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ORIGINAL RESEARCH

Clinicopathological phenotypes of singleton stillbirth: A retrospective cohort study

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Abstract

Introduction: Interpreting the histopathology report after stillbirth and applying it to care in a subsequent pregnancy can be challenging.

Material and Methods: A retrospective cohort study of singleton stillbirths in Iceland 1996–2021 ($n = 338$). Clinical information and description of placenta and umbilical cord were reviewed, and microscopic slides re-evaluated according to the Amsterdam Consensus. Clinical and histopathological findings, including major patterns of placental injury and umbilical cord at risk, were correlated and compared between gestational age groups: <28 weeks ($n = 102$), ≥28 but <37 weeks ($n = 114$), and ≥37 weeks ($n = 122$).

Results: Placental slides were reviewed for 96.4% (326/338) of singleton stillbirths and classified into major patterns of placental injury. Maternal vascular malperfusion (MVM) was diagnosed in 19.0% of placentas (62/326), fetal vascular malperfusion (FVM) in 31.6% (103/326), acute chorioamnionitis (ACA) in 32.2% (105/326), chronic villitis of unknown etiology (VUE) in 15.9% (52/326), and none of the major patterns in 27.9% (91/326). More than one pattern of placental injury was found in 7.7% of placentas (25/326), most often at term. A similar proportion of MVM was found irrespective of gestational age; FVM was more common after 28 weeks, ACA before 28 weeks, but VUE most frequent at term. A higher proportion of MVM was found in stillbirths with small for gestational age (SGA) infants than non-SGA (23.0 vs. 6.1%), as well as in stillbirths with maternal hypertensive disorder of pregnancy than in stillbirths with a normotensive mother (23.9 vs. 11.8%). The latter association was not seen with high-grade FVM nor VUE. The umbilical cord was at risk in 53.8% (175/326) of singleton stillbirths, increasing with gestational age to 71.7% (86/120) at term. Hypercoiled, excessive long, and wrapped cords were most common. Term stillbirths with cord at risk often also had placental MVM or VUE.

Abbreviations: ACA, acute chorioamnionitis; CNS, central nervous system; FPR, fetoplacental ratio; FVM, fetal vascular malperfusion; GA, gestational age; HDP, hypertensive disorder of pregnancy; MVM, maternal vascular malperfusion; SGA, small for gestational age; VUE, villitis of unknown etiology.

Conclusions: Understanding major patterns of placental injury and their correlation with clinical phenotypes can help counseling after stillbirth. Stillbirths with placental MVM often had clinical signs suggesting a high-risk pregnancy. However, term stillbirths with placental VUE or FVM and umbilical cord at risk were commonly without recognized risk factors.

KEYWORDS
Amsterdam placental workshop consensus, placental histopathology, stillbirth

1 | INTRODUCTION

One of the first questions usually asked after stillbirth is why the baby died. The need for answers encourages investigations after stillbirth such as histopathological examination of the placenta and autopsy,[1] which may provide explanations that were not recognized before the fetal death. Understanding the cause of death and risk of recurrence can help come to terms with the loss[2] as well as planning the mother's antenatal care in subsequent pregnancies.[3] However, attributing cause of death can be complicated and subjective. The fact that there are over 80 classification systems for stillbirth[4,5] does not help.

The Amsterdam consensus to standardize definitions of placental lesions was first published in 2016[6] and further described in 2018 as "Four major patterns of placental injury".[7] Placental pathology can be divided into vascular and inflammatory categories.[8] The former consists of maternal vascular malperfusion (MVM) and fetal vascular malperfusion (FVM). MVM reflects failure of deep trophoblast implantation and spiral artery remodeling in early pregnancy. Formerly called uteroplacental insufficiency, it is associated with pre-eclampsia, fetal growth restriction (FGR), as well as stