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Can information regarding the index stillbirth determine risk of adverse outcome in a subsequent pregnancy? Findings from a single-center cohort study

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Abstract

Introduction: Women with a history of stillbirth have an almost five-fold increased risk of stillbirth in a subsequent pregnancy, as well as increased risk of other adverse maternal and neonatal outcomes. The reasons for this association are not well understood but could relate to recurrent causes. We aimed to determine whether information from the time of index stillbirth, including cause, is associated with outcome of a subsequent pregnancy.

Material and methods: A retrospective cohort study was conducted at a UK tertiary maternity center. Cases were included if stillbirth was investigated, subsequent pregnancy care was provided, and the birth occurred in the same unit. Data on maternal characteristics, findings of investigations, and classification of death using the ReCoDe system were extracted, and logistic regression was performed to determine whether these factors were associated with adverse outcome in the subsequent pregnancy.

Results: In this cohort (n = 266), there were 69 adverse outcomes, including three perinatal deaths. Preterm delivery (16.2%) and birthweight <10th centile (12.4%) were the most common adverse outcomes. Of the preterm births, 69.8% were iatrogenic and 47% of these were due to abnormalities of fetal growth. On multivariate analysis women with a preexisting medical condition (adjusted odds ratio [aOR] 2.12, 95% CI 1.10-4.12) and those who smoked in their subsequent pregnancy (aOR 6.80, 95% CI 1.99-23.30) were at increased risk of adverse outcome. Neither ReCoDe classification of stillbirth ($P = .61$) nor gestation of stillbirth ($P = .36$) were associated with subsequent pregnancy outcome. Placental histopathological findings of maternal vascular malperfusion (aOR 11.34, 95% CI 2.20-58.62), fetal vascular malperfusion (aOR 9.27, 95% CI 1.09-78.82), and chorioamnionitis (aOR 6.35, 95% CI 1.16-34.78) in the index stillbirth were associated with adverse outcome in subsequent pregnancy. These associations were independent of maternal characteristics.

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; MVM, maternal vascular malperfusion; ReCoDe, Relevant Condition at Death.

Conclusions: Placental examination at time of stillbirth is important, as certain placental disorders inform the risk of adverse outcome in subsequent pregnancy. In this cohort, information regarding maternal characteristics and classification of cause of stillbirth do not provide significant prognostic information about the risk of adverse outcome in subsequent pregnancies. Optimal management of maternal medical disorders and access to smoking cessation are essential.

KEYWORDS

chorioamnionitis, maternal vascular malperfusion, placenta, recurrence, stillbirth, subsequent pregnancy

1 | INTRODUCTION

Stillbirths represent a significant burden of avoidable deaths,[1] one approach to reduce stillbirths in high-income countries is to identify pregnancies at increased risk and alter their management to mitigate the risk of stillbirth. In 2015, a large systematic review and meta-analysis of 13 cohort and 3 case-control studies including 3 412 079 pregnancies found that women who experience a stillbirth in their first pregnancy are 4.8 times more likely to experience a stillbirth in their second pregnancy.[2] Previous stillbirth also increases the risk of other adverse outcomes including fetal growth restriction, preeclampsia, placental abruption, and prematurity in subsequent pregnancy.[3,4] Hence, stillbirth represents an important risk factor for adverse pregnancy outcome. However, there is uncertainty surrounding the recurrence risk for specific causes of stillbirth, as few studies have examined the cause of death in recurrent cases and the large meta-analysis was unable to answer this question.[2] Two cohort studies that include robust information on the cause of index stillbirth have examined recurrence risk.[5,6] The larger study, including 273 babies concluded that stillbirths associated with maternal placental vascular disorders had an increased risk of recurrent adverse pregnancy outcome compared with those with an index stillbirth of unknown cause or 'other' cause.[5] In their study of 125 women Nijkamp et al found recurrence in prematurity and placental disorders with an association between cause of death in index stillbirth and in subsequent pregnancy in half of cases; however, the sample size was too small to evaluate this further.[6]

The uncertainty surrounding the recurrence risk for specific causes of stillbirth makes counseling women and their families challenging, as well as making decisions about care provision to mitigate the increased risk of stillbirth in subsequent pregnancies more difficult. Consequently, practice as to how women are cared for during a pregnancy following stillbirth varies between maternity units, which may result in some women having inadequate surveillance in their pregnancies or receiving excessive intervention.[7] Individualizing care for women who have previously experienced a stillbirth would not only benefit women, but could also have benefits because investigations would be focused to the needs of those at highest risk of adverse outcomes, saving resources, and saving time and anxiety for women and their families.[7-10]

Key message

Adverse outcomes in pregnancies after stillbirth were not related to the assigned classification, but were more frequent in women who smoke cigarettes, those with maternal medical disorders, and in the presence of specific placental conditions (maternal vascular malperfusion and chorioamnionitis).

