When the Fetus Goes Still and the Birth Is Tragic

The Role of the Placenta in Stillbirths

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KEYWORDS

• Placenta • Stillbirth • Perinatal death • Investigation of stillbirth • Cause of stillbirth • Autopsy • Placental abruption • Chorioamnionitis

KEY POINTS

- Reducing stillbirth remains a significant challenge to maternity services in high-income countries (HICs).
- Pathologic conditions within the placenta are the most frequent cause of stillbirth in HICs.
- The relationship between specific placental lesions and stillbirth is less clear, due to variations in placental sampling and definitions of placental abnormalities.
- Information obtained from the placental examination reduces the likelihood of an unexplained stillbirth and provides prognostic information regarding subsequent pregnancies.
- Following stillbirth, the placenta should be sent for histopathological assessment.

INTRODUCTION

Stillbirth is defined as the death of an infant before birth. There is significant variation internationally regarding the lower gestational age limit, with the World Health Organization (WHO) using a definition of 22 weeks' gestation or a birthweight of 500 g when gestational age is unknown. However, to compare among countries, the WHO uses a definition of 28 weeks' gestation or a birthweight of 1000 g.[1] Applying this definition, there are an estimated 2.6 million stillbirths each year globally, ~98% of which occur in low and middle-income countries (LMICs).[2] However, this should not lead one to underestimate the burden of stillbirths in high-income countries (HICs). There are approximately 23,000 stillbirths per year in the United States, where stillbirth is defined as the death of an infant before birth after 20 weeks of gestation.[3]

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Obstet Gynecol Clin N Am 47 (2020) 183–196
https://doi.org/10.1016/j.ogc.2019.10.005
obgyn.theclinics.com

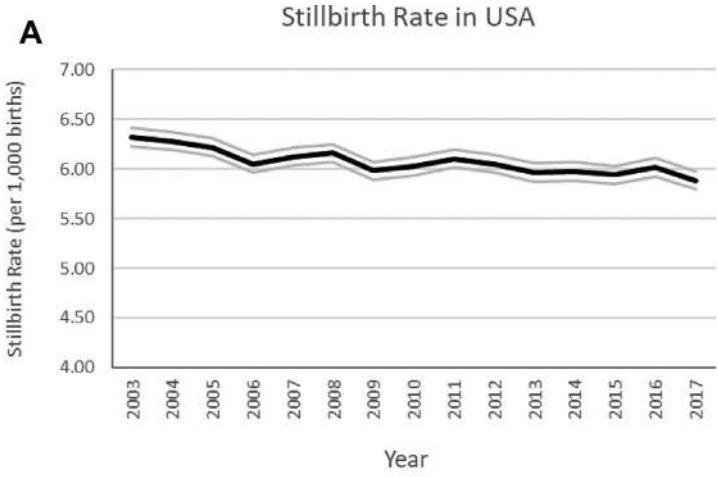
Applying the WHO definition for international comparison, the stillbirth rate in the United States after 28 weeks' gestation is 3.0 per 1000 stillbirths, placing the United States 27th of 49 HICs.[4] Of greater concern is that the annual rate of reduction of stillbirths after 28 weeks' gestation in the United States between 2000 and 2015 was only 0.4%, placing it 48th of the 49 HICs studied (**Fig. 1**A).[4] In addition, there is significant variation among states ranging from 3.37 stillbirths per 1000 live births in New Mexico up to 9.87 per 1000 total births in Mississippi (**Fig. 1**B).[3] Comparing the 5-year average stillbirth rates from 2003 to 2007 to 2013 to 2017, there is also significant variation between states with regard to reduction in stillbirth, with decreases of more than 1 per 1000 births seen in New York, Louisiana, South Carolina, Virginia, West Virginia, and Connecticut, but increases greater than 0.5 per 1000 births seen in Kansas, Oregon, Rhode Island, Utah, Tennessee, and South Dakota (see **Fig. 1**B). As stillbirths place significant psychological, social, and economic burden on families, health services and wider society efforts are urgently needed to reduce the burden of stillbirth.[5,6] Understanding risk factors for stillbirth and the underlying pathologic processes is proposed as a means to reduce the stillbirth rate.

