



The Pre-Pregnancy Risk Factors of Stillbirth in Pregnant Iranian Women: A Population-Based Case-Control Study

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Abstract

Background: Stillbirth is an important economic, cultural, and health index that has a higher prevalence in developing countries.

Objectives: The present research was conducted to determine the pre-pregnancy risk factors of stillbirth in Iran.

Methods: This research is a national population-based case-control study on the risk factors of stillbirth in Iran. A total of 3,085 women presenting to public healthcare centers of ten provinces/cities of Iran entered the study, including 1,459 women who their last pregnancy ended in a stillbirth as the case group and 1,626 women who their last pregnancy ended in a live birth as the control group. Data were collected with a researcher-made questionnaire and were then analyzed by SPSS-19 using the chi-square and the logistic regression tests. P values less than 0.05 were considered statistically significant.

Results: The results revealed a relationship between the last pregnancy ending in a stillbirth and a previous history of stillbirth (OR = 2.64, CI: 1.81 - 3.85, P = 0.001), miscarriage (OR = 1.57, CI: 1.21 - 2.03, P = 0.001) irregular menstruation (OR = 1.29, CI: 1.02 - 1.64, P = 0.029), age over 35 (OR = 1.58, CI: 1.17 - 2.14, P = 0.001), low level of education (OR = 3.50, CI: 2.30 - 5.33, P = 0.001), and the use of oral contraceptives.

Conclusions: There are several risk factors for stillbirth, including a previous history of stillbirth, miscarriage or irregular menstrual cycle, most of which can be controlled through pre-pregnancy training. Educational interventions are, therefore, required to improve the knowledge of women at childbearing age and preventive measures should be taken to reduce the number of stillbirths in pregnant women.

Keywords: Stillbirth, Risk Factors, Case-Control, Pregnancy, Miscarriage

1. Background

Stillbirth is known as one of the most unpleasant consequences of pregnancy (1) that is defined by the World Health Organization (WHO) as a baby born without vital

signs or as fetal death after 28 weeks of pregnancy with a birth weight of 1,000 grams or a body length of 35 cm (2). Most stillbirths occur at the end of pregnancy and their main cause is mostly unknown (3). The Center for Disease Control and Prevention (CDC) has classified still-

birth as early stillbirth (death in the 20th to 27th weeks of pregnancy), late stillbirth (death in the 28th to 36th weeks of pregnancy), and term stillbirth (death in the 37th or 38th weeks of pregnancy or at delivery) (4).

Epidemiological studies show that 3 million stillbirths occur around the world every year (5). The majority of stillbirths (nearly 98%) occur in low- and middle-income countries and more than half of them (55%) occur in rural sub-Saharan Africa (6). Although some developed countries have reported the rate of stillbirth as three per thousand live births (7), a ten-fold increase has been observed in sub-Saharan Africa and Southeast Asia compared to in high-income countries; thus the rate of stillbirth in these countries is 30 per thousand live births (8). In the Middle East and neighboring countries of Iran, the rate of stillbirth varies from eight per thousand live births in Qatar to 38 per thousand in Afghanistan (9). According to the reports of the WHO collaborative centers in Argentina, Egypt, India, Peru, South Africa, and Vietnam, the rate of stillbirth is 12.5 per thousand live births. In the past two decades, the rate of stillbirth has varied from 12.8 to 40.0 per thousand live births in different regions of Iran (10).

The risk factors of stillbirth consist of bacterial infection, congenital diseases, chromosomal abnormalities, congenital diabetes, high blood pressure (preeclampsia), mother's drinking and smoking or chemical drug use, placental abruption, trauma, exposure to radiation, female genital mutilation (11), umbilical cord problems (12), mother's age, multiple pregnancy, a previous history of stillbirth and miscarriage, low maternal education and premature rupture of the membranes in women over the age of 35 (13).

