CEOG Clinical and Experimental Obstetrics & Gynecology

Clinical characteristics and etiological analysis of late fetal death

Jing-lan Liu*, Yan Chen*, Yu-na Guo

The International Peace Maternity & Child Health Hospital of The China Welfare Institute, Shanghai (China)

Summary

With the continuous improvement of obstetric quality, the death of the fetus caused by serious pregnancy complications showed a downward trend. However, the etiological analysis of late fetal death is still an urgent health problem and early detection is required to reduce the risk of stillbirth. This study aimed to investigate the clinical and pathological features of late fetal death, and to propose the intervention measures to reduce the incidence of perinatal mortality. This was a retrospective analysis with 131 cases of fetal death of more than 28 gestation weeks from February 2009 to December 2015 in International Peace Maternity and Child-health Hospital. The related factors of maternal and umbilical cord were analyzed by STATA software. Among the 131 cases of dead fetuses in the late stage, 71 (54.2%) cases died of umbilical cord factor. Maternal age of late fetal death usually occurred from 25~35 years (83.97%). History of hysteromyoma, syphilis, thyroid disease, diabetes or uterine abnormalities of pregnant women are risk factors contributed to fetal death. Most pregnant women had regular prenatal examination 107 (89.9%), among which the number of stillbirths with ultrasound screening abnormalities was 69 (58.0%), 47 (39.5%) cases with D-Dimer abnormal of blood coagulation function, and 32 (26.9%) cases with positive bacterial culture results of fetal death. There were no statistically significant differences in fetal death rate between fasting blood glucose, platelet counts, ultrasound of fetal biparietal diameter, and pregnancy age, with or without abortion history (all $p > 0.05$). Umbilical cord torsion, edema, necrosis, and funisitis were the most common factors associated with late fetal death. In conclusion, perinatal healthcare management and monitoring should be strengthened, and the umbilical cord length, diameter, spiral coil index, blood flow, with or without torsion, and other conditions should be classified as routine examination of fetal structural screening in the second trimester ultrasound.

Key words: Late fetal death; Pathological characteristics; Umbilical cord lesions; Maternal.

Introduction

In recent years, although with the continuous improvement of perinatal medicine and obstetric quality, perinatal mortality showed a downward trend and the death of the fetus decreased slightly, which mostly contributed to the perinatal mortality in China [1]. Late fetal death is known to be associated with a number of maternal diseases as serious pregnancy complications. However, umbilical cord is a major cause of fetal death that is difficult to prevent and timely detect [2].

Umbilical cord is a remarkable organ that carries out hundreds of vital functions for fetuses, but it is vulnerable to different types of congenital and acquired anomalies, such as malformations, lesions and infections, which could influence the health of fetus. When the damage of umbilical vein or arterial blood flow reaches a certain level, fetal injury or death occurs [3, 4].

The purpose of the present study was to investigate the risk factors related to clinical and pathological features of late fetal death, and to propose the intervention measures to reduce the incidence of intrauterine fetal death, while ensuring the health and safety of mother and fetus.

Materials and Methods

A retrospective investigation was conducted via collecting a large number of fetal death cases from February 2009 to December 2015 in International Peace Maternity and Child-health Hospital. Diagnostic criterion takes reference from the 7th edition of Obstetrics and Gynecology [5]. Fetuses due to therapeutic and non-plan-birth induced labor were excluded.

Among the 131 cases of dead fetuses of more than 28 gestation weeks from February 2009 to December 2015, 71 cases of intrauterine fetal death caused by umbilical cord factor occurred in 54.2% of the fetal death. Maternal age of stillbirth that was caused by umbilical cord factors were 22~40 years, mean age was 30.56 ± 3.81 years. Fetal death of umbilical cord abnormalities usually occurred during 28~41 weeks, the percentage of stillbirth during 28~33 weeks was 58.7%, at 34~36 weeks it was 20.6%, and at 37~41 weeks was also 20.6%. Most pregnant women with fetal deaths were primiparas (79.4%), number of singleton pregnancy was 119 (90.8%) cases, and twins were 12 (9.2%) cases.

All of the fetal deaths in this study received regular prenatal examination except one case; 46 (73%) cases underwent Down's syndrome prenatal screening and 38 (60.3%) cases received oral glucose tolerance test (OGTT).