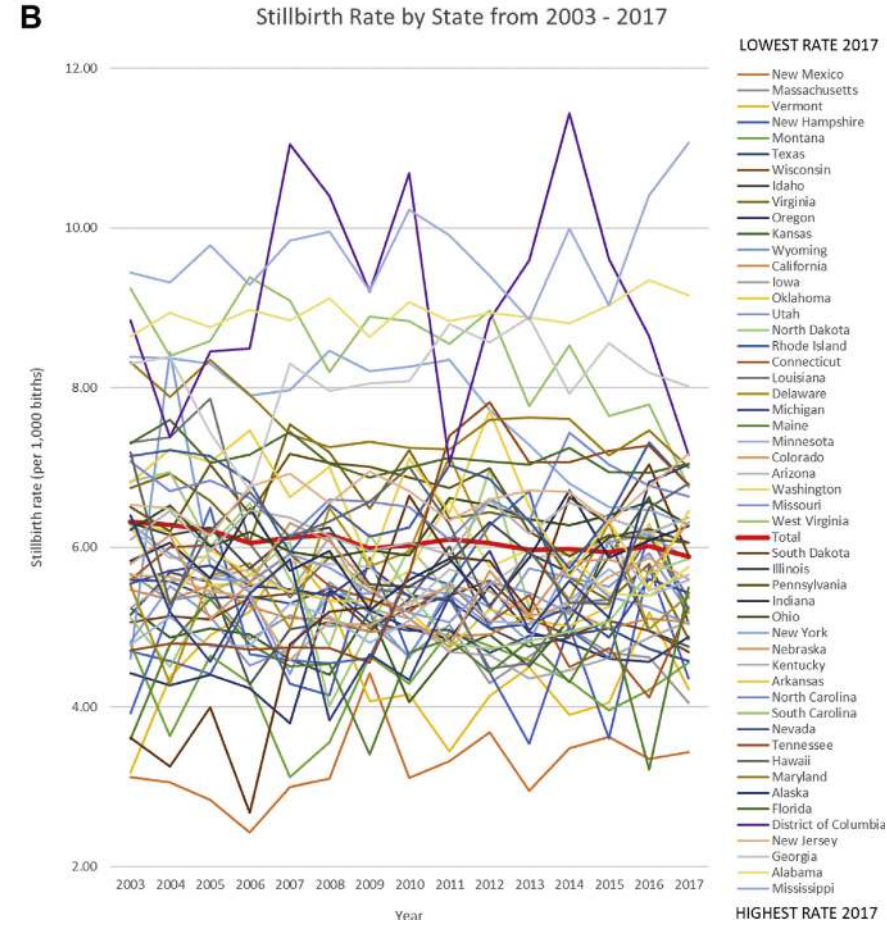
This article reviews the evidence for the role of the placenta in the etiology of stillbirth, initially considering epidemiologic studies of risk factors for stillbirth and how these may mediate their effects through the placenta. We then consider placental abnormalities reported in cases of stillbirth and how the placental etiologies change across gestation. We postulate that the presence of selective placental abnormalities is of significance in future pregnancies.

RISK FACTORS FOR STILLBIRTH IN HIGH-INCOME COUNTRIES

In HICs, stillbirths usually occur in the antepartum period, in contrast to LMICs, where approximately 50% of stillbirths occur during labor. A review of 15,840 stillbirths occurring in the United States during 2014 found that the largest proportion (30%) were unexplained.[7] Where a cause of death was reported, complications with the placenta, cord, or membranes were most the frequently cited cause (28% of deaths), followed by maternal complications (14%) and congenital abnormalities (10%). Importantly, these classifications incorporated findings from autopsy in only 11.7% of cases and histopathological examination of the placenta in 47.7% of cases, which may account for the high proportion of "unexplained" stillbirths.[7] Factors associated with stillbirth have been extensively investigated using a variety of epidemiologic methods, including large retrospective cohort and prospective case-control studies, in some cases there have been sufficient numbers of studies to undertake meta-analyses. In the United States, the Stillbirth Collaborative Research Network (SCRN) has undertaken and published a case-control study on a well-characterized group of 614 stillbirths and 1816 live births.[8] In this study, examples of factors occurring before pregnancy that were independently associated with stillbirth are shown in **Table 1** with their respective adjusted odds ratios (aORs). However, these factors are present in only 19% of stillbirths, indicating that the bulk of stillbirths occur in women who do not have risk factors present in early pregnancy.[8]