2. Objectives

The high rate of stillbirth is a major public health concern that demonstrates the rate of population growth. Given the lack of sufficient evidence and knowledge about stillbirth and its pre-pregnancy risk factors in Iran and the absence of comprehensive studies at the national level, as well as the ethnic differences between countries, the present study was conducted to determine some of the pre-pregnancy risk factors of stillbirth in mothers presenting to healthcare centers across different regions of the country.

3. Methods

The present population-based case-control study was conducted to review the pre-pregnancy risk factors of still-

birth in ten provinces/cities of Iran, including Fars, Hormozgan, Kermanshah, Hamadan, Kohgiluyeh and Boyer-Ahmad, Yazd, South Khorasan, and Golestan provinces and the cities of Mashhad and Zahedan. A total of 1,459 (47.3%) women who their last pregnancy ended in stillbirth and a total of 1,626 (7.52%) women who their last pregnancy ended in a live birth presenting to primary healthcare centers (PHC) across the country entered the study. Data were collected from different geographical regions and ethnic groups of Iran so as to enable the generalization of the results to the entire Iranian population.

As defined by the CDC, stillbirth is classified into three categories, including early stillbirth (death in the 20th to 27th weeks of pregnancy), late stillbirth (death in the 28th to 36th weeks of pregnancy) and term stillbirth (death in the 37th or 38th weeks of pregnancy or at delivery). This study collected the overall records of stillbirth from the PHCs of the mentioned provinces and cities. The intended urban and rural PHCs were taken as clusters from which the household health records and indexes and hospital death certificates were randomly selected. PHCs are established to follow up pregnant women who do not refer to the centers for care. Any woman reporting a stillbirth is asked specific questions to ensure her diagnosis and the recorded data is then announced to the health network and the health network receives records of stillbirth from each hospital and compares it against the statistics provided by the PHCs, and if a hospital reports a case of infant death that the center takes into account as stillbirth, the center is informed so that they can correct the statistics and record accurate data.

In the present study, data were collected using a researcher-made questionnaire, household health records from public healthcare centers and interviews with the women. The interviews inquired about the parents' personal information (mother's age, parents' education, parents' occupation, place of residence, ethnicity, family relationship, etc.) and pregnancy information (number of pregnancies, outcome of previous pregnancies, birth spacing, planned or unplanned pregnancy, method of contraception, menstrual cycle regularity, etc.). The validity of the questionnaire was approved by experts and its Cronbach's alpha reliability was estimated as 0.66 through a pilot study of 50 mothers in Kermanshah province. Stillbirth was the dependent variable and the independent variables included the mother working on night shifts, the mother's place of residence, ethnicity, birth order, menstrual cycle regularity, parents' age at delivery, parents' nationality, parents' education, parents' occupation, con-

sanguineous marriage, mother's pre-pregnancy weight, mother's height, outcome of previous pregnancies, pregnancy spacing (time since last pregnancy), planned or unplanned pregnancy, type of delivery, reason for cesarean section, method of contraception, the smoking and drinking history of the mother and her relatives, a previous history of miscarriage and stillbirth and mother's history of chronic diseases such as diabetes and mental disorder.

Ten provinces/cities of Iran, including Fars, Hormozgan, Kermanshah, Hamadan, Kohgiluyeh and Boyer-Ahmad, Yazd, South Khorasan and Golestan provinces and the cities of Mashhad and Zahedan, were selected through cluster sampling and based on their geographical location. The provincial capital and four cities of each province (including cities from the North, South, East, and West of each province) were selected as the clusters. One urban and one rural PHC were selected from each cluster and the women who presented to the PHCs were given the questionnaires to fill out. Ten cases of stillbirth filled out the questionnaires in each center. If the cases of stillbirth were less than ten in any of the centers, the closest center was selected so as to complete the remaining questionnaires. If, however, the cases of stillbirth were more than ten in the centers, ten of them were randomly selected to fill out the questionnaires. The controls were also randomly selected from the centers on the same day as the cases. Data were collected from these centers by trained interviewers based on a common guideline. A prerequisite of the study was to have an equal number of samples from each center in the case and control groups. The sample size was calculated as 800 per group with the design effect estimated at two. Given that 24 independent variables were under study, the overall sample size was increased to 1,040 per group, making for a total of 2,080 samples. During data collection, this sample size further increased due to the good cooperation of some of the provinces and in order to increase the accuracy of the findings. The data collected were then entered the Excel and analyzed by SPSS software. P values less than 0.05 were considered statistically significant.