We hypothesized that information on the cause of the index stillbirth can be used to inform care in a subsequent pregnancy. To address this hypothesis, data were obtained from the index pregnancy including maternal characteristics, results from investigations conducted after the stillbirth, and the assigned cause. These were then combined with data regarding the outcome of subsequent pregnancies in a contemporaneous maternity population.

2 | MATERIAL AND METHODS

A retrospective, single center, cohort study was conducted at a UK tertiary maternity center. Women were included in the study if both the index stillbirth and subsequent pregnancy care and delivery were at the center as this ensured completeness of data. All cases of perinatal death since January 2012 have been recorded on the unit's perinatal mortality database; this database includes information from the index pregnancy such as baseline maternal demographic characteristics, preexisting medical conditions, body mass index, maternal smoking status, alcohol and drug use, scan frequency and findings, complications in pregnancy, and events leading to the stillbirth diagnosis. The gestational age, birthweight, and the results of any investigations performed, (eg autopsy, placental histopathological examination, chromosomal analysis, and maternal hematological and biochemical tests) are included. Investigation of stillbirth is conducted according to a

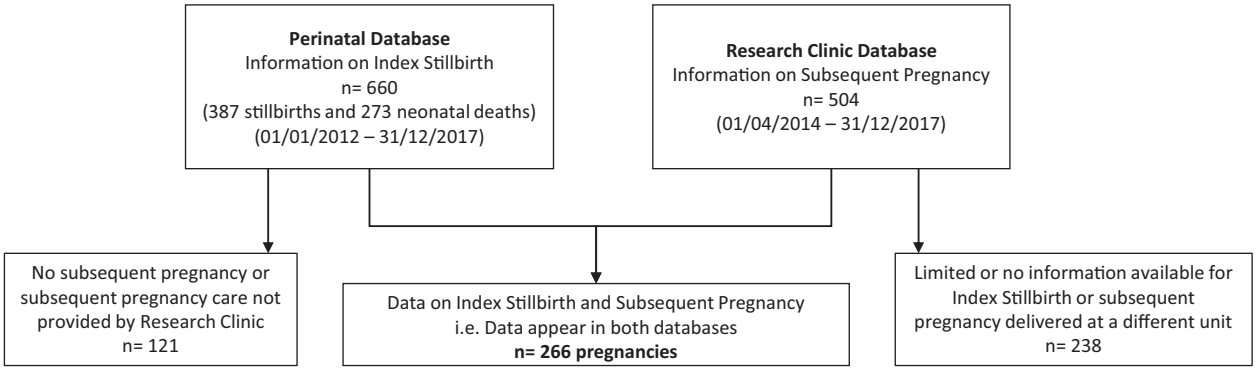

FIGURE 1 Flow chart to indicate sources of information and number of participants who have complete data for clinical analysis

prespecified protocol based upon guidance from the Royal College of Obstetricians and Gynaecologists.[11] The Relevant Condition at Death (ReCoDe) classification system was used according to the author's instructions for use,[12] following review of investigation results and multidisciplinary team discussion. ReCoDe is a hierarchical classification system, considering conditions relevant to the fetus, the placenta (including placental histology), and the mother, as well as timing of death (antenatal or intrapartum). Findings from histopathological examination of the placenta were classified using Turowski's classification system.[13]

At this maternity unit, women in a subsequent pregnancy following perinatal loss are cared for by a dedicated specialist antenatal service. An electronic system is used to record baseline maternal demographic characteristics, women's previous obstetric history, their medication use, ultrasound scan measurements, and management plans (Viewpoint, General Electric, Version 5.0). Delivery details, including mode of delivery, date of delivery, gestational age, and birthweight, were obtained from a separate electronic intrapartum system (K2MS Athena, K2 Medical Systems UK, Version 4.2.01101.1). Customized birthweight centile was calculated using the gestational age optimal weight (GROW) calculator Version 6.7 (UK) (Gestation Network).

Women were included in the study if they had received care in the antenatal clinic and delivered at the unit over a 4-year period from 2014 to 2017, and data from their stillbirth was included on the perinatal database. Participants were excluded if the stillbirth was managed and investigated at a different maternity unit, if subsequent pregnancy care was not in the antenatal clinic, if the index stillbirth was not investigated, or there was no information available. Women were also excluded if their subsequent pregnancy had a fetal anomaly as defined in the fetal anomaly screening program checklist (https://www.gov.uk/topic/population-screening-programmes/fetal-anomaly) or there the subsequent pregnancy was a multiple pregnancy. Women were classified as having significant past medical history if they had diabetes, hypertension, thrombophilia, cardiac disease, autoimmune disorders, epilepsy, or other disorders requiring medical therapy. Women with a history of anxiety, depression, or other psychiatric disorders requiring therapy were classified as having mental health disorders.

