Madeleine ter Kuile, Jan Jaap H.M. Erwich and Alexander E.P. Heazell*

Stillbirths preceded by reduced fetal movements are more frequently associated with placental insufficiency: a retrospective cohort study

https://doi.org/10.1515/jpm-2021-0103
Received March 3, 2021; accepted June 25, 2021;
published online July 15, 2021

Abstract

Objectives: Maternal report of reduced fetal movements (RFM) is a means of identifying fetal compromise in pregnancy. In live births RFM is associated with altered placental structure and function. Here, we explored associations between RFM, pregnancy characteristics, and the presence of placental abnormalities and fetal growth restriction (FGR) in cases of stillbirth.

Methods: A retrospective cohort study was carried out in a single UK tertiary maternity unit. Cases were divided into three groups: 109 women reporting RFM, 33 women with absent fetal movements (AFM) and 159 who did not report RFM before the diagnosis of stillbirth. Univariate and multivariate logistic regression was used to determine associations between RFM/AFM, pregnancy characteristics, placental insufficiency and the classification of the stillbirth.

Results: AFM or RFM were reported prior to diagnosis of stillbirth in 142 (47.2%) of cases. Pregnancies with RFM prior to diagnosis of stillbirth were independently associated with placental insufficiency (Odds Ratio (OR) 2.79, 95% Confidence Interval (CI) 1.84, 5.04) and were less frequently associated with maternal proteinuria (OR 0.16, 95% CI 0.07, 0.62) and previous pregnancy loss <24 weeks (OR 0.20, 95% CI 0.07, 0.70). When combined, AFM and RFM were less frequently reported in twin pregnancies ending in stillbirth and in intrapartum stillbirths.

Conclusions: The association between RFM and placental insufficiency was confirmed in cases of stillbirth. This provides further evidence that RFM is a symptom of placental insufficiency. Therefore, investigation after RFM should aim to identify placental dysfunction.

Keywords: absent fetal movement; decreased fetal movement; perinatal mortality; placenta.

Introduction

Stillbirth is an extensive problem that receives little attention from worldwide initiatives [1]. Although only 2% of the 2.8 million stillbirths each year occur in high-income countries (HICs), this still accounts for significant number of deaths [2]. Stillbirth prevention is a major challenge; despite efforts to reduce it, the stillbirth rate has only decreased at 1.4% per year in the UK since 2000 [3]. In 2015, the UK stillbirth rate (3.9 per 1,000 live births after 28 weeks' gestation) was still in excess of the European average [3]. If all HICs achieved a stillbirth rate comparable to the six best performing countries it is estimated that over 20,000 stillbirths could be prevented [3]. Therefore, further efforts for improvement are needed.

Common causes of stillbirth in HICs include placental pathologies which may be associated with fetal growth restriction (FGR), congenital and karyotype anomalies and maternal medical diseases [4–6]. Placental abnormalities were found to be causal or contributory in over 60% of stillbirths [7]. A wide variety of maternal and fetal characteristics are risk factors for stillbirth (e.g. obesity, advanced maternal age, smoking, nulliparity, low socioeconomic status), several of which are associated with altered placental structure or function [8–10]. However, stillbirth often occurs in the absence of recognised risk factors, 86% of stillbirths at or after 24 weeks gestation occurred in women with no risk factors in the first trimester [11]. Although 14% of stillbirths are diagnosed at routine antenatal visits without antecedent signs [12], in other cases women had symptoms and signs including: antepartum haemorrhage, abdominal pain and

***Corresponding author: Professor Alexander E.P. Heazell**, PhD, Maternal and Fetal Health Research Centre, University of Manchester, St Mary's Hospital, Manchester, UK, Phone: +44 161 701 0889, Fax: +44 161 276 6134, E-mail: alexander.heazell@manchester.ac.uk
Madeleine ter Kuile, Department of Obstetrics, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands; and Faculty of Biology, Medicine and Health, Maternal and Fetal Health Research Centre, School of Medical Sciences, University of Manchester, Groningen, the Netherlands
Jan Jaap H.M. Erwich, Department of Obstetrics, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands. https://orcid.org/0000-0003-1362-4501

hypertension, but most commonly, the perception of reduced fetal movements (RFM) [12].

RFM is regarded as a marker of a vulnerable fetus, due to its association with a variety of pregnancy complications, including: oligohydramnios, neuromuscular abnormalities, brain injuries, small for gestational age fetuses (SGA) and FGR [13], and stillbirth [14, 15]. The proposed link between RFM, FGR and stillbirth is supported by evidence of placental dysfunction in women presenting with RFM who go on to have a live birth [16–18]. However, this finding has not been investigated in women who had RFM who went on to have a stillbirth.

Presently, there is a need to improve the prediction of stillbirth and FGR following RFM. As RFM when used alone has a low positive predictive value for adverse outcome, additional testing is required, which ideally has high sensitivity and specificity. A better understanding of the associations between RFM, stillbirth and placental dysfunction could assist in better understanding of underlying pathology and recommend investigations after RFM. This study aimed to determine whether the frequency of placental insufficiency and other characteristics differed in stillbirths preceded by RFM compared to those with normal movements.

