Ann Ig 2021; 33(3): 231-241 doi:10.7416/ai.2021.2430

Incidence and maternal-fetal risk factors of stillbirth. A population-based historical cohort and a nested case-control study

Z. Maleki[1], H. Ghaem[2], M. Seif[3], S. Foruhari[4]

Key words: Pregnancy, Cohort, Fetal death, Stillbirth, Risk factors
Parole chiave: Gravidanza, Coorte, Morte fetale, Nato morto, Fattori di rischio

Abstract

Background. *For parents, stillbirth is a tragic experience; thus, identifying the associated risk factors can be beneficial in order to prevent this event. This study aimed to investigate the incidence and risk factors associated with stillbirth.*

Methods. *In this historical cohort study, a total of 18,129 birth records were investigated. The outcome variable was having or not having stillbirth. For each case of stillbirth, three live birth infants on the same day and same hospital were selected as controls, which were matched for gestational age. The data were collected using a researcher-made checklist. Finally, data were analyzed using STATA, 13.0 with Cox proportional hazards regression model at the significance level of 0.05.*

Results. *The cumulative incidence of stillbirth was 9.48 per 1,000 live births. Based on multivariate Cox regression model, five risk factors for stillbirth were identified, including male gender, fetal diseases, gestational hypertension, gestational diabetes, and maternal hypothyroidism, (all hazard ratios > 1 and p<0.05), and - for the first time in Iran - maternal hypothyroidism, oligohydramnios, and polyhydramnios were shown as risk factors for stillbirth, which were not evaluated in any previous study.*

Conclusion. *The findings of this study suggest that some maternal and fetal risk factors can be recognized as predictors of stillbirth, which might help to detect and prevent high-risk parents at early stages in order to avoid adverse health consequences in the mother and her neonate.*

Background

According to the World Health Organization (WHO), stillbirth is defined as a baby born without signs of life with a birth weight ≥1000 g, or - if missing - born at ≥28 completed weeks gestation, or - if missing - with body length ≥35 cm (1). Despite the increasing attention toward maternal, neonatal and child health, stillbirths still remain a major public health concern, as neither counted in the Millennium Development Goals, nor in the Current Sustainable Development Goals (2). In recent years, attempts were made, using documented data to establish

[1] *Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran*
[2] *Non-Communicable Diseases Research Center, Department of Epidemiology, School of Health, Shiraz University of Medicl Sciences, Shiraz, Iran*
[3] *Department of Epidemiology, School of Health, Shiraz University of Medical Sciences, Shiraz, Iran*
[4] *Infertility Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*

standard cut-offs for pregnancy and birth weight (3). In 2015, WHO estimated 2.6 million stillbirths, with more than 7,178 deaths a day. The stillbirth rate in sub-Saharan Africa is approximately 10 times that of developed countries (29 vs. 3 per 1,000 births) (4). About 98 percent of stillbirths occur in low- and middle-income countries, especially in sub-Saharan Africa and South Asia (5-7). Stillbirth rate is 10 times higher in the developing countries than in the developed ones (3, 8). Almost 47,000 stillbirths occur every year in Tanzania (7). Generally, the rate of stillbirth in developing countries is estimated at 25.5 per 1,000 births (3). There are many maternal and fetal risk factors for stillbirth, including smoking, alcohol consumption, number of delivery ≥3, high maternal age (over 35 years), low maternal education, chronic maternal diseases, preeclampsia, multiparity, gestational diabetes, antepartum hemorrhage, premature rupture of membranes, hypertensive conditions in pregnancy, caesarean section, cephalo-pelvic disproportion, prolonged / obstructed labor, and congenital abnormalities, lack of antenatal care, poor maternal nutrition, infections during pregnancy, birth asphyxia, and intra- uterine growth restriction (9-16).

Since stillbirth might cause severe psychological problems such as stress, anxiety and depression for the involved mother and her family, this issue can lead to irreparable mental damage and high burden of costs to the family and healthcare system, affecting future pregnancies (17).