As subsequent stillbirth is infrequent, we could not conduct an adequately powered study with a primary outcome of stillbirth. Therefore, in common with previous studies, we used a composite measure of adverse neonatal outcome. Our composite outcome included: stillbirth or neonatal death, 5-minute Apgar score of less than 7, umbilical artery pH of less than 7.05, admission to neonatal intensive care for more than 24 hours, preterm birth less than 37^{+0} weeks of gestation, or birthweight less than the 10th centile on a customized growth chart. Data were also collected on other relevant maternal and neonatal outcomes including mode of delivery, whether labor was spontaneous or induced (to calculate the proportion of intervention), gestation at delivery (to calculate the proportion of preterm births), birthweight and birthweight centile (to calculate the proportion of small-for-gestational-age <10th centile), and maternal conditions including preeclampsia, gestational diabetes, and placental abruption.

Data were collected from source databases and collated using Microsoft Excel. Statistical analysis was conducted using STATA Version 15. Before further analysis, numerical data were transformed to categorical data; body mass index (BMI) was categorized using the World Health Organization classification, maternal age was separated into 5-year groups as these are known to have different frequencies of adverse outcome.[14] Differences in distribution of groups were assessed by chi-squared or Fisher's exact test. Univariate logistic regression was used to investigate associations between variables and adverse pregnancy outcome. For maternal characteristics multivariate logistic regression was used to adjust for the effects of potential confounding factors including maternal age, parity, BMI, cigarette smoking status, past medical history, and inter-pregnancy interval as these factors are related to the risk of stillbirth.[15] For placental classification, multivariate logistic regression was used to adjust for gestation of stillbirth, maternal age, parity, BMI, cigarette smoking, and past medical history as these conditions are known to affect placental morphology.

2.1 | Ethical approval

A favorable ethical opinion was granted by South East Coast – Surrey Research Ethics Committee (Ref 16/L0/1666) and approval was given by the Health Research Authority on 20 September 2016.

TABLE 1 Frequency of adverse outcome in pregnancies after stillbirth

Pregnancy outcome	Whole population (n = 266)	Women giving birth preterm in subsequent pregnancy (n = 43)	Women giving birth at term in subsequent pregnancy (n = 223)
Uncomplicated pregnancy	197 (74.1)	0 (0)	197 (88.3)
Any adverse pregnancy outcome[a]	69 (25.9)	43 (100)	26 (11.7)
Preterm birth <37 weeks	43 (16.2)	43 (100)	0 (0)
Birthweight <10th centile	35 (13.2)	16 (45.7)	19 (8.5)
Admission to NICU >24 h	29 (11.0)	23 (53.4)	6 (2.7)
5-min Apgar score <7	7 (2.6)	6 (14.0)	1 (0.5)
Umbilical cord arterial pH <7.05	3 (1.1)	0 (0)	3 (1.3)
Stillbirth	2 (0.8)	2 (4.7)	0 (0)
Neonatal death	1 (0.4)	1 (2.3)	0 (0)

[a]Nota bene pregnancies could have more than one adverse outcome, so the total number of adverse outcomes are greater than the column total who had any adverse outcome. All columns are number (%).

TABLE 2 Details of iatrogenic preterm births associated with preeclampsia, antepartum hemorrhage, and suspected abnormalities in fetal growth

	Iatrogenic preterm births		
	Associated with preeclampsia (n = 5)	Associated with antepartum hemorrhage (n = 4)	Associated with abnormalities in fetal growth (n = 16)
FGR in index stillbirth	5 (100%)	4 (100%)	12 (75%)
Hypertension in index stillbirth	3 (60%)	0 (0%)	3 (18.8%)
APH in index stillbirth	0 (0%)	0 (0%)	0 (0%)
MVM in index stillbirth	4 (80%)	3 (75%)	11 (68.8%)
Birthweight <10th centile in subsequent pregnancy	3 (60%) all <3rd centile	0 (0%)	9 (56.3%)
Gestation at delivery in subsequent pregnancy (wk)	30 (range 25-34)	35 (range 35-36)	33 (range 28-37)

Abbreviations: APH, antepartum hemorrhage; FGR, fetal growth restriction; MVM, maternal vascular malperfusion.

3 | RESULTS

Complete data were obtained for 266 women (Figure 1), adverse pregnancy outcome was observed in 69 (25.9%) subsequent pregnancies, with a perinatal death recurrence rate of 1.2% (two stillbirths [0.8%] and one neonatal death [0.4%]) (Table 1). The most frequently observed adverse pregnancy outcome was preterm birth, occurring in 16.2% of cases, 69.8% of which were iatrogenic. The median gestation of the preterm birth group was 245 days (range 173-259 days). The majority of adverse outcomes (birthweight <10th centile, admission to neonatal intensive care unit, and Apgar score <7 at 5 minutes) occurred in women who gave birth preterm. Overall, 13.2% of infants had a birthweight less than the 10th centile, but 45.7% of infants born preterm had birthweight less than the 10th centile. (Table 1).