The related factors of late fetal death and umbilical cord were analyzed using STATA 12. Continuous descriptive variables were analyzed by analysis of variance (ANOVA), and categorical descriptive variables by the chi-square test. Significant levels were

*Contributed equally.

Revised manuscript accepted for publication March 28, 2017

Table 1. — *Demographic and physiologic characteristics of pregnant women.*

Risk factors		n	%
Number of fetuses	Singleton	119	90.84%
	Twins	12	9.16%
Method of pregnancy	Conceived naturally	122	93.13%
	Assisted reproductive technology	9	6.87%
Age (years)	< 25	10	7.63%
	25-35	110	83.97%
	> 35	10	7.63%
Pregnancy history	Full-term	22	16.79%
	Premature birth	2	1.53%
	Abortion	42	32.06%
History of disease	Hysteromyoma	5	3.82%
	History of syphilis	2	1.53%
	Thyroid disease	2	1.53%
	Diabetes	2	1.53%
	Uterine abnormalities	2	1.53%

reported at $p < 0.05$.

Results

The demographic and physiologic characteristics of pregnant women are presented in Table 1. Of the 131 intrauterine fetal death, the fetal death rate of singleton pregnancy was significantly higher ($p < 0.05$) than twins. Natural pregnant was the most common factor associated with late fetal death and occurred in 93.13% (122/131) of the fetal deaths. The mother age of late fetal death usually occurred during 25~35 years (83.97%). History of hysteromyoma, syphilis, thyroid disease, diabetes or uterine abnormalities of pregnant women were also risk factors contributed to fetal death.

As shown in Table 2, 113 natural singleton pregnant of fetal deaths (95.8%) combined with maternal factors. Most pregnant women had regular prenatal examination 107 (89.9%), among which the number of stillbirths with ultrasound screening abnormalities was 69 (58.0%), 47 (39.5%) cases with D-Dimer abnormal of blood coagulation function, and 32 (26.9%) cases with positive bacterial culture results of fetal death. However, there was a large number of pregnant women did not have the OGTT test (51.3%), fetal echocardiography (85.7%), and chromosomes of umbilical cord blood (94.1%).

Correlations between clinico-pathological data of singleton pregnant women and pregnant age, and with or without abortion history in late fetal death are shown in Tables 3 and 4. As demonstrated, there were no statistically significant differences in fetal death rates between fasting blood glucose, platelet counts, ultrasound of fetal biparietal diameter, and pregnant age, with or without abortion history (all $p > 0.05$).

In this study, there were 32 (26.9%) singleton pregnancies with fetal deaths combined with placental lesions, among which five (15.6%) cases had placental infarction, three cases were velamentous, two cases were placental abruption, battledore placenta eight cases, and immature placenta six cases. In the development of villous maturation, six cases were mature, 12 cases were immature, and 25 cases had retarded villous maturation.

Of the 131 intrauterine fetal deaths, umbilical cord torsion, edema, necrosis, and funisitis were the most common factors associated with late fetal death. As shown in Tables 5 and 6, there were no statistically significant differences in fetal death rates between umbilical cord lesions and pregnancy age, with or without abortion history (all $p > 0.05$).

The etiology of multiple fetal stillbirth mainly included placental fusion (8/12), umbilical cord abnormal attachment (6/12), umbilical cord torsion or edema (1/12), and retarded villous maturation (7/12).

Among the late fetal deaths of singleton pregnancies, nine cases had thoracic diseases (chest hemorrhage one case, capillary pathological changes in one, and pleural effusion two cases). Three cases had pericardial effusion, two agenesis of gallbladder, 12 cases with pulmonary manifestations (pulmonary hemorrhage two cases, pneumonia in one, alveolar expansion in one, lung hypoplasia in two, amniotic fluid inhalation in five, and pulmonary vasodilation one case) were observed. There were also one case of hepatic ischemic lesions and two cases of cerebral ischemia (data were not shown).

In this study, a total of 83 cases had a bacterial culture. Fifty-one cases were negative and 36 cases had bacterial infection. Infectious causes included E.coli, candida albicans, staphylococcus epidermidis, enterococcus faecalis, ureaplasma urealyticum, mycoplasma hominis, coagulase negative staphylococcus, streptococcus bovis, E. faecium, and streptococcus agalactiae (data were not shown).

