Original Article

Consanguinity in Unexplained Recurrent Pregnancy Loss and Preterm Delivery among Saudi Females

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Abstract

Objectives: Consanguinity is considered as a factor which influences reproductive health. This study aimed to investigate the role of cousin marriages on the occurrence of recurrent pregnancy loss (RPL) and preterm delivery (PTD) in Saudi females. **Methods:** The study included 300 Saudi women (RPL = 100; PTD = 50; control = 150). Demographic and clinical data were entered on forms specially designed for the study, and the women were interviewed about the relationship with their husbands. The degree of consanguinity as the first and second cousins was recorded, and the prevalence of PTD and RPL was calculated in consanguineous and nonconsanguineous marriages. **Results:** The results revealed that consanguinity occurs at a higher frequency in RPL and PTD (RPL = 55%; PTD = 52%) compared to the control group (36%) and the difference compared to the controls were statistically significant for both PTD and RPL ($P < 0.05$). **Conclusion:** The results of this study show that the frequency of consanguinity is significantly higher in the females giving preterm birth (PTB) and those with RPL. Since consanguinity increase homozygosity of autosomal recessive conditions, our result implicates the involvement of some autosomal recessive genes, in the pathogenesis of PTD and RPL. Further studies are required to identify gene mutations or polymorphisms which are involved in early fetal loss and PTD, conduct genetic screening for such genetic mutations and polymorphisms, and conduct genetic counseling to decrease the frequency of both conditions. Furthermore, there is a greater need to increase awareness about complications that may occur among consanguineous families, in an attempt to decrease the frequency of consanguinity.

Keywords: Consanguinity, first cousin marriages, preterm delivery, recurrent pregnancy loss, Saudi Arabia

Introduction

Recurrent pregnancy loss (RPL) and preterm delivery (PTD) are problems that have unexplained etiologies in most patients. Spontaneous miscarriage is defined as "a pregnancy loss before the 20th week of gestation," whereas, RPL refers to three or more consecutive pregnancy losses (before the 20th week of gestation).[1] PTD, also referred to as "preterm birth" according to the World Health Organization is the birth of a baby before the 37th week of pregnancy.[2] Based on the available data from 184 countries in 2015, the Centre for Disease Control and prevention reported that every year about 15 million babies are born preterm and the rate of PTD ranges from 5% to 18% of all the live births. The prevalence of PTD is high in certain racial and ethnic groups, and the rate has increased over the past 20 years due to increased maternal age, problems associated with the maternal health (i.e., diabetes and high blood pressure), and increase in the number of pregnancy-related complications such as gestational diabetes and multiple pregnancies.[2,3]

Premature delivery is considered as the biggest global killer of children primarily in the developing countries causing mortalities in millions, of children every year due to related complications.[4,5] Hence, PTD is regarded as a major contributor to infant death, long-term morbidity, neurological disabilities, and cognitive outcomes in children.[6-9]

Access this article online

Quick Response Code:

Website: www.jnsmonline.org

DOI: 10.4103/JNSM.JNSM_5_19

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Submission: 06-02-2019 **Revision:** 18-03-2019
Acceptance: 12-06-2019 **Published:** 06-01-2020

How to cite this article: Warsy AS, Alkhuriji A, Al-Marry BA, Alraqibah AA, Alharbi AA, Babay Z, *et al*. Consanguinity in unexplained recurrent pregnancy loss and preterm delivery among Saudi females. J Nat Sci Med 2020;3:33-8.

Several factors play a role in increasing the prevalence of RPL and PTD, including environmental and genetic factors indicating a multifactorial etiology.[10-11] Well-documented risk factors implicated in RPL, include maternal smoking, advanced maternal age, previous spontaneous miscarriage, and fetal chromosomal abnormalities. The factors involved in PTD include smoking, maternal body mass index (BMI), hypertension, stress, preeclampsia, premature rupture of membrane, hormonal factors, genetic factors, urinary tract infection, oligohydramnios, bleeding or spotting, and previous history of PTD.[12-17] Consanguinity has also been considered as one of the predisposing factors in a few studies conducted in some populations.[17-22] However, there are several contradictory reports in the literature. Furthermore, the data available on the effect of consanguinity are limited due to the low frequency of consanguinity in the Western societies such as Europeans and North Americans, where consanguinity is not favored and is disliked on historical and religious grounds. Contrary to this, populations in Asia and the Arab World show a strong preference for consanguineous marriages, most frequently contracted between first cousins, and the marriage outside the family is perceived as a risky and disruptive option.[23-27]