Analysis of stillbirths in other HICs confirms the relationship between these factors and stillbirth. Systematic reviews coupled with large meta-analyses suggest the odds ratio (OR) for stillbirth in women with a previous stillbirth is 4.83 (95% confidence interval [CI] 3.77–6.18),[9] for women $\geq$40 years of age it is 2.12 (95% CI 1.86–2.42),[10] and with cigarette smoking the OR is 1.43 (95% CI 1.32–1.54).[11] These meta-analyses suggest that the data from the SCRN study are consistent with information from many studies performed across a variety of international settings.


A
Stillbirth Rate in USA
Stillbirth Rate (per 1,000 births)
7.00
6.50
6.00
5.50
5.00
4.50
4.00
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year


B
Stillbirth Rate by State from 2003 - 2017
Stillbirth rate (per 1,000 births)
12.00
10.00
8.00
6.00
4.00
2.00
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
Year
LOWEST RATE 2017
New Mexico
Massachusetts
Vermont
New Hampshire
Montana
Texas
Wisconsin
Idaho
Virginia
Oregon
Kansas
Wyoming
California
Iowa
Oklahoma
Utah
North Dakota
Rhode Island
Connecticut
Louisiana
Delaware
Michigan
Maine
Minnesota
Colorado
Arizona
Washington
Missouri
West Virginia
Total
South Dakota
Illinois
Pennsylvania
Indiana
Ohio
New York
Nebraska
Kentucky
Arkansas
North Carolina
South Carolina
Nevada
Tennessee
Hawaii
Maryland
Alaska
Florida
District of Columbia
New Jersey
Georgia
Alabama
Mississippi
HIGHEST RATE 2017

Studies examining the impact of risk factors that develop during pregnancy have shown consistent associations between a small for gestational age (SGA) fetus and stillbirth (relative risk [RR] 8.0, 95% CI 6.5–9.9; aOR 6.22, 95% CI 3.79–0.23),[12] as well as the development of hypertensive disorders of pregnancy/preeclampsia (RR 2.8, 95% CI 1.5–5.1; adjusted RR 1.45, 95% CI 1.20–1.76)[12,13] and maternal perception of reduced fetal movements and stillbirth (RFM; aOR 3.54, 95% CI 2,44–5.15).[14] In particular, the association between SGA fetuses and stillbirth are thought to reflect fetal growth restriction (FGR), where the fetus does not achieve its genetic growth potential. There are also relationships between FGR and hypertensive disorders of pregnancy and FGR and RFM.

The risk factors presented here for stillbirth in HICs provide some initial clues to the relationship between placental dysfunction and stillbirth. Many of the risk factors for antepartum stillbirth described here, including obesity,[15] maternal age $\geq$40,[16] cigarette smoking,[17] reduced fetal movements,[18] FGR,[19] and hypertensive disorders of pregnancy,[20] are associated with abnormalities of placental structure and/or function. Although a detailed review of these ex vivo studies is beyond the scope of this article, a significant body of work has described changes in placental morphology, cell proliferation, cell death, and inflammation in the presence of these risk factors. Placental dysfunction, culminating in a failure to meet the oxygen and nutrient requirements of the fetus, may be a common pathway linking epidemiologic risk factors to stillbirth.[21]

Further evidence regarding the important role of the placenta in stillbirth and pregnancy loss can be inferred from the increased rate of stillbirth and SGA infants seen in confined placental mosaicism (CPM). CPM is a condition in which the placenta has a numerical or structural chromosomal abnormality, whereas the fetus has normal chromosomes. Analysis of 115 cases of CPM identified by prenatal testing compared with 230 unaffected controls found an increased rate of SGA infants (15% compared with 5%),[22] and a review of cases of CPM reported before 2011 found that 9.3% were associated with FGR and 7.2% of cases ended in stillbirth or spontaneous miscarriage.[23] This finding suggests that even when abnormalities are restricted to the placenta, they exert an important effect on fetal growth and survival.

