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ORIGINAL ARTICLE

# Consanguineous Marriage and Early Pregnancy Loss in Rural to Peri-Urban India

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## Abstract

**Background** Consanguineous marriage (CM) has been linked to spontaneous abortion (SAB), although studies have largely been cross-sectional and likely underestimated early loss. We aimed to determine the relationships between CM and SAB in a prospective pregnancy cohort study in Telangana State, India.

**Methods** Data from 661 participants aged 15–35 years in the Longitudinal Indian Family hEalth (LIFE) study actively followed for pregnancy and pregnancy loss were analyzed. SAB was classified as early (< 8) or late (8–22) weeks gestation. We used logistic regression to model the relationships between CM, defined by first-cousin marriage, and SAB, adjusted for maternal age.

**Results** Women in CM were at a modestly increased risk of any ($OR_{adj}$ 1.15, 95% CI 0.69, 1.91) and early ($OR_{adj}$ 2.03, 95% CI 0.85, 4.83) SAB compared to women in non-CM, although results were not statistically significant. There was no relationship between CM and late SAB.

**Conclusion** Among couples in southern India, there was a modest increase in early but not late SAB among CMs which may be explained by the expected influence of chromosomal abnormalities and lethal homozygous recessive disease on early loss. Pre- and Peri-marital Health Counseling that addresses this risk may be warranted.

**Keywords** Consanguineous marriage · Cousin marriage · Spontaneous abortion · India · Pregnancy loss

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## Background

The prevalence of consanguineous marriage (CM), the union between two individuals who are related as second cousins or closer [1], varies globally with rates as low as 5% in the USA, Western Europe, and Australia [2] and up to 70% in regions such as the Middle East [3]. In India, rates differ depending on the geographic region within the country in addition to the size, diversity and divergent attitudes toward CM [4]. Rates vary from 1–10% in northern states to 20–60% in southern India [5]. Although proportions have declined overall since the early 1990s [4], rates remain high in Telangana State, with over 40% of women reporting being in a related marriage [6]. Globally, and in India, first-cousin marriages are the most common form of consanguineous relationships, comprising roughly 20–30% [2].

Marriage between related individuals has been shown to result in a number of adverse outcomes among offspring. Several studies have reported an increased risk of death among offspring of consanguineous couples [7, 8]. The most commonly studied and well-known association with CM is congenital anomalies. Offspring of related individuals are more likely to have rare autosomal recessive conditions that are uncommon in offspring of non-consanguineous couples [2, 9]. Absolute risk varies by population and outcome and has been found to be 1.7–2.8% higher for the children of first cousins than for those from non-related couples [2].

CM may also result in a spontaneous abortion (SAB) [10–12], a common outcome occurring in 15–20% of all clinically recognized pregnancies [13, 14]. Chromosomal abnormalities are implicated in roughly 50% of early losses, yet early pregnancies and pregnancy losses are often missed in cross-sectional studies and studies that recruit women later in the first trimester [13]. Studies of SAB are methodologically challenging, as early miscarriages often occur before women are aware of the pregnancy, increasing the likelihood of misclassification and missed identification of cases. For this reason, most studies looking at the association between CM and SAB have been cross-sectional in nature and derived from survey data, and results from these studies have been conflicting [10–12, 15–18].

To address these research gaps, we conducted a prospective pregnancy cohort study in Telangana which utilized active identification of early pregnancies as well as SABs, providing data on SABs that might be missed using cross-sectional and self-report data. In addition, southern India, especially the state of Telangana, is understudied in terms of both CM and birth outcomes. This paper aims to explore the association between first-cousin marriages and SAB in this region to provide an evidence base for medical professionals and women looking to conceive.

## Methods

### Study Population

The Longitudinal Indian Family hEalth (LIFE) study is a prospective cohort of 1,227 childbearing age women from Medchal Mandal, a rural to peri-urban region outside of Hyderabad, India. Design and conduct of the cohort is detailed elsewhere [19]. Briefly, women ages 15–35 were eligible to participate in the study if they lived in one of the non-transient villages in Medchal Mandal, planned to have more children, were not pregnant beyond the first trimester, and if neither the woman nor her husband had undergone a sterilization procedure. Preconception and prenatal demographic variables, health status, behavioral factors and environmental exposures were ascertained using questionnaires at enrollment and in the first and third trimesters.

