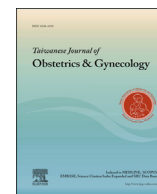




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Review Article

Major risk factors for stillbirth in different trimesters of pregnancy—A systematic review



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ABSTRACT

Stillbirth remains an event that has an important impact on global health issues. Different levels of health care between countries suggest that the stillbirth rate may be one of the indicators of the quality of a country's medical system. In this review, major risk factors for stillbirth will be discussed, especially in different trimesters of pregnancy. Early identification of risk factors for stillbirth and appropriate antenatal management may reduce preventable stillbirths and improve general outcomes of pregnancy.

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Introduction

A stillbirth indicates a fetus born after 20 completed weeks of pregnancy without spontaneous breath or heartbeat. It is equivalent to intrauterine fetal demise in which no fetal heartbeat is detected after 20 weeks of gestation. The estimated number of stillbirths is 3.2 million a year worldwide. The incidence of stillbirth varies from 5 to 32/1000 in different nations [1,2]. Developing countries have higher stillbirth rates, up to 97%, than developed countries [3,4]. Different levels of health care between countries suggest the stillbirth rate may be one of the indicators of the quality of a country's medical system. In Taiwan, the overall stillbirth rate was 0.9–0.98% from 1999 to 2011 [5,6]. Our stillbirth rate was lower than 2.3% of East Asia but still higher than 0.3–0.5% of developed countries when comparing to international stillbirth rates in 2000 [1,3]. Stillbirth has multifactorial etiologies. Early identification of risk factors for stillbirth and appropriate antenatal management may reduce preventable stillbirths and improve the general outcomes of pregnancy.

Maternal characteristics

Advanced maternal age and increased maternal body mass index (BMI) are identified as risk factors of stillbirths [7,8]. The mean maternal age at delivery has been increasing and gives a 1.6- to 2.6-

fold risk increase for adverse perinatal outcomes [5,9]. In terms of maternal BMI at delivery, the ethnic and cultural diversity, social and economic conditions, and nutritional transitions are contributors to different average BMIs of the world's population. The increased stillbirth risk of the 3rd trimester compared to the 2nd trimester may be attributable to a reasonable maternal body weight increase as pregnancy progresses. Pregnant women and their physicians should follow a well-controlled weight increase to obtain better perinatal outcomes.

Smoking during pregnancy or exposure to environmental smoke causes an increased risk of stillbirth [10–12]. Furthermore, smoking carried into the 3rd trimester is found to have a more significant influence on the risk of stillbirth than smoking during the 2nd trimester [6]. This may be attributable to the longer duration of cigarette exposure and the greater impact on the fetoplacental circulation. Smoking is a modifiable lifestyle choice, and its effect should be preventable.

“Small for gestational age” is defined as a birth weight below the 10th percentile for the gestational age. Nearly half of stillbirths are small for their gestational age [7,13]. Besides the pathologic factors, the time of recognition of intrauterine fetal demise may not be the exact gestational age at which it happens. In Taiwan, regular antenatal visits by government support staff are arranged every 1–4 weeks, depending on the gestational age. The earlier the pregnancy stage, the longer the interval between antenatal visits. Therefore, without notice of decreased fetal movement and early diagnosis of stillbirth, there is reasonable intrauterine growth restriction data related to stillbirth. The reported fetal weight at delivery is smaller in Asia than in America [14,15]. To avoid the misdiagnosis of intrauterine growth restriction, it is necessary to

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use an appropriate growth chart. In the case of existing intrauterine growth restrictions, adequate diagnosis and management offer a significant opportunity to improve outcomes and reduce potentially preventable stillbirths [16]. Ultrasound accompanied by well-managed control of illness should be used more frequently to monitor fetal growth in the case of pregnancy complicated with a high risk of placental dysfunction.

Umbilical cord pathology

Umbilical cord pathology includes prolapse, true knots, stricture, and strangulation of the fetus. The risk increases as the pregnancy continues and may lead to more fetal demise outcomes in late pregnancy, ranging from 19% to 56.6% of all stillbirths and a rate of 5.7 per 1000 deliveries [2,17] (Table 1). Both a relatively small intrauterine space and more frequent fetal movement are found in late pregnancy. The risk of cord problems resulting in vessel compression and cessation of blood flow as well as fetal perfusion in the 3rd trimester is higher [18,19]. Because most cord accidents are sudden and unpredictable, pregnant women need to pay attention to subjective fetal movement to prevent delayed diagnosis. Fortunately, the prognosis for future pregnancies is believed to be favorable.

Unexplained causes

Despite extensive evaluations, stillbirths from uncertain reasons account for 25–60% of total events, a rate of 2.8/1000 births [20,21]. In term pregnancy, the incidence of unexplained fetal demise could be as high as 0.9/1000 births [22]. This number may be overestimated because of insufficient diagnostic experience and equipment in some nations. However, recognition of the potential risk factors for stillbirth may indicate the possibility of problems that can be addressed and solved with appropriate care. For those with a high-risk pregnancy, paying more attention to the perinatal period may be of benefit to preventing intrauterine fetal demise.