ASSOCIATION BETWEEN PLACENTAL ABNORMALITIES AND STILLBIRTH

Placental size is routinely measured as part of the macroscopic assessment of the placenta during histopathological examination, and placental weight relative to birthweight is associated with stillbirth. A large cohort study found that placental weight is lower in stillbirths than in live births at all gestational ages. The proportion of stillbirths with fetal:placental weight ratio in the top 10% for gestational age, increased with advancing weeks' gestation, from 29% of stillbirths between 25 and 26 weeks' gestation to 36% between 39 to 40 weeks' gestation.[24] Two smaller studies provide

Fig. 1. (*A*) The stillbirth rate ($\geq$20 weeks' gestation) for all reported births in the United States from 2003 to 2017 showing an overall annual rate of reduction of 0.28% per year. Light grey lines indicate 95% confidence interval. (*B*) The stillbirth rates for individual states from 2003 to 2017, ranging from those with the lowest to highest rates in 2017 demonstrating wide variation in stillbirth rates throughout the country. For comparison, the average stillbirth rate for the United States is shown in red. (*Data from* Centers for Disease Control and Prevention (CDC). National Center for Health Statistics. Vital Statistics Online Data Portal. Available at: https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm. Accessed Sept 30 2019.)

Table 1
Characteristics in early pregnancy and their association with stillbirth

Characteristic (Comparison)	Adjusted Odds Ratio (95% Confidence Interval)
Non-Hispanic black ethnicity (vs non-Hispanic white)	2.12 (1.41–3.20)
Previous stillbirth (vs previous live birth)	5.91 (3.18–11.00)
Diabetes (vs no diabetes)	2.50 (1.39–4.48)
Obesity ($\geq$35 kg/m^2) (vs. appropriate weight)	1.73 (1.23–2.45)
Maternal age $\geq$40 (vs 20–24 y)	2.41 (1.24–4.70)
Cigarette smoking $\geq$10 per day (vs nonsmoker)	1.55 (1.02–2.35)
History of drug misuse (vs none)	2.08 (1.12–3.88)

Data from Stillbirth Collaborative Research Network Writing Group. Association between stillbirth and risk factors known at pregnancy confirmation. JAMA 2011;306(22):2469-2479.

conflicting data as to whether or not placental weight is related to the recorded cause of stillbirth. The first study of 126 singleton stillbirths found the placental weight was less than 10th percentile in 57% of cases; the fetal:placental weight ratio was in the top decile in 58% of stillbirths due to FGR, 57% due to placental insufficiency, and in 47% of stillbirths from unknown cause.[25] In contrast, another study of 145 singleton stillbirths found that placental weight was reduced only in stillbirths associated with placental pathology, but not other causes.[26] Therefore, whether or not placental size predisposes to stillbirth, or is simply an indicator of underlying placental dysfunction, remains unknown.

A systematic review to determine the likelihood of diagnosing a cause of stillbirth from placental examination identified 41 studies that met the inclusion criteria.[27] There was considerable variation among included studies, as 63% were retrospective, sample sizes varied between 5 and 750 participants, and diagnostic criteria were specified in only 29% of studies. In the 13 studies of 3636 cases that investigated the frequency that placental lesions caused stillbirth, there was a large variation in conditions reported as placental causes of stillbirth, with more than 30 different "causes" recorded. Placental abruption was the most frequently attributed placental cause of death, although this was reported in only 10 (77%) of 13 studies and placental abruption accounted for 7% to 14% of deaths in these studies. Other frequently reported placental causes of stillbirth included infarction (54% of studies), chorioamnionitis, and villous dysmaturity (both reported by 38% of studies).[27] The lack of comparability between the recording of placental pathology and the classification system used meant that the proportion of stillbirths attributed to a placental cause of death varied considerably from 11% to 65%. There was a relationship between the number of categories of placental disease in the classification system and the proportion of cases determined as having a placental cause of death, which indicates that the ability of the classification system to record placental conditions may affect the cause of death attributed. In addition, a further 5 studies of 934 cases found that placental abnormalities, including placental abruption, praevia, vasa praevia, placental insufficiency, and other placental abnormalities, were associated with 17% of stillbirths. This study highlighted the need for consensus in the definition of placental lesions and application of classification systems that facilitate recording of placental pathology.[27]