Of the iatrogenic cases of preterm birth (n = 30), 16 (53)% were as a result of ultrasound scan abnormalities in fetal growth (reduced or static fetal growth rate) and/or umbilical artery Doppler ultrasound measurements (raised pulsatility index or absent or reversed end diastolic flow), 5 (17%) had preeclampsia, 4 (13%) as a result of significant antepartum hemorrhage and 1 case had a pathological antenatal fetal heart rate trace; the remaining 4 cases (13%) had intervention based upon their history alone. Of those delivered preterm because of preeclampsia all had fetal growth restriction in the index stillbirth, and 60% had previous hypertension in pregnancy (Table 2). Of those delivered preterm with a significant antepartum hemorrhage, all had fetal growth restriction in the index stillbirth, none had a previous history of antepartum hemorrhage, and none had a previous nor current history of hypertension.

There was no statistically significant relation between maternal characteristics of age, parity, BMI, cigarette smoking in the index pregnancy, and ethnicity and the likelihood of an adverse outcome in the subsequent pregnancy (Table 3). There was a strong relation between current smoking status and adverse outcome (adjusted odds ratio [aOR] 6.80, 95% CI 1.99-23.30). Those

TABLE 3 Association of maternal characteristics with an adverse outcome in pregnancy after stillbirth

	All (n = 266)	Normal outcome (n = 197)	Adverse outcome (n = 69)	*P* value chi-squared test	Univariate analysis (95% CI)	Multivariate analysis [a] (95% CI)	*P* value for multivariate analysis
Age (yr)	30.6 (17-45)	31.2 (18-45)	28.6 (17-41)				
<25	50 (18.8)	33 (16.8)	17 (24.6)	0.21	1.11 (0.52 – 2.38)	0.98 (0.41 –2.33)	0.97
26-30	76 (28.6)	52 (26.4)	24 (34.8)		Reference	Reference	—
31-35	87 (32.7)	71 (36.0)	16 (23.2)		0.49 (0.24– 1.01)	0.49 (0.22 –1.10)	0.09
36-40	49 (18.4)	38 (19.3)	11 (15.9)		0.63 (0.27– 1.43)	0.51 (0.19 –1.39)	0.19
41+	4 (1.5)	3 (1.5)	1 (1.5)		0.72 (0.07 –7.30)	0.76 (0.07 –8.81)	0.82
Gravidity	3.7 (2-12)	3.7 (2-12)	3.9 (2-11)	0.76			
Parity	1.7 (0-8)	1.7 (0-8)	1.7 (0-6)	0.45	0.99 (0.83 –1.18)	1.05 (0.82 –1.30)	0.67
BMI (kg/m^2)	28.0 (18-46)	27.8 (18-46)	28.4 (19-43)	0.76			
<18.5	5 (1.9)	5 (2.5)	0 (0)	0.24	—	—	—
18.5-24.9	91 (34.2)	64 (32.5)	27 (39.1)		Reference	Reference	—
25.0-29.9	92 (34.6)	74 (37.6)	18 (26.1)		0.58 (0.29 –1.14)	0.57 (0.27 –1.24)	0.16
30.0-39.9	70 (26.3)	49 (24.9)	21 (30.4)		1.01 (0.51 –2.01)	1.01 (0.47 –2.19)	0.82
>40	8 (3.0)	5 (2.5)	3 (4.4)		1.42 (0.32 –6.38)	1.07 (0.16 –7.33)	0.95
Smoker in index pregnancy	30 (11.3)	19 (9.6)	11 (15.9)	1.78	0.99 (0.80 –3.95)	1.43 (0.55 –3.72)	0.47
Amount smoked (cig./day)	9.5 (2-20)	9.6 (2-20)	9.3 (5-20)	0.44			
Smoker in current pregnancy	16 (6.0)	5 (2.5)	11 (15.9)	<0.001	7.28 (2.43 –21.81)	6.80 (1.99–23.30)	<0.001
Amount smoked (cig./day)	9 (2-20)	4 (2-10)	10 (5-20)	0.04			
Ethnicity							
Asian	57 (21.4%)	44 (22.3%)	13 (18.8%)	0.39	0.58 (0.29 –1.13)	0.94 (0.41 –2.16)	0.88
Black	54 (20.3%)	35 (17.7%)	19 (27.5%)		0.54 (0.24 –1.25)	1.85 (0.85 –4.01)	0.12
White	147 (56.3%)	112 (56.9%)	35 (50.7%)		Reference	Reference	
Other	8 (3.0%)	6 (3.1%)	2 (2.9%)		0.61 (0.11 –3.34)	1.28 (0.22 –7.58)	0.95
Past medical history							
None	166 (62.4%)	130 (66.0%)	36 (52.1%)	0.05	Reference	Reference	
Mental illness	19 (7.1%)	15 (7.6%)	4 (5.8%)		0.96 (0.30 –3.08)	0.83 (0.23 –3.02)	0.78
Medical illness	81 (30.5%)	52 (26.4%)	29 (42.0%)		2.01 (1.12 –3.62)	2.10 (1.07 –4.13)	0.03
Inter-pregnancy interval (mo)	25.5	25.8	24.4	0.26			
<12 months	49 (18.4%)	30 (15.2%)	19 (27.5%)	0.16	2.33 (1.15 –5.08)	2.51 (1.10 –5.75)	0.03
13-24 months	106 (39.9%)	84 (42.6%)	22 (31.9%)		Reference	Reference	
25-36 months	54 (20.3%)	41 (20.8%)	13 (18.8%)		1.21 (0.55 –2.64)	0.96 (0.41 –2.27)	0.93
37-48 months	45 (16.9%)	32 (16.2%)	13 (18.8%)		1.55 (0.69 –3.44)	1.37 (0.57 –3.27)	0.48
49+ months	12 (4.5%)	10 (5.1%)	2 (2.9%)		0.76 (0.16 –3.74)	0.79 (0.15 –4.11)	0.78