Table 2. — *Clinicopathologic analysis of singleton pregnancy in late fetal death.*

Risk factors		n	%
Method of pregnancy	Conceived naturally	113	95.8
	Assisted reproductive technology	5	4.2
Age (years)	< 35	105	88.2
	> 35	13	11.8
Pregnancy history	Full-term	21	17.6
	Premature birth	39	32.8
	Abortion	2	1.7
History of disease	Thyroid disease	4	3.4
	Uterine abnormalities	7	5.9
	Ovarian diseases	1	0.8
	Others	4	3.4
Prenatal examination	Never or first time	12	10.1
	Regular	107	89.9
Blood type	A	30	25.2
	B	15	12.6
	AB	30	25.2
	O	41	34.5
	Unknown	3	2.5
OGTT test	Negative	50	42
	Positive	8	6.7
	Unknown	61	51.3
Ultrasound screening	Normal	37	31.1
	Abnormal	69	58
	Unknown	13	10.9
Fetal echocardiography	Abnormal	8	7.7
	Normal	9	7.6
	Unknown	102	85.7
Chromosomes of umbilical cord blood	Abnormal	1	0.8
	Normal	6	5.1
	Unknown	112	94.1
Blood biochemical index	Abnormal	15	12.6
	Normal	99	83.2
	Unknown	5	4.2
D-Dimer	Negative	71	60
	Positive	47	39.5
	Unknown	1	0.5
FDP	Negative	67	56.3
	Positive	2	1.7
	Unknown	50	42
Pregnancy complications	No	85	77.3
	Yes	25	22.7
Bacterial culture results	Negative	51	42.9
	Positive	32	26.9
	Unknown	36	30.3

Discussion

The main objective in the present study was to identify maternal and fetal factors associated with stillbirth. The vast majority of stillbirths occurred after 28 weeks of pregnancy, and most pregnant women feel fetal movement anomaly before the fetal death. However, they have not paid enough attention, leading to delay in diagnosis and treatment.

Maternal disease (e.g., hysteromyoma, syphilis, thyroid disease, diabetes, uterine abnormalities) presumably related to fetal death was found in most mothers of stillbirths. Abruption of the placenta was also an important risk factor contributing to fetal death. There was evidence that some enterovirus infections may provoke pregnancy loss possibly by affecting the placenta [6]. In the present study, the authors found a high prevalence of singleton pregnant of fetal deaths combined with placental lesions.

Umbilical cord was found to be the most recognized factor associated with stillbirth, which is an important link to maintain the life of the fetus, but less attention has been de-

Table 3. — *Correlation between clinico-pathological parameters of singleton pregnant women and pregnant age in late fetal death.*

	< 35	≥ 35	*t*	*p*
	105	13		
Fasting blood glucose	4.42 ± 0.53	3.92 ± 1.35	1.321	0.189
Basic platelet counts	235.52 ± 56.98	217.69 ± 64.97	0.945	0.347
Platelet counts after admission	192.88 ± 91.23	195.44 ± 65.1	-0.127	0.899
Ultrasound of fetal biparietal diameter	73 ± 24.68	76.53 ± 19.33	-0.601	0.549

Table 4. — *Correlation between clinico-pathological parameters of singleton pregnant women and with or without abortion history in late fetal death.*

	With abortion history	Without abortion history	*t*	*p*
	28	79		
Fasting blood glucose	4.01 ± 1.5	4.04 ± 1.15	-0.115	0.909
Basic platelet counts	75.07 ± 23.58	75.92 ± 19.61	-0.108	0.862
Platelet counts after admission	194.67 ± 69.71	193.98 ± 71.14	0.044	0.965
Ultrasound of fetal biparietal diameter	212.37 ± 65.34	224.05 ± 65.96	-0.807	0.421

Table 5. — *Correlation between umbilical cord lesions of singleton pregnant women and pregnant age in late fetal death.*

Umbilical cord lesions		< 35	≥ 35	*p*
Torsion	Yes	30	2	0.838
	No	37	2	
Edema	Yes	25	1	0.619
	No	42	3	
Necrosis	Yes	8	1	0.446
	No	59	3	
Funisitis	Yes	12	0	0.353
	No	55	4	

Table 6. — *Correlation between umbilical cord lesions of singleton pregnant women and with or without abortion history in late fetal death.*

Umbilical cord lesions		Without abortion history	With abortion history	*p*
Torsion	Yes	24	8	0.761
	No	28	11	
Edema	Yes	18	8	0.562
	No	34	11	
Necrosis	Yes	6	3	0.634
	No	46	16	
Funisitis	Yes	9	3	0.88
	No	43	16	

voted to abnormalities of umbilical cord [7]. At present, the authors have not used the detection of umbilical cord lesions as a routine. Many pathological changes of the umbilical cord can harm the health of the fetus and even be fatal, but the diagnoses were often made after birth or missed as the cause of death remained unknown [8]. The most common cord lesions associated with fetal death are umbilical cord torsion, umbilical cord edema, necrosis, arteriovenous hemorrhage, velamentous, and entanglements [9].