Drawing conclusions about whether a placental abnormality caused or was associated with stillbirth can be challenging. In a series of analyses of live births, Pathak and colleagues[28] described that histopathological abnormalities of the placenta, including

ascending genital tract infection, chronic placental underperfusion, intervillous thrombus, and villitis of unknown etiology, could be seen in apparently uncomplicated pregnancies (in 11.3%, 7.7%, 5.0%, and 3.7% of cases, respectively; **Table 2**). Other abnormalities, such as massive perivillous fibrin deposition, were seen more frequently in pregnancies complicated by hypertensive disorders of pregnancy (4%) or SGA (2%) infants compared with uncomplicated pregnancies (0.2%), suggesting these disorders may be more specific to adverse outcomes.[28]

To address the issue that placental pathology is seen in apparently healthy placentas, both case and control groups within the SCRN study were used to determine the frequency of placental abnormalities in stillbirth, reducing the potential for selection bias. Pinar and colleagues[29] reported findings from 518 singleton stillbirths and 1200 live births that found a similar proportion of live births reported chorioamnionitis to the study by Pathak and colleagues[28] (12%). However, all reported placental abnormalities were found more frequently in stillbirths (see **Table 2**). The most frequently reported abnormalities in stillbirth were acute chorioamnionitis of the free membranes (30%) or chorionic plate (23%), retroplacental hematoma (24%), and fetal vascular thrombi in the chorionic plate (23%).[29] Importantly, Pinar and colleagues[29] examined the relative frequency of placental lesions across gestation and found that lesions associated with infection, including chorioamnionitis and funisitis, were most common in births before 24 weeks' gestation, and were more common in live births than stillbirths before 31 weeks' gestation. In contrast, retroplacental hematoma was seen in equal proportions of live births and stillbirths before 24 weeks' gestation, but after that time, such hematomas were always more common in stillbirths. Although these disorders were most common at earlier gestations, distal villous immaturity, villous infarction, and fetal vascular thrombi were more frequent in cases of stillbirth after 32 weeks' gestation.[29] Thus, the placental lesion should be considered in the context of the gestation of the stillbirth and the clinical information surrounding the fetal death.

Man and colleagues[30] provide further information about the differing frequency of placental lesions in 946 cases of fetal death and stillbirth, of which 32% were deemed to have a placental cause of death. A placental cause of death was more common after 24 weeks' gestation compared with earlier losses. Of the 307 cases with a placental cause of death, the most frequent observation was ascending genital tract infection, chorioamnionitis, which was evident in 57% of cases (see **Table 2**). Man and colleagues[30] also reported the frequency of placental abnormalities (55/307) that were felt to have direct significance for the cause of death, most frequently maternal vascular malperfusion and fetal vascular occlusion, with rare causes including massive perivillous fibrin deposition and chronic histiocytic intervillositis. In addition, there were 54 cases in which placental lesions were seen (eg, focal villitis of unknown etiology) but were of uncertain clinical significance. As with Pinar and colleagues,[29] this cohort study also demonstrated variation in the frequency of lesions across gestation, with maternal vascular malperfusion noted to be more common in stillbirths occurring between 24 and 30 weeks' gestation compared with cases after 35 weeks' gestation. Later losses (>35 weeks' gestation) were more likely to have either no placental abnormalities or have the presence of lesions of uncertain significance.

These 2 large-scale studies of placental morphology after stillbirth clearly show that a diverse range of placental pathologies may be seen in stillbirth. Ptacek and colleagues[27] identified a total of 20 studies including 1447 cases of stillbirths that investigated the role of specific lesions in stillbirth, including chorioamnionitis, cord abnormalities, delayed villous maturation, fetal thrombotic vasculopathy, hemorrhagic endovasculitis and villitis of unknown etiology. Most studies (89%) replicated the

Table 2
Frequency of placental lesions in 3 large studies: Stillbirth Collaborative Research Network (SCRN) case-control study, a UK single-center cohort study of stillbirths, and a single UK center cohort study of live births