Interestingly, consanguinity is a complex and multifaceted topic, with claimed social and cultural advantages, despite several medical disadvantages. The rate at which cousin marriages exists varies from one population to another and within a population group, there is variability between different tribes, communities, and ethnic groups.[28] Among the European countries, the marriages within families are rare (<0.5%), whereas in Saudi Arabia, North Africa, and Western and Southern Asian countries, consanguineous unions range from 22% to 55%.[23-27] In several states of the United States of America, cousin marriages are illegal under the statutes passed during the 19th and 20th centuries.[29]

In Saudi Arabia, el-Hazmi *et al*.[26] investigated the prevalence of consanguinity and reported 60.8%, 52.1%, 67.7%, 54.2%, and 59.1% cousin marriages in the central, northern, north-western, south-western, and eastern regions of Saudi Arabia, respectively. Other more recent investigations also highlighted the differences in rates of cousin marriages in different regions of Saudi Arabia.[28] In a community-based cross-sectional study, El Mouzan *et al*.[30] showed a close association between consanguinity and major genetic disorders in Saudi children. A recent investigation showed that the frequency of consanguinity has not changed much over the past two generations, despite an increase in the education level and awareness.[31]

Tadmouri *et al*.[32] reviewed the influence of consanguinity on the reproductive health among Arabs and commented that though there was an increase in the prevalence of congenital malformation in consanguineous marriages, there were no major differences reported in the few studies comparing postnatal mortality, fetal wastage, fertility, or birth anthropometric measurements. More recently, Chaman *et al*.[33] reported that first cousin marriages are an important risk factor for neonatal deaths and found a positive association between neonatal deaths and prematurity, low birth weight and older maternal age.

During our investigations on Saudi women suffering from RPL and PTD, we identified several couples who were consanguineous, with a higher level of pregnancy-related complications. This study was designed to identify the role of consanguinity in reproductive health and presents the results of our investigation into the association between consanguinity and the occurrence of unexplained RPL and PTD in Saudi women.

Methods

The study was conducted as a case–control study on women attending the Obstetrics' and Gynaecology Clinics at King Khalid University Hospital (KKUH), Riyadh. The study protocol was approved by the Institutional Review Board at the College of Medicine, King Saud University, Riyadh, Saudi Arabia (Committee Reference Number: E-10-132 and E-14-1295). The aim of this study was clearly explained in Arabic, and informed consent was obtained. Only those females who volunteered were enrolled in the survey. Each subject included in the study was required to sign an informed consent form. The patients with RPL were recruited from the "Recurrent Abortion Clinic" at KKUH, and the inclusion criteria were as follows: women suffering from three or more consecutive spontaneous miscarriage. Exclusion criteria included non-Saudi females, females suffering from any major illness (insulin-dependent diabetes mellitus, congenital heart disease, renal disease, cardiovascular disease, and systemic lupus erythamatosus (SLE)), women with any risk factor for RPL (inborn errors of metabolism, kidney disease, congenital heart disease, etc.), and cervical incompetence. All miscarriage cases with a chromosomal abnormality or congenital malformation were also excluded from the study. The PTD patients were recruited from the delivery room. The inclusion criteria were women who delivered spontaneously before the 37th week of gestation in this last pregnancy. The exclusion criteria were placenta previa, multiple pregnancies, preeclampsia, infections, and babies born with any malformation. (As a policy at KKUH, all patients with PTD have vaginal swap examination, and infection was not reported in any of the women included in this study). The control group was recruited from the delivery room, with full-term spontaneous delivery and no previous history of RPL or PTD. The controls were matched with the patients in terms of age and BMI. Parental karyotyping was done to exclude balanced chromosomal aberration in all cases. The study included a total of 309 women, namely, 105 suffering from RPL, 54 had PTD, and 150 were the controls without RPL or PTD. Of these, nine women were not included in this study. Five of these did not satisfy the inclusion criteria (only one miscarriage) and 4 satisfied the exclusion criteria (non-Saudis = 2, placenta previa = 1, multiple pregnancies = 1).

Essential demographic data were recorded for all the women on specially designed forms. The clinical data were collected for the PTD and RPL patients.

A purpose-designed questionnaire was prepared, and each woman was interviewed in Arabic. The age, height, weight, number of previous pregnancies (including ectopic pregnancy, miscarriages, and PTD), age at first pregnancy, the number of children, number of miscarriages, any still birth's, previous RPL or PTD, relationship with her husband, and the level of consanguinity (i.e., first cousin [1st cousins share grandparents] or second cousins [2nd cousins share great grand patents]), were recorded. The BMI (weight [kg]/height^2 [m^2]) for each subject was calculated. The files of the PTD patients and controls were also assessed to see if there was any history of gestational diabetes, hypertension, or any other pregnancy-related complication. For the PTD patients and controls, the gestational age and babies' weight were recorded.

