



Stillbirth and intrauterine fetal death

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Stillbirth
and
intrauterine
fetal
death:
role
of
routine
histopathological
placental
findings
to
determine
cause
of
death

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KEYWORDS:
histology; miscarriage; placenta; stillbirth

ABSTRACT

Objectives

Placental abnormalities are a common cause of death in stillbirth, ranking second only to unexplained deaths, though there is wide variation in the proportion attributed to placental disease. In clinical practice, interpretation of the significance of placental findings is difficult, since many placental features in stillbirths overlap with those in live births. Our aim was to examine objectively classified placental findings from a series of > 1000 autopsies following intrauterine death in order to evaluate the role of placental histological examination in determining the cause of death.

Methods

As part of a larger study evaluating several aspects of autopsy findings in intrauterine death, a dedicated database was used to collate antenatal and postmortem examination details for all cases examined between 2005 and 2013 at two tertiary specialist centers in London, UK. Histological findings for placentas were evaluated in relation to the final cause of death.

Results

Among 1064 intrauterine deaths, 946 (89%) cases had the placenta submitted for examination as part of the autopsy. Of these, 307 (32%) cases had the cause of death assigned to abnormalities of the placenta, cord or membranes. Around one third of stillbirths (= 24 weeks) had some isolated placental histological abnormality

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identified, many of uncertain significance, a significantly greater proportion than in cases of second-trimester intrauterine fetal demise ($P < 0.0001$). The cause of death was ascending infection in 176/946 (19%) cases, peaking at 22 weeks' gestation, with significantly more black mothers having ascending infection compared with other ethnicities ($P < 0.0001$). Maternal vascular malperfusion

was the largest category of placental abnormalities in stillbirth, with peak prevalence in the early third trimester. There were 18 (2%) cases with specific histological abnormalities, including chronic histiocytic intervillitis and massive perivillous fibrin deposition.

Conclusions

Placental pathologies represent the largest category of cause of intrauterine death. Placental histological examination is the single most useful component of the autopsy process in this clinical setting. A minority of cases are associated with specific placental pathologies, often with high recurrence rates, that can be diagnosed only on microscopic examination of the placenta. Many deaths remain unexplained, although placental histological lesions may be present which are of uncertain significance. A rigorous, systematic approach to placental pathology research and classification may yield better understanding of the significance of placental findings and reduce the rate of unexplained intrauterine deaths. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

Placental abnormalities are the most common cause of stillbirth, ranking second only to unexplained deaths¹. A review of over 40 studies, examining placental pathology findings in association with stillbirth, reported that the placenta was the likely cause of fetal demise in 11–65% of cases, with placental abruption being the most frequent specific cause². There are no first- or second-trimester tests of placental function in routine clinical use which can predict stillbirth reliably, although uterine artery Doppler indices and maternal serum pregnancy-associated plasma

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Table

1

Summary of histological findings of cord, membranes and placenta in 931 intrauterine deaths with complete placental histology results

Histology Early IUFD Late IUFD Stillbirth All

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Normal cord, membranes and placenta 94 (47) 70 (42) 172 (30) 336 (36)
Isolated abnormality in placenta 38 (19) 31 (19) 196 (34) 265 (28)
Isolated abnormality in cord or membranes 11 (6) 21 (13) 50 (9) 82 (9)
Placental abnormality with abnormality in membranes or cord 55 (28) 43 (26) 150
(26) 248 (27)
Total 198 165 568 931

Data are given as n (%) or n. Early intrauterine fetal death (IUFD) was defined as intrauterine death < 20 weeks, late IUFD was death at 20–23 weeks and stillbirth was death = 24 weeks. Fifteen cases with absent or incomplete placental histology have been excluded.

protein-A levels show promise³. Therefore, the diagnosis of placental disease is often determined only after fetal death, based on placental histological examination⁴.

There are a range of specific placental pathologies reported in association with stillbirth^{5,6} which can usually be identified in addition to any changes occurring secondary to intrauterine retention following fetal death⁷. The difficulty in clinical practice is that differences in frequencies of specific lesions or pathologies in stillbirths compared with live births based on population studies are not helpful in determining the clinical significance of findings in an individual case, since there is overlap in the frequency distributions of these populations.

