AOGS
ACTA Obstetricia et Gynecologica Scandinavica

AOGS ORIGINAL RESEARCH ARTICLE

Consanguineous marriage, prepregnancy maternal characteristics and stillbirth risk: a population-based case–control study

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Key words

Adverse pregnancy outcome, consanguineous marriage, consanguinity, cousin marriage, Golestan province, Iran, maternal characteristics, stillbirth

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Conflicts of interest

All authors have stated explicitly that there are no conflicts of interest in connection with this article.

Please cite this article as: Maghsoudlou S, Cnattingius S, Aarabi M, Montgomery SM, Semnani S, Stephansson O, et al. Consanguineous marriage, prepregnancy maternal characteristics and stillbirth risk: a population-based case–control study. Acta Obstet Gynecol Scand 2015; 94: 1095–1101.

Received: 28 January 2015
Accepted: 13 June 2015

DOI: 10.1111/aogs.12699

Abstract

Introduction. Consanguineous marriage is associated with increased risks for congenital anomalies, low birthweight, and other adverse perinatal outcomes. In this population-based, case–control study we investigated the association between consanguineous marriage (first-cousin marriage) and stillbirth risk, using prospectively collected information from prepregnancy visits. *Material and methods.* From 2007 to 2009, we identified 283 stillbirths (cases) and 2088 randomly selected live control births through prepregnancy visits in rural Golestan, Iran. The associations between consanguinity and prepregnancy maternal characteristics and stillbirth risk were examined using multivariate logistic regression. *Results.* The rate of consanguineous marriage was 19.4% among cases and 13.6% among controls. Consanguinity was associated with increased stillbirth risk [odds ratio (OR) 1.53; 95% CI 1.10–2.14]. The association was significantly increased for preterm stillbirth (< 37 gestational weeks) (OR 2.43; 95% CI 1.46–4.04) but not for term stillbirth (≥ 37 weeks) (OR 1.14; 95% CI 0.75–1.74). Low and high maternal age, underweight, obesity, nulliparity, a history of infertility or miscarriage, previous obstetric complications (preeclampsia, preterm delivery, and stillbirth in previous pregnancies) were also associated with increased stillbirth risks. *Conclusions.* Consanguineous marriage is associated with increased risk of stillbirth, particularly preterm stillbirth. Findings for other maternal risk factors for stillbirth in rural Iran are consistent with previously reported findings from high-income countries.

Abbreviations: BMI, body mass index; OR, odds ratio; SGA, small-for-gestational age.

Key Message

A population-based case–control study showed that consanguineous marriage associated with a >50% increased risk of stillbirth. The association was increased significantly for preterm but not for term stillbirth.

Introduction

More than five stillbirths occurs for every 1000 deliveries in many high-income countries (1) and this rate is up to

10-fold higher in low-income countries (2). During recent decades, some countries have experienced substantial reductions in stillbirth rates; whereas in other countries stillbirth rates have been stable or slightly declining (3).

The changes in stillbirth rates may be a result of changes in prevalence of risk factors, including high and low maternal age, primiparity and grand multiparity, maternal smoking, overweight and obesity (3). In addition, increased access to obstetric services, including better pregnancy supervision and modern interventional strategies during labor may contribute to declining stillbirth rates (4).

Iran has moved to be a middle-income country over the recent decades (5), which could influence stillbirth rates, both by changes in maternal characteristics, living conditions and medical care. Most pregnancies are planned and mothers have regular antenatal care through the primary healthcare system. Importantly, Iran has also a scheduled prepregnancy visit for all women when planning a pregnancy, the visit is valid for 1 year and is followed by eight antenatal visits, all women receive folate supplements and women with high-risk pregnancies are identified. Some 95% of mothers deliver their infants in hospitals and the rate of caesarean section is more than 45% (6). The incidence of stillbirth in Iran is reported to be around 10/1000 (7).