3.1. Data Analysis

The univariate analysis examined the relationship between each independent variable and stillbirth. If P value was less than 0.25 in the analysis, the independent variable was deemed suitable for undergoing multivariate analysis, which is a type of analysis that examines the effects of several independent variables on the dependent variable simultaneously in order to control the different confound-

ing variables. The chi-square test and a binary logistic regression model were, therefore, used to describe and analyze the univariates and the multivariates. Logistic regression models help describe the relationship between a dependent binary variable and one or several continuous or discrete independent variables. The dependent variable examined in this study was "having experienced a stillbirth or not". The binary model of logistic regression was used in this study to control the variables that are likely to have confounding effects (14).

The modeling was performed using selected variables, including the parents' demographic information (mother's age, education, occupation, working on night shifts, place of residence and ethnicity), previous history of miscarriage and stillbirth, birth spacing, outcome of previous pregnancy, birth order, and menstrual cycle regularity. The variables were selected for the final model using a forward logistic regression and included the mother's education, age and disease history, a previous history of stillbirth, menstrual cycle regularity, a history of miscarriage and pregnancy spacing.

4. Results

Table 1 presents the demographic characteristics of the participants using univariate analysis. The raw analysis of the data showed that the chance of stillbirth is higher in women over 35 than in those below the age of 35. The odds ratio of stillbirth was also higher in men over 37 than in those below the age of 37; however, after that, the mothers' age was entered the model, the fathers' age was removed, which may suggest extreme linearity between the two variables. The odds ratio of stillbirth was much higher in women with low levels of education compared to women from the other education groups. The analysis of the relationship between education and stillbirth using the chi-square test led to consistent results. A remarkable finding of the mother's education is that this variable was significant in all models. The variable of occupation in both mothers and fathers had a significant relationship with stillbirth using the univariate analysis; however, this variable did not remain in any of the models. The odds ratio of stillbirth was higher in women with Kurd, Turk or Turkmen ethnicity compared to women with other ethnicities.

Table 2 presents the pre-pregnancy and pregnancy risk factors of stillbirth in women. Based on the results, the odds ratio of stillbirth was higher in women who did not use any contraceptive methods compared to those who did. The odds ratio of stillbirth was also higher in women

Table 1. Demographic Characteristics of the Cases and Controls and Univariate Analysis