Field staff called or visited enrolled women monthly to determine the most recent date of the participant's last menstrual period (LMP). Women found to be more than 5 weeks post-LMP were provided with a urine pregnancy test. Throughout the first and second trimester, women were monitored for losses. At 10–20 weeks' gestation, a field worker visited the women to discuss her plans for the pregnancy and delivery and to perform a urine pregnancy test at confirmation of a progressing pregnancy. Women also reported known losses to field staff members. A pregnancy loss questionnaire was administered to all women who had a pregnancy that ended in anything other than a live birth.

This analysis was limited to women who were not pregnant at registration ($n=661$), contributed at least one singleton pregnancy to the study, and had either had a SAB or had a pregnancy that was confirmed to be continuing past 22 weeks' gestation as ascertained at the third trimester visit. For women who contributed more than one pregnancy to the study, only the first was used (Fig. 1). Preliminary data from a subset of 286 pregnancies from this cohort are described in a publically available dissertation (http://d-scholarship.pitt.edu/18625/1/Eastman_ETD_FINAL_2.pdf).

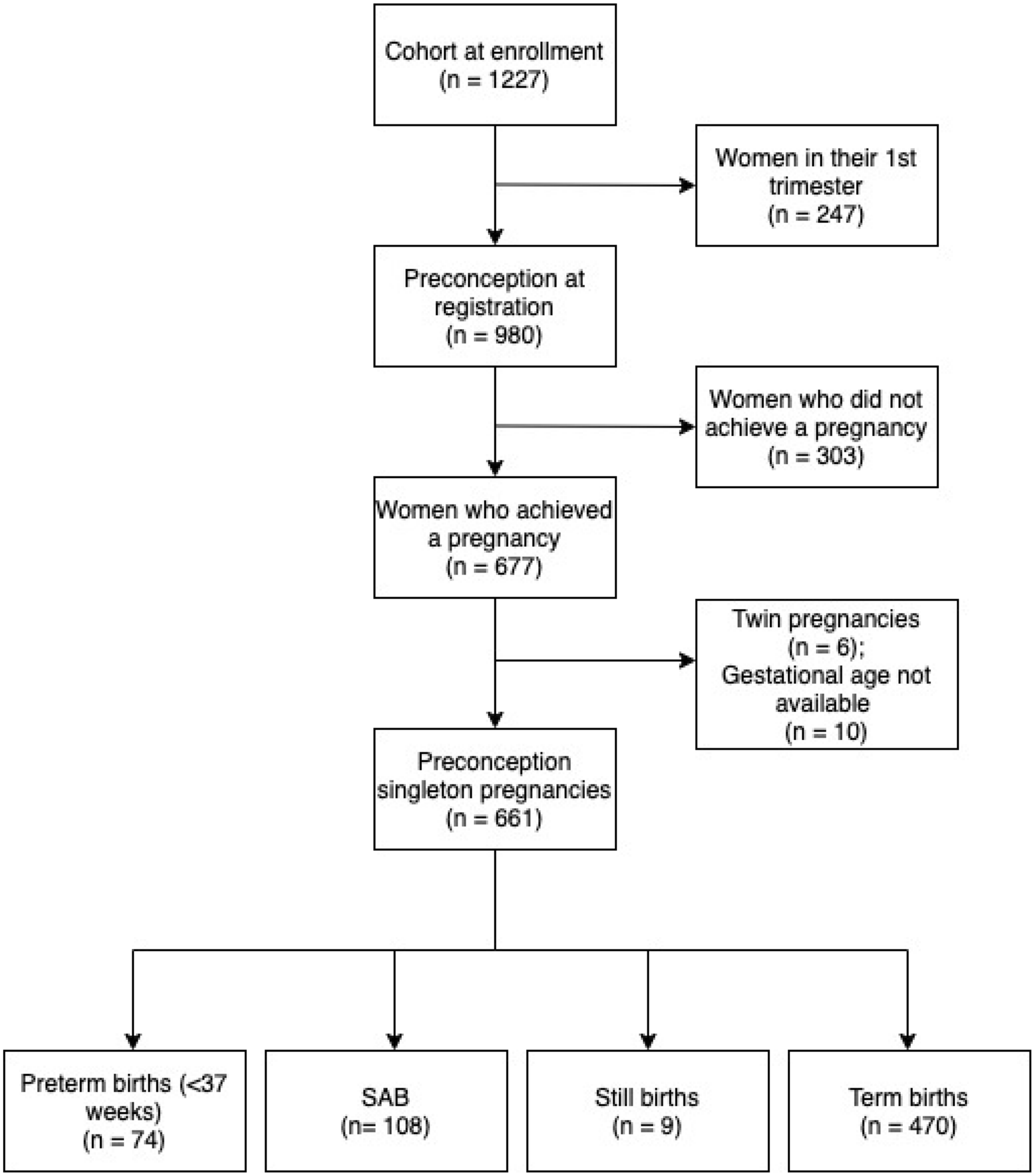


**Fig. 1** Flow chart of the LIFE study

### Related Marriage Definition

Women were asked at enrollment whether they were related to their husband prior to marriage. Those who answered in the affirmative were then asked to identify the nature of the relationship based on a provided list of common consanguineous relationships. Women who identified relationships that did not meet the standard definition of a CM or who were unable to provide information on the relationship were excluded. As most participants who reported being in a related marriage reported being in a first-cousin marriage (130/661, 19.6%), analyses were limited to those in non-CMs and those in first-cousin marriages. Women who reported being in a relationship with their husbands beyond the first-cousin marriage were excluded ($n=26$).

