

Fetal, neonatal, and infant death in central China (Hubei)

A 16-year retrospective study of forensic autopsy cases

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Abstract

Data based on forensic autopsy in neonates and infants in China are rare in the literature. The purpose of this study is to evaluate the characteristics of fetal, neonatal, and infant death and to determine the main cause of death among them.

A retrospective analysis of fetal and infant forensic autopsies referred to the Tongji Forensic Medical Center (TFMC) in Hubei, central China, during a 16-year period between January 1999 and December 2014, was performed.

In this period, there were 1111 males and 543 females; the total male-to-female ratio (MFR) was 2.05:1. There were 173 fetal and infant autopsies conducted, comprised of 43 fetal, 84 neonatal (<28 days) and 46 infant (4 weeks to 1 year) cases. The annual case number ranged from 5 in 2004 to 18 in 2014 (annual mean of 10.8). MFR was 1.75:1. About 94% of these deaths (163/173) resulted from natural causes, 6 cases (3.5%) were accidental deaths, and 4 (2.3%) resulted from homicide (4 abandoned babies). Among fetuses, the most common causes of death were placental and umbilical cord pathologies (28%, 12/43), followed by intrapartum asphyxia resulting from amniotic fluid aspiration (AFA) or meconium aspiration syndrome (MAS) (18.6%, 8/43), congenital malformation (14%, 6/43), and intrapartum infection (9.3%, 4/43). A majority of neonatal deaths (66.7%, 56/84) died within 24 hours of birth. The main causes of neonatal death were asphyxia resulting from AFA, MAS, or hyaline membrane disease, and congenital malformation. The main causes of infant (1–12 months) death were infectious diseases, including pneumonia, meningitis, and viral brainstem encephalitis.

This study was the 1st retrospective analysis of autopsies of fetal, neonatal, and infant death in TFMC and central China. We delineate the common causes of early demise among cases referred for autopsy, and report a male preponderance in this population. Our data observed that placental and/or umbilical cord pathology, asphyxia due to AFA, and/or MAS, and pneumonia were the leading causes of fetal, neonatal, and infant death, respectively. And it can inform clinical practitioners about the underlying causes of some of the most distressing cases in their practices.

Abbreviations: AFA = amniotic fluid aspiration, CDH = congenital diaphragmatic hernia, EV71 = enterovirus 71, GA = gestational age, HFMD = hand-foot and mouth disease, IMR = infant (1–12 months) mortality rates, LBWR = lung weight to body weight ratio, MAS = meconium aspiration syndrome, MFR = male-to-female ratio, SIDS = sudden infant death syndrome, TFMC = Tongji Forensic Medical Center.

Keywords: cause of death, fetal death, forensic autopsy, infant death, manner of death

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1. Introduction

The death of an infant is a tragic event for a family and for medical practitioners. Within developed countries, the stillbirth rate is estimated to be 4.2 to 6.8 per 1000 live births, whereas in the developing world, this rate is 20 to 32 per 1000 live births.^[1] Infant (1–12 months) mortality rates (IMRs) widely vary among countries. In China, the estimated average IMR level in 2010 for 31 provinces was 1.23% for males and 1.07% for females,^[2] whereas the IMR in the United States was 0.68% in 2007 and 0.596% in 2013, respectively.^[3,4] Autopsy improves definitive diagnosis, informs genetic counseling, and assists in medical malpractice evaluation and resolving medical disputes.^[5–9] It is additionally useful in criminal investigation.

However, data based on forensic autopsy in fetuses, neonates and infants in China remains rarely reported. The purpose of the study is to evaluate the characteristics of these deaths referred for autopsy, and to identify the risk factors for mortality in this select group of cases.

1.1. Ethical statements

The research protocols were approved by the ethics committee of Huazhong University of Science and Technology. Informed consent was obtained from each claimed case.