Variable	Case (%)	Control (%)	OR (95% CI)	P Value
Address				
Urban	658 (46.4)	761 (53.6)	1.06 (0.92 - 1.23)	0.387
Rural	760 (47.9)	825 (52.1)		
Age of mother			2.14 (1.65 - 2.78)	0.001
Less than or equal 35	1257 (45.4)	1514 (54.6)		
Greater than 35	173 (64.1)	97 (35.9)		
Age of father			1.42 (1.16 - 1.73)	0.001
Less than or equal 37	1166 (45.6)	1390 (54.4)		
Greater than 37	259 (54.4)	217 (45.6)		
Nationality				
Fars	830 (44.9)	1019 (55.1)	1	-
Lor	93 (46.3)	108 (53.7)	1.05 (0.78 - 1.41)	0.020
Turk	257 (50.7)	250 (49.3)	1.26 (1.03 - 1.53)	0.002
Kurd	34 (68)	16 (32)	2.60 (1.43 - 4.76)	0.002
Arab	19 (54.3)	16 (45.7)	1.42 (0.74 - 2.85)	0.271
Baloch	99 (49.5)	101 (50.5)	1.20 (0.89 - 1.61)	0.214
Turkmen	74 (54.4)	62 (45.6)	1.46 (1.03 - 2.07)	0.032
Other*	15 (37.5)	25 (62.5)	0.73 (0.38 - 1.40)	0.354
Education level of a mother				
Illiterate	108 (61.4)	68 (38.6)	3.39 (2.33 - 4.94)	0.001
Elementary	395 (55.6)	315 (44.4)	2.68 (2.05 - 3.50)	0.001
Guidance	363 (51.1)	347 (48.9)	2.23 (1.71 - 2.91)	0.001
High school	475 (42.3)	648 (57.7)	1.56 (1.22 - 2.01)	0.001
Collegiate	115 (31.9)	246 (68.1)	1	Reference
Mother's history of night shift			0.51 (0.27 - 0.95)	0.035
Yes	15 (32.6)	31 (67.4)		
No	1315 (48.5)	1394 (51.5)		
Education level of father				
Illiterate	69 (57)	52 (43)	2.29 (1.51 - 3.46)	0.001
Elementary	290 (55.1)	236 (44.9)	2.12 (1.62 - 2.76)	0.001
Guidance	471 (52)	434 (48)	1.87 (1.47 - 2.38)	0.001
High school	475 (42.5)	642 (57.5)	1.27 (1.01 - 1.61)	0.040
Collegiate	150 (36.7)	259 (63.3)		Reference
Mother's occupation				
Housewife	1339 (48.3)	1433 (51.7)		Reference
Employee	65 (32.5)	135 (67.5)	0.51 (0.38 - 0.69)	0.001
Agricultural livestock	25 (56.8)	19 (43.2)	1.40 (0.77 - 2.56)	0.264
Other	18 (48.6)	19 (51.4)	1.01 (0.53 - 1.94)	0.967
Father's occupation				
Businessman	937 (48.5)	993 (51.5)		Reference
Governmental employee	178 (37.4)	298 (62.6)	0.63 (0.51 - 0.77)	0.001
Farmer	104 (49.1)	108 (50.9)	1.02 (0.76 - 1.35)	0.888
Rancher	30 (53.6)	26 (46.4)	1.22 (0.71 - 2.08)	0.459
Other	201 (52.1)	185 (47.9)	1.15 (0.92 - 1.43)	0.206

with a history of stillbirth and miscarriage compared to those with no such history (OR: 2.99 [2.12 - 4.22]). Finally, 11 of the 24 variables were entered the multivariate analysis. [Table 3](#) shows the results.

According to [Table 3](#), the results of the multivariate logistic regression showed that stillbirth was related only to seven of the 11 variables selected for entering the multivariate analysis model, which include, in the order of impor-

Table 2. Univariate analysis of maternal factors before pregnancy related to stillbirth

