency of RM cases due to consanguineous marriages in our series (around 27%). A consanguineous marriage between relations has substantiated to predispose for genetics related risks due to an increased probability of harbouring the similar allele types. The impact of consanguineous marriages on mortality is still a debatable issue^[34-38]. An alarming percentage of RM in our cases due to consanguinity has been found in other populations also^[34,39,40,41-43]. But there are some reports where relationship between RM and consanguinity could not be ascertained^[44-47].

Kashmiri population is genetically conserved and people don't prefer to marry outside their ethnic territorial boundaries. It has been observed Kashmir Valley has the custom of consanguineous marriages since centuries. Considering this fact, consanguinity in our study may impact the live births irrespective of other risk factors as seem to be customary in various human societies that lead to an increased prevalence of severe genetic disorders^[48].

Hence, consanguinity and genetic disorders, being related to serious health problems, are always considered most important in genetic studies^[49].

As the continuous research shows that most of RM cases are associated with advanced maternal age but our series of cases defy that norm and showed a random pattern of RM. So, there are certain undefined underlying factors behind this phenomenon which need to be identified for the development of more successful treatment and continuous improvement of the outcome of future pregnancies in women experiencing RM.

CONCLUSION

We conclude that frequency of RM is very high in our region and interestingly considerable frequency of cases was observed in consanguineous group and with known family history. Apart from consanguinity and family history, the patterns of these events observed defies the norm of it being more prevalent in advanced maternal age but were observed with nearly equal frequency in both age groups. A comprehensive approach needs to be applied to rule out the factors responsible for the RM in our region which includes genetic predisposition also.

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Ethical approval and patient consent: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A written informed consent was obtained from each

recruited patient in the language they fully understood.

Ethical approval was obtained from Institutional Ethical Committee (SKIMS Study ref: IEC-SKIMS Protocol P 244/12014).

Conflict of Interest: All the authors declare no conflict of interest.

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