In Iran, consanguineous marriage is culturally acceptable and the overall rate of marriage between first cousins is high (8). Consanguineous marriage has been associated with increased risks of asthma, mental retardation, epilepsy, subfertility (9), infertility (10), and diabetes in the offspring (11) as well as infant and child mortality (12,13). Consanguineous marriage is also related to low birthweight (14) and congenital malformations (15), which are associated with increased stillbirth risk. The few studies investigating the association between consanguineous marriage and stillbirth risk have suffered from methodological problems such as small sample sizes (16,17).

The aim of this population-based case–control study from a rural area in northeast Iran was to investigate the association between consanguineous marriage and stillbirth risk. We also estimated the associations between prepregnancy maternal characteristics, previous obstetric history, and stillbirth risk.

Material and methods

The study was performed in rural areas of the Golestan Province, in northeast Iran. Golestan Province has a population of approximately 1 700 000 inhabitants (50% living in rural areas), and annually there are approximately 17 000 births. Based on the public healthcare system in Iran, each rural health house is responsible for providing care and recording information before and during pregnancy, and after delivery. Such information is prospectively recorded in the family health files held by rural health houses.

All identified singleton stillbirths in rural areas of Golestan Province between 2007 and 2009 (n = 501) were selected as cases. Stillbirth was defined as delivery of a baby without any vital signs at 28 weeks of gestation or later. Controls were selected using the block randomization method. We determined each region as a block and calculated block sample sizes based on the population growth rate of the region. All pregnancies during the study period in the region were listed and numbered based on date of delivery. Thereafter, we selected controls using random digits created by computer. We aimed to have at least five controls per case after excluding births before 28 gestational weeks, multiple births, and stillbirths. The control group included 2918 live singleton births with a gestational age of at least 28 completed weeks.

Information on maternal and pregnancy characteristics were collected from medical records by midwives who work as healthcare providers for pregnant women at the health centers. Data were abstracted from both prepregnancy, pregnancy, and delivery records, and information was computerized by 10 specially trained medical students. A consanguineous marriage was defined as a marriage between first cousins, as recorded in the health files. Infertility was defined as inability to naturally achieve pregnancy within 1 year. A self-reported previous miscarriage was defined as a miscarriage before onset of the index pregnancy. Gestational age was based on the time interval between date of delivery and date of the first day of the last menstrual period. A preterm birth was defined as a live birth before 37 completed weeks of pregnancy. As a proxy for fetal growth restriction, we used small-for-gestational age (SGA), which was defined as a birthweight below the 10th centile (in the control group) for gestational age (week) and sex. Because of the limited number of preterm births in the control group, we could not estimate appropriate cut-off limits for SGA in preterm deliveries. Socio-economic status was based on father's profession (unskilled manual worker, skilled manual worker, self-employed, farmer, other occupations, and unemployed).

As a quality control, we collected and computerized 10% of the data for a second time. The variables that had more than 5% mismatches were recollected and the data were re-entered for all study subjects. If the data for a health center had more than 5% mismatches, all data were recollected and re-entered for the center. In total, 283 cases and 2120 controls had both prepregnancy and pregnancy visits, and were included in the study.

We used univariate and multivariate logistic regression models for estimating odds ratios (OR) and 95% CI for the associations between exposures and stillbirth. The multivariate models were adjusted for maternal age, body mass index (BMI), height, parity, history of miscarriage, history of infertility, region of residence, and father's occupational classification. Due to possible differences in the causes of stillbirth in relation to gestational age, we also performed analysis stratified for preterm and term birth. We also analyzed term stillbirths stratified into SGA and non-SGA stillbirths.

We estimated OR for maternal age (≤ 19, 20–24, 25–29, 30–34, and ≥ 35 years), mother's BMI (< 18.5, 18.5 to < 25, 25 to < 30, 30 to < 35, and ≥ 35 kg/m^2), and mother's height (< 150, 150–154, 155–159, 160–164, and ≥ 165–cm), parity (nulliparous, 1–2 and ≥ 3 previous births), and history of miscarriage (yes, no) as categorical variables.