### Outcomes

SAB was defined as a spontaneous loss occurring < 22 weeks' gestation. Last self-reported LMP and self-reported date of pregnancy loss were used to determine gestational age at pregnancy loss. SABs were then classified as having occurred early (< 8 weeks' gestation), $n=25$ or late (8– < 22 weeks' gestation), $n=83$. Stillbirth was defined as the loss of a baby at 22 weeks or later of pregnancy or during delivery. Fetal death was defined as a spontaneous intrauterine death of the fetus at any time during pregnancy. These include SABs (pregnancy loss of < 22 weeks of gestation) and stillbirth (pregnancy loss occurring at 22 weeks of gestation or greater). Preterm birth (PTB) was defined as the birth of the baby before 37 completed weeks of pregnancy.

### Statistical Analysis

Analyses were performed using R version 3.6.1. Maternal characteristics were compared between those in related and unrelated marriages using the Student t test for continuous variables and the Chi-squared test of proportions for categorical variables. In the case of low expected cell counts, Fisher's exact test was substituted for the Chi-squared test. We used logistic regression to characterize the odds ratios of SAB for those in first-cousin marriages compared to those in unrelated marriages. Left truncation was used to reduce the variability in gestational age at which the pregnancy was identified. Maternal age, caste, self-reported health status at first trimester, education level, parity, and religion were considered as confounders. Risk factors that had a $p$ value < 0.25 from the univariate analysis were considered for inclusion in the final model. Additional analyses were performed to examine the risk of early SAB and risk of later SAB.

As pregnancies resulted in either pregnancy loss or a live birth which may occur at or prior to term, we considered PTB as a competing risk to stillbirth. We estimated cumulative incidence function (CIF) for pregnancy loss due to stillbirth with live birth as the competing risk after week 21 when a live birth is viable. The estimated CIFs between pregnancy outcomes from CM and those from normal marriages were compared via the log-rank test [20]. All pregnancies with missing data on exposure and outcome variables and those that ended in a SAB were excluded from these analysis. The CIFs for PTBs at week 26 (beginning of the third trimester), week 36 (end of the at-risk period for PTB), and week 31 (chosen as the middle of the two earlier time points) across CM and normal marriages were also presented. We calculated the cumulative incidences of stillbirth and PTB accordingly.

