



Analysis of High-Risk Factors of Stillbirth Among Pregnant Women in China

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ABSTRACT

The objective of this study was to explore the high-risk factors of stillbirth after the two-child policy was fully opened. 327 cases of stillbirth were collected in the Obstetrics and Gynecology Hospital of Zhejiang University from January 2015 to December 2020. All cases were analyzed retrospectively, including general profile, high-risk factors of stillbirth in different years and different gestational periods. The incidence of stillbirth was 2.75%. The peak period of stillbirth during pregnancy was 28~28+6, 30~30+6, and 31~31+6 weeks, respectively. It remained at a low level after 38 weeks of pregnancy. The top 5 high-risk factors leading to stillbirth were umbilical cord factor, unexplained causes, maternal factor, fetal factor and placental factor. In 2015, unexplained causes, maternal factor and umbilical cord factor were the top three high-risk factors leading to stillbirth. Since 2016, umbilical cord factor, maternal factor and unknown cause have become the top three high-risk factors. Of all 327 cases, early stillbirth (28~36+6 weeks of gestation) accounted for 81.7%, with umbilical cord factor, maternal factor and unexplained cause as the top three high-risk factors. Late stillbirth (pregnancy ≥ 37 weeks) accounted for 18.3%, of which umbilical cord factor, unexplained cause and maternal factor were the top three high-risk factors. The findings of this study emphasize on managing the complications in maternal pregnancy, strengthening prenatal fetal monitoring and terminating pregnancy timely, which may help to reduce the incidence of stillbirth.

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Authors' Contribution

XW and HT participated in conceiving the design of the study and collecting and reviewing the data and coordination of project. HD, QX and XB participated in doing literature review, collecting the data and analysis and in preparing the manuscript. JF and XB helped in critical revision and finalizing the manuscript. All authors read, revised, and approved the final manuscript.

Key words

Stillbirth, Risk factors, Pregnancy complications, Torsion of cord, Fetal monitoring

INTRODUCTION

Stillbirth refers to the absence of signs of life at birth, the cessation of breathing, heartbeat and umbilical blood flow, and spontaneous muscle contraction (Nijkamp *et al.*, 2022; Da Silva *et al.*, 2016). The diagnostic criteria for the birth weight and gestational age of stillbirth have not

been unified worldwide (Dudley *et al.*, 2010). According to the definition of WHO, intrauterine fetal death is the death of the fetus before birth, regardless of gestational age. This issue is one of the midwifery problems that can be prevented with prenatal care in many cases. Otherwise, repeating this problem causes mothers to suffer physical and mental complications. WHO also defines stillbirth as a newborn with no signs of life at 28 weeks of gestation. The gestational age of stillbirth in China is 28 weeks. With the improvement of obstetric and neonatal asphyxia resuscitation technology, the incidence of stillbirth and neonatal death has decreased significantly (Feresu *et al.*, 2005; Watson, 2020). This paper retrospectively analyzed the clinical data of 327 cases of stillbirth in the Obstetrics and Gynecology Hospital Affiliated to the Medical College of Zhejiang University since 2015, and discussed

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the high-risk factors of stillbirth, with the hope to provide some case-based medical evidence for the prevention of stillbirth and reduce the incidence of stillbirth.

MATERIALS AND METHODS

Data source

From January 2015 to December 2020, the total number of hospitalized deliveries in the Obstetrics and Gynecology Hospital Affiliated to the Medical College of Zhejiang University was recorded as 11,8785, including 327 stillbirths. Women were eligible to join the study if they met the following inclusion criteria: clear diagnosis of stillbirth and complete clinical data. Women with missed abortion before 28 weeks of gestation, late spontaneous abortion, cessation of embryo development, selective induction of labor due to fetal malformation or social factors during pregnancy ≥ 28 weeks, and incomplete clinical data were excluded from the present study.

Methods

Analysis indicators: The clinical data of stillbirth were retrospectively analyzed, and some relevant information of medical history was registered, including (1) General information: the delivery age of the pregnant woman, the age of the spouse, the gestational week of delivery, the number of pregnancies, the sex of the fetus, the educational level, the history of smoking or drinking, the history of toxic exposure during pregnancy, the history of adverse pregnancy or childbirth, and fetal movement. (2) Maternal complications. (3) Fetal abnormalities: structural abnormalities and chromosomal abnormalities. (4) Umbilical cord abnormalities. (5) Placenta condition. (6) Amniotic fluid volume. (7) Autopsy of stillbirth and pathological examination of placenta.

Diagnostic criteria of stillbirth: The fetus dies in the uterus after 28 weeks of pregnancy.