Statistical analysis

The data obtained were filled on spreadsheets and analyzed using the SPSS version 22 (IBM Corp. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp). The mean and standard error of the mean were calculated, and groups were compared using the Student's *t*-test. Prevalence rates between groups were compared using the Chi-square (χ^2) analysis using either 2 × 2 or 2 × 3 contingency tables. Odds ratio, 95% confidence intervals, χ^2, and *P* value were obtained from the program. For all data comparison, $P < 0.05$ was considered statistically significant.

Results

Tables 1 and 2 present the demographic and clinical data in the PTD and RPL patients, respectively, in comparison with the controls. The patients and controls were age, and BMI matched for PTD patients, and the RPL patients matched for BMI in controls). The PTD group was slightly younger, while the RPL cases were older than the controls, but the differences in age were not statistically significant for both groups.

The prevalence of consanguinity in the RPL, PTD patients, and controls are presented in Table 3. The total consanguinity (1st + 2nd cousins combined) for RPL and PTD patients, were 55% and 52%, respectively, compared to the 36% in controls. The frequency of total consanguinity (1st + 2nd cousin) was significantly higher both in the RPL ($P = 0.003$) and PTD ($P = 0.045$) compared to the control group. The major form of consanguinity was first cousin marriages (33%, 30%, and 22% in the RPL, PTD, and control groups, respectively). This was followed by second cousin marriages in all the three groups (22%, 22%, and 14% in the RPL, PTD, and control groups, respectively). When the frequency of the first and second cousin marriage was compared in each of the patient's group with the controls using 2 × 3 contingency tables, the significance was still observed in the RPL compared to controls ($\chi^2 = 8.82$ $P = 0.012$; df = 2). However, in the PTD group, the difference was not significant ($\chi^2 = 4.1$; $P = 0.129$; df = 2).When the frequency of the 1st and 2nd cousin marriages were separately compared in the RPL and PTD group, only the 1st cousin marriages almost reached significance in the RPL group ($P = 0.053$), but not in the PTD. Second cousin marriages were not significantly different.

Discussion

This study has investigated the influence of cousin marriages on pregnancy outcome, and the results have shown that the prevalence of both RPL and PTD is higher in couples who are related as cousins. Previously, many studies have documented that consanguinity is associated with increased risks for rare autosomal recessive genetic disorders, congenital anomalies, low birth weight, and other adverse neonatal outcomes.[34-37] Reports on the relationship between consanguinity and RPL and PTD have been diverse, where some studies have reported a

Table 1: Comparison of the demographic and clinical data of the preterm delivery patients and controls

Parameter	Mean±SEM		*P*
	PTD patients (*n*=50)	Controls (*n*=150)	
Age (years)	28.9±0.9	28.1±0.5	NS
BMI (kg/m^2)	28.4±0.9	29.9±0.6	NS
Number of pregnancies	3.2±0.4	2.6±0.2	NS
Number of children	2.3±0.26	2.2±0.2	NS
Number of miscarriages	2.0±0.3	None	-
Weight (kg) of baby	1.5±0.1	3.2±0.1	0.0001
Parameter	**Percentage**		**Fisher exact probability test**
	PTD patients (*n*=50)	Controls (*n*=150)	
Previous PTD	100	0	-
Previous PROM	42	0	-
Infections	0	0	-
Smoking	0	0	-
Survival of the new born	90	100	0.0001

SEM: Standard error of the mean, BMI: Body mass index, PTD: Preterm delivery, PROM: Premature rupture of the membrane, NS: Not significant