Maternal medical conditions

In general, the stillbirth rate would be 6–7/1000 when pregnancies are complicated with maternal diseases. There is about 10% of all stillbirths being related to maternal medical illnesses [23].

Table 1
Stillbirth causes.

	% (in total stillbirths)	Rate (per 1000 births)
Umbilical cord pathology	19–56.6	5.7
Unexplained causes	25–60	0.9–2.8
Maternal medical conditions		
Overall	10	6–7
Hypertension	4–9	5–52
Diabetes mellitus	3	5–35
Hypothyroidism	0.83	0–125
SLE	3.6–7.1	40–150
Congenital anomaly and malformations and chromosomal abnormalities	6–20	0.5–0.9
Uterine complications		
PROM (PPROM)	0.8	0.03
Chorioamnionitis	22.6–36.9	0.83
Multifetal gestation complications	7.3	12–57
Placental abruption	9–15.2	0.5

PROM = premature rupture of membranes; PPRM = preterm premature rupture of membranes; SLE = systemic lupus erythematosus.

Among these diseases, hypertension and diabetes mellitus are the most common.

Hypertensive pregnancy includes chronic hypertension, which represents elevated blood pressure prior to the gestational age of 20 weeks, and pregnancy-induced hypertension, which means high blood pressure that occurs after 20 weeks of pregnancy. Hypertension is one of the most common medical conditions that complicate pregnancy with an incidence of 7–10% [24,25]. The disease would complicate proteinuria, often called preeclampsia. About 5.6–9.4% of pregnancies complicated by preeclampsia end in intrauterine fetal demise [26,27]. Hypertensive pregnancies are responsible for 4–9% of all fetal deaths. The stillbirth rate is 5–52/1000 births, depending on the severity of complications from hypertension [23]. The pressure on the vascular system, including maternal–fetal circulation, indicates the same progressive vascular effect on pregnancy. Complete antenatal diagnosis for preeclampsia severity and education to prevent underestimation of high-risk pregnancy and resulting tragedy are basic in perinatal management. Prevention of the progression of preeclampsia and consequent complications such as placenta abruption, which is also a possible cause of intrauterine fetal demise, is still a major goal of this high-risk pregnancy care.

As for diabetic pregnancy, when diabetes mellitus is diagnosed before 20 weeks of pregnancy, it is called overt diabetes. There is a 2- to 5-fold risk of stillbirth for overt diabetes mellitus [28–30]. Risks of complication such as preeclampsia and stillbirth are also increased in type 1 diabetic pregnancy as compared to pregnancy in the general population, giving an odds ratio of 4.47 and 3.34, respectively [31]. When diabetes mellitus is found after 20 weeks of gestation, it is defined as gestational diabetes mellitus. Diabetic pregnancy is responsible for about 3% of all stillbirths. The stillbirth rate for pregnancies complicated by diabetes mellitus is 5–35/1000 [20,23]. The complication would have a progressive effect on the overall maternal and fetal system in pregnancy. The screen for gestational diabetes is done at 24–28 weeks of pregnancy. In some cases, unknown fetal demise that occurs prior to 24 weeks may be part of the cause of gestational diabetes mellitus. The risk of diabetic pregnancy and stillbirths may be underestimated. Under adequate treatment of gestational diabetes, the pregnancy outcome is similar to that of the general population [32].

Autoimmune and endocrine diseases, which occur more frequently in women than in men, should be diagnosed for their possible adverse pregnancy outcome. Hypothyroidism is a known risk factor for pregnancy-induced hypertension, intrauterine growth restriction, and intrauterine demise [33]. The prevalence of overt and subclinical hypothyroidism is 0.1–2% and 2.3–8%, respectively [34,35]. Hypothyroidism accounts for about 0.83% of the total number of stillbirths [6]. The stillbirth rate is 0–125 of 1000 births [20]. It has an autoimmune process and has all the aspects of the influence of pregnancy, including hypertension or fetal anomalies. Delayed management of thyroid function creates a higher risk of fetal complications such as fetal demise. Under adequate treatment and well-managed control of hypothyroid disease, the risk of fetal demise would be no more increased than in women without thyroid disease [36].

Systemic lupus erythematosus (SLE) is an autoimmune disease with a cluster of phenomena. It mainly affects young women during their reproductive age, and pregnancy is therefore a major issue. The overall stillbirth rate is 3.6–7.1% for pregnancy complicated by SLE [37,38]. The stillbirth rates of 40–150 of 1000 births were observed among women diagnosed with SLE prior to pregnancy [20]. Antiphospholipid syndrome (APS), one kind of autoimmune-related coagulation disorder, presents as recurrent spontaneous pregnancy losses and repeated vascular thromboses. It can be a

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