A multiple imputations method was used to provide data for the missing values for father's profession (seven among cases and 45 among controls) and mother's height (70 among cases and 64 in controls). The MI procedure (SAS software) with five imputations was used for multiple imputations (18).

Restricting the study to those who had data from prepregnancy visits may potentially cause selection bias. We therefore performed a sensitivity analysis using information from all singleton stillbirths (n = 501) and live births (n = 2918). We estimated the association for some variables that were available for all mothers (with or without a prepregnancy visit), including maternal age, maternal weight, history of miscarriage, and infertility. We also compared characteristics of women with and without pre-pregnancy visits.

SAS software version 9.3 was used for analyzing the data.

Ethics approval for this study was obtained from the ethics committees of Golestan University of Medical Sciences, Iran (35/2633-p/g, 17 January 2011) and Karolinska Institute regional ethics committee (2011/1657-31/3).

Results

The frequencies of consanguineous marriage among the 283 cases and 2120 controls were 19.4% and 13.4%, respectively. Prepregnancy characteristics of cases and controls, stratified by consanguinity, are presented in the Supplementary material (Tables S1 A–C).

Associations between maternal prepregnancy characteristics and risk of stillbirth are presented in Table 1. Consanguinity was associated with a 50% increased stillbirth risk in the adjusted analysis. Compared with 20- to 24-year-old mothers, teenage mothers, and especially mothers who were 35 years or older had an increased stillbirth risk. Compared with mothers with normal BMI (18.5 to < 25 kg/m^2), underweight mothers (BMI < 18.5 kg/m^2), mothers with mild obesity (BMI 30.0 to < 35 kg/m^2), and especially mothers with severe obesity (BMI > 35 kg/m^2) had increased stillbirth risks. We also found that nulliparity, a history of infertility, and a history of miscarriage were associated with increased stillbirth risks. We observed that risk of stillbirth was higher in Galikesh and Gomishan regions, and lower in Gorgan, Aghghala and Minoodasht regions compared with Gonbad. Due to the paucity of exposure, it was not possible to estimate the association for smoking (no smokers among cases and 1.2% among controls), opium use (1.8% and 2.4%, respectively), or chronic maternal disease (1.1% and 1.5%, respectively).

In analysis of preterm and term stillbirths, we found that consanguinity was associated with a more than two-fold increased risk for preterm stillbirth (OR 2.43; 95% CI 1.46–4.04) (Table 2). Among term deliveries the OR (95% CI) for the associations of consanguinity and SGA stillbirth and with non-SGA stillbirth were 1.40 (0.72–2.72) and 1.01 (0.54–1.88), respectively.

Characteristics of previous pregnancies and stillbirth risks in parous women are presented in Table 3. A positive history of preeclampsia was associated with an almost four-fold increased stillbirth risk. A history of preterm delivery was associated with a more than four-fold increase in risk and a previous stillbirth was associated with a more than ten-fold increase in risk.

We also investigated the importance of some risk factors available in all registered singleton stillbirths (n = 501) and 2918 randomly selected singletons live birth pregnancies (with or without a prepregnancy visit) between 2007 and 2009. Compared with 20- to 24-year-old mothers, risks of stillbirth for younger mothers and those who were 35 years or older were 1.34 (0.95–1.89) and 2.64 (1.79–3.89), respectively. Among all mothers, both a history of miscarriage and a history of infertility were associated with increased risks (OR 1.41; 95% CI 1.08–1.84 and OR 2.40; 95% CI 1.40–4.13, respectively).

Discussion

In this case–control study, we found that consanguineous marriage was associated with an increased stillbirth risk. The association was stronger for preterm than term stillbirths and only statistically significant for preterm stillbirths. Prepregnancy maternal characteristics, including low and high maternal age, underweight, obesity, infertility, and previous adverse obstetric history (a history of abortion, preeclampsia, preterm delivery, and stillbirth in previous pregnancies) were also associated with increased stillbirth risk.