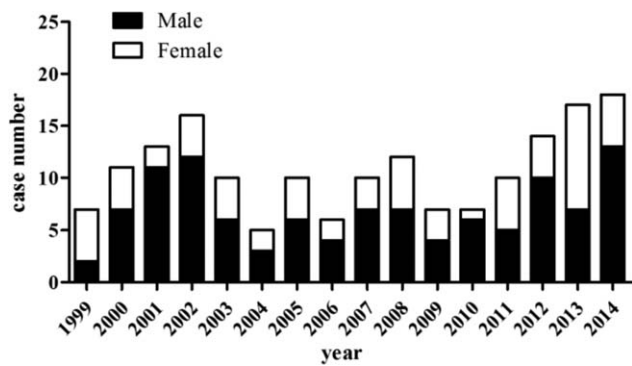


Figure 1. Number of cases and gender by years (1999–2014).

2. Materials and methods

Wuhan is the capital of Hubei Province in central China, with a population of 10.1 million in 2012. Forensic pathologists in Tongji Forensic Medical Center (TFMC) in Hubei are primarily responsible for forensic examination of sudden unexpected deaths, accidental deaths, and suicide cases in Hubei Province and the surrounding provinces including Henan and Hunan. Thorough investigation of such deaths includes review of police reports and medical records, as well as a complete medicolegal autopsy performed within 24 hours of death. Tissue samples from brain, heart, lung, liver, spleen, pancreas, kidney, adrenal, stomach, and intestine were collected. Placenta and umbilical cord in all fetal and early neonatal death cases were provided for pathological examination, including gross inspection and histopathologic examination (hematoxylin-eosin stain), performed by 2 or more pathologists. Special stains, virology, biochemistry, and genetics tests were conducted in some cases. Final determination as to the cause of death was reached by comprehensive analysis of all of this available information.

In this study, all the autopsy cases conducted in TMFC during January 1999 to December 2014 were reviewed, and cases of fetal and infant death were analyzed. These cases were grouped into fetal deaths, neonatal deaths (<28 days of life) and infant deaths (from 4 weeks to 1 year of life). All documents were reviewed by the authors together. The manners and causes of these deaths and other characteristics were noted and discussed.

3. Results

From January 1999 to December 2014, a total of 1654 autopsy cases were conducted in TFMC. Of these cases, there were 1111

males and 543 females, the total male-to-female ratio (MFR) was 2.05:1. A total of 173 (10.4%) cases involved fetal, neonatal, and infant death and were identified for inclusion in this study. The annual case number ranged from 5 to 18, and a mean case number of 10.8 (Fig. 1).

Of the 173 cases, there were 110 males and 63 females, the MFR was 1.75:1 (Table 1). There were 43 fetal, 84 neonatal, and 46 infant cases. For neonatal deaths, 66.7% (56/84) died in first 24 hours of birth, with an MFR was 1.80:1.

Gestational age (GA) of each case is reported in Table 2. In fetal death cases, GA ranged from 20 to 41 weeks: 25.6% (11/43) cases at 20 to 28 weeks, 37.2% (16/43) at 29 to 36 weeks, and 37.2% (16/43) at 37 to 41 weeks. About 38 cases died soon prior to delivery, while 5 showed evidence of earlier demise, such as maceration. GA was preterm in 8/84 neonatal death cases and term (85.7%, 72/84) or unknown (2/84) in the remainder. GA was unknown in the majority (90.7%, 39/43) of infant death cases.

In regards to the manner of death, the majority of these cases (94.2%, 163/173) were from natural causes, 6 cases (3.5%) were accidental death. About 4 (2.3%) were homicides, all of which were abandoned babies with traumatic brain injury (Table 3). Based on the police reports and positive results of hydrostatic test of lung and stomach, these 4 abandoned babies were probably live born.

3.1. Causes of fetal death

In fetal death cases, the main causes of death are reviewed and listed in Table 4. All these cases were singleton pregnancies. The most common causes of death were placental and umbilical cord pathologies (27.9%, 12/43), including placental insufficiency, infection and infarction, and umbilical cord abnormalities. GA ranged from 25 to 41 weeks in these cases. Other causes of death included intrapartum asphyxia resulting from amniotic fluid aspiration (AFA) or meconium aspiration syndrome (MAS) (18.6%, 8/43), congenital malformation (14%, 6/43), and intrapartum infection (9.3% 4/43). The other causes, including fetomaternal hemorrhage (3/43), fetal mediastinal tumor, and maternal factors are listed as well. There was no clear explanation for death in 7 of the cases.