[a]Multivariate model includes adjustment for maternal age, parity, body mass index (BMI), current cigarette smoking status, past medical history and inter-pregnancy interval.

with an existing medical condition were at increased risk of adverse outcome compared with those with no medical conditions (42% and 26.4%, respectively; aOR 2.10, 95% CI 1.07-4.13). The most frequent existing medical conditions in those experiencing an adverse outcome were hypertension (17.4%), thrombophilia (11.6%), autoimmune disorders (7.2%), and diabetes (5.8%). A shorter inter-pregnancy interval of <12 months increased the risk of adverse outcome (Table 3).

There was no statistically significant difference between pregnancy outcomes when compared with the different primary ReCoDe classifications given for the index stillbirth (Table 4). When placental causes and factors were considered in more detail (Table 5), there

TABLE 4 Classification of the cause of stillbirth using primary ReCoDe classification and association with adverse pregnancy outcome in subsequent pregnancy

Primary ReCoDe for Index Stillbirth	Normal outcome (%)	Adverse outcome (%)	*P* value
A1 Lethal congenital anomaly	14 (7.1)	7 (10.1)	0.49
A2 Fetal infection	5 (2.5)	1 (1.5)	
A5 Feto-maternal hemorrhage	2 (1.0)	0 (0)	
A6 Twin to twin transfusion syndrome	3 (1.5)	0 (0)	
A7 Fetal growth restriction	87 (44.2)	38 (55.1)	
A8 Fetal (other)	11 (5.8)	4 (5.8)	
B2 Umbilical cord constricting loop	4 (2.0)	0 (0)	
C1 Placental abruption	16 (8.1)	6 (8.7)	
C4 Placental insufficiency	19 (9.6)	7 (10.1)	
D1 Chorioamnionitis	9 (4.6)	5 (7.3)	
D4 Amniotic fluid 'other'	1 (0.5)	0 (0)	
F8 Maternal (other)	1 (0.5)	0 (0)	
G1 Intrapartum asphyxia	5 (2.5)	0 (0)	
I1 and I2 Unclassified	20 (10.2)	1 (1.5)	

was no increase in adverse pregnancy outcome in a subsequent pregnancy in those women whose stillbirth was attributed to placental insufficiency, placental abruption or fetal growth restriction by the ReCoDe classification system. There was also no difference observed in subsequent pregnancy outcome based upon the gestational age of the stillbirth.

Considering the placenta, 87% (n = 232) of women had placental weight recorded for the index stillbirth, and full histopathology report available. Those with a small placenta in their index stillbirth, defined as placental weight less than the 10th centile for gestation, did not have an increased risk of adverse pregnancy outcome in the subsequent pregnancy. Using the Turowski classification system for placental histopathology, those with normal placenta, implantation abnormalities or genetic anomalies seen on the stillbirth placenta were least likely to have an adverse outcome in the subsequent pregnancy and those with maternal vascular malperfusion (MVM) were at greatest risk. Those with MVM (aOR 11.34), fetal vascular malperfusion (aOR 9.27), and chorioamnionitis (aOR 6.35) seen on the stillbirth placenta were at an increased risk of adverse pregnancy outcome in the subsequent pregnancy independent of maternal characteristics (Table 5). When pregnancies with MVM were compared with all other causes of stillbirth, there was an increased risk of adverse outcome (aOR 2.98, 95% CI 1.37-4.86). There was a weak association between MVM in the index pregnancy and subsequent small-for-gestational-age birth; of the babies born small for gestational age, 55.2% had MVM in the index stillbirth compared with 38.9% of babies that were born appropriate for gestational age ($P = .06$). Where placental histology was available, none of the babies born small for gestational age in a subsequent pregnancy (n = 29) had normal placental histology in the index stillbirth.