## Results

This study included 661 women who enrolled in the study and became pregnant between August 2009 and July 2011 (Table 1). One hundred and thirty women (19.7%) reported being in a first-cousin marriage. Overall, the mean ± SD age of the study population at time of pregnancy was 22.9 ± 3.1 years. The majority of participants were Hindu (90.0%), had a primary school education (84.7%), belonged to a Backward caste (57.8%), reported their health status at the first trimester as either very good or good (86.4%), and reported at least one prior live birth (45.1%). Pregnancies in this analysis were identified at a mean ± SD gestational age of 7.2 ± 3.4 weeks. Women in CMs were more likely to be from Scheduled caste and reported very good or good health status, compared to women in non-CM. In other respects, there were no significant differences among baseline characteristics of women in unrelated marriages compared to those in first-cousin marriages.

SAB occurred among 108 pregnancies (108/661 = 16.3%), with 85 (85/531 = 12.9%) occurring among women in non-consanguineous relationships and 23 (23/130 = 17.7%) among women in first-cousin relationships. Less than a quarter of SABs were classified as early SABs ($n=25$, 19.2%). Women in first-cousin marriages had a higher percentage of their SABs in the early period (8/130, 6.2%) compared to women in non-related marriages (17/531 = 3.2%).

Of the potential confounding factors investigated, only maternal age at the time of pregnancy met the criteria to be included in the final model. In the unadjusted analysis,

**Table 1** Baseline characteristics ($N = 661$)

| | Overall n (%) | CM = 0 n (%) | CM = 1 n (%) | p value |
|---|---|---|---|---|
| n | 661 | 531 | 130 | |
| Age at baseline (mean (SD)) | 21.73 (2.89) | 21.78 (2.84) | 21.51 (3.11) | 0.334 |
| Age at pregnancy (mean (SD)) | 22.86 (3.08) | 22.91 (3.07) | 22.65 (3.13) | 0.389 |
| Homemaker (%) | 506 (76.6) | 409 (77.0) | 97 (74.6) | 0.642 |
| Religion (%) | | | | 0.936 |
| Hindus | 595 (90.0) | 477 (89.8) | 118 (90.8) | |
| Muslims | 40 (6.1) | 33 (6.2) | 7 (5.4) | |
| Christians/other | 26 (3.9) | 21 (4.0) | 5 (3.8) | |
| Caste (%) | | | | 0.002 |
| Scheduled caste | 134 (20.3) | 102 (19.2) | 32 (24.6) | |
| Scheduled tribe | 47 (7.1) | 29 (5.5) | 18 (13.8) | |
| Backward caste | 382 (57.8) | 316 (59.5) | 66 (50.8) | |
| Other | 98 (14.8) | 84 (15.8) | 14 (10.8) | |
| Education (%) | 560 (84.7) | 449 (84.6) | 111 (85.4) | 0.921 |
| Health status (very good/good) (%) | 571 (86.4) | 451 (84.9) | 120 (92.3) | 0.040 |
| Parity (%) | | | | 0.302 |
| Nulliparous | 268 (40.5) | 211 (39.7) | 57 (43.8) | |
| Primiparous | 298 (45.1) | 247 (46.5) | 51 (39.2) | |
| Multiparous | 95 (14.4) | 73 (13.7) | 22 (16.9) | |
| Gestational age at pregnancy reported (mean (SD)) | 7.22 (3.35) | 7.19 (3.26) | 7.33 (3.72) | 0.692 |

**Table 2** Logistic regression models: First-cousin marriage and spontaneous abortion

| | Unadjusted OR (95% CI), p value | Adjusted OR[a] (95%CI), p value |
|---|---|---|
| Any spontaneous abortion ($n = 108$) | 1.13 (0.68, 1.87), 0.642 | 1.15 (0.69, 1.91), 0.60 |
| Early spontaneous abortion ($n = 25$) | 1.98 (0.83, 4.70), 0.12 | 2.03 (0.85, 4.83), 0.11 |
| Late spontaneous abortion ($n = 83$) | 0.89 (0.49, 1.61), 0.70 | 0.90 (0.49, 1.63), 0.72 |

[a]Model adjusted for maternal age at pregnancy

women in first-cousin marriages were at a modestly increased risk of SAB compared to women in non-related marriages both before (OR 1.13, 95% CI 0.68, 1.87) and after adjustment for maternal age ($OR_{adj}$ 1.15, 95% CI 0.69, 1.91), although results were not statistically significant (Table 2). There was a trend for an increased risk of early SAB among women in first-cousin marriages both before (OR 1.98, 95% CI 0.83, 4.70) and after adjustment for maternal age ($OR_{adj}$ 2.03, 95% CI 0.85, 4.83). There was no relationship between CM and late SAB.