higher prevalence of PTD and RPL in consanguineous matings, while others have failed to show any association. In a study, reported almost 22 years ago on the Saudi population, it was shown that consanguinity plays a role in reducing the gestational age.[18] However, an earlier study from the same population had failed to show any association between consanguinity and PTD. Similarly, a study published in 1989 from Lebanon[38] showed no association between consanguinity and PTD, while a later study reported a 1.6-fold increase in the risk of PTD in the same population.[19] Studies from Jordan[21] and Norway[39] have revealed that consanguinity does pose an increased risk for PTD, but a similar study from India failed to show any association in the gestational period of consanguineous and nonconsanguineous deliveries.[40] Regarding the RPL, similar contradictions have frequently been encountered. A study conducted during the 1980s in Kuwait, reported higher prenatal losses in consanguineous mating (14.2%) compared to the nonconsanguineous mating (13.97%), but the difference was not statistically significant.[41] A major study conducted on the Turkish population from 1970 to 1988, exhibited an increased prevalence of miscarriage in consanguineous compared to the nonconsanguineous pregnancies.[42] A more recent study from India has also reported a strong association between consanguinity and miscarriages.[40] Other reports also showed an increased prevalence of miscarriages in cousin marriages among Egyptians[43] and Tunisian populations.[44] However, studies from the United Arab Emirates, Spain, an Arab community in Israel, Jordan and Tunisia, did not show any increase in the prevalence of reproductive wastage in consanguineous marriages compared to the nonconsanguineous ones.[44-49]

Table 2: Demographic and clinical of the recurrent pregnancy loss patients and controls

Parameter	Mean±SEM		*P*
	RPL (*n*=100)	Control (*n*=150)	
Age (years)	33.2±0.6	28.1±0.5	0.037
BMI (kg/m^2)	29.50±0.7	29.94±0.6	0.472
Number of pregnancies	6.41±0.3	2.64±0.2	0.0001
Number of children	1.95±0.2	2.22±0.2	0.01
Number of miscarriages	4.51±0.2	0	-
Infections	0	0	
Smoking	0	0	

RPL: Recurrent pregnancy loss, BMI: Body mass index, SEM: Standard error of the mean

Since there are several contradictory reports, in the literature, on the effect of consanguinity on reproductive outcome, sometimes even from the same population group, it is necessary to conduct further studies, to elucidate the adverse influence of consanguinity on the reproductive loss and gestational age. The possible cause/s for such diverse findings is/are not clear. Since both RPL and PTD are believed to have a multifactorial etiology with the interplay between several genetic and multiple environmental factors, it is possible that along with environmental factors several contributing genes, and mutations or polymorphisms in these genes are influencing the occurrence of miscarriages and PTB. Since the prevalence and types of gene mutations and polymorphisms differ in different ethnic groups, the prevalence of PTD and RPL also differs. Furthermore, consanguinity increases the chance of co-inheritance of abnormal mutations from the two parents, resulting in a homozygous state, thus it may be one of the several factors that influence the prevalence of PTB and RPL. In addition, the studied populations may be different in their lifestyle, food habits, and other environmental factors which influence pregnancy outcome. More recently, epigenetic factors have been implicated in the etiology of several diseases, and such factors may also be contributing to RPL and PTD occurrence. Further studies are required to search for genetic loci which are contributing to the causation of RPL and PTD, particularly those inherited recessively, since consanguinity increase homozygosity. Such studies are possible in populations conventionally preferring cousin marriages, such as the Saudi population.

Conclusion

In the present study on the Saudi population, we examined females who were suffering from RPL and PTD, the obtained

Table 3: Prevalence of consanguinity in preterm delivery and recurrent pregnancy loss cases compared to consanguinity in control group

Group	Total number	Consanguinity				Stats of total consanguinity in comparison with control (using 2 × 3 contingency tables)
		None, *n* (%)	1st cousin, *n* (%)	2nd cousin, *n* (%)	Total, *n* (%)	
Control	150	96 (64)	33 (22)	21 (14)	54 (36)	
RPL*	100	45 (45)	33 (33)	22 (22)	55 (55)	OR=2.17 95% CI=1.30-3.64 χ^2=8.81 *P*=0.003
PTD**	50	24 (48)	15 (30)	11 (22)	26 (52)	OR=1.93 95% CI=1.01-3.68 χ^2=4.0 *P*=0.045

Stats using 2 × 3 contingency tables. *χ^2=8.82, *P*=0.012; df=2, **χ^2=4.1, *P*=0.129; df=2. RPL: Recurrent pregnancy loss, PTD: Preterm delivery, OR: Odd's ratio, CI: Coefficient of variation, *P*: Significance

results suggest that pregnancy loss and delivery-before-term are more common in consanguineous marriages compared to those in couples who were not related. Since PTD is associated with several long-term complications in the baby, and since RPL has a devastating effect on the family often leading to psychosocial problems, the control of both of these conditions requires special attention. To confirm these results, further large scale studies are required. There is also a need to identify genetic and environmental factors that increase susceptibility to both of the studied conditions. Genetic screening of couples such as whole-exome sequencing, in particular, those who are related, followed by proper counseling may play a role in lowering the incidence of these two studied states. The major weakness of this study is the small number of patients group. Further larger studies are needed to confirm these findings.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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