4 | DISCUSSION

In common with earlier studies, this study found that women with a history of stillbirth are at high risk of adverse pregnancy outcomes in a subsequent pregnancy.[2-4] Information regarding maternal characteristics and ReCoDe classification of stillbirth does not provide significant prognostic information for adverse outcome in subsequent pregnancies, but certain placental conditions were associated with adverse outcomes in a subsequent pregnancy.

This study was strengthened by the amount of information available about each case and the use of a standardized protocol to investigate stillbirths. The classification of stillbirth by an independent multidisciplinary team shortly after the time of stillbirth reduced reporting bias towards specific diagnoses. This study was of a comparable size to the largest existing detailed data set of women with previous stillbirths,[5] but as this study was conducted in a single tertiary maternity center in the UK it may not be representative of women who have a history of stillbirth in other settings. Restricting analysis to cases in which the initial stillbirth was investigated, and the subsequent pregnancy care was provided in a single tertiary hospital may have led to selection bias. Even though a standardized investigation protocol was in place, following stillbirth data were sometimes incomplete, potentially leading to misclassification of the index stillbirth. Nevertheless, the frequency of post-mortem and placental histopathological examinations are consistent with contemporaneous UK reports.[16] The size of the study prevented division of outcomes by gestational age. As preterm births were associated with a higher proportion of adverse outcomes, a larger study or individual participant data meta-analysis of existing studies could be performed to investigate whether

TABLE 5 Association of characteristics of stillbirth and placental examination identified after the index stillbirth with outcome of subsequent pregnancy

Characteristic	Total (n = 266)	Normal outcome (n = 197)	Adverse outcome (n = 69)	*P* value chi-squared or Fisher's exact test	Univariate analysis (95% CI)	Multivariate analysis (95% CI)	*P* value for multivariate analysis
Gestation of stillbirth (wk^{+d})	32^{+2} (20^{+1}-42^{+0})	32^{+5} (21^{+0}-42^{+0})	31^{+2} (20^{+1}-42^{+0})	0.06			
≤28 weeks	100 (37.6%)	73 (37.1%)	27 (39.1%)	0.22	1.46 (0.74 –2.85)	1.56 (0.77 –3.17)	0.22
29-36 weeks	72 (27.1%)	49 (24.9%)	23 (33.3%)		1.85 (0.91 –3.75)	1.70 (0.81–3.59)	0.16
≥37 weeks	94 (35.3%)	75 (38.1%)	19 (27.5%)		Reference	Reference	
Any classification of:							
Placental insufficiency (C4)	133 (50.0%)	93 (47.2%)	40 (58.0%)	0.12	1.54 (0.89 –2.68)	1.45 (0.80 –2.62)	0.22
Placental abruption (C1)	28 (10.5%)	19 (9.6%)	9 (13.0%)	0.43	1.40 (0.60 –3.27)	1.51 (0.61 –3.74)	0.37
Fetal growth restriction (A7)	129 (48.5%)	90 (45.7%)	39 (56.3%)	0.12	1.55 (0.89 –2.69)	1.59 (0.89 –2.85)	0.12
Placental weight centile (n = 229 had placental weight centile recorded)							
<10th centile	101 (44.1%)	70 (40.9%)	31 (53.5%)	0.06	1.55 (0.68 –3.52)	1.69 (0.67 –4.27)	0.27
10th-50th centile	66 (28.8%)	49 (28.7%)	17 (29.3%)		1.21 (0.50 –2.97)	1.39 (0.53 –3.67)	0.50
50-90th centile	45 (19.7%)	35 (20.5%)	10 (17.2%)		Reference	Reference	
>90th centile	17 (7.4%)	17 (9.9%)	0		-	-	
Histological classification (n = 232 index stillbirths had histopathology report)							
Normal, implantation, genetic or other abnormality	30 (12.9%)	28 (16.2%)	2 (3.4%)	0.003	Reference	Reference	
Chorioamnionitis	48 (20.7%)	36 (20.8%)	12 (20.3%)		4.67 (0.96 –22.57)	6.35 (1.16 –34.78)	0.03
Villitis	17 (7.3%)	15 (8.7%)	2 (3.4%)		1.87 (0.24 –14.61)	3.43 (0.37 –32.12)	0.28
Maternal vascular malperfusion	95 (41.0%)	59 (34.1%)	36 (61.0%)		8.54 (1.91 –38.02)	11.34 (2.20 –58.62)	0.004
Fetal vascular malperfusion	11 (4.7%)	8 (4.6%)	3 (5.1%)		5.25 (0.74 –37.05)	9.27 (1.09 –78.82)	0.04
Delayed villous maturation	31 (13.4%)	27 (15.6%)	4 (6.8%)		2.07 (0.35 –12.27)	2.84 (0.43 –18.64)	0.28

Multivariate analysis adjusted for gestation of stillbirth, maternal age, parity, body mass index, cigarette smoking in the index pregnancy and past medical history.

maternal or placental factors are differentially related to adverse outcomes preterm or at term.