		SCRN Study[29]		Man et al,[30] 2016	Pathak et al,[28] 2011
Lesion Type	Placental Feature	Stillbirth, %, n = 518	Liveborn Control, %, n = 1200	Stillbirth, %, n = 946	Healthy Live Birth, %, n = 935
Infective	Acute chorioamnionitis (membranes)	30.4	12.0	—	—
Infective	Acute chorioamnionitis (chorionic plate)	23.2	11.9	—	—
Infective	Ascending genital tract infection	—	—	18.6	11.3
Vascular	Placental abruption/ retroplacental hematoma	23.8	4.5	4.0	Study stated this lesion would be examined but none reported
Vascular	Multifocal or diffuse parenchymal infarction	13.7	4.5	—	—
Vascular	Chronic maternal underperfusion	—	—	4.4	7.7
Inflammatory	Chronic diffuse villitis/villitis of unknown etiology	1.6	0.5	Not specified	3.7
Inflammatory	Chronic histiocytic intervillositis	—	—	0.3	0.2
Inflammatory	Massive perivillous fibrin deposition	9.2	1.5	0.6	0.2
None	Normal histology	—	—	35.5	71.6

The SCRN study was a case-control study, so the frequency of lesions between stillbirth (case) and livebirth (control) could be directly compared, as the descriptions of abnormalities by individual studies showed minor differences. Data shown as % of participants within each column. -, no data reported regarding the lesion in this study.

finding of Pinar and colleagues that placental lesions were more commonly seen in cases of stillbirth. Yet, none of the lesions seen were either specific to stillbirth or a specific cause of stillbirth. This is best exemplified by fetal thrombotic vasculopathy, which was reported in association with various possible causes of death, including cytomegalovirus infection and umbilical cord accidents or abnormal cord coiling.[31–33]

Exploring the reported associations between rare placental lesions and stillbirths can be challenging because of the large sample sizes required. Useful information has been obtained from aggregate data in systematic reviews for chronic histiocytic intervillositis (CHI) and villitis of unknown etiology (VUE). By pooling data from 67 cases Contro and colleagues[34] demonstrated that CHI was associated with FGR in 66.7% of cases and the rate of live birth was 53.6%. Derricott and colleagues[35] reported the findings of VUE described in 10 studies including 2527 women with VUE and 20,590 controls; VUE was seen more frequently in cases of SGA and stillbirth, but only SGA demonstrated a significantly higher frequency of VUE compared with unaffected controls (28.6% vs 15.6%, $P<.001$), although this may be because of a lack of statistical power to detect a difference in stillbirths compared with live births (7.1% vs 5.1; $P = .14$). Critically, most of the placental lesions described in the preceding paragraphs are made following qualitative examination of the placenta by perinatal pathologists who not only identify lesions but grade their severity. As noted earlier, many studies do not include or refer to definitions of placental lesions and may also not obtain samples from the placenta in a standardized manner, limiting the comparability of data between studies. To address this, a multidisciplinary group was convened in Amsterdam in 2014 to agree to a standardized method for placental sampling and definitions of commonly occurring placental lesions.[36] To date, this document has been cited by more than 230 publications and hopefully, standardizing definitions of placental abnormalities will improve the accuracy of reporting of placental lesions and the generalizability of study findings.

CLINICAL UTILITY OF PLACENTAL EXAMINATION AFTER STILLBIRTH

Not surprisingly, examination of the placenta is recommended in clinical practice guidelines for the investigation of stillbirth. The systematic review of placental pathology in stillbirth found that in 9 studies of 1779 cases, the proportion of stillbirths with evidence of useful placental pathology ranged from 31.5% to 84.0% and the proportion of placental causes that were diagnosed from information found in the placenta ranged from 15.4% to 87.0%.[27] A study of 144 cases of stillbirth from a single center in the United States found that clinical and laboratory investigations found a cause of death in 24% of cases, placental examination increased the proportion with a probable cause to 61% of cases, and addition of autopsy results gave a probable cause in a total of 74% of cases.[37] Thus, placental examination had the largest incremental value in identifying the probable cause of death (with a rise of 37%). Importantly, this study found the information available altered clinical management in 36% of cases. A small study of 71 cases of stillbirth was used to determine the contribution of histopathological examination of the placenta to the classification of the cause. This study found placental assessment significantly reduced the likelihood of stillbirth being classified as unexplained (OR 0.17; 95% CI 0.04–0.70).[38] The findings of placental investigation were included in the classification of stillbirth in 47% of cases and in 16% the cause of death was determined primarily by placental examination. A study of 125 stillbirths from Scotland found that 79 (61%) showed placental changes that were considered to have caused death and a further 21 (16%) showed findings likely to influence the management of subsequent pregnancies. Interestingly, this article compared the

frequency of detection of placental lesions with that of genetic abnormalities that were present in 3% of cases.[39] Although these 3 studies are comparatively small single-center cohorts, their findings are similar, indicating that placental examination is the investigation most likely to identify a cause of stillbirth. Consequently, histopathological investigation of the placenta is one of the most cost-effective tests to identify information regarding the cause of stillbirth and may influence care in subsequent pregnancies.