Studies have shown that umbilical cord torsion is an uncommon cause of intrauterine fetal death [10], but in the present study, umbilical cord torsion was the most common factor associated with late fetal death, and usually occurred during 28~33 weeks. These results concur with those seen in other studies [1, 11]. Umbilical cord torsion has usually been regarded as the second leading cause of fetal death [12]. Umbilical cord torsion can block the umbilical cord blood vessels in the absence of predisposing constriction and resulting in fetal death [13]. The degree of torsion of the umbilical cord is proportional to the speed of the death of the fetus. Results of this study suggest that non maternal risk factors affect the torsion of the cord. It has also been demonstrated that torsion of the umbilical cord can be recognized by prenatal ultrasonography. If the vein-to-vein pitch is < 2 cm, then it indicates that the umbilical cord is torsion [14]. In clinics, woman often experienced reducing fetal movement even disappearing before coming to the hospital; if women can detect fetal abnormalities and go to the hospital as soon as possible, these can be avoided.

Umbilical cord edema is also one of the important reasons for fetal death in the present study. The cause of cord edema may be associated with pregnancy complicated with diabetes, placental early stripping, maternal fetal blood group incompatibility, and pregnancy-induced hypertension [15, 16]. Unfortunately, in the present analyses the au-

thors did not see significant associations of these maternal complications with umbilical cord lesions.

Velamentous umbilical cord is a defect in the insertion of the umbilical cord attached to the membranes of the placenta before reaching the placental margin, resulting from the atrophy of portions of the developing placenta. Studies have reported that the occurrence rate of velamentous umbilical cord was 3.65% in term singleton placentas [17, 18]. The two stillbirths of the present study were all one of the twin pregnancy and terminated the pregnancy at 29^{+5} weeks and 36^{+4} weeks, which may be related to congenital malformation.

Bacterial infections are the most common pathological features of late fetal death among fetal development abnormalities [19], with an incidence ranging from 14.7% to 33.7% of all deliveries [20]. However, the present authors only found 36 cases of bacterial infections in this study; in severe cases, fetal death can occur. Amniotic fluid infection has been shown to be the most common cause of stillbirth and may be responsible for some of the unexplained deaths encountered in the present study [21].

Some limitations should be considered in the interpretation of this study. First, this study was conducted with a small sample size in a single institution. Moreover, although in this study the authors demonstrated the associations of relevant maternal risk factors with different factors such as umbilical cord lesions, but the authors did not control confounders that might have affected the associations above. Thus, a larger study sample size is needed to further examine the relationships of multiple risk factors and late fetal death, as well as an interventional study design.

In conclusion, umbilical cord lesion was the most common factor associated with late fetal death. The present study suggests that perinatal healthcare management and monitoring should be strengthened, and the umbilical cord length, diameter, spiral coil index, blood flow, with or without torsion, and other conditions should be classified as routine examination of fetal structural screening in the second trimester ultrasound. Attempts to reduce maternal morbidity by extensive screening of the pregnant women for risk factors associated with stillbirth may ultimately reduce perinatal losses.

Acknowledgement

The study was supported by Health and Family Planning Commission Project, Shanghai (Grant No.: 201540194).

References

[1] Zhang J., Zhao X.F., Zhang Q.: "Fetal death related risk factor analysis on 279 women in middle and late pregnancy". *Chin. J. Women Children*, Health, 2012, *3*, 135.

[2] Shinde K.K., Bangal V.B., Kwatra A., Borawake S.K.: "Lessons learnt from umbilical cord accidents: are these stillbirths preventable?" *Int. J. Students' Res.*, 2012, *2*, 14. Available at: http://connection.ebscohost.com/c/case-studies/90156000/lessons-learnt-from-umbilical-cord-accidents-are-these-stillbirths-preventable

[3] Tantbirojn P., Saleemuddin A., Sirois K., Crum C.P., Boyd T.K., Tworoger S., *et al.*: "Gross abnormalities of the umbilical cord: related placental histology and clinical significance". *Placenta*, 2009, *30*, 1083.