To date, no study has investigated risk factors for stillbirths, using statistical modeling through a population-based study, and most of the studies using small sample size have examined merely the incidence of stillbirths. Although, a few studies in other countries have identified the risk factors associated with stillbirth, maternal and fetal variables were not simultaneously evaluated. Therefore, to our knowledge, this is the first study with a large sample size determining the incidence of stillbirths through a population-based cohort study, by identifying risk factors for stillbirth according to maternal and fetal causes.

Methods

Study procedure

This study design was conducted through a historical cohort of pregnant women and their fetuses and a nested case-control on stillbirth-livebirth babies.

Phase 1: Historical cohort of pregnant women and their fetuses

This study reviewed a total of 18,129 medical records in five major midwifery hospitals (three tertiary and two private hospitals) in Shiraz, the capital of Fars province, Iran, using census method, between March 2016 and March 2017. The cohort included all cases of pregnant women who referred to these hospitals for delivery around the end of their pregnancy, including vaginal delivery, cesarean section, and stillbirth. It should be mentioned that all standard forms of the Ministry of Health were added to the patients' medical records, and were completed by midwives and operating room nurses.

Phase 2: Nested case-control study on stillbirth-livebirth babies

For each case of stillbirth, three controls were randomly selected from those who had not experienced stillbirth, and had given live births in the same hospital on the same day. Cases and controls differ only on the presence/absence of stillbirth respectively. In both cases and controls groups, week of gestation was acknowledged as a time-matched variable, and the required data were obtained using a researcher-made checklist.

Study variables were maternal characteristics, such as age, ABO blood

group, blood Rh factor, number of labors, number of abortion, mode of delivery, maternal disease during pregnancy (at least having one of following diseases: gestational diabetes mellitus, gestational hypertension (blood pressure≥ 140/90 mm Hg) and hypothyroidism); and fetal characteristics, including fetus gender, birth weight, fetal disease (at least having one of following diseases: Intrauterine growth restriction (IUGR), congenital anomaly, chromosomal disorder, oligohydramnios, polyhydramnios, brain disorder and severe hydrops). All female residents of Shiraz with Iranian nationality, who referred to the obstetrics units of the selected hospitals, were eligible for recruitment in this study. This study used a time-to-event method for weeks of gestation in both case and control, and Cox regression model was implemented to investigate factors associated with stillbirth. The positive of HR means that the variable is considered as a risk factor and the negative as a protective factor for risk of still birth. For modelling, the variables with $p<0.2$ were entered into the multivariate Cox regression model. All study variables were analyzed using STATA software, version 13.0. Descriptive data are presented as mean and Standard Deviation (± SD) for continuous variables and frequency (%) for categorical ones. The differences between subgroups were compared using independent-sample t-test and Chi-square test. All quantitative variables were tested for normal distribution by Kolmogorov-Smirnov test and statistical graphs (i.e. histogram and box-plot). Univariate and multivariate Cox regression analyses were applied and reported separately for both maternal and fetal variables.

Results

Maternal risk factors

The average age for mothers was 28.72 ± 5.99 years, ranging 16-45 years. Table 1 shows demographic and clinical characteristics of the participants.

In our study, the cumulative incidence of stillbirth was 9.48 per 1,000 live births (95% Confidence Interval (CI) 8-11). The incidence of stillbirth was 0.38 (95% CI 0.1-0.7), 7.72 (95% CI 6-9) and 1.37 (95% CI 0.8-2) per 1,000 live births amongst mothers under the age of 20, 20 to 35, and over 35 age, respectively.

Among maternal variables, maternal age, number of abortions, number of deliveries, blood ABO group, blood Rh Factor, maternal diseases (e.g. gestational hypertension, gestational diabetes mellitus, and hypothyroidism) were associated with stillbirth in maternal Univariate analysis (Table 2). For modelling, the variables with $p<0.2$ in univariate analysis, including maternal age, blood ABO group, gestational hypertension, maternal hypothyroidism, gestational diabetes mellitus, fetus gender, fetal diseases, fetal weight (g) and number of abortions were entered into the multivariate Cox regression model. Eventually, in modelling using multivariate Cox regression analysis, three maternal variables remained as the most important predictors of stillbirth, including pregnancy hypertension (HR=2.38; 95%CI 1.38-4.12; p-value=0.002), hypothyroidism (HR=2.24; 95%CI 1.37-3.63; p-value=0.001), and gestational diabetes mellitus (HR=1.94; 95%CI 1.17-3.24; p-value=0.010) (Table 3 and Figure 1).