All the cases involving intrapartum asphyxia occurred at 36 to 41 weeks GA. Severe aspiration of squamous cells and/or meconium was identified by histopathologic examination in the fetus's airways and alveolar spaces. Risk factors for these episodes might include prolonged 2nd stage of labor, macrosomia, and atypical placental abruption. Congenital malformations (6 cases), were found in the cardiovascular and central nervous system, and included congenital heart disease and neural tube defects. Intrapartum infection induced by cytomegalovirus (3 cases) and rubella virus (1 case) were found in fetal deaths that occurred at 25 to 29 weeks GA.

Table 1
Overview of fetal, neonatal, and infant death autopsy cases.

	Gender		Total	%	MFR
	Male	Female			
Fetal death	23	20	43	24.9	1.15:1
Neonatal death					
<24 h	36	20	56	32.4	1.80:1
1–28 d	22	6	28	16.2	3.67:1
Infant death (4 wks to 1 yr)	29	17	46	26.6	1.71:1
Total	110	63	173	100.00	1.75:1

MFR = male-to-female ratio.

Table 2
Gestational age (GA) distribution.

GA	Fetal death		Neonatal death		Infant death		Total
	Male	Female	Male	Female	Male	Female	
≥20 and <28 wks	7	4					11
>28 and ≤36 wks	7	9	8				24
>37 and ≤42 wks	9	7	48	24	4	5	97
>42 wks			2				2
Unknown				2	25	12	39
Total	23	20	58	26	29	17	173

Table 3
Manner of death.

Manner of death	Male	Female	Total (%)
Homicides			4 (2.3)
Abandoned baby (traumatic brain injury)	1	3	
Accidents			6 (3.5)
Asphyxia (inhalation of milk and peanut)	2		
Fire	1		
Fall	1		
Drug anaphylactic reaction	1		
Maternal trauma resulting in fetal death	1		
Natural death	103	60	163 (94.2)
Total	110	63	173 (100.0)

3.2. Causes of neonatal death

In neonatal death cases, 36.9% (31/84) died from asphyxia resulting from AFA and/or MAS, of which 25 deaths occurred within 24 hours after birth. These may indicate a problem in neonatal care and emergency treatment that could induce medical malpractice claims. There were 25 cases in which malpractice claims were prosecuted in court.

The 2nd most cause of neonatal death was congenital malformation (27.4%, 23/84), including pulmonary hypoplasia (8/23), congenital heart disease (7/23), congenital diaphragmatic hernia (CDH, 6/23), and cerebral arteriovenous malformation (2/23).

Ten cases diagnosed were hyaline membrane disease, also known as Neonatal Respiratory Distress Syndrome. Pneumonia contributed 7.1% of neonatal deaths.

Four babies abandoned by their parents or relatives died from traumatic brain injury (homicide). All of these babies were born outside of a hospital.

Table 4
Causes of fetal death.

Cause of death	Male	Female	Total (%)
Placental and umbilical cord pathology			12 (27.9)
Placental chorioamnionitis		2	
Oligohydramnios	2		
Placental dysplasia		1	
Placental infarction	1		
Single umbilical artery		2	
Constricting loop or knot of umbilical cord	1	1	
Stricture of umbilical cord		1	
Umbilical artery thrombus		1	
Intrapartum asphyxia due to AFA or MAS	3	5	8 (18.6)
Congenital malformations			6 (14.0)
Cardiovascular system (heart)	2	1	
CNS (anencephalus, meningocele)	3		
Intrapartum infection			4 (9.3)
Cytomegalovirus	1	2	
Rubella virus	1		
Others			4 (9.3)
Fetomaternal hemorrhage	2	1	
Fetal mediastinal tumor		1	
Maternal factor			2 (4.7)
Maternal trauma	1		
Uterus septus	1		
Unexplained death	5	2	7 (16.3)
Total	23	20	43 (100.0)

AFA=amniotic fluid aspiration, CNS=central nervous system, MAS=meconium aspiration syndrome.