Table 1. Maternal prepregnancy characteristics and risk of stillbirth in Golestan, Iran.

	Cases		Controls		Odds ratio (95% CI)			
	n	(%)	*n*	(%)	Crude		Adjusted[a]	
Consanguineous marriage								
No	228	80.6	1805	86.4	Reference		Reference	
Yes	55	19.4	283	13.6	1.54	1.12–2.12	1.53	1.10–2.14
Mother's age, years								
≤19	48	17.0	278	13.3	1.70	1.14–2.52	1.74	1.15–2.62
20–24	68	24.0	668	32.0	Reference		Reference	
25–29	75	26.5	556	26.6	1.32	0.94–1.87	1.26	0.87–1.83
30–34	48	17.0	411	19.7	1.15	0.78–1.69	1.09	0.70–1.69
≥35	44	15.5	175	8.4	2.47	1.63–3.74	2.61	1.61–4.22
Body mass index, kg/m^2								
<18.5	21	9.9	153	7.5	1.55	0.96–2.48	1.74	1.05–2.87
18.5 to <25	92	43.2	1148	56.7	Reference		Reference	
25 to <30	59	27.7	505	24.9	1.46	1.07–2.00	1.31	0.94–1.82
30 to <35	30	14.1	174	8.6	1.95	1.27–3.01	1.75	1.12–2.75
≥35	11	5.2	46	2.3	2.81	1.51–5.20	2.29	1.18–4.44
Missing	70		62					
Mother's height, cm								
<150	22	10.3	136	6.7	1.37	0.84–2.23	1.28	0.77–2.13
150–154	51	23.9	455	22.5	0.98	0.70–1.37	1.02	0.72–1.44
155–159	87	40.8	743	36.7	Reference		Reference	
160–164	27	12.7	385	19.0	0.82	0.57–1.19	0.81	0.55–1.19
≥165	26	12.2	307	15.1	0.77	0.49–1.22	0.84	0.52–1.34
Missing	70		62					
Parity								
0	143	50.5	960	46.0	1.27	0.98–1.64	1.48	1.09–2.00
1–2	118	40.7	1004	48.1	Reference		Reference	
≥3	22	7.8	124	5.9	1.51	0.92–2.47	1.26	0.74–2.14
History of miscarriage								
No	225	79.5	1787	85.6	Reference		Reference	
Yes	58	20.5	301	14.4	1.53	1.12–2.09	1.41	1.01–1.98
History of infertility								
No	271	95.8	2047	98.0	Reference		Reference	
Yes	12	4.2	41	2.1	2.21	1.15–4.26	2.33	1.18–4.60
Father's profession								
Unskilled manual	112	41.3	952	46.8	Reference		Reference	
Skilled manual	31	11.4	195	9.6	1.35	0.88–2.07	1.12	0.59–2.12
Self-employed	50	18.4	247	12.1	1.70	1.18–2.44	1.51	0.86–2.66
Farmer	43	15.9	373	18.3	0.99	0.68–1.43	0.90	0.52–1.56
Other occupations	25	9.2	207	10.2	1.06	0.68–1.67	0.78	0.38–1.58
Unemployed	10	3.7	62	3.0	1.47	0.74–2.93	2.17	0.89–5.30
Missing	12		52					
Region								
Aghghala	21	7.4	302	14.5	0.33	0.20–0.55	0.35	0.17–0.75
Aliabad	20	7.1	137	6.6	0.70	0.41–1.19	0.89	0.42–1.88
Azadshahr	23	8.1	86	4.1	1.28	0.77–2.16	1.89	0.85–4.20
Bandargaz	2	0.7	46	2.2	0.21	0.05–0.88	0.29	0.04–2.36
Galikesh	13	4.6	40	1.9	1.56	0.80–3.06	2.76	1.10–6.97
Gomishan	29	10.2	88	4.2	1.59	0.98–2.57	2.38	1.12–5.03
Gonbad	81	28.6	390	18.7	Reference		Reference	
Gorgan	14	4.9	242	11.6	0.28	0.15–0.50	0.24	0.09–0.64
Kalaleh	25	8.8	210	10.1	0.57	0.35–0.92	0.62	0.29–1.30
Kordkoy	8	2.8	71	3.4	0.54	0.25–1.17	1.15	0.41–3.24
Maraveh	14	4.9	108	5.2	0.62	0.34–1.14	0.82	0.33–2.00
Minoodasht	12	4.2	212	10.1	0.27	0.14–0.51	0.42	0.18–0.99