Fetal risk factors

The incidence of stillbirth amongst males and females were 8.32 (95% CI 7-9) and 1.15 (95% CI 0.7-1) per 1,000 live births, respectively. Among fetal variables, male gender, birth weight and fetal diseases (i.e. IUGR, congenital anomaly, chromosomal disorder, oligohydramnios, polyhydramnios, brain disorder and severe hydrops) were associated with stillbirth in fetal univariate analysis (Table 2). Finally, results of

Table 1 - Maternal and fetal demographic/clinical characteristics

Characteristics	Case (n=172) N (%)	Control (n=516) N (%)	P value
Maternal age (year)			0.09
<20	7 (4.1)	45 (8.7)	
20-35	140 (81.4)	411 (79.7)	
>35	25(14.5)	60 (11.6)	
Gestational hypertension			<0.001
No	152 (88.4)	516 (100)	
Yes	20 (11.6)	0 (0)	
Gestational hypothyroidism			<0.001
No	147 (85.5)	515(99.8)	
Yes	25 (14.5)	1(0.2)	
Gestational Diabetes mellitus			<0.001
No	145 (84.3)	516 (100)	
Yes	27 (15.7)	0 (0)	
Type of delivery			
Cesarean	5 (3)	248 (48)	<0.001
Vaginal	167 (97)	268 (52)	
Fetus gender			<0.001
Female	21 (12.2)	240 (46.5)	
Male	151 (87.8)	276 (53.5)	
Fetal diseases			<0.001
No	102 (59.3)	516 100)	
Yes	70 (40.7)	0 (0)	
Birth weight (g)			<0.001
<1500 (or 1000-1500)	167 (97.1)	0 (0)	
1500-2490	2 (1.2)	31 (6.0)	
2500-3990	3 (1.7)	471 (91.3)	
≥4000	0 (0)	14 (2.7)	

statistical modelling with multivariate cox regression showed that two fetal variables remained as the most important predictors of stillbirth, including male gender (HR=3.45; 95%CI 2.16-5.50; p-value=0.001) and fetal diseases (IUGR, congenital anomaly, chromosomal disorder, oligohydramnios, polyhydramnios, brain disorder and severe hydrops) (HR=3.23; 95%CI 2.30-4.54; p-value=0.001) (Table 3 and Figure 1).

Discussion

In this historical cohort study conducted among 18,129 hospital records, the following results were reached: the cumulative incidence rate of stillbirth was 9.48 per 1000 live birth. In a study conducted by Tshibumbu et al., (18) in Namibia, the rate of stillbirth was reported as 12.0 per 1,000 births, and Tilahun et al., (19) the incidence of the stillbirth in hospital in few months was reported 8% or 80 per 1,000 births. However, Blencowe et al., (20) estimated the rate of stillbirth as 23 per 1,000 live births in India. Our estimates of stillbirth incidence was much lower, which can be due to ethnic, environmental, and socioeconomic differences or variations in data collection methods. Consistent with other studies in this area (21-23), our study suggests an increased risk of stillbirth for the age-group 20-35 but then a decreased risk in the age-group >35. One reason for the high cumulative incidence of stillbirths

Table 2 - Univariate analysis on the relationship between the study factors and stillbirth*

Variables	Cox regression		
	n	HR (95% CI)	P value
Maternal age (year)			
<20 (reference)	52	1	
20-35	551	1.94 (0.91-4.16)	0.086
>35	85	2.77 (1.20-6.42)	0.017
Blood Rh			
Positive(reference)	649	1	
Negative	39	1.11 (0.60-2.06)	0.722
Blood group			
AB (reference)	231	1	
A	168	3.47 (1.87-6.44)	<0.001
B	173	3.78 (2.05-6.95)	<0.001
O	116	10.79 (6.12-19.03)	<0.001
Gestational hypertension			
No (reference)	668	1	
Yes	20	9.31 (5.80-14.94)	<0.001
Maternal hypothyroidism			
No (reference)	662	1	
Yes	26	6.23 (4.06-9.54)	<0.001
Gestational Diabetes mellitus			
No (reference)	661	1	
Yes	27	7.02 (4.62-10.67)	<0.001
Fetus gender			
Female (reference)	261	1	
Male	427	4.82 (3.05-7.61)	<0.001
Fetal diseases			
No (reference)	618	1	
Yes	70	5.35 (3.94-7.27)	<0.001
Fetal weight (g)			
<1500 (reference)	167	1	
1500-2490	33	2.95 (1.25-6.96)	<0.001
2500-3990	474	1.76 (4.31-7.17)	<0.001
≥4000	14	1.25 (4.66-7.58)	<0.001
Number of abortions	688	1.49 (1.22-1.81)	<0.001
Number of labors	688	1.10 (0.94-1.29)	0.200