The other causes of death were neonatal jaundice, neonatal scleredema, neonatal pneumothorax, and others (as listed in Table 5).

3.3. Causes of infant death

The cause of death in more than a half in these cases (60.9%) was respiratory system infection, including pneumonia (24 cases), bronchopneumonia (3 cases), and laryngotracheobronchitis (1 case). Pneumonia was caused by influenza virus, cytomegalovirus, mycoplasma, and others.

Meningitis, including viral meningitis and purulent meningitis caused by poliovirus, pneumococcus, and diplococcal meningitis, were identified in 4 cases. Human enterovirus 71 (EV71) infection induced hand-foot and mouth disease (HFMD) was identified in 3 cases. Viral brainstem encephalitis in these patients with HFMD was determined to be the main cause of death. Sudden infant death syndrome (SIDS) was diagnosed in 2 cases.

Other causes of infant death are listed in Table 6, including congenital heart disease, endocardial fibroelastosis, Reye syndrome, postoperative short bowel syndrome, accidents, and others.

4. Discussion

Complete autopsy and histopathologic examination serve important roles in forensic investigation of fetal, neonatal, and infant death, as well as providing valuable insights for clinical obstetrics and pediatrics.^[10,11] In a “verbal autopsy,” a poor outcome is reviewed by obstetricians and pediatricians to help them identify contributors to the death. However, completion of a true post mortem examination generally provides further information helpful for definitive diagnosis. Autopsy of non-criminal deaths is optional in China and mainly performed by a forensic practitioner. The autopsy rates for fetuses and infants are very low in China. The National Health and Family Planning Commission of PR China requires that hospitals belonging to the III and II grades must attain autopsy rates of at least 15% and

Table 5
Causes of neonatal death.

Cause of death	Male	Female	Total (%)
Asphyxia due to AFA and/or MAS	23	8	31 (36.9)
Congenital malformation			23 (27.4)
Neonatal pulmonary hypoplasia	6	2	
Congenital heart disease	6	1	
Congenital diaphragmatic hernia	3	3	
Cerebral arteriovenous malformation	2		
Hyaline membrane disease	7	3	10 (11.9)
Pneumonia	4	2	6 (7.1)
Abandoned baby (traumatic brain injury)	1	3	4 (4.8)
Kernicterus	1	1	2 (2.4)
Neonatal sclerema and premature birth	1		1 (1.2)
Neonatal pneumothorax		1	1 (1.2)
Traumatic brain injury resulting from vacuum extraction		1	1 (1.2)
Asphyxia resulting from milk aspiration	1		1 (1.2)
Hypoxic-ischemic encephalopathy	1		1 (1.2)
Viral myocarditis		1	1 (1.2)
Necrotizing enterocolitis	1		1 (1.2)
Purulent peritonitis	1		1 (1.2)
Total	58	26	84 (100.0)

AFA=amniotic fluid aspiration, MAS=meconium aspiration syndrome.

Table 6
Causes of infant death.

Cause of death	Male	Female	Total (%)
Respiratory system			28 (60.9)
Pneumonia	16	8	
Bronchopneumonia	1	2	
Laryngotracheobronchitis		1	
Nervous system			8 (17.4)
Meningitis	2	2	
Viral brainstem encephalitis (infected by EV71)	2	1	
Traumatic brain injury resulting from fall	1		
Cardiovascular system			2 (4.4)
Congenital heart disease		1	
Endocardial fibroelastosis	1		
Digestive system			2 (4.4)
Reye syndrome		1	
Postoperative short bowel syndrome	1		
SIDS	1	1	2 (4.4)
Others			3 (6.5)
Drug anaphylactic reaction	1		
Injury sustained in a fire	1		
Asphyxia resulting from inhalation of peanut	1		
Unexplained death	1		1 (2.2)
Total	29	17	46(100.0)

EV71 = enterovirus 71, SIDS = sudden infant death syndrome.