Materials and methods

This retrospective cohort study was conducted using a database of perinatal deaths at a single tertiary maternity unit in the UK. As this analysis used anonymised routinely collected data, approval from a Research Ethics Committee was not required. The database contained all perinatal deaths at the institution from 2010 to 2017. Women who had perinatal deaths were not necessarily at risk *a priori*; thus low-risk as well as high-risk pregnancies that ended in stillbirth were included. Patient information regarding the stillbirths was incorporated into a spreadsheet database (Microsoft Excel). The original database consisted of 619 cases (Figure 1); duplicate cases, neonatal deaths and terminations of pregnancy for fetal abnormality were excluded resulting in 343 antepartum and intrapartum stillbirths. There was initially no patient exclusion based on maternal age, twin pregnancy or fetal congenital abnormalities. The UK definition of stillbirth was used, thus all fetal deaths before the gestational age of 24 weeks were excluded, as were babies known to have died before 24 weeks [19]. Following these exclusions 301 cases met the inclusion criteria.

Participants in the study were divided into two groups based on whether they reported reduced or absent fetal movements shortly before the stillbirth was diagnosed or not (Figure 1). The group which described no evidence of an altered perception of fetal movements included women whose patient notes contained a confirmation of normal movements and women whose notes did not disclose any information specifically about an altered movement pattern. When women had an episode of RFM earlier in the pregnancy, but

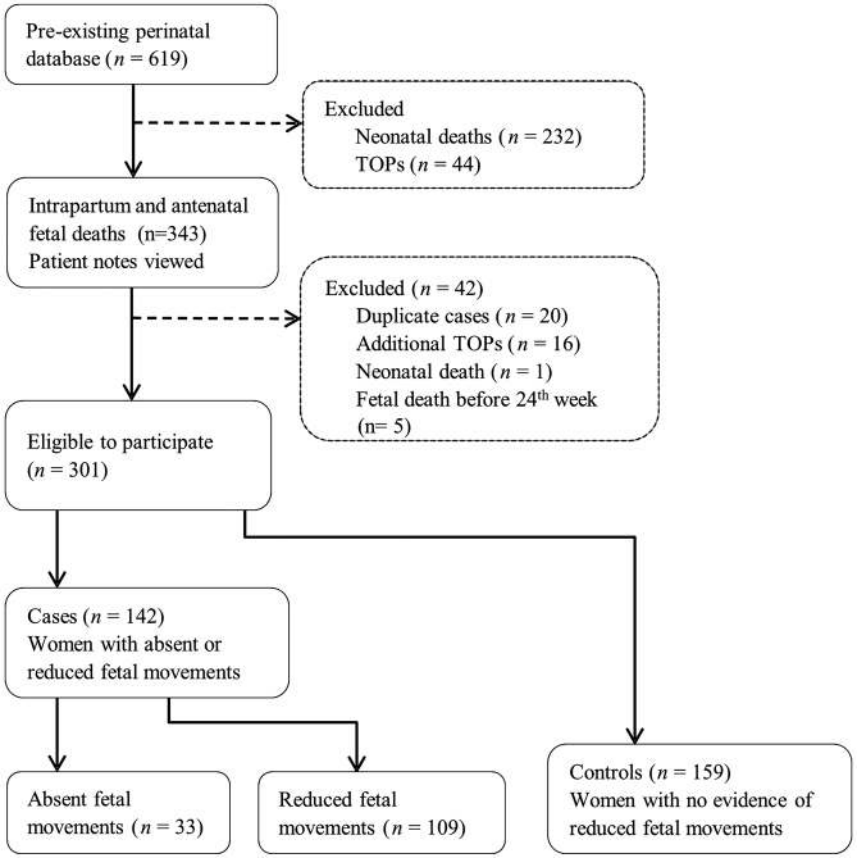

Figure 1: Patient recruitment and study design. TOP=termination of pregnancy.

experienced normal fetal movements after that up until the stillbirth, they were allocated to the normal fetal movement group.

A range of variables regarding pregnancy and investigations after birth were recorded; these were chosen based on their potential relationship to either stillbirth or RFM (e.g. maternal age, body mass index (BMI), parity, previous pregnancy loss ≤24 weeks, ethnicity, smoking, maximum blood pressure, diabetes, birthweight and placental weight centile). Data were collected whether the stillbirth was antepartum or intrapartum and classified according the ReCoDe system [4]. "Placental insufficiency" was defined as evidence of significant placental lesion(s) on pathological examination, such lesions included placental abruption, infarction, maternal vascular malperfusion, fetal vascular malperfusion, villous maturation disorders, inflammatory disorders and placental hypoplasia [20]. The significance of the placental lesions was determined by a multidisciplinary team reviewing the case.

For analysis, maternal ethnicity was clustered into four groups: European, Asian, African or other origin. For the calculation of birthweight centiles, the specific ethnic group of the individual mother was used. Pregnancy induced hypertension was defined as a systolic BP ≥140 mmHg or a diastolic BP ≥90 mmHg or a mean arterial pressure (MAP) of ≥105 mmHg or higher [21]. Women were considered to have diabetes if they had a history of diabetes, positive oral glucose tolerance test, a random blood glucose ≥11.1 mmol L^{-1} or an HbA_{1c} >5.8%.