The clinical utility of the findings of placental histopathological examination is dependent on how the information obtained is integrated into the clinical care for women whose infants are stillborn. First, as Miller and colleagues[37] highlight, some causes of stillbirth may be apparent from maternal history and clinical observations. Cases in point include a massive placental abruption presenting with abdominal pain or vaginal bleeding, or a pregnancy with a high level of suspicion of FGR from antenatal ultrasound scans. This information should be passed on to the pathologist so they can interpret histopathological observations in the correct clinical context.[40] Second, the clinical meaning of placental lesions should be conveyed; for example, increased syncytial knots or syncytial nuclear aggregates are indicative of accelerated villous maturation, Such lesions are seen in maternal vascular malperfusion, which may be of particular relevance in the presence of FGR or preeclampsia.[41,42] One proposal from Turowski and colleagues[43] is a clinically orientated classification that combines individual placental findings into 9 clinically informative categories: (1) placenta with normal morphology, according to gestational age; (2) placenta with chorioamnionitis; (3) placenta with villitis and intervillositis; (4) placenta with maternal circulatory disorders (decidual vasculopathy); (5) placenta with fetal circulatory disorders; (6) placenta with delayed villous maturation; (7) placenta with findings suggestive of genetic aberration; (8) placenta with implantation disorders; and (9) placenta with other lesions. Applying this system to 315 placentas from pregnancies that ended in stillbirth found good levels of interobserver agreement (0.79). In this cohort, chorioamnionitis was a relatively rare diagnosis (3.8%), with the largest group comprising maternal circulatory disorders (75.9%); in agreement with other studies reported here, villitis/intervillositis and features suggestive of genetic aberrations were rare (frequencies of 1.9% and 1.3%, respectively), suggesting that this classification produces information that is consistent with other studies and has good interobserver reliability. A subsequent analysis of view from 62 obstetricians and maternal-fetal medicine consultants believed that implementing the reporting system would aid interpretation of placental pathology reports, which can then be used by mothers to plan future pregnancies with the help of health care professionals.[44]

There is a paucity of studies that have examined the effect of placental causes of stillbirth on the outcome of subsequent pregnancies. A large meta-analysis of 16 studies of 3,412,079 pregnancies found women who had a history of stillbirth had an independently high risk of stillbirth in a subsequent pregnancy (aOR 4.83%, 95% CI 3.77–6.18) with an absolute risk of 2.5%.[9] As few studies separated their analysis depending on the cause of stillbirth, the reasons for this increased risk are unclear. However, placental conditions likely have a role, as placental abruption, preeclampsia, and low-birthweight infants, all of which relate to placental dysfunction, are more common in pregnancies after stillbirth.[45] Two smaller studies have attempted to identify whether specific placental conditions increase the risk of adverse pregnancy outcomes after stillbirth. A study of 163 women in the Netherlands who had a pregnancy loss after 16 weeks' gestation described a further loss in a subsequent pregnancy in 11 cases.[46] Clinical information identified a cause for 7 of the subsequent stillbirths; these included placental conditions such as massive perivillous fibrin deposition,

placental bed pathology/failure of conversion of spiral arteries, prelabor rupture of membranes, and, in 2 cases, neither the cause of the index or subsequent stillbirth could be determined.[46] A larger study of 273 women from 3 Italian hospitals found a frequency of adverse outcome (perinatal death, FGR, preterm birth <34 weeks' gestation, respiratory distress) in late pregnancy was 24.5%, including 2 further perinatal deaths.[47] Monari and colleagues[47] found that adverse neonatal outcome was more frequent in women who had maternal vascular malperfusion in their index stillbirth compared with those who had an unexplained stillbirth or other causes (aOR 2.1, 95% CI 1.2–3.8), this study also found maternal obesity was independently associated with increased risk of perinatal outcome (aOR 2.1, 95% CI 1.1–4.3).