Table 1. Continued

	Cases		Controls		Odds ratio (95% CI)			
	n	(%)	n	(%)	Crude		Adjusted[a]	
Ramian	10	3.5	66	3.2	0.73	0.36–1.48	1.00	0.39–2.54
Torkaman	11	3.9	90	4.3	0.59	0.30–1.15	1.28	0.59–2.80

[a]Adjusted for all variables in the table.

Table 2. Consanguineous marriage and risks of preterm and term stillbirth.

	Preterm stillbirth[a]					Term stillbirth[b]				
	Cases		Controls			Cases		Controls		
Consanguineous marriage	n	%	n	%	OR[c] (95% CI)	n	%	n	%	OR[c] (95% CI)
No	66	73.3	1805	86.4	Reference	162	83.9	1613	86.2	Reference
Yes	24	26.7	283	13.5	2.43 (1.46–4.04)	31	16.1	258	13.8	1.14 (0.75–1.74)

[a]Analysis included 90 preterm stillbirths and 2120 controls with complete information on covariates
[b]Analysis included 193 term stillbirths and 1904 controls with complete information on covariates
[c]Adjusted for all variables provided in Table 1.

Table 3. Odds ratio and 95% CI for the associations between previous obstetric history and stillbirth in parous mothers.

	Cases		Controls		Odds ratio (95% CI)	
	n	(%)	n	(%)	Crude	Adjusted[a]
History of neonatal death						
No	131	93.6	1100	97.5	Reference	Reference
Yes	9	6.4	28	2.5	2.66 (1.18–6.00)	2.31 (0.98–5.44)
History of preeclampsia						
No	128	91.4	1099	97.4	Reference	Reference
Yes	12	8.6	29	2.5	3.35 (1.63–6.87)	3.82 (1.79–8.18)
History of preterm delivery						
No	124	88.6	1100	97.5	Reference	Reference
Yes	16	11.4	28	2.5	5.07 (2.67–9.63)	4.66 (2.29–9.45)
History of stillbirth						
No	105	75.0	1092	96.8	Reference	Reference
Yes	35	25.0	36	3.2	10.11 (6.09–16.78)	10.67 (6.05–18.82)

[a]Adjusted for all maternal characteristics (provided in Table 1).

Our finding of a positive association between consanguineous marriages and stillbirth risk is consistent with the results of a Norwegian study: Stoltenberg et al. found a moderately increased risk of stillbirth in mothers with Pakistani origin, among whom consanguineous marriage is common (19). In contrast to the Norwegian study, we looked at consanguinity more directly rather than inference by ethnic origin. A case–control study with 84 cases and 1978 controls in Egypt found a strong association between consanguineous marriage and stillbirth (OR 10.6) (20). A positive association between consanguinity and pregnancy loss or self-reported pregnancy wastage (a combination of abortion and stillbirth) and consanguineous marriage was also reported in Palestinian mothers (16,21).

The association between consanguinity and stillbirth was restricted to preterm stillbirths. Consanguinity is associated with increased risks of low birthweight (14), preeclampsia (22), and congenital anomalies (23), which in turn are risk factors for stillbirth (17), especially preterm stillbirth (24,25). It has also been shown that there is an association between lethal recessive alleles in consanguinity and diseases in offspring. Culprit genes have been identified in associations between consanguinity and hearing loss (26), familial Mediterranean fever (27), intellectual disability (28), and many other disorders. We therefore suggest that our finding of a positive association between consanguineous marriages and preterm stillbirth risk may be the result of either a genetic disposition for poor placentation (giving a higher risk of fetal growth restriction and preeclampsia), lethal recessive alleles associated with congenital anomalies, or both.