Statistical analysis

Statistical analysis was performed using SPSS Statistics (Version 22, IBM). First, absent (AFM) or reduced fetal movements (RFM) was compared to those with 'no evidence' of abnormal fetal activity. Individual variables were analysed separately to identify significant factors to incorporate into a logistic regression model. The normality of continuous data was checked both visually using histograms, and statistically using Kolmogorov–Smirnov test. Most variables were not normally distributed; thus the Mann Whitney U test was used for continuous variables. Categorical data were analysed using the Chi square test or Fisher's exact test. Statistical significance was set at a p-value <0.05. For both categorical and continuous data, the Bonferroni correction was applied to adjust for the alpha inflation. Factors which are known to be associated with stillbirth or RFM were identified from the analysis were incorporated into a directed acyclic graph (Figure 2) which was used to identify the minimal adjusted data set required for multivariate regression using Dagitty (Version 2.3, Institute for Computing and Information Sciences, Radboud University Nijmegen). Due to the need for appropriate group sizes and the different pattern of associations between AFM and RFM, only RFM was compared to women with no evidence of abnormal fetal activity in the regression model. A sample size calculation using placental insufficiency as the primary outcome measure demonstrated that at least 96 cases were needed in each group to have 80% power to detect a difference of 20% in placental insufficiency with two-sided p-value of 0.05.

Results

The cohort of 301 cases of stillbirth included 142 women (47.2%, 95% confidence interval 46.1–52.8%) which presented with AFM or RFM and 159 (52.8%) who had no evidence of abnormal fetal activity; 109 women had RFM and 33 reported AFM. The maternal characteristics of the participants are shown in Table 1. Women presenting with

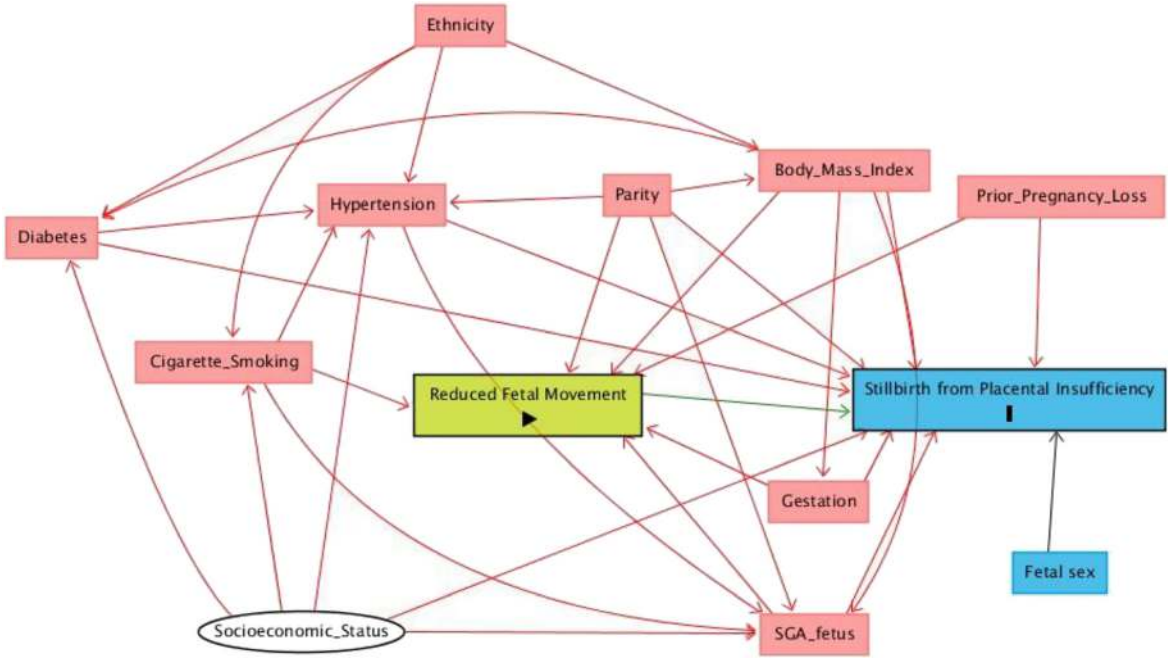

Figure 2: Directed acyclic graph showing relationship of potential interactions between different factors which may affect the association between reduced fetal movements (exposure) and placental insufficiency (outcome). Unmeasured factors are shown in grey oval, measured factors are shown in red boxes. This identified that the minimum variables required for adjustment for covariates was body mass index, smoking status, gestation, number of pregnancies and the frequency of small for gestational age infants.

RFM had a lower gravidity than women with no evidence of RFM. Parity showed a trend to be lower amongst RFM women, although this was not statistically significant (p=0.11). No significant relationship between RFM and age, BMI, ethnicity, blood group, presence of rhesus D antigen or consanguinity was found (Table 1 and Supplementary Table 1).

Medical and pregnancy-related characteristics are presented in Table 2. Women with a stillbirth of at least one baby of a twin pregnancy reported AFM or RFM less frequently (0 and 2.8% respectively) than women with no evidence of RFM (8.8%). Women with AFM or RFM had a lower systolic, diastolic and mean arterial blood pressure and a lower proportion of hypertension (10.0 and 19.4% respectively) than the group with no evidence of reduced movement (31.2%). A higher proportion of women with no evidence of RFM had significant proteinuria. There was no significant difference in gestational age, frequency of IVF pregnancies, smoking, alcohol, drugs and diabetes between the different groups.