Preliminary data from a detailed comparison of placental structure in index stillbirths (n = 10 in each group) found that syncytial nuclear aggregates were increased in index stillbirths and subsequent pregnancies compared with gestation age–matched controls, whereas other features, such as villous vascularity, returned to normal levels in subsequent pregnancies (Ganguly, unpublished data, 2017). This ex vivo evidence is consistent with persistence of maternal vascular malperfusion in a proportion of cases. The recurrence risk of other related placental conditions also has been explored in pregnancies that did not necessarily end in stillbirth or adverse pregnancy outcomes. Again, there is strong evidence that placental conditions may recur in subsequent pregnancies. Placental abruption is much more common in women with a history of placental abruption compared with unaffected index pregnancies (aOR 93, 95% CI 62–139).[48] Contro and colleagues[34] described that CHI is associated with a recurrence risk of 80%, and only 50% of pregnancies result in the birth of a liveborn infant and a single-center study found high-grade VUE recurred in 7 (37%) of 19 cases, and in those who had recurrent VUE, 3 were SGA (43%).[49] This provides evidence that histopathological findings from the index pregnancy can provide information regarding the prognosis of a subsequent pregnancy.

USING KNOWLEDGE ABOUT THE PLACENTA TO PROVIDE CARE IN A PREGNANCY AFTER STILLBIRTH

Given the evidence regarding the risk of recurrence of placental conditions in pregnancies after stillbirth, additional measures should be implemented to maximize placental health; for example, stop cigarette smoking, optimize maternal weight, and consideration should be given to giving aspirin to reduce the risk of placental disease.[50] There is very little evidence originating from studies of women with prior stillbirth to support a recommendation of aspirin,[51] but it extrapolates from a large systematic review that found commencing aspirin at a prophylactic dose before 16 weeks' gestation reduced the risk of perinatal death in late pregnancy (RR 0.41 vs 0.93).[52] Other novel treatment regimens are also now being established for other placental conditions, including CHI, which may improve outcomes.[53] However, these approaches should be regarded as empirical and further intervention studies are needed.

Because of the increased risk of an SGA fetus in a pregnancy following stillbirth, additional screening should be put in place to ensure normal fetal growth until birth. In addition to routine assessment of fetal growth, ultrasound also has been used to assess placental structure. Importantly, abnormal uterine or umbilical artery flow with a thickened placental disc may reflect the underlying disease process (eg, maternal vascular malperfusion or placental bed disorders), and these observations are associated with complications such as FGR and stillbirth.[54] Toal and colleagues[55] examined the predictive accuracy of a combination of maternal serum screening (16–18weeks), second trimester uterine artery Doppler, and placental morphologic

condition (shape and/or texture), and found there were no cases of unexpected stillbirth in the cohort, and no cases of severe early-onset FGR after a normal placental profile. Combining ≥2 abnormal components of the test predicted 14 of 19 pregnancies that developed severe early-onset intrauterine growth restriction (sensitivity 74%) and 15 of 22 pregnancies that ended in stillbirth (sensitivity 68%). This approach could allow antenatal surveillance to be directed to women who have the greatest chance of adverse pregnancy outcomes, as this is informed by the possibility of recurrent placental disease. Further studies are needed to determine how information about the placenta in the index stillbirth can be combined with assessment of placental morphology in a subsequent pregnancy to predict neonatal outcome.

SUMMARY

Because of the crucial role the placenta plays in determining the outcome of pregnancy, its pivotal role in stillbirth is expected. A wide range of placental abnormalities have been reported in cases of stillbirth, and although for some of these features there is a clear relationship to the cause of death (eg, placental abruption), for others further work is needed to understand the pathophysiology and how other factors including gestation, maternal ethnicity, and health behaviors may interact to produce the placental phenotype and lead to stillbirth. Importantly, translating the findings from histopathological investigation of the placenta into clinical practice reduces the proportion of unexplained stillbirths and provides information that informs care of subsequent pregnancies. Consequently, sending the placenta for histopathological examination after stillbirth or perinatal death is essential to provide valuable information for bereaved parents that may be of benefit in subsequent pregnancies.

DISCLOSURE

The authors had no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and have no other relationships or activities that could appear to have influenced the submitted work.

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