Table 3 shows the estimated cumulative incidences of stillbirth among CMs at weeks 26, 31, and 36 were numerically higher at 0.0188, 0.0280, and 0.0280, respectively (log-rank test $p = 0.29$). In contrast, the cumulative incidence of PTB among women in a CM was similar or numerically lower at 0.0000, 0.0000, and 0.1028 at weeks 26, 31, and 36, respectively (log-rank test $p = 0.36$). The cumulative incidences of both stillbirth and PTB among CM compared to non-CM was similar at these occasions. Figure 2a shows that the risks of PTB among women in a consanguineous relationship versus a non-consanguineous relationship are similar up to 31 weeks of gestation, but the cumulative incidence increased dramatically for both consanguineous and non-consanguineous relationships to 10.3% and 14.3%, respectively. On the other hand, the risk of stillbirth among women in a consanguineous relationship versus a non-consanguineous relationship is consistently higher after the first 21 weeks of gestation even though the difference was not statistically significant due to limited sample size and the nature of stillbirth being a rare event (Fig. 2b). As expected, the cumulative incidence rate of stillbirths at 36 weeks was much lower among normal marriages (0.68%) than that among CMs (2.8%).

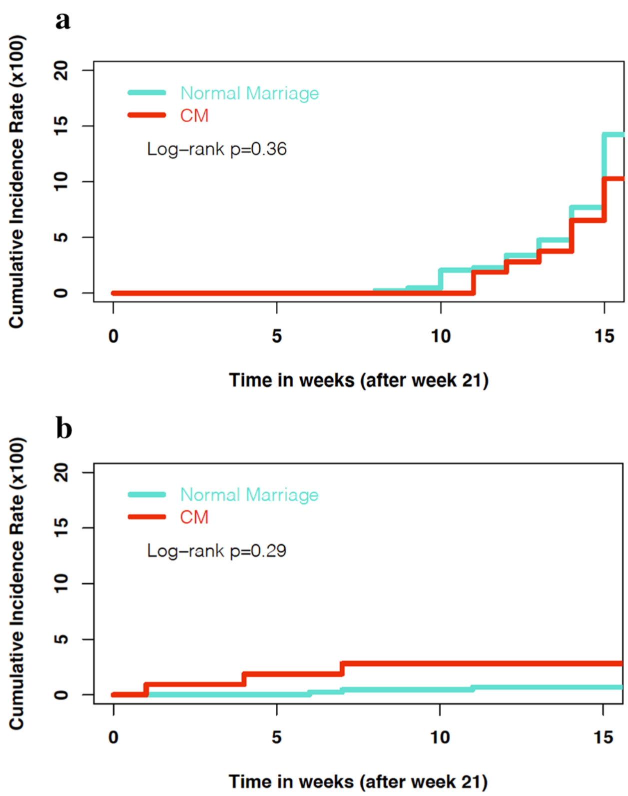


**Fig. 2** **a** Competing risk for PTB between CM and non-CM. **b** Competing risk for Stillbirth between CM and non-CM

## Discussion

CM is common in many parts of the world, including South India. Our results showed an increase in the risk of early SAB among women in consanguineous versus unrelated marriage independent of maternal age, although results were of borderline statistical significance. On the other hand, we did not find that CM increased the odds of later gestation SAB. This pattern may reflect the greater influence of chromosomal abnormalities and lethal homozygous recessive disease in early SAB [21], as many early SABs are the result of chromosomal abnormalities, whereas late SABs may be more influenced by environmental exposures [22, 23]. In fact, chromosomal abnormalities are much more common in consanguineous relationships, which may suggest that recessive genetic mutations inherited from a common ancestor can lead to adverse prenatal outcomes [24].