[4] Bangal V.B., Shinde K.K., Gavhane S.P., Borawake S.K.: Twisting of the umbilical cord causing intrauterine fetal death". *Int. J. Biomed. Adv. Res.*, 2012, *3*, 656.

[5] Le J.: "Obstetrics and Gynecology". Beijing: People's Medical Publishing House, 2008, 141.

[6] Basso N.G., Fonseca M.E., Garcia A.G., Zuardi J.A., Silva M.R., Outani H.: "Enterovirus isolation from foetal and placental tissues". *Acta Virol.*, 1990, *34*, 49.

[7] Shenai J.P.: "Interpreting umbilical cord blood gases for clinicians caring for the fetus or newborn". *J. Perinatol. Off. J. Calif. Perinat. Assoc.*, 2013, *33*, 578.

[8] Ugurlucan F.G., Atil Yuksel M.D.: "Is complete umbilical cord scanning possible at the second-trimester ultrasound scan?" *J. Clin. Ultrasound*, 2014, *43*, 249.

[9] Ferguson V.L., Dodson R.B.: "Bioengineering aspects of the umbilical cord". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2009, *144*, S108.

[10] Atin H., Sailesh R., Saswati H.., Martinez J.M., Torné A.: "Umbilical cord torsion; a rare cause of intra-uterine fetal death". *J. Turkish-German Gynecol. Assoc.*, 2009, *10*, 128.

[11] Zhang G.L., He P.: "Clinical analysis of umbilical cord in fetal death". *J. Practical Med. (Chin.)*, 2008, *24*, 1758.

[12] Bendon R.W., Brown S.P., Ross M.G.: "In vitro umbilical cord wrapping and torsion: possible cause of umbilical blood flow occlusion". *J. Matern. Fetal Neonatal Med.*, 2014, *27*, 1462.

[13] Fletcher S.: "Chirality in the umbilical cord". *Br. J. Obstet. Gynaecol.*, 1993, *100*, 234.

[14] Tian C.F., Kang M.H., Wu W., Fu L.J.: "Relationship between pitch value or S/D ratio of torsion of cord and fetal outcome". *Prenat. Diagn.*, 2010, *30*, 454.

[15] Stanek J.: "Periarterial stem villousedemais associated with hypercoiledumbilicalcordand stem obliterative endarteritis". *Open J. Obstet. Gynecol*., 2013, *3*, 9.

[16] Yamashita E., Yashiro K., Suzuki S.: "Prenatal ultrasonographic findings of large pseudocysts and edema of the umbilical cord". *J. Med. Ultrason*., 2011, 38, 59-61.

[17] Ebbing C., Kiserud T., Johnsen S.L., Albrechtsen S., Rasmussen S.: "Prevalence, risk factors and outcomes of velamentous and marginal cord insertions: a population-based study of 634,741 pregnancies". *PLoS One*, 2013, *8*, e70380.

[18] Suzuki S., Kato M.: "Clinical significance of pregnancies complicated by velamentous umbilical cord insertion associated with other umbilical cord/placental abnormalities". *J. Clin. Med. Res.*, 2015, *7*, 853.

[19] Sheiner E., Abramowicz J.S., Levy A., Silberstein T., Mazor M., Hershkovitz R.: "Nuchal cord is not associated with adverse perinatal outcome". *Arch. Gynecol. Obstet.*, 2006, *274*, 81.

[20] Kong C.W., Chan L.W., To W.W.: "Neonatal outcome and mode of delivery in the presence of nuchal cord loops: implications on patient counselling and the mode of delivery". *Arch. Gynecol. Obstet.*, 2015, *292*, 283.

[21] Naeye R.L., Ross S.M.: "Amniotic fluid infection syndrome". *Clin. Obstet. Gynaecol.*, 1982, *9*, 593.

Corresponding Author:
YU-NA GUO, M.D.
The International Peace Maternity & Child Health Hospital of The China Welfare Institute
910 Hengshan Road, Xuhui District
Shanghai 200030 (China)
e-mail: yu_naguo@163.com