10%, respectively. However, these percentages are not achieved in many hospitals,^[5] mainly because of parental refusal, lack of awareness of the importance of autopsy, neglect of medical workers, helpless pathologists, and so on. From 1998 to 2008, the autopsy rates in China's different representative hospitals were 0.04% to 2.04%, and some hospitals did not perform a single autopsy for years.^[5,12] In TMFC, the mean annual autopsy number was only 10.8, though there has been a rising tendency since 2010. In this study, the purposes of these autopsies were mainly for the following reasons: investigation of unexpected fetal or infant deaths for the purpose of medical litigation claims; identification of the cause of unexpected fetal death as guidance for subsequent pregnancies; and criminal investigations. The total MFR was 2.05:1, and fetal and infant autopsies was 1.75:1, indicating that the autopsy application and medical liability disputes were more common in the setting of male death.

In this study, we present the manners and causes of fetal, neonatal, and infant death investigated with autopsy. There were 4 cases determined as abandoned baby died from traumatic brain injury. Their parents abandoned them for different reasons. In South Africa, the rate of abandoned babies was 0.2 per 100,000 live birth and showed no marked difference in the gender of them. However, in China the situation of abandoned bodies was gender specific, 90% were girls and 10% were boys.^[13,14] And female infants are more often killed in countries such as China, Taiwan, South Korea, and Pakistan.^[15] Consistent with this, in our study, there were 3 female babies killed and 1 male.

Our findings regarding fetal deaths are consistent with previous reports.^[10,16–19] Placental and/or umbilical cord factors were the leading cause of intrauterine fetal death with the GA widely distributed between 25 and 41 weeks. These anomalies can result deficient maternal blood supply, fetal growth restriction, intrauterine hypoxia, and result in intrauterine fetal death. It is necessary to examine placental and umbilical cord whenever possible.

Asphyxia significantly contributes to fetal and neonatal morbidity and mortality and determines the prognosis of future

development.^[20] AFA and/or MAS can be identified by histopathologic examination, but there are not precisely defined markers to distinguish perinatal asphyxia.^[21] In our study, intrauterine/neonatal asphyxia was confirmed by signs of asphyxia and findings of squamous cells and/or meconium in the airways and alveolar space. In previous reports, AFA was present in 8% to 20% of all deliveries, especially in term and postterm infants, while the mortality rate reaches 39.3% in MAS and 13.5% in pure AFA.^[22] The risk factors of asphyxia include mother's disease associated with inadequate oxygenation of blood, reduction of blood flow from the placenta to the mother's body, inadequate blood flow from the placenta to the fetal body, failure of gas exchange in the placenta, and conditions in the fetus associated with increased demands for oxygen. About 90% of the causes of asphyxia occurs prenatally and during labor.^[21] Amniotic fluid and meconium removal from the airways by tracheal intubation and suction, oxygen inhalation, and pulmonary surfactant treatment can help prevent death from AFA and MAS.

Congenital malformations were observed in 6 fetal cases (14%) and 23 neonatal cases (27.4%), respectively. Ventricular septal defect, anencephalus, and meningocele were responsible for fetal death. They could be predicted by undergoing prenatal ultrasonography in time to allow for therapeutic planning or induced abortion when indicated. In neonates, congenital malformations mainly included neonatal pulmonary hypoplasia, severe congenital heart disease, CDH, and cerebral arteriovenous malformation. The incidence of pulmonary hypoplasia varies from 9 to 11 per 10,000 live births, with a high mortality rate of 50% to 70%.^[23] It can be caused CDH, congenital cystic adenomatoid malformation, bronchopulmonary sequestration, cardiac or mediastinal masses, pleural effusion, severe oligohydramnios, genitourinary anomalies, and others.^[24] The lung weight to body weight ratio (LBWR) is the simplest method to diagnose pulmonary hypoplasia at autopsy. Lungs are classified as hypoplastic if the LBWR is <0.015 before 28 weeks of GA, or <0.012 beyond 28 weeks of GA. An additional criterion is measurement of the mean radial alveolar count.^[24] In our study, CDH was listed as a separate and important cause of neonatal death with an impact similar to congenital heart disease. Intrauterine infections mainly occur between 20 and 28 weeks.^[23] Infection may cause stillbirth by a number of mechanisms including direct infection, placental damage, and severe maternal illness. Cytomegalovirus is the leading viral intrauterine fetal infection in the United States,^[25] as well as in our study. The involved fetus presents small for GA, and with positive virology results.