Although evaluations against other cohort studies can be made (see Table 6), direct comparisons are limited by the use of different classification systems and gestational age definitions for stillbirth. The observed frequency of adverse pregnancy outcomes in our study is comparable to that found by Monari et al (25.9% vs. 24.5%).[5] The rate of recurrent stillbirth was 7.5/1000 (0.8%), which is higher than reported by Monari et al (3.7/1000; 0.4%),[5] but the rarity of this outcome means that estimates are imprecise. Applying the definition of adverse outcome (only including preterm birth <34 weeks of gestation and assuming that any infants with intraventricular hemorrhage, necrotizing enterocolitis, or hypoxic-ischemic encephalopathy would have gone to the neonatal intensive care unit) there were 59 adverse outcomes in this cohort (22.1%). However, using a sensitivity analysis found minimal effect in the observed associations of the multivariable analysis model.

Of the three perinatal deaths in our cohort, one was a neonatal death that occurred in the infant of a mother with recurrent late second trimester/early third trimester losses due to a recurrent genetic condition. One of the stillbirths was a recurrent placental abruption, on both occasions occurring during the late third trimester, and placental histology demonstrated recurrent MVM. In the other, a recurrent third trimester loss of the same gestation, both pregnancies were affected by severe fetal growth restriction with small placentas and the same histological finding of chronic histiocytic intervillositis. Interestingly, the recurrent perinatal deaths observed by Monari et al, all resulted from recurrent placental vascular disorders in the third trimester.[5] While Nijkamp et al reported recurrent fetal deaths only,[6] 3 of the 11 deaths were related to placental bed pathology or placental pathology consistent with MVM. In addition to the perinatal deaths, cases in this study ending in iatrogenic preterm birth frequently had MVM in the index stillbirth. Hence, this lesion should be viewed as a recurrent placental disorder that may lead to adverse outcome in pregnancies after stillbirth.

The most frequently observed adverse pregnancy outcome in our cohort was preterm birth, with 16.2% of women giving birth before 37 weeks of gestation, this is almost double the rate reported for Europe (8.7%)[17] but is similar to Monari et al[5] and Black et al[4] who reported preterm birth rates of 18.7% and 18.1%, respectively. In our study 69.8% of preterm births were iatrogenic due to abnormalities of fetal growth detected on ultrasound scan or Doppler velocimetry, preeclampsia, and antepartum hemorrhage. Unfortunately, only a small proportion of placentas were sent for histopathological analysis after subsequent pregnancy, which meant that the recurrence of maternal or fetal vascular malperfusion, and their relation to iatrogenic preterm birth, cannot be determined. However, as preterm fetal growth restriction, preeclampsia, and antepartum hemorrhage are closely related to placental disease,[18] particularly in preterm disease, it is plausible that this pathology underpins the increased incidence of preterm birth in this population. Further research, comparing the histopathological phenotype of index stillbirth and subsequent pregnancies, is needed to address this question.

Few maternal characteristics examined here were related to outcome in a subsequent pregnancy. Smoking at the time of index stillbirth was not related to outcome of the subsequent pregnancy, probably because 45.2% of women had stopped smoking by this time, which is consistent with observations that women who experience a stillbirth are more likely to stop smoking.[19] However, women who continued to smoke cigarettes had a strongly increased risk of adverse outcome in their subsequent pregnancy. This underpins the need to promote smoking cessation to this high-risk group. We did not see a relation between obesity and increased risk of adverse pregnancy outcome seen elsewhere.[15,20-22] Mean BMI increased from 26.9 to 28.0 kg/m^2 from the index stillbirth to the subsequent pregnancy, with almost half of this cohort (48.4%) gaining weight between pregnancies resulting in 29% of women in this study being classified as obese and 35% overweight in their subsequent pregnancy. This lack of association between obesity and adverse pregnancy outcomes does not diminish the importance of addressing this important modifiable risk factor, but our data also demonstrate the difficulties in reducing BMI, even though this group of women are generally highly motivated to improve a future pregnancy outcome. Women with a preexisting medical condition were at a statistically significant increased risk of adverse outcome in the subsequent pregnancy; although one cannot infer causality, as these conditions may predispose to fetal growth restriction and preeclampsia, pre-conception counseling and optimization of disease control is advised in affected mothers.