* For modelling, the variables with p<0.2 in univariate analysis, including Maternal age, Blood group, Gestational hypertension, maternal hypothyroidism, Gestational Diabetes mellitus, Fetus gender, fetal diseases, fetal weight (g) and number of abortions were entered into the multivariate Cox regression model.

in the age group 20-35 years may be due to the high frequency of births in this age range. Another reason for a decreased cumulative incidence of stillbirth in women over 35 years is that they are at their second and more pregnancy and are more likely to have a healthy fetus(24).

Maternal factor associated with stillbirth

Among maternal causes, gestational hypertension was identified as the first risk factor associated with increased amount of stillbirth. In addition, Neogi et al. (25), Newtonraj et al. (26), Ashish et al. (27), Liu et al. (28), Al-Kadri et al. (29), Mutihir et al

Table 3 - Statistical modelling on the relationship between the study factors and stillbirth using multiple Cox regression

Variables	Cox model		
	n	HR (95% CI)	P value
Gestational Hypertension			
No (reference)	668	1	
Yes	20	2.38 (1.38-4.12)	0.002
Gestational hypothyroidism			
No (reference)	662	1	
Yes	26	2.24 (1.37-3.63)	0.001
Gestational Diabetes mellitus			
No (reference)	661	1	
Yes	27	1.94 (1.17-3.24)	0.010
Fetus gender			
Female (reference)	261	1	
Male	427	3.45 (2.16-5.50)	0.001
Fetal disease*			
No (reference)	618	1	
Yes	70	3.23 (2.30-4.54)	0.001

*Fetal disease (i.e. IUGR, congenital anomaly, chromosomal disorder, oligohydramnios, polyhydramnios, brain disorder and severe hydrops)

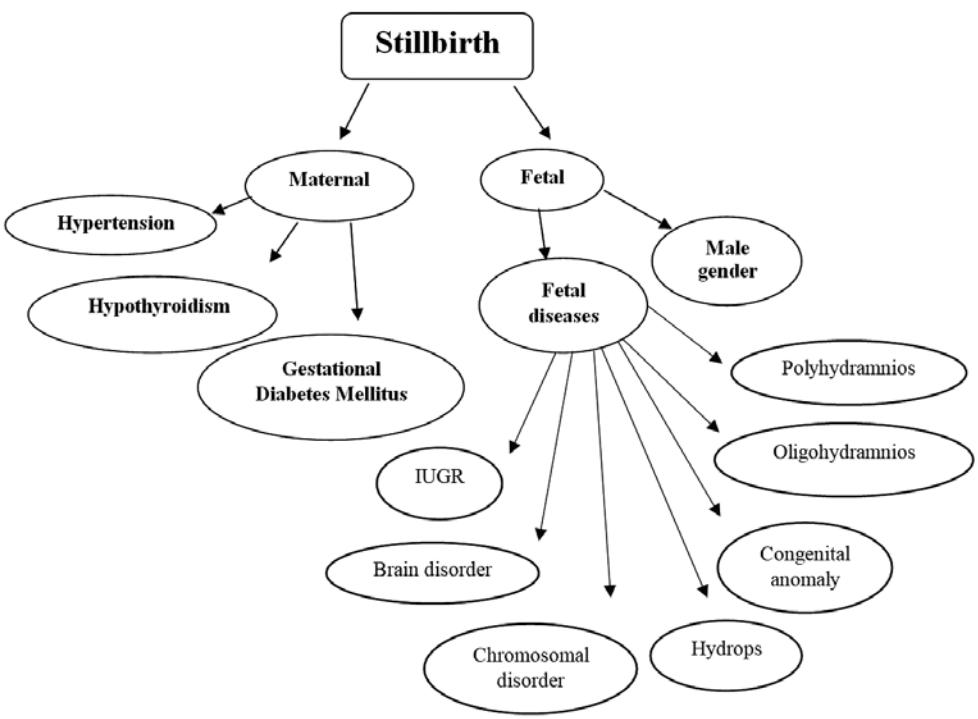

Figure 1 - The maternal and fetal risk factors of stillbirth based on final modelling