The main causes of infant (1–12 months) death were infectious diseases. Pneumonia deaths occur much more frequently in low-income countries.^[26,27] In China, the mortality rates attributable to pneumonia in postneonates (1–11 months) between 2011 and 2013 were 20.6 and 118.9 per 100,000 live births in urban areas and rural areas, respectively.^[28] In a community-based study using verbal autopsy in rural Western China, pneumonia was the leading cause of death, consistent with our study.^[29] Pneumonia can be caused by viruses, bacteria, fungi, and parasites, resulting in respiratory and circulatory failure. Infants with pneumonia often have a wet cough and a fever, or develop sweaty and clammy skin. However, in many cases, they can present with reduced mental status, excessive sleepiness, and/or have a decreased appetite. Uncommon presentations may result in delayed diagnosis and clinical management. An unexpected infant death could cause medical liability disputes.

The EV71 infection presents with manifestations including HFMD and neurologic symptoms.^[30] When the central nervous system is involved, the EV71 can damage neurons, cause cluster necrosis of neurons, and brainstem encephalitis.^[31] It was responsible for 90.2% (83/92 cases) HFMD fatality cases in mainland China from 2008 to 2014.^[32] The diagnosis was confirmed by histopathologic and EV71 RNA sequence analysis in this study.

The SIDS is one of leading causes of death in infancy, with an incidence of 6.4 cases in 10,000 births and an incidence decline tendency from 1995 to 2004.^[33] However, SIDS deaths are rare in Asians and are more common in native Americans and African-American populations.^[34] In 2013 in the United States, there were 1563 infant deaths from SIDS, constituting 6.7% of total infant deaths.^[35] In our study, 2 of 130 infants (<1 year of life) deaths were attributed to SIDS based on complete autopsy, review of infant's clinical history, and detailed death scene investigation, showing a higher incidence of SIDS. That may due to smaller sample size and low infant autopsy rate in China. Not all forensic practitioners in China used the SIDS as cause of death, an issue also noted in the United States.^[36] There was no shaken baby syndrome observed in present study.

In total, there were 8 cases determined as unexplained deaths, including 7 fetal deaths. These causes may be attributed to chromosome abnormalities, maternal hormonal factors, environmental radiation, and so on, which were difficult to confirm due to lacks of economic and technical supports.

Our study differs from the clinical expectations of obstetricians and pediatricians and should not be considered to reflect the causes and characteristic of deaths in the broader population. Our study focused on a select group of deaths, those referred in our region for forensic evaluation. One of the most common reasons for such a referral is to inform malpractice litigation cases. The majority of our cases indeed were associated with medical disputes. Referrals to forensics are uncommon when the psychologic expectations of the mother already incorporate the risk of fetal or neonatal death. For example, in our cases, there were no maternal risk factors for fetal or neonatal death represented, such as hypertensive disorders or preeclampsia or diabetes. Setting appropriate expectations likely deters malpractice lawsuits as well. Joint evaluation by forensic pathologists and clinicians confirmed that about one third of these claims were adjudicated as medical malpractice cases. These cases mainly occurred in county-level hospitals and rural clinics lacking treatment experience and advanced resuscitative measures.

In conclusion, this study was the 1st retrospective analysis of fetal, neonatal, and infant death as referred to and assessed by forensic autopsy in TFMC and central China. These cases showed a predominance of male gender, and most were associated with potential medical litigation. Placental and/or umbilical cord pathology, asphyxia due to AFA and/or MAS, and pneumonia were the leading causes of fetal, neonatal, and infant death, respectively. Our data can inform clinical practitioners about the underlying causes of some of the most distressing cases in their practices, as well as potentially help families and practitioners to have appropriate expectations about the reality that this period of life is statistically the most dangerous of all.

Author contributions

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