The aim of this study was to examine, in a large series of > 1000 cases of intrauterine death which were autopsied at two tertiary specialist centers in London, the objectively classified placental findings, in order to evaluate the role of placental histological examination in determining cause of intrauterine death.

METHODS

This study was part of a larger project examining several aspects of autopsy practice in a series of intrauterine deaths. Cases were included from two specialist pediatric and perinatal pathology units in London (Great Ormond Street Hospital and St George's Hospital). For each case,

> 400 data fields were extracted and entered into a dedicated research Microsoft Access Autopsy Database (Microsoft Corp., Redmond, WA, USA) including autopsy and antenatal details. Cases included early intrauterine fetal deaths (IUFD) (< 20 weeks' gestation), late IUFDs (20–23 weeks) and stillbirths (= 24 weeks), from 2005–2013 inclusive.

For the purposes of this study, for each data field, predefined objective criteria were used for classification⁸, based on recorded autopsy findings, to ensure data consistency. Placental cause of death was diagnosed in cases with clear clinical and/or pathological features of abruption, those with unequivocal features of underlying maternal vascular malperfusion (MVM)⁹, and those with other specific and well-defined placental pathologies, such as chronic histiocytic intervillitis (CHI). Cases with only histological changes of uncertain significance, such as mild patchy villitis of unknown etiology and patchy increased syncytial knot formation, were classified as 'placental

lesion of unknown significance' rather than placental cause of death.

Non-identifiable data were extracted and analyzed through queries and statistical tests run using Microsoft Access and Microsoft Excel (Microsoft Corp.), GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA) and Stats Direct (StatsDirect Ltd., Altrincham, UK). Proportions were compared using the chi-square test and continuous variables using the Mann-Whitney U-test, with $P <$

0.05 being considered statistically significant. The study was approved by the local research ethics committee.
RESULTS

Of the total of 1064 intrauterine deaths with results available from autopsy, 946 (89%) had the placenta submitted as part of the postmortem examination, including 203/246 (83%) cases of early IUFD, 168/179 (94%) cases of late IUFD and 575/639 (90%) stillbirths. Approximately one third of all deaths had completely normal histology of the cord, membranes and placenta (Table 1), while 307 (32%) cases had a cause of death assigned to abnormalities of the placenta (Table 2); 57% of these were cases of ascending infection, associated mainly with second-trimester loss.

Around one third of stillbirths had at least some abnormality identified on histological examination of the placenta with normal membranes and cord (Table 1), a significantly greater proportion than in cases of IUFD ($z = 5.7$, $P < 0.0001$). There was a placental cause of

Table
2

Cause of intrauterine death (COD) related to abnormalities of the placenta, including those with COD based on clinical history

Placental COD	n (%)
Abruption	38 (12)
Ascending genital tract infection	176 (57)
Antenatally diagnosed fetal growth restriction	17 (6)
Placental lesion	60 (20)
Fetal vascular occlusion*	9/60 (15)
Chronic histiocytic intervillitis*	3/60 (5)
Massive perivillous fibrin deposition*	6/60 (10)
Maternal vascular malperfusion	42/60 (70)
Clinical pre-eclampsia	16 (5)
Total	307

*Specific details of these cases are given in Table 3.

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Placental histology and cause of intrauterine death

Table
3

Details of specific cases of intrauterine death with definitive histological

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abnormalities other than non-maternal vascular malperfusion which were the likely cause of death

Degree of GA Maternal Maternal MA
Placental pathology Type of death maceration (weeks) ethnicity BMI (kg/m2)
(years)

Fetal vascular occlusion

Case 1 Intrauterine death >
24 h Moderate 37 white NA 18
Case 2 Intrauterine death >
24 h Present but N/S 41 white 51.1 28
Case 3 Intrauterine death >
24 h Mild 25 Black NA 29
Case 4 Intrauterine death >
24 h Severe 29 white 23.1 40
Case 5 Intrauterine death >
24 h Severe 38 white 23.2 30
Case 6 Intrauterine death >
24 h Present but N/S 34 white 23.2 31
Case 7 Intrauterine death >
24 h Severe 28 white NA 39
Case 8 Intrauterine death >
24 h Severe 40 white 36.2 30
Case 9 Intrauterine death >
24 h Severe 36 NA NA 26

Chronic histiocytic intervillitis

Case 1 Intrauterine death >
24 h Present but N/S 26 white 24.5 39
Case 2 Fresh intrapartum death None 24 NA NA 27
Case 3 Intrauterine death >
24 h Moderate 29 Asian NA 41

Massive perivillous fibrin deposition

Case 1 Intrauterine death >
24h Mild 35 NA NA NA
Case 2 Intrauterine death <
24 h None 17 Black 26.2 30
Case 3 Intrauterine death >
24 h Severe 39 Asian 28 30
Case 4 Intrauterine death >
24 h Severe 35 white NA 20
Case 5 Intrauterine death <
24 h Mild 27 white NA 35
Case 6 Intrauterine death >24 h Mild 41 white NA 40

Cases with chronic histiocytic intervillitis all occurred in the late second/early third trimester, whereas cases of massive perivillous fibrin deposition affected all gestational ages from second trimester to term. BMI, body mass index; GA, gestational age at delivery; MA, maternal age; NA, not available; N/S, not specified.

death in 168/575 (29%) stillbirths, including 59 cases 16 of ascending infection, 30 of placental abruption, 24 14

31 33 35 37 39 >40

with changes associated with antenatally diagnosed fetal

growth restriction (FGR) or pre-eclampsia (PE) and

55 with definite histological placental abnormalities of

likely direct significance for the cause of death (including

mainly MVM (n =

39), but also massive perivillous fibrin

Percent of cases

12

10

8

6

4

deposition (MPVFD), CHI and fetal vascular occlusion

(Table 3)). In addition, there were 54 (8%) stillbirths

2

with definite placental lesions, but of uncertain clinical significance (such as focal villitis of unknown etiology).

There was ascending infection in 176 (19%) cases, with associated intrauterine death peaking at 22 weeks' gestation (Figure 1). Black mothers were significantly more likely to have ascending infection compared with mothers of other ethnicity ($z = 7.04, P < 0.0001$). There

were two gestational-age peaks in cases with histological evidence of MVM, one at 24 weeks' gestation and a smaller peak at 28–29 weeks. 90% of MVM-associated cases were IUFDs with an intrauterine retention time of at least 24 h, death occurring in the absence of labor or other maternal symptoms; 98% of fetuses with MVM had some degree of maceration, with the majority being severely macerated, as a result of the prolonged intrauterine interval after death.

Other than ascending genital tract infection, MVM represented the largest proportion of histological placental abnormalities within the 'placental lesion' cause of death category. However, there were 18 (2%) other cases with specific histological abnormalities of the placenta, including extensive fetal vascular occlusion (fetal thrombotic vasculopathy), CHI, MPVFD (Table 3,

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0

13 15 17 19 2123252729
Gestational age (weeks)

Figure

1

Gestational age at intrauterine death in 176 cases with features of ascending genital tract infection. There was a clear peak in the late second trimester of pregnancy consistent with such cases presenting as spontaneous miscarriage. The line indicates the four-period moving average (percent of cases).

Figures 2 and 3), most (83%) of which were deaths with an intrauterine retention time of > 24 h and fetal maceration. The median gestational age in these cases was 34.5 weeks.