Variable	Case (%)	Control (%)	OR (95% CI)	P Value
The cause of cesarean				
Elective cesarean	19 (30.6)	43 (69.4)	Reference	Reference
History of cesarean	88 (31.2)	194 (68.8)	1.02 (0.56 - 1.86)	0.931
Lack of labor progress	62 (36.3)	109 (63.7)	0.28 (0.69 - 2.40)	0.427
Embryonic problems or abnormal fetal presentation	148 (67.9)	70 (32.1)	4.78 (2.59 - 8.80)	0.001
Other	51 (41.5)	72 (58.5)	1.60 (0.83 - 3.06)	0.154
Type of delivery				
Natural	1063 (48.7)	1120 (51.3)	Reference	Reference
Cesarean	380 (43.2)	500 (56.8)	0.80 (0.68 - 0.93)	0.006
Distance from a previous pregnancy				
More than 3 years	379 (41.5)	534 (58.5)	Reference	Reference
1 to 3 years	412 (48.8)	432 (51.2)	1.34 (1.11 - 1.62)	0.002
Less than a year	119 (68)	56 (32)	2.99 (2.12 - 4.22)	0.001
First pregnancy	519 (47.6)	572 (52.4)	1.27 (1.07 - 1.52)	0.007
The use of contraceptive methods				
Yes	583 (41.8)	811 (58.2)	Reference	Reference
No	862 (51.9)	799 (48.1)	1.50 (1.30 - 1.73)	0.001
Type of contraception				
Pill	242 (46.5)	278 (53.5)	Reference	
IUDs	29 (36.3)	51 (63.8)	0.65 (0.40 - 1.06)	0.08
Ampoules of injection Depo-provera	53 (43.1)	70 (56.9)	0.87 (0.58 - 1.29)	0.49
Condom	178 (39)	278 (61)	0.73 (0.57 - 0.94)	0.01
Other	80 (37.6)	133 (62.4)	0.69 (0.49 - 0.95)	0.02
Regular menstruation				
Yes	1207 (46.6)	1384 (53.4)	Reference	
No	218 (53.4)	190 (46.6)	1.31 (1.06 - 1.62)	0.010
History of stillbirth				
Yes	130 (73.4)	47 (26.6)	3.28 (2.33 - 4.62)	0.001
No	1329 (45.7)	1579 (54.3)	Reference	
History of abortion				
Yes	225 (60.5)	147 (39.5)	1.83 (1.47 - 2.28)	0.001
No	1234 (45.5)	1479 (54.5)	Reference	
Mother's background diseases				
Yes	116 (8.1)	72 (4.5)	1.86 (1.38 - 2.53)	0.001
No	1312 (91.9)	1522 (95.5)	Reference	

tance, mother's education, history of stillbirth, pregnancy spacing, history of other diseases, age, history of miscarriage and menstrual cycle irregularity.

5. Discussion

The results of the study showed that the risk of stillbirth is higher in women over 35 compared to those younger than 35, which is consistent with the results of other studies (15). Hajian-Tilaki et al. stated that this higher risk may be associated with increased maternal age, the history of stillbirth, multiparity and placental abruption, the combination of which increases the risk of stillbirth

in older women (16). Age may have no effects on the likelihood of stillbirth per se, and studies have shown that the increased risk of stillbirth in older women may be associated with their development of chronic diseases at this age (hypertension etc.) and pregnancy complications such as diabetes, gestational hypertension, multiparity, and previous history of miscarriage (17). Reddy et al. argued that although an increased maternal age is associated with an increased risk of stillbirth, maternal hypertension and diabetes are two common pregnancy complications at the age of 35 and above that are considered the confounding factors of this relationship and are responsible for the significant relationship between maternal age and stillbirth (18).

Table 3. Modeling of the Maternal Factors Before and During Pregnancy and Demographics with Stillbirths

Variable	OR (95% CI)	P Value
History of stillbirth		
Yes	2.64 (1.81 - 3.85)	0.001
No	1	
History of abortion		
Yes	1.57 (1.21 - 2.03)	0.001
No	1	
Education level of mother		
Illiterate	1	
Elementary	3.50 (2.30 - 5.33)	0.001
Guidance	2.79 (2.07 - 3.76)	0.001
High school	2.60 (1.63 - 3.51)	0.001
Collegiate	1.81 (1.37 - 2.40)	0.001
Regular menstruation		
Yes	1	0.029
No	1.29 (1.02 - 1.64)	
Age of mother		
≥ 35	1	
≤ 35	1.58 (1.17 - 2.14)	0.003
Distance from previous pregnancy		
Less than a year	2.64 (1.80 - 3.87)	0.001
One to three years	1.35 (1.09 - 1.66)	0.005
More than three years	1.72 (1.40 - 2.10)	0.001
First pregnancy	1	-
Mother's background diseases		
Yes	79.1 (52.2 - 28.1)	0.001
No	1	-

Studies also have shown that increased maternal age is an independent risk factor for stillbirth even after controlling the effect of maternal morbidities (1). They did not find a significant relationship between higher maternal age and the risk of stillbirth, which is attributed to the elimination and exclusion of congenital anomalies and they explained since a higher maternal age increases the risk of congenital anomalies, the relationship between maternal age and stillbirth remains unidentified after eliminating and excluding these factors. Owing to the present study had a large sample size, it can be argued that the increased risk of stillbirth was associated with higher maternal age rather than with maternal factors. Preconception counseling and improving prenatal care can help reduce the risk of still-

birth in older women (18).