A lower proportion of intrapartum stillbirths was found in women with AFM and RFM group as opposed to those with no evidence of abnormal fetal activity although due to the small numbers of intrapartum stillbirths this was not statistically significant (3.0 and 2.8% vs. 8.8%, Table 3). No significant difference was found for gender, birthweight, birthweight centile, placental weight and feto:placental weight ratio (absolute values and centiles). The ReCoDe classification differed between RFM and those with and no evidence of RFM. Women that presented with RFM showed a higher proportion of stillbirths due to placental insufficiency (51.2 vs. 38.4% in no evidence of RFM). However, the proportion of FGR and other placental conditions (e.g. placental abruption) combined showed no significant difference between the groups.

The association between different variables and RFM were analysed by univariate and multivariate regression informed by the DAG (Table 4). This analysis was limited to singleton pregnancies as twin pregnancies were not associated with RFM. Only placental insufficiency was independently associated with RFM (adjusted OR (aOR) 2.76, 95% CI 1.45, 5.26; p<0.001). More than two previous pregnancy losses before 24 weeks (aOR 0.27, 95% CI 0.08, 0.92; p=0.04) and proteinuria ≥2 + (aOR 0.16, 95% CI 0.08, 0.85; p=0.03) were less frequently seen in women who experienced RFM. As there was an interaction between hypertension and proteinuria, hypertension was not independently reduced in women with RFM. None of the additional variables had a significant association with RFM.

Discussion

In this retrospective study, cases of stillbirth were investigated to identify associations with RFM. The main finding was the confirmation of the relationship between RFM and placental insufficiency in this population. Furthermore, women with RFM prior to their stillbirth were significantly less likely to have significant proteinuria and previous

Table 1: Demographic characteristics of women who had a fetal death *in utero* divided by whether there was absent (AFM) or reduced fetal movements (RFM) or no evidence of absent or reduced fetal movements (ARFM).

Maternal characteristic		AFM (n=33)	RFM (n=109)	No evidence of ARFM (n=159)	p-Value AFM vs. no evidence	p-Value RFM vs. no evidence
Age, years (range)		29(19–42)	29(16–41)	30(14–46)	0.85	0.46
BMI, kg/m^2 (range)		27(21–40)	25(18–47)	26(17–63)	0.50	0.31
Gravidity (IQR)		3(2–4)	2(1–3)	3(1–4)	0.82	0.006
Parity (IQR)		1(1–2)	0(0–2)	1(0–2)	0.38	0.11
Previous pregnancies <24 weeks[a] (range)		0(0–2)	0(0–5)	0(0–8)	1.00	0.06
Ethnicity, n, %	European	17(51.5%)	57(52.3%)	74(46.5%)	0.74	0.74
	African	8(24.2%)	15(13.8%)	29(18.2%)		
	Asian	5(15.2%)	27(24.8%)	41(25.8%)		
	Other	3(9.1%)	10(9.2%)	15(9.4%)		
Smoking, n, %		5(15.2%)	17(15.6%)	38(24.1%)	0.36	0.12
Unknown		–	–	1	–	–
Alcohol, n, %		–	3(2.5%)	4(2.5%)	1.00	1.00
Unknown		–	1	1	–	–
Drugs, n, %		–	1(0.9%)	3(1.9%)	1.00	1.00
Unknown		–	–	1	–	–

IQR, interquartile range. [a]Includes termination of pregnancy and spontaneous miscarriages.

Table 2: Maternal medical characteristics of women who had a fetal death *in utero* divided by whether there was absent (AFM) or reduced fetal movements (RFM) or no evidence of absent or reduced fetal movements (ARFM).

Characteristic	AFM (n=33)	RFM (n=109)	No evidence of ARFM (n=159)	p-Value AFM vs. no evidence	p-Value RFM vs. no evidence
Gestational age in days at birth (IQR)	238(187–276)	242(195–266)	233(191–262)	0.39	0.33
Gestation grouped, n, %					
Early (<27 weeks)	9(27.3%)	27(24.8%)	46(28.9%)	0.35	0.65
Late (27–38 weeks)	10(30.3%)	44(40.4%)	65(40.9%)		
Late-term (>38 weeks)	14(42.4%)	38(34.9%)	48(30.2%)		
IVF pregnancy, n, %	1(3.0%)	–	7(4.4%)	1.00	0.09
Twin pregnancy, n, %	0(0.0%)	4(3.7%)	14(8.8%)	0.26	0.28
Max BP systolic (IQR)	120(110–130)	120(110–130)	123(112–142)	0.20	0.06
Max BP diastolic (IQR)	70(64–80)	70(64–82)	75(65–89)	0.10	0.07
Mean arterial pressure (IQR)	87(80–93)	89(80–97)	91(83–107)	0.14	0.06
Hypertension, n, %[a]	3(10.0%)	21(19.4%)	49(31.2%)	0.05	0.07
Unknown	3	1	2	–	–
OGTT 2h, glucose level in mmol L^{-1} (IQR)	6.0(4.9–7.1)	5.5(5.0–6.3)	6.0(4.8–6.7)	0.75	0.45
Diabetes, n, %[b]	3(11.5%)	7(7.6%)	13(12.9%)	0.86	0.23
Unknown	7	17	58	–	–
Maximum proteinuria, n, %					
No	17(56.7%)	65(69.1%)	83(58.5%)	0.83	0.04
Trace	4(13.3%)	13(13.8%)	17(12.0%)		
1+	3(10.0%)	10(10.6%)	9(6.3%)		
2+	4(13.3%)	3(3.2%)	8(5.6%)		
3+	–	1(1.1%)	9(6.3%)		
4+	2(6.7%)	2(2.1%)	16(11.3%)		
Unknown	3	15	17		