The most common factor associated with adverse outcome in subsequent pregnancy (Table 6) is placental bed/placental vascular disorders and chorioamnionitis. Over half (57.2%) of all adverse outcomes seen in this cohort had MVM on placental histology of the index stillbirth. When the recurrence of adverse outcome was compared between stillbirth with and without MVM, similar results were found in our cohort and that of Monari et al (aOR 2.98 vs aOR 2.1).[5] The relation between placental abnormalities and subsequent pregnancy outcome highlights the importance of placental histopathological examination after stillbirth to gain appropriate information to aid counseling and future pregnancy management. One of the main differences between the studies in Table 6 is the variation in proportion of stillbirths classified as unknown cause (44.3%, 21.5%, and 7.9%, respectively). As histopathological examination of the placenta after stillbirth reduces the proportion of stillbirths labeled as unexplained,[23] it also reduces cost to healthcare systems, as a subsequent pregnancy to an unexplained stillbirth bears greater cost than if the cause is known.[24] Although a logical area of exploration, to date there have been no basic science or histopathological studies comparing the placental changes seen in a subsequent pregnancy following stillbirth and the index stillbirth to ascertain whether specific placental lesions that lead to stillbirth recur. Paired studies (of the same mother) would help understand whether placental abnormalities or histopathological disorders recur even if the pregnancy is managed differently and ends in a live birth.

TABLE 6 Comparisons between the three studies reporting subsequent pregnancy outcomes depending upon the cause of index stillbirth

	Monari et al[5]	Nijkamp et al[6]	This study
No. of participants	273 babies	125 babies	266 babies
Study design	Prospective observational	Retrospective cohort	Retrospective cohort
Setting	3 University Hospitals	Single tertiary center	Single tertiary center
Location	Italy	The Netherlands	United Kingdom
Study period	Jan 2005-June 2013	Jan 1999-Dec 2004	Jan 2012-Dec 2017
Stillbirth definition	>22/40	>16/40	>20/40
Stillbirth classification system	CoDAC	Tulip	ReCoDe
Factors associated with stillbirth			
Placental	20.9%	47.8%	18.0%
FGR <10th centile	18.7%	—	47.0%
Unexplained	44.3%	21.5%	7.9%
Primary outcome	Composite adverse neonatal outcome - Perinatal death - FGR - PTB <33^{+6} - HIE - Intercranial hemorrhage - Respiratory distress requiring ventilation	Recurrent fetal death - Miscarriage < 16/40 - Miscarriage 16-22/40 - Stillbirth > 22/40 - Neonatal death	Composite adverse neonatal outcome - Perinatal death - FGR < 10th - PTB < 37^{+0} - 5-min Apgar < 7 - Umbilical artery pH < 7.05 - - NICU admission > 24 hrs
Findings			
SB in subsequent pregnancy	0.37% (1/273)	Overall 8.8% (11/125) - 4.8% 17-22 weeks' - 4% >22/40 weeks'	0.8% (2/266)
NND in subsequent pregnancy	0.37% (1/273)	—	0.4% (1/266)
Overall composite adverse outcome	24.5% (67/273)	—	25.9% (69/266)
PTB <37weeks in subsequent pregnancy	18.7%	—	16.2%
Birthweight centile <10th in subsequent pregnancy	17.9%	—	13.2%
Obesity	Independent risk factor	Study sample too small to evaluate	No statistically significant association
Conclusions re recurrent adverse outcome	Highest risk of recurrent adverse outcome (32.4%) if cause of index SB was placental vascular disorder compared with other index SB causes (19.4%)	Cause-specific recurrence seen with prematurity and placental disorders. Association between cause of death in index SB and cause of death in subsequent pregnancy in half of cases	Risk of recurrent adverse outcome increased if maternal or fetal vascular malperfusion. Classification of cause of index stillbirth does not affect risk of adverse outcome in subsequent pregnancy. Cause-specific recurrence seen in all three cases of recurrent perinatal loss

Abbreviations: FGR, fetal growth restriction; HIE, hypoxic-ischemic encephalopathy; NND, neonatal death; PTB, preterm birth; SB, stillbirth.

5 | CONCLUSION

Few factors known at the conclusion of investigations of the index stillbirth identify women at greatest risk of adverse outcome in a subsequent pregnancy. Placental examination remains important after stillbirth as MVM and related placental bed disorders have now been identified in three independent cohort studies, as being associated with recurrent problems, as have other rarer inflammatory disorders of the placenta. However, as there is no reliable way to accurately predict risk in this group of women, there is a

need for increased surveillance in all pregnancies after stillbirth at present.

CONFLICT OF INTEREST

None.

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