Other studies on the risk of SAB among consanguineous couples in India have reported mixed results. A study in Tamil Nadu reported a significant increase in SAB [12], while others conducted in various regions of South India, excluding Telangana State, have shown insignificant [16–18] or mixed results [11]. All of these studies may have missed capturing early SABs that might go unnoticed in non-planning populations with little access to healthcare. Further, these studies did not distinguish between early and late SABs. In addition, diverse geographical and ethnic groups in India have different marriage customs and levels of overall relatedness. The effects of CM within one region may not be indicative of the risk in another. The results of this study along with previous research demonstrate a need for larger prospective studies that are able to identify early pregnancies and losses among a variety of populations.

Our study has a number of notable strengths. First, to our knowledge this is the first prospective pregnancy cohort study in this region to actively follow women for pregnancy and pregnancy loss, allowing us to examine predictors of accurately measured SAB, including CM. Despite the high rate of CM in Telangana, information on the degree of relatedness of couples in the area and the impact on pregnancies has not been previously reported. Our study also has limitations. First, women were asked to self-report their consanguineal kinship to their husband. No information on ancestral relationship between the couple was available in this study. Some couples may be more related than measured in the current analysis. Future studies using blood samples may be able to determine the true degree of relatedness among participants. Second, approximately a quarter of SABs were identified as occurring early, and models of CM and SAB may have been underpowered. Still, our study identified a trend for an increased risk of early SAB and no increased risk of late SAB, which was in line with a priori hypotheses. Additional prospective studies including sufficient numbers of early and late SABs in a variety of regions and ethnic groups are needed to replicate our findings. Finally, there may be misclassification of the outcome variable. SABs were ascertained through staff follow-up and participant self-report, but several days or weeks may have passed between the actual

**Table 3** Cumulative incidence of preterm birth and stillbirth

| Outcome | Week 26 | | Week 31 | | Week 36 | |
|---|---|---|---|---|---|---|
| | Cum. inc. (SE) among CM = 0 | Cum. inc. (SE) among CM = 1 | Cum. inc. (SE) among CM = 0 | Cum. inc. (SE) among CM = 1 | Cum. inc. (SE) among CM = 0 | Cum. inc. (SE) among CM = 1 |
| PTB ($n$ = 74) | 0.0000 (0.0000) | 0.0000 (0.0000) | 0.0045 (0.0032) | 0.0000 (0.0000) | 0.1425 (0.0166) | 0.1028 (0.0295) |
| Stillbirth ($n$ = 9) | 0.0000 (0.0000) | 0.0188 (0.0132) | 0.0045 (0.0032) | 0.0280 (0.0160) | 0.0068 (0.0039) | 0.0280 (0.0160) |

loss and when the women became aware of the loss. For those who were near the cutoff of 22 weeks of gestation, they may have been classified as having had a stillbirth. To determine whether this was a potential problem in our analysis, a single fetal death variable consisting of both SABs and still births ($n = 117$) was used in subsequent analysis. Overall, this change had did not change the conclusion (Table SI).

We demonstrated an increased risk of pregnancy loss, particularly early SAB, among women in a region of India with high rates of CM, suggesting that efforts to counsel reproductive aged women and married couples may be warranted [25]. As evidence suggests that prenatal morbidity and mortality rates increase due to intrafamilial marriages [25–27], pre-marital Health Counseling (PMHC) is a growing trend among nations where CM rates are high. Our study provides additional findings for evidenced-based counseling of populations at risk. Both pre-marital counseling and peri-marital counseling on the risk of SAB may help healthcare providers better counsel patients who are experiencing recurrent miscarriages.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s13224-021-01498-7.

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## Declarations

**Conflicts of interest** The investigators have no conflicts of interest.

**Informed Consent** Informed consent was obtained for all participants in the study.

**Ethics approval** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1964 Helsinki Declaration of and its later amendments or comparable ethical standards. This study was a population based prospective study and was approved by the Institutional Review Board of the MediCiti Institute of Medical Sciences (MIMS) hospital and was conducted within the tenets of the Declaration of Helsinki.

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