We also found that prepregnancy maternal characteristics were associated with stillbirth risk, including low and high maternal age, underweight, obesity, primiparity, history of miscarriage, and history of infertility. A large, well-designed, systematic review and meta-analysis of 96 population-based studies found similar results for maternal age, BMI, and primiparity in high-income nations (3).

The results from our study indicate that previous obstetric history (a history of preeclampsia, miscarriage, preterm delivery, stillbirth, or neonatal death) is associated with stillbirth risk, which is supported by previous findings (3,29,30). These results may help health providers to identify a risk group for more intense supervision during pregnancy. Moreover, development of public health orientation and improving knowledge about maternal risk factors such as underweight, obesity, teenage pregnancy, and high maternal age, and discouraging consanguineous marriage might be helpful to reduce stillbirth rate.

Strengths of the study include using the data from prepregnancy visits. This provides a possibility to investigate the effects of different factors on pregnancy outcomes with less risk of bias. Second, there is only limited information on the incidence of adverse pregnancy outcomes in low/middle-income countries, and this study adds important population-based data from rural areas in Iran. Finally, this study was conducted in rural areas of Golestan province, where most pregnancies are planned, and women have a scheduled prepregnancy visit, several pregnancy visits and an "after delivery visit". Some 97% of pregnant women are in contact with the primary healthcare system and receive nutritional supplements during pregnancy (6). We included all cases and randomly selected controls and extracted prospectively collected data from family health files, so striving to minimize risks of selection and recall bias.

This study also has some potential limitations. We limited the study to data included in family health files from rural areas. Consanguinity was registered as a first-cousin marriage in the health files. Therefore, the unexposed group includes both second cousin and non-cousin couples. This may cause an underestimation of the association between consanguinity and stillbirth risk. As we aimed to investigate the association for prepregnancy factors, we only included cases and controls with prepregnancy visits. As this restriction might cause selection bias, we performed a sensitivity analysis. We found that there were no differences in stillbirth risks related to maternal age, a history of miscarriage, and a history of infertility among mothers with a prepregnancy visit compared with all mothers. Misclassification of miscarriage and induced abortions could be a potential concern. Induced abortion is illegal in Iran, and some women may have not reported a history of induced abortion. As we used prospectively collected information before and during pregnancy, information on miscarriage and induced abortions based on self-report could not represent a recall bias. Hence, a potential misclassification would be non-differential, and if anything, would shift the association toward the null. Another limitation of this study is that father's profession, which is used as measure of socio-economic conditions for families, may not be sufficiently discriminatory. The observed higher risk of stillbirth in two most deprived regions of the province (Galikesh and Gomishan) could be due to residual confounding by socio-economic status. There may also be concern regarding generalizability of the results. However, the age and BMI distributions in our control group are similar to previously reported age and BMI distributions among pregnant women in other parts of Iran (31). Finally, we did not have any data to determine the cause of the stillbirth, specifically genetic testing, autopsy, placental pathology, or congenital defects.

This study provides evidence that consanguineous marriage is a risk factor for stillbirth, particularly for preterm stillbirth. These findings also suggest that many risk factors for stillbirth, such as consanguineous marriage, underweight, obesity, teenage pregnancy, and high maternal age, are partly preventable. Hence, in theory, a significant reduction in stillbirth rate is possible.

Acknowledgments

We are indebted to the members of the primary healthcare system of Golestan University of medical sciences, particularly maternal healthcare units in rural area of Golestan in northern Iran.

Funding

This work was entirely funded by internal funding of Karolinska Institute.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Characteristics of the cases and controls by consanguineous marriage.

Table S2. Frequency of adverse pregnancy outcomes of the cases and controls by consanguineous marriage among term pregnancies.

Table S3. Characteristics of the cases and controls by consanguineous marriage among parous mothers.