High-risk factors of stillbirth: The high-risk factors of stillbirth mainly include: maternal factors, fetal factors, placental factors, umbilical cord factors and unknown causes. These factors can act alone or in combination with multiple factors.

Maternal factors refer to the maternal complications leading to fetal hypoxia and stillbirth during pregnancy, including the single high-risk factors such as pregnancy-induced hypertension, pregnancy-induced intrahepatic cholestasis, pregnancy-associated infection, diabetes, liver disease, kidney disease, heart disease, thyroid gland disease, blood system disease, reproductive organ malformation and immune diseases.

Fetal factors refer to those factors triggering stillbirth caused by fetal abnormal development, including fetal

chromosomal abnormalities, structural abnormalities and other single high-risk factors.

Placental factors refer to those accounting for stillbirths caused by placental insufficiency, including placental abruption, placenta previa, twin transfusion syndrome and other single high-risk factors.

Umbilical cord factors refer to those responsible for the deaths caused by enough damage to the blood flow of the umbilical cord, including single high-risk factors such as umbilical cord entanglement, torsion, prolapse, knot, etc., which interrupt the blood exchange between the fetus and mother, and thus result in fetal hypoxia death.

Unknown cause refers to the factors of stillbirth which cannot be attributed to an identifiable fetal, placenta, umbilical cord, maternal or obstetric cause.

Statistical analysis

SPSS software was used for statistical analysis of data. Since our quantitative data did not meet the normal analysis, *m* (*q*) was used for description. The difference between the two groups was compared by two independent sample rank sum test. The test statistic *Z*, $P \leq 0.05$, indicated the statistically significant difference. The difference of multiple groups was compared with the rank sum test. The test statistic *H*, $P \leq 0.05$ suggested that the difference was statistically significant. Qualitative data were described in frequency and percentage. Chi square test was used to compare the differences and test the statistics. Multivariate logistic regression analysis was used to analyze the factors affecting the cause of death. The data were statistically significant when $P \leq 0.05$.

RESULTS

During the study, the overall incidence of stillbirth in our hospital was 2.75%, of which the lowest incidence year was 2019 (1.51%), and the highest year was 2015 (4.20%). The relevant data were presented in Table I. The delivery age of the pregnant woman was 30 ± 4.6 years old, the age of the husband was 32 ± 5.2 years old, and the gestational week was 32.7 ± 3.5 weeks. The average number of pregnancies was 2.2 ± 1.3 , and the average number of births was 0.8 ± 0.7 . Among 327 pregnant women, the proportion of those who received standardized prenatal examination was 98.2%. The lowest weeks of stillbirth occurrence were 41~41+6 weeks (0.3%), 40~40+6 weeks (3.1%) and 38~38+6 weeks, respectively. The highest number of stillbirth in the gestational weeks were 28~28+6 weeks ($n=45$, 13.8%), 30~30+6 weeks ($n=44$, 13.5%) and 31~31+6 weeks ($n=30$, 9.2%), respectively. The number of stillbirth remained at a low level after 38 weeks of pregnancy.

Table I. Analysis of stillbirth rate and general conditions in different years.

Year	2015	2016	2017	2018	2019	2020	Total
Total delivery	15228	21604	20552	19708	21836	19857	118785
Stillbirth (n, %)	63(0.41)	58(0.27)	60(0.29)	67(0.34)	33(0.15)	46(0.23)	327(0.28)
Age ($\bar{x} \pm s$)	30.6 $\pm$ 4.8	29.3 $\pm$ 4.4	31.6 $\pm$ 4.5	31.1 $\pm$ 4.6	28.7 $\pm$ 4.7	29.7 $\pm$ 3.8	30.0 $\pm$ 4.6
Weeks ($\bar{x} \pm s$)	31.9 $\pm$ 3.4	32.7 $\pm$ 3.7	33.1 $\pm$ 3.5	33.4 $\pm$ 3.4	32.0 $\pm$ 5.4	31.1 $\pm$ 3.8	32.7 $\pm$ 3.5
Prenatal examination (n, %)	62(98.4)	56(96.6)	60(100)	65(97.0)	33(100)	45(97.8)	321(98.2)
History of adverse pregnancy (n, %)	14(22.6)	12(21.4)	12(20.0)	14(20.9)	2(6.10)	6(13.3)	60(18.3)

Table II. Composition ratio and sequence of high risk factors for stillbirth.