There were 74 cases (15 early IUFDs, five late IUFDs and 54 stillbirths) with histological abnormalities of the placenta that were either not sufficiently severe to be the likely cause of death, or whose significance was uncertain but which could not be discounted completely as having contributed to death. These cases were labelled 'unexplained with placental lesion of unknown significance' (Figure 4) and included abnormalities such as isolated subjective increased syncytial knots/accelerated maturation, villitis of unknown etiology, scattered intervillous thrombi, focal areas of sclerotic villi with no other features

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70

8

60

7

50

40

Percent of cases

MVM FTV MPVFD CHI Abr/PET

24-30 31-34 35 to term

Percent of cases

30

20

10

2

0

1

Gestational age (weeks)

0

Placental disease

Figure

4

Relationship between gestational age and selected placental pathology categories, as percentage of total cases per group within each included gestational age category: unexplained

Figure

2

Relative frequencies of specific patterns of placental

cases with no risk factors or lesions (

); unexplained cases with

placental histological lesion of unknown significance, e.g. patchy disease in 575 stillbirth cases in which the placenta was examined.

Abr/PET, abruption/pre-eclamptic toxemia; CHI, chronic histiocytic intervillitis; FTV, fetal thrombotic vasculopathy/vascular occlusion; MPVFD, massive perivillous fibrin deposition; MVM, maternal vascular malperfusion.

low-grade villitis of unknown etiology (

); and maternal vascular malperfusion (MVM,

). MVM was relatively more common in the early third trimester, whereas lesions of uncertain significance were more common at term.

of fetal thrombotic vasculopathy, plasma cell deciduitis and small infarcts. The majority (72%) of these unexplained deaths were retained intrauterine deaths, with a retention period of > 24 h associated with maceration.

The gestational age of these cases peaked at 35–42 weeks' gestation, suggesting that such abnormalities were either incidental and more frequent with increasing gestational age or, if clinically significant, were associated with late stillbirth. There was no significant difference in gestational age or in maternal age between cases with unexplained placental lesions and those with specific placental abnormalities ($P = 0.32$ and $P = 0.40$, respectively).

DISCUSSION

There are three main findings of this study. First, placental pathologies represent a major category of cause of intrauterine death, and placental histological examination is a useful component of the autopsy process in this clinical setting. Second, whilst placental abruption and MVM represent the most common subgroups of placental pathologies, a minority of cases are associated with specific conditions, such as CHI, which can only be identified on histological examination. Third, in addition to cases with clear pathologies, there are numerous deaths which remain unexplained but in which there are placental histological lesions of uncertain significance (which also occur in normal live births)¹⁰; further research is required to better determine the pathophysiological significance of such lesions in individual cases.

In this large series of autopsies following intrauterine death, the placenta was submitted for examination in almost all (89%) cases. The majority of stillbirths were associated with some degree of placental abnormality on

Figure

3

Photomicrographs of placental parenchyma from

stillbirths, demonstrating: (a) placental pathology likely related directly to the cause of death (maternovascular malperfusion with histological examination, a significantly greater propor

ation than for second-trimester IUFDS, and in around 25% abnormality of uncertain significance (patchy villitis (original of stillbirths, placental abnormalities were the likely cause magnification × 100)); (b) histological

tion than for second-trimester IUFDS, and in around 25%

abnormality of uncertain significance (patchy villitis (original of stillbirths, placental abnormalities were the likely cause magnification × 100)). of death (including those in whom the diagnosis was based

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on clinical history, such as acute placental abruption). Of all intrauterine deaths in the study, around one third had an attributed placental cause of death, including placental abruption, ascending infection, FGR, pre-eclampsia and specific placental histological abnormalities. Placental causes of death therefore represent a major group of IUFDS in whom a cause is determined, consistent with previous data^{1,2,8}. Cases of ascending genital tract infection are usually associated with fresh mid-trimester loss and intrapartum deaths, in keeping with established associations between preterm labor and chorioamnionitis¹¹. However, around 20% of deaths were related to specific histological abnormalities of the placental parenchyma, of which MVM accounted for a large majority (70%); MVM cases were usually IUFDS with retention, almost all showing evidence of fetal maceration. The prevalence of these mechanisms varied with gestational age, deaths due to ascending infection peaking in frequency at around 22 weeks' gestation whilst deaths due to MVM were most frequent at 24–28 weeks. Black mothers were significantly more likely to be affected by ascending infection compared with white mothers. A previous American study similarly reported that intrapartum and early stillbirths are more common in non-Hispanic black women¹². The peak in frequency of MVM cases in the early third trimester is also consistent with published data on prediction of stillbirth using maternal serum biochemistry

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and/or maternal uterine artery Doppler velocimetry¹³. These approaches are relatively effective at detecting the underlying pathological process of maternal vasculopathy and placental malperfusion, and hence may identify cases of FGR, pre-eclampsia and intrauterine deaths due to typical early-onset MVM, as illustrated here. However, cases of clinically unexplained stillbirth at or near term much more rarely demonstrate such underlying pathology and hence prediction of these late intrauterine deaths is unlikely to be achieved based on such screening methods.