(30), concluded that gestational hypertension was one of the factors associated with stillbirth, which is in line with the results of our study. Gestational hypertension increases by twofold the risk that placenta is separated earlier, leading to fetal-growth disorders, and by threefold the risk of maternal mortality (31). The findings also showed that gestational diabetes was the other risk factor associated with stillbirth, which increased the risk by twofold. Furthermore, gestational diabetes mellitus was shown to be significantly associated with stillbirth, which is consistent with the systematic review of Liu et al. (28), indicating that gestational diabetes mellitus increased the risk of stillbirth by 2 to 5 folds. This was also supported by the results of Siddiqui et al. (32), Casson et al. (33), Dunne et al. (34), Dunne et al. (35). Birth weight greater than 4,000g is shown to be associated with the increased stillbirth in diabetic mothers (36).

There is evidence that fetus of diabetic mothers, classified as large for gestational age, is at greater risk of stillbirth (37). Even with a strong efficient patient monitoring system, women with gestational diabetes mellitus are still at high risk of stillbirth (38). In fact, certain increase in blood glucose level or a sudden onset of diabetes mellitus in the third trimester of pregnancy might lead to fetal death (39). Pregnant women with hypothyroidism were twice more likely to have stillbirth than healthy pregnant women. In addition, it was concluded that hypothyroidism could lead to stillbirth, which was consistent with the results of Liu et al., and other previous studies (28, 40-42). This is justifiable, since endocrine disorders (thyroid dysfunction) occur mainly in women, and its prevalence amongst women in Shiraz, is high (43). Leung et al. (44), concluded that maternal hypothyroidism during pregnancy leads to placenta abruption, prematurity and low birth weight, intrauterine growth restriction, congenital malformations and stillbirth. In addition, thyroid disease is very common in Iran, especially among women, and many women of childbearing age who have hypothyroidism are unaware of their illness (45). Chen et al. (46) proposed that hypothyroidism leads to IUGR, hypertension and premature rupture of membranes.

Fetal factors associated with stillbirth

Amongst fetal causes, male gender increased the risk of still birth by more than threefold. Fetal disease (i.e. IUGR, congenital anomaly, chromosomal disorder, oligohydramnios, polyhydramnios, brain disorder and severe hydrops) was identified as the other main factor associated with stillbirth, which increased the risk by threefold. For the first time in Iran, maternal hypothyroidism, oligohydramnios and polyhydramnios were shown as a risk factors for stillbirth, which were not evaluated in any previous study.

Rate of stillbirth amongst male gender is 3 times higher than females, which is supported by Mutihir et al. (30). This can be due to higher susceptibility of the male gender in the embryonic period, as well as higher rate of male birth (47-52). As a new achievement, according to the findings of this study, fetal diseases (IUGR, congenital anomaly, chromosomal disorder, oligohydramnios, polyhydramnios, brain disorder and severe hydrops) were associated with increased risk of stillbirth by threefold, which was consistent with results of Newtonraj et al. (26), Siddiqui et al. (32), Liu et al. (40), and Patel et al. (53). Importantly, in the present study, univariate analysis without considering the confounding effect of some covariates such as maternal age, mother's blood group, number of abortions and fetal weight were shown to be associated with stillbirth. However, after taking into account the confounding effect, these variables did not remain as risk factors. Therefore, interpretation of the results

without considering the confounding effect would be misleading.