Category	Cases	Percentage	Order
Umbilical factor	103	31.5	-
Cord torsion	35	10.7	1
Cord wrapped around neck	28	8.6	3
Cord congestion	10	3.1	5
True knot	8	2.4	-
Cord presentation vascular preposition	5	1.5	-
Single umbilical artery	4	1.21	-
Cord edema	3	0.9	-
Cord prolapse	3	0.9	-
Vein thrombosis	2	0.6	-
Cord winding	2	0.6	-
Cord rupture	2	0.6	-
Cord cyst	2	0.6	-
Short cord	1	0.3	-
Unknown reason	72	22	-
Maternal factor	70	21.4	-
PIH	31	10.4	2
Complicated with infection	10	3.1	4
Gestational diabetes	8	2.4	-
Autoimmune diseases	6	1.8	-
Liver disease	6	1.8	-
Maternal diseases (others)	9	2.8	-
Fetal factor	46	14.1	-
Structural abnormality	9	3.1	-
Fetal edema	8	2.4	-
Chromosomal abnormalities	5	1.5	-
Growth restriction	5	1.5	-
Placental factor	35	10.7	-
Total	327	100.0	-

The order of high-risk factors for stillbirth was listed as follows: umbilical cord factor (31.5%), unknown cause (22.0%), maternal factor (21.4%), fetal factor (14.4%), and placental factor (10.7%). The top 5 single high-risk factors for stillbirth were recognized as umbilical cord torsion (10.7%), pregnancy induced hypertension (PIH) (10.7%), umbilical cord around the neck (8.6%), umbilical cord congestion (3.1%), and fetal structural abnormalities (3.1%). The data, correspondingly, were listed in [Table II](#).

In 2015, unknown causes, maternal factors and umbilical cord factors were the top three high-risk factors leading to stillbirth. Since 2016, umbilical cord factor has been the main high-risk factor causing stillbirth. From 2015 to 2020, the proportion of unexplained high-risk factors in stillbirth was 22/63 (34.9%), 15/58 (25.9%), 9/60 (15%), 7/67 (10.4%), 8/33 (24.2%), 11/46 (23.9%), respectively. The proportion of umbilical cord factors of stillbirth from 2015 to 2020 was 10/63 (15.9%), 16/58 (27.6%), 26/60 (43.3%), 21/67 (31.3%), 15/33 (45.5%), 14/46 (30.4%). The difference in umbilical cord factors and unexplained factors from 2015 to 2020 was statistically significant ($P \leq 0.05$), while there was no significant difference in fetal factors, placental factors and maternal factors in different years. The relevant data were provided in [Table III](#).

Table III. Top high risk factors of stillbirth in different years (cases, %).

Year	Unknown factor	Maternal factor	Cord factor
2015 (n=63)	22(34.9%)	18(28.6%)	10(15.9%)
2016 (n=58)	16(29.3%)	15(24.1%)	11(19.0%)
2017 (n=60)	26(43.3%)	11(18.3%)	9(15.0%)
2018 (n=67)	21(31.3%)	17(25.4%)	12(17.9%)
2019 (n=33)	15(45.5%)	8(24.2%)	7(21.2%)
2020 (n=46)	14(30.4%)	11(23.9%)	8(17.4%)

DISCUSSION

In this study, the incidence of stillbirth in our hospital in the past six years is 0.275%, which is far lower than the

incidence of stillbirth in the world and the United States (MacDorman and Gregory, 2015). Umbilical cord torsion, PIH, umbilical cord around the neck and body, pregnancy-associated infection and umbilical cord congestion are the top five single high-risk factors for stillbirth. Therefore, attention should be paid to the management of abnormal fetal movement during pregnancy, and electronic fetal monitoring should be carried out for those with abnormal fetal movement timely. Pregnant women should be alert to sudden changes in fetal movement, especially when they are not hospitalized after full-term. Also, they should focus on finding the abnormalities as soon as possible, terminating pregnancy timely and prevent the maternal pregnancy complications, especially PIH and maternal infection. Collectively, improving the prenatal screening and diagnostic technology is conducive to reducing the incidence of stillbirth.

The incidence of stillbirth decreased from 35 % in 1980 to 15 % in 2015 globally. The reduced incidence of stillbirth is associated with the improved antenatal care, skilled birth attendants and attention to the known risk of stillbirth (GBD, 2015). In this study, the incidence of stillbirth is 0.275% (0.156% - 0.419), which is far lower than the global average incidence of stillbirth, and far lower than the United States (where the average incidence was 5.95 % in 2013 (MacDorman and Gregory, 2015)). The occurrence of stillbirth is related to the demographic characteristics, delivery age of pregnant women, social status, education level, income, the number of prenatal examinations, etc. Nearly 98% of stillbirths occur in low or middle-income countries (Lawn *et al.*, 2011). In this study, 65.2% of pregnant women have college degree or above, and the standardized prenatal examination rate is as high as 98.1%, both of which may be the reasons for the low incidence of stillbirth.