[a]Hypertension based on highest measure during antenatal visits: systolic ≥140 mm Hg, diastolic ≥90 mm Hg or mean arterial pressure (MAP) ≥105 mm Hg. [b]Diabetes was defined as any of the following: known diabetes mellitus type 1 or 2, a fasting plasma glucose level ≥5.6 mmol/L during pregnancy, a 2-h plasma glucose level of ≥7.8 mmol/L after OGTT in pregnancy, a random glucose >11.1 mmol/l in pregnancy or a plasma HbA1c >5.8% shortly after birth. IQR, interquartile range.

pregnancy losses <24 weeks compared to women who did not have any evidence of RFM.

This is the first study to investigate the relationship between RFM and factors including placental insufficiency specifically in stillbirths, as opposed to studies that compared stillbirths to live births or investigated live births only [16, 17, 22]. As all stillbirths in the unit were included in the database, and many different variables were assessed, this study offered a realistic representation of the current situation and known confounding variables were unlikely to be missed. The calculation of individual percentiles for birthweight, placental weight and feto:placental weight ratio facilitated comparisons between different groups avoided potential effects of gestational age [23, 24]. As often with retrospective studies using clinically derived data, necessary data were not always available for all cases. Efforts were made to find missing values to achieve a complete database, but if variables were still missing the incomplete cases were not used in the analysis. Critically, the classification of AFM, RFM or normal movements depended on both personal interpretation of the mothers' description of fetal movements and later, the interpretation of these descriptions from the patient notes. Thus, cases of AFM could be recorded as RFM or the other way around, which may have led to misclassification. However, the proportion of stillbirths with RFM was only slightly lower than a previous study (47.2 vs. 54.7%) [12]. Differences in the proportion of RFM may be due to changes in maternal education or in the way this information is recorded in maternal case notes.

Interestingly, the results of the AFM and RFM group appeared to be divergent, which suggests that the

Table 3: Statistical analysis of fetal characteristics. Continuous variables are represented as medians with ranges or interquartile ranges (IQR).

Fetal characteristic	AFM or RFM (n=142)	AFM (n=33)	RFM (n=109)	No evidence of AFM or RFM (n=159)	p-Value ARFM vs. no evidence	p-Value AFM vs. no evidence	p-Value RFM vs. no evidence
Gender							
Male	76(52.8%)	18(54.5%)	57(52.3%)	89(56.0%)	0.74	0.76	0.39
Female	66(46.5%)	14(42.4%)	52(47.7%)	68(42.8%)			
Indeterminate	1(0.7%)	1(3.0%)	–	2(1.3%)			
Birthweight (IQR)	1,889(900–2,735)	1,560(915–2,876)	1950(880–2,660)	1,500(580–2,720)	0.08	0.19	0.12
Birthweight centile (IQR)	5.7(0.4–26.2)	7.0(1.0–22.4)	5.2(0.3–32.8)	2.9(0.0–32.0)	0.06	0.27	0.08
Placenta weight (IQR)	301(200–413)	322(186–460)	300(210–400)	280(188–394)	0.18	0.36	0.23
Placental weight centile (IQR)	2.6(0.3–11.9)	4.2(0.3–15.1)	2.4(0.3–11.8)	3.0(0.3–14.2)	0.70	0.77	0.51
Feto:placental weight ratio (IQR)	6.0(4.3–7.5)	6.0(3.6–7.2)	6.0(4.4–7.7)	5.6(3.8–6.9)	0.07	0.48	0.06
Feto:placental weight ratio centile (IQR)	91.8(59.6–99.3)	92.2(68.1–99.0)	91.7(59.5–99.3)	90.9(51.1–98.3)	0.20	0.65	0.17
Type of stillbirth, n, %							
Antepartum	138(97.2%)	32(97.0%)	106(97.2%)	145(91.2%)	0.05	0.64	0.14
Intrapartum	4(2.8%)	1(3.0%)	3(2.8%)	14(8.8%)			
Stillbirth cause (ReCoDe classification), n (%)[a]							
Group A: fetus							
Lethal congenital anomaly	10(7.0%)	5(15.2%)	5(4.6%)	17(10.7%)	0.002	0.92	0.001
Infection	0(0.0%)	0(0.0%)	0(0.0%)	1(0.6%)			
Acute infection	5(3.5%)	3(9.1%)	2(1.8%)	11(6.9%)			
Non-immune hydrops	1(0.7%)	0(0.0%)	1(0.9%)	1(0.6%)			
Fetomaternal haemorrhage	0(0.0%)	0(0.0%)	0(0.0%)	1(0.6%)			
Twin-twin transfusion	1(0.7%)	0(0.0%)	1(0.9%)	1(0.6%)			
Fetal growth restriction	69(48.6%)	15(45.5%)	54(49.5%)	67(42.1%)			
Other	2(1.4%)	0(0.0%)	2(1.8%)	4(2.5%)			
Group B: umbilical cord							
Prolapse	0(0.0%)	0(0.0%)	0(0.0%)	1(0.6%)			
Constricting loop or knot	2(1.4%)	1(3.0%)	1(0.9%)	1(0.6%)			
Group C: placenta							
Abruptio	3(2.1%)	1(3.0%)	2(1.8%)	16(10.1%)			
Other placental insufficiency	18(12.7%)	2(6.1%)	16(14.7%)	4(2.5%)			
Group D: amniotic fluid							
Chorioamnionitis	1(0.7%)	0(0.0%)	1(0.9%)	2(1.3%)			
Polyhydramnios	0(0.0%)	0(0.0%)	0(0.0%)	1(0.6%)			
Other	1(0.7%)	0(0.0%)	1(0.9%)	0(0.0%			
Group F: mother							