The risk of stillbirth was higher in illiterate women than in those with university education, which is consistent with the results of other studies (19) and can be attributed to the greater knowledge in educated mothers about the outcomes of pregnancy, their greater adherence to pregnancy health and their more frequent visits to healthcare centers for receiving prenatal care.

According to the findings, the risk of stillbirth was higher in women with a history of stillbirth or miscarriage compared to those with no such history, which is consistent with the findings of other studies (20). Akolekar et al. demonstrated that the risk of stillbirth increases in women with a history of miscarriage and depends on their gestational age at pregnancy loss. In this regard, the risk of stillbirth is 1.6 times higher in women with a history of miscarriage before 16th week of pregnancy, 6.3 times higher in those with miscarriage between 16th and 23th weeks and three times higher in those with miscarriage at later weeks. Akolekar et al. also showed that the risk of stillbirth is 50% lower in women with successful previous pregnancies than in women with a history of stillbirth or miscarriage in their previous pregnancy (21). In another study, Bhattacharya et al. showed that a history of stillbirth is associated with the risk of stillbirth in the current pregnancy as well as obstetric complications such as preterm delivery, low birth weight, and pre-eclampsia in subsequent pregnancies (22).

Samueloff et al. compared women with a previous history of stillbirth and women with their first experience of stillbirth and found hypertension and diabetes as probable reasons for stillbirth (23). Pariente et al. reported significantly higher rates of cardiovascular or renal diseases in women with a history of one or more stillbirths (24). History of stillbirth is known to be a risk factor of stillbirth in pregnant women; however, the underlying causes of previous stillbirths cannot be detected and identifying these factors can, therefore, help health service providers mark high-risk women for further supervision and pregnancy care. Promoting public health and increasing awareness about the risk factors of stillbirth can also help reduce the rate of stillbirth (25).

The risk of stillbirth was also higher in women with less than three years between their pregnancies compared to others, which is also in line with the findings of other studies (26). Different studies have found that short pregnancy intervals does not allow the mother's body to compensate for the complications and pressures of the previous pregnancy, delivery, and breastfeeding and leads to negative

outcomes such as low birth weight, preterm delivery, stillbirth, miscarriage, and bleeding in late pregnancy (27). Short pregnancy interval is also associated with more pregnancy bleeding, which may be caused by the disruption in the normal reconstruction of the endometrial blood vessels after delivery followed by a new pregnancy. In this regard, the placental blood flow decreases inside the uterus; thus the risk of bleeding increases in late pregnancy. Therefore, training women to change their poor reproductive behaviors and observe optimal pregnancy intervals by improving their access to contraceptive methods are essential.

According to the present findings, some pre-pregnancy risk factors are significantly associated with stillbirth. Educational interventions to improve the awareness of women of childbearing age and performing effective health measures can help reduce the risk factors of stillbirth and the prevalence of this complication. Considering that this study was a case-control research that interviewed patients about their history of pregnancy and diseases, a recall bias may have occurred for some of the independent variables, which is a common disadvantage of retrospective studies; nonetheless, the researcher made great efforts to reduce this bias via selecting objective variables that could have a higher recall and lower recall error.

5.1. Study Limitations and Ethical Issues

This study was designed in such a way to yield minimum limitations; however, no studies can evade limitations completely. The multiplicity of the interviewers may have led to some inter-interviewer variation. To fix this variation, the researcher prepared a common guideline for the interviewers and distributed it among all the centers.

Footnotes

Conflict of Interests: It is not declared by the authors.

Ethical Consideration: No ethical considerations.

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