Rare cases of stillbirth demonstrated significant other

specific placental pathologies as the likely cause of death, at an average gestational age of around 32 weeks. The two main rare but specific histological diagnoses associated with intrauterine death were CHI and MPVFD. Both of these conditions are of uncertain etiology, but are postulated to be autoimmune in origin, with significant recurrence risks of around 80% and 20%, respectively^{16,17}. CHI is characterized by diffuse infiltration of the intervillous space by maternal CD68+ histiocytes, with or without associated fibrin deposition^{18,19}, whilst MPVFD demonstrates large areas of intervillous space filled with perivillous fibrin¹⁷, into which trophoblast may proliferate, preventing normal maternal perfusion. Both entities are not detectable reliably with maternal serum biochemistry or antenatal sonography and hence require routine placental histological evaluation for their diagnosis. CHI is of particular importance in those with recurrent pregnancy failure, since this condition may present with intrauterine death from the first through to the third trimester and may

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also be associated with other complications such as FGR¹⁶.

Importantly, there was an additional group, representing around 20% of all cases, in which the placenta showed some histological abnormality which was of uncertain significance. The majority of these otherwise unexplained deaths were retained intrauterine deaths and occurred predominantly at or near term. Several of the features in this group, such as patchy villitis of unknown etiology and non-specific isolated changes of abnormal villous maturation, such as hypermaturity, have been reported more frequently in complicated pregnancies and intrauterine deaths than in normal live births²⁰. However, in large unselected populations they are also reported frequently in clinically normal pregnancies delivering at term, and therefore the positive predictive values for their clinical significance is low¹⁰. At present there is no 'gold standard' or objective test to determine whether, in an individual case, such findings contributed to the cause of death; this is an important area for further research.

Whilst previous studies have reported on placental
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findings in autopsies following intrauterine death^{6,21}, our current findings are based on a large dataset with predefined objective criteria for classification of cause of death. This dataset also allows exploration of the relationship between gestational age, across the full range of second- and third-trimester intrauterine deaths, and placental findings. Broadly speaking, our findings are consistent with those of previous studies, suggesting that formal placental examination is an important investigation to determine cause of intrauterine death. Although several stillbirth classification systems have been described, it is only recently that attempts have been made to incorporate histological evidence of ascending maternal genital tract infection and MVM as discrete entities^{26,27}. In addition, it should be noted that, for the purposes of this study, abnormalities of the umbilical cord such as abnormal coiling index or non-specific findings possibly associated with cord compression, were

not included as definite causes of death since reliable diagnostic criteria for their interpretation in individual cases do not exist. This uncertainty regarding interpretation, in addition to the subjective and non-specific nature of terminology within many classification systems are likely to be major contributing factors to the considerable variation in intrauterine death rates attributed to placental pathologies². Improved understanding of the mechanisms of intrauterine death require scientifically rigorous, objective criteria in order to separate truly pathological placental findings from incidental features that may overlap extensively with those of normal populations. Recent research demonstrates that a quantitative approach to placental morphology²¹ and placentally derived hormones²⁸ may help to better identify lesions of pathological significance.

In conclusion, the findings of this study demonstrate that placental pathology represents a major category of cause of intrauterine death. Specific placental histological abnormalities represent a significant cause of stillbirth,

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especially MVM in the early third trimester. There remain a range of placental histological findings of uncertain significance, particularly in late stillbirth. Placental examination is an important contributor to determining the cause of intrauterine death at all gestational ages, and should therefore be encouraged strongly, even for parents who decline full autopsy examination.

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