Table 3: (continued)

Fetal characteristic	AFM or RFM (n=142)	AFM (n=33)	RFM (n=109)	No evidence of AFM or RFM (n=159)	p-Value ARFM vs. no evidence	p-Value AFM vs. no evidence	p-Value RFM vs. no evidence
Diabetes	1(0.7%)	1(3.0%)	0(0.0%)	3(1.9%)			
HDP[b]	0(0.0%)	0(0.0%)	0(0.0%)	3(1.9%)			
Drug misuse	1(0.7%)	0(0.0%)	1(0.9%)	0(0.0%)			
Other	1(0.7%)	0(0.0%)	1(0.9%)	1(0.6%)			
Group G: intrapartum							
Asphyxia	0(0.0%)	0(0.0%)	0(0.0%)	6(3.8%)			
Group I: unclassified							
No relevant condition available	26(18.3%)	5(15.2%)	21(19.3%)	15(9.4%)			
No information available	0(0.0%)	0(0.0%)	0(0.0%)	3(1.9%)			
Placental insufficiency[c]	77(51.2%)	12(36.4%)	65(59.6%)	61(38.4%)	0.008	1.00	0.002
Any placental cause, n, %[c]	79(55.6%)	13(39.4%)	66(60.6%)	82(51.6%)	0.49	0.50	0.34
FGR (<10th centile), n (%)[c]	71(50.0%)	16(48.5%)	55(50.5%)	75(47.2%)	0.65	0.89	0.70

[a]The first listed cause in ReCoDe classification order. [b]HDP = Hypertensive disease in pregnancy. [c]As one of the causes of stillbirth according to ReCoDe classification.

Table 4. Logistic regression of factors associated with in women with singleton stillbirths stillbirth associated with RFM. Multivariable model adjusted for body mass index, cigarette smoking, gestation, history of prior pregnancy loss and a small for gestational age fetus in addition to the variables shown in the table.

Characteristic	RFM	No evidence	Univariate logistic regression Odds ratio (95% CI), p-Value	Multivariate logistic regression Odds ratio (95% CI), p-Value
Gravidity, n, %	n=109	n=159		
1	48(44.0%)	49(30.8%)	Reference	Reference
2	23(21.1%)	30(18.9%)	0.78(0.40, 1.54), 0.48	1.27(0.0.51, 3.09), p=0.60
≥ 3	38(34.9%)	80(50.3%)	0.49(0.28, 0.84), 0.01	0.88(0.39, 2.02), p=0.78
Previous pregnancy loss <24 weeks, n, %	n=109	n=159		
0	79(72.5%)	101(63.5%)	Reference	Reference
1	24(22.0%)	25(15.7%)	1.23 (0.65, 2.31), 0.53	1.42 (0.0.58, 3.46); p=0.45
≥ 2	6(5.5%)	33(20.8%)	0.23 (0.09, 0.58), 0.002	0.29 (0.08, 0.97),p=0.04
Hypertension in pregnancy, n, %[a]	n=108	n=157		
No	87(79.8%)	108(68.8%)	Reference	Reference
Yes	21(20.2%)	49(31.2%)	0.44(0.240, 0.81), p=0.008	0.54(0.23, 1.27), p=0.16
Proteinuria, n, %	n=94	n=142		
1+or less	88(93.6%)	109(76.8%)	Reference	Reference
2+ or more	6(6.4%)	33(23.2%)	0.23(0.09, 0.56), 0.001	0.0.27(0.08, 0.89), p=0.03
Interaction of hypertension × proteinuria	n=104	n=152		
Hypertension and no or trace proteinuria	98(94.2%)	123(80.9%)	Reference	Reference[b]
Hypertension and 1+ proteinuria	2(1.9%)	4(2.6%)	0.29(0.09, 2.64), p=0.27	0.26(0.03–2.68), p=0.26[a]
Hypertension and ≥2+ proteinuria	4(3.8%)	25(24.0%)	0.19(0.07, 0.58), p=0.003	0.20(0.06, 0.62), p=0.006[a]
Placental insufficiency, n, %	n=109	n=159		
No	44(40.4%)	98(61.6%)	Reference	Reference
Yes	65(59.6%)	61(38.4%)	2.28(1.36, 3.80), p=0.002	3.15(1.57, 6.32), p=0.002

[a]Hypertension defined as maximum blood pressure ≥140/90 mmHg or MAP ≥105 mmHg. [b]Multivariate regression for the combined variable did not include hypertension and proteinuria due to co-linearity.

diagnostic value of reported RFM and AFM is not the same. Further research needs to be carried out to identify the reasons behind these findings. Possible causes for the variances between the two groups would be that AFM occurs after the fetus has already died, or after a sudden cause of death (e.g. cord occlusion) or the movements had been absent during the whole pregnancy. Therefore, the proposed mechanism of fetal adaptation as a reaction to insufficient metabolic supply would not apply in the case of AFM [25].