The high-risk factors of fetal birth are different among the developing and developed countries and between the early and late pregnancy. In developing countries, obstructive and prolonged delivery, preeclampsia and maternal infection are common causes of stillbirth. In developed countries, however, fetal congenital structural or chromosomal abnormalities, placental abnormalities with fetal growth restriction and maternal complications are recognized as the common causes (McClure *et al.*, 2006). In this study, umbilical cord factors are high-risk factors leading to fetal stillbirth, and the most common factors are cord torsion and nuchal cord encirclement, which accounts for 61.2% of all umbilical cord factors. Meanwhile, the unknown factors and maternal factors are the second and third high-risk factors for fetal stillbirth. The main maternal factors are PIH and maternal infection, accounting for 62.9% of all maternal factors.

Prevention of stillbirth

Strengthen prenatal fetal monitoring: some techniques, including ultrasound monitoring, non-stress test (NST) and fetal movement count, should be taken into account. According to ACOG guidelines on the treatment of stillbirth, it is recommended to start prenatal fetal monitoring (such as NST and ultrasound monitoring) before 1-2 weeks of the last stillbirth week of gestation or 32-34 weeks of gestation (Smith and Fretts, 2007). Any complaints of reduced fetal movement can increase the risk of poor prognosis, including stillbirth, and nearly half of stillbirth is accompanied with reduced fetal movement (Holm *et al.*, 2009). The results of this study also showed that 23% of pregnant women had obvious fetal movement abnormalities from the last week to half day before fetal death. After 37 weeks, the number of stillbirths with substantial umbilical cord pathological results due to umbilical cord torsion and umbilical cord around neck and body was significantly increased. Fetal movement assessment is the oldest and most commonly used method to evaluate fetal status, and is the only prenatal fetal monitoring method recommended to all pregnant women. Normal fetal movement is a specific hint of good fetal status. However, reduced fetal movement means perinatal complications, especially fetal growth restriction, suggesting that pregnant women should take further evaluation. At present, it is believed that fetal movement counting can indeed improve perinatal outcomes compared with non-counting, and the mother's obvious perception of fetal movement reduction is the most important definition of fetal movement reduction (Saastad *et al.*, 2011). Therefore, it is necessary to emphasize the significance of strictly counting the fetal movements of pregnant women in the third trimester and strengthen the awareness of prevention. For women with high-risk factors of stillbirth, such as those having previous stillbirth history, oligohydramnios, PIH during pregnancy, pregnancy complicated with infection, and abnormal fetal structure, it is recommended to start NST monitoring or biophysical scoring once or twice a week from the 32nd week of pregnancy.

Pay attention to the treatment of maternal complications during pregnancy: clinicians should pay attention to the management of maternal complications, especially maternal hypertensive diseases during pregnancy, preeclampsia, thrombophilia and immune related diseases to reduce the early stillbirth. According to the data of ACOG pre-pregnancy health care working group (American College of Obstetricians and Gynecologists, 2005), among the women aging 18-44, 80% have dental or other oral diseases, 50% are overweight or obese, 9% have diabetes, 6% have asthma, 3% have heart disease,

3% have hypertension and 1% have thyroid disease. The results of this study showed that umbilical cord torsion and PIH are the top two risk factors for stillbirth, and nearly 1/4 of stillbirth may be related to these two factors. Accordingly, the following techniques are expected after the disease is cured or controlled: active pre-pregnancy examination, full evaluation of maternal complications (such as hypertension, diabetes, thyroid disease, heart disease and autoimmune disease), control on infection, etc., and pregnancy planning.

Timely termination of pregnancy: Smith found that during the gestation, the incidence of stillbirth was 1/2000 at 37 weeks, 1/500 at 42 weeks and 1/200 at 43 weeks (Smith, 2001). In this study, the highest period of peak stillbirth caused by placental or maternal factors was before 37 weeks, while umbilical cord factors tend to occur after term pregnancy. Combining the results of Smith and our study, in order to reduce the incidence of stillbirth, the following induction strategies are proposed.

CONCLUSION

For those women with gestational hypertension, twin blood transfusion syndrome, placenta previa, placental exfoliation, placental dysfunction, oligohydramnios, previous history of stillbirth and other diseases, we recommended to terminate the pregnancy before 37 weeks of gestation, although the fetus can survive. For those full-term pregnant women without having high-risk factors but with umbilical cord-caused adverse outcome through the auxiliary examination, we suggested that they should terminate the pregnancy as soon as possible.

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IRB approval

This study was approved by the Women's Hospital, School of Medicine, Zhejiang University.

Ethical approval

This study approved by the Ethics Committee

of Women's Hospital, School of Medicine, Zhejiang University (Approval number: IRB-20220354-R).

Statement of conflict of interest

The authors have declared no conflict of interest.

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