Conclusions

For the first time, in Iran, the cumulative incidence rate of stillbirth was revealed to be 9.48 per 1,000 live births in this population-based historical cohort study. This study indicates that the factors associated with stillbirth include fetus gender, gestational hypertension, gestational hypothyroidism, gestational diabetes mellitus and fetal diseases (IUGR, congenital anomaly, chromosomal disorder, oligohydramnios, polyhydramnios, brain disorder and severe hydrops). Importantly, the findings of our study suggest that maternal hypothyroidism, oligohydramnios and polyhydramnios were risk factors for stillbirth, which were not evaluated in any previous study. Also, our study confirmed that without considering the confounding effect through statistical modelling, the interpretation of the result would be ambiguous.

Strengths and limitations

This study benefitted from several strengths. The population-based design and large sample size of the study provided generalizability as well as adequate power to detect a reduction in composite maternal and fetal outcomes. Another strength of the study was its cost-effectiveness from an economic point of view. One other strong point of the study was that the two groups were matched with respect to gestational age. However, the study limitations included non-registration of the parents' smoking status, mother's education level and socio-demographic variables, therefore these variables could not be examined.

Acknowledgments
This article was a part of Zahra Maleki's M.Sc. thesis approved and financially supported by the Research Vice-chancellor of Shiraz University of Medical Sciences (grant No. 97-01-04-18095). This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1397.912). Hereby, the authors would like to express their gratitude to all staff of the Medical Records Department of Obstetrics and Gynecology wards of Shiraz hospitals for their cooperation. Thanks also go to Ms. A. Keivanshekouh at the Research Improvement Center of Shiraz University of Medical Sciences for improving the quality of English in the manuscript.

Financial support and sponsorship
This study was financially supported by the Shiraz University of Medical Sciences.

Conflicts of interest
The authors declare no conflict of interests regarding the publication of this article.

Availability of data records and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations
WHO: world health organization
IUGR: Intrauterine growth restriction
HR: Hazard Ratio
SD: Standard Deviation
CI: confidence interval

Riassunto

Incidenza e fattori di rischio materno-fetali di natimortalità. Uno studio su coorte storica di popolazione ed un nested case-control study

Premessa. Per i genitori, un nato morto rappresenta un'esperienza traumatizzante. Pertanto, riuscire ad identificare i fattori di rischio associati alla natimortalità rappresenta la premessa per poter formulare piani di prevenzione. Lo studio qui descritto aveva lo scopo di studiare l'incidenza del fenomeno, nonché i fattori di rischio adesso associati.

Metodi. In questo studio di coorte storica sono state prese in carico 18.129 cartelle di nascita, e la variabile considerata è stata la natimortalità. Per ogni caso di natimortalità sono stati selezionati tre controlli, appresentati da altrettanti nati vivi nello stesso giorno e nello stesso ospedale, appaiati per età gestazionale. I dati sono stati raccolti con una check-list preparata dai ricercatori stessi. I dati raccolti sono stati analizzati usando STATA versione 13.9, con il modello di rischio proporzionale di Cox ed un livello di significatività di 0,05.

Risultati. L'incidenza cumulativa di nati morti è stata di 9,48/1.000 nati vivi. Sulla base del modello di regressione multivariata di Cox sono stati identificati

cinque fattori di rischio di natimortalità, e cioè: genere maschile, presenza di malattie fetali, ipertensione in gravidanza, diabete in gravidanza, ed ipotiroidismo (tutti i rapporti con valore >1 e p<0.05) e, per la prima volta, l'ipotiroidismo materno. Anche oligo-idramnio e poli-idramnio sono stati documentati come fattori di rischio per la natimortalità, mentre non erano mai stati segnalati in precedenti studi.

Conclusioni. Le evidenze emerse da questo studio suggeriscono che alcuni fattori di rischio, sia materni che fetali, rappresentano fattori di rischio di natimortalità, e questa conoscenza può rappresentare la base per la prevenzione, permettendo di identificando in fase precoce i genitori a più alto rischio, e di tentare così di evitare conseguenze sanitarie negative per madre e figlio.

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Corresponding author: Haleh Ghaem, Non-Communicable Diseases Research Center, Department of Epidemiology, School of Health, Shiraz University of Medical Sciences, School of Health, Al-zahra Bolvar, Shiraz, Iran. Postal code 14336-71348.
e-mail: hale.ghaem.sums@gmail.com
e-mail: ghaemh@sums.ac.ir