Importantly, the causes of stillbirth were not solely classified based upon post mortem examinations or histopathological examination of the placenta, but were determined using a multidisciplinary approach which led to the assignation of one or more conditions according to the ReCoDe classification and maternal history of fetal activity was not taken into account when these decisions were made. Therefore, there was a low risk of classification bias in this study.

The significant relationship between RFM and placental insufficiency mirrors that seen in livebirths [16, 17]. This provides additional support for the hypothesis that RFM is a symptom of placental insufficiency leading to decreased nutrient or oxygen support and the fetus conserving energy as a result. However, FGR was not found to be significantly associated with RFM. This may reflect that the classification of FGR was based on birthweight centile, and there might have been FGR stillbirths that were not below the 10th centile. In such cases placental histopathology probably offers more reliable information about the cause of stillbirth than birthweight alone. Another possible explanation for the lack of association between FGR and RFM in this sample, is that placental insufficiency occurred later in pregnancy when primary adaptation (reduced fetal growth) would be not as evident when the baby died, which is consistent with the trend towards higher fetal:placental weight ratio in RFM (6.0 vs. 5.6, p=0.06).

Both increased proteinuria and hypertension were found less often in women with RFM in univariate analysis. Blood pressure of women with RFM was on average 4 mmHg lower than women with no evidence of RFM. Arguably the difference in overt hypertensive disease (≥140/90 mmHg) was more interesting. However, this does not appear to be an independent association with RFM as the effect was not significant following multivariate regression. This may be due to its correlation with proteinuria, which may reflect preeclampsia. Although

preeclampsia can be associated with some types of placental insufficiency, this study showed that RFM was negatively associated with signs of preeclampsia, this may be due to additional antenatal checks and fetal monitoring identifying compromise in cases of preeclampsia.

This study found that absent and RFM occurred more often in antepartum stillbirths. One study found that in 8% of stillbirths contractions were misinterpreted as fetal movements [26]. This means that women with intrapartum stillbirths possibly had RFM, but did not recognise this as such. This phenomenon was addressed as a confounding factor in this study due to limited information in these cases. However, as there were only 18 intrapartum stillbirths (6%) in the study, of which 14 (4.7%) felt normal movements, possible misinterpretations were unlikely to significantly influence the results.

This study also showed that AFM and RFM occur less in twin pregnancies. Potential explanations for this observation is that twin fetuses move less than singletons [27], that movements between twins are usually asynchronous and as the survivor keeps moving this makes it difficult for the mother to identify a reduction in movements. This merits further exploration in specific studies of fetal movements in multiple pregnancies.

Although this study found a relationship between placental insufficiency and RFM in cases of stillbirth, specific causes of placental insufficiency were not investigated. In a previous study of livebirths, it was shown that RFM is associated with a greater area with signs of infarction, a higher density of syncytial knots which is consistent with maternal vascular malperfusion [17]. Future studies could determine whether specific placental or fetal conditions are associated with RFM. This could identify underlying pathologic processes which would enable specific testing to be instituted to identify fetal compromise. Another suggestion for future work would be the effect of recurrent RFM. In this study, only cases with RFM shortly before birth were used. The prognostic value of a reduction in movement earlier in the pregnancy, which apparently does not immediately lead to fetal death, still needs to be investigated. It would be interesting to investigate if a higher frequency of RFM in pregnancy is associated with a greater degree of placental pathology.

Efforts are needed to reduce stillbirth in high-income countries. Maternal perception of fetal movements is a simple and adequate way to confirm fetal viability and if reduced, recognise increased risk of fetal compromise. However, the recently reported AFFIRM study found that a combination of information about fetal movements and standardised management (including induction of labour from 37 weeks' gestation) did not give the anticipated 30% reduction in stillbirth [28]. One possibility raised in an editorial was that the study was underpowered [29]. Our study, which found that just under half of stillbirths had ARFM, means that the intervention would have had to reduce stillbirths in this group by over 60% to achieve this degree of reduction. Thus, directing intervention after RFM to focus on women with objective evidence of placental insufficiency or fetal compromise may be more appropriate; this is currently being explored by a multicentre pilot study [30].

Research funding: This project received no specific financial support. AEPH receives salary support from Tommy's Charity, UK.

Author contributions: AEPH and JJHME were responsible for the project design. AEPH maintained the perinatal mortality database. MtK and AEPH undertook the statistical analysis. All authors contributed to the writing and review of the manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Not applicable.

Ethical approval: As this analysis used anonymised routinely collected data, approval from a Research Ethics Committee was not required.

References

1. Froen JF, Friberg IK, Lawn JE, Bhutta ZA, Pattinson RC, Allanson ER, et al. Stillbirths: progress and unfinished business. Lancet 2016; 387:574–86.
2. Lawn JE, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I, et al. Stillbirths: where? When? Why? How to make the data count? Lancet 2011;377:1448–63.
3. Flenady V, Wojcieszek AM, Middleton P, Ellwood D, Erwich JJ, Coory M, et al. Stillbirths: recall to action in high-income countries. Lancet 2016;387:691–702.
4. Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. Br Med J 2005;331:1113–7.
5. Korteweg FJ, Gordijn SJ, Timmer A, Erwich JJ, Bergman KA, Bouman K, et al. The Tulip classification of perinatal mortality: introduction and multidisciplinary inter-rater agreement. BJOG 2006;113: 393–401.
6. Froen JF, Pinar H, Flenady V, Bahrin S, Charles A, Chauke L, et al. Causes of death and associated conditions (Codac): a utilitarian approach to the classification of perinatal deaths. BMC Pregnancy Childbirth 2009;9:22.
7. Ptacek I, Sebire NJ, Man JA, Brownbill P, Heazell AE. Systematic review of placental pathology reported in association with stillbirth. Placenta 2014;35:552–62.
8. Higgins L, Mills TA, Greenwood SL, Cowley EJ, Sibley CP, Jones RL. Maternal obesity and its effect on placental cell turnover. J Matern Fetal Neonatal Med 2013;26:783–8.
9. Lean SC, Derricott H, Jones RL, Heazell AEP. Advanced maternal age and adverse pregnancy outcomes: a systematic review and meta-analysis. PloS One 2017;12:e0186287.

10. Zdravkovic T, Genbacev O, McMaster MT, Fisher SJ. The adverse effects of maternal smoking on the human placenta: a review. Placenta 2005;26:S81–6.
11. Stillbirth Collaborative Research Network Writing Group. Association between stillbirth and risk factors known at pregnancy confirmation. Jama 2011;306:2469–79.
12. Efkarpidis S, Alexopoulos E, Kean L, Liu D, Fay T. Case-control study of factors associated with intrauterine deaths. Med Ged Med 2004;6:53–8.
13. Heazell AE, Froen JF. Methods of fetal movement counting and the detection of fetal compromise. J Obstet Gynaecol 2008;28: 147–54.
14. Heazell AEP, Budd J, Li M, Cronin R, Bradford B, McCowan LME, et al. Alterations in maternally perceived fetal movement and their association with late stillbirth: findings from the Midland and North of England stillbirth case-control study. BMJ Open 2018;8:e020031.
15. Stacey T, Thompson JM, Mitchell EA, Ekeroma A, Zuccollo J, McCowan LM. Maternal perception of fetal activity and late stillbirth risk: findings from the Auckland stillbirth study. Birth 2011;38:311–6.
16. Warrander LK, Batra G, Bernatavicius G, Greenwood SL, Dutton P, Jones RL, et al. Maternal perception of reduced fetal movements is associated with altered placental structure and function. PloS One 2012;7:e34851.
17. Winje BA, Roald B, Kristensen NP, Froen JF. Placental pathology in pregnancies with maternally perceived decreased fetal movement–a population-based nested case-cohort study. PloS One 2012;7:e39259.
18. Levy M, Kovo M, Izaik Y, Luwisch Cohen I, Schreiber L, Herman HG, et al. Reduced fetal movements at term in singleton low risk pregnancies-Is there an association with placental histopathological findings? Acta Obstet Gynecol Scand 2020;99: 884–90.
19. Still-Birth Definition Act 1992, Curr Law Statut Annot GB: Great Britain 1.
20. Khong TY, Mooney EE, Ariel I, Balmus NC, Boyd TK, Brundler MA, et al. Sampling and definitions of placental lesions: Amsterdam placental workshop group consensus statement. Arch Pathol Lab Med 2016;140:698–713.
21. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. Pregnancy Hypertens 2014;4:97–104.
22. Tuffnell DJ, Cartmill RS, Lilford RJ. Fetal movements; factors affecting their perception. Eur J Obstet Gynecol Reprod Biol 1991; 39:165–7.
23. Thompson JM, Irgens LM, Skjaerven R, Rasmussen S. Placenta weight percentile curves for singleton deliveries. BJOG 2007;114: 715–20.
24. Clausson B, Gardosi J, Francis A, Cnattingius S. Perinatal outcome in SGA births defined by customised versus population-based birthweight standards. BJOG 2001;108:830–4.
25. Maulik D. Doppler velocimetry for fetal surveillance: adverse perinatal outcome and fetal hypoxia. In: Maulik D, editor Doppler ultrasound in Obstetrics and Gynecology. New York: Springer-Verlag; 1997.
26. Linde A, Pettersson K, Radestad I. Women's experiences of fetal movements before the confirmation of fetal death–contractions misinterpreted as fetal movement. Birth 2015;42:189–94.
27. Mulder EJ, Derks JB, de Laat MW, Visser GH. Fetal behavior in normal dichorionic twin pregnancy. Early Hum Dev 2012;88: 129–34.
28. Norman JE, Heazell AEP, Rodriguez A, Weir CJ, Stock SJE, Calderwood CJ, et al. Awareness of fetal movements and care package to reduce fetal mortality (AFFIRM): a stepped wedge, cluster-randomised trial. Lancet 2018;392:1629–38.
29. Gidlof S. When will we stop encouraging awareness of fetal movements? Acta Obstet Gynecol Scand 2019;98:137–8.
30. Armstrong-Buisseret L, Mitchell E, Hepburn T, Duley L, Thornton JG, Roberts TE, et al. Reduced fetal movement intervention Trial-2 (ReMIT-2): protocol for a pilot randomised controlled trial of standard care informed by the result of a placental growth factor (PlGF) blood test versus standard care alone in women presenting with reduced fetal movement at or after 36(+0) weeks gestation. Trials 2018;19:531.

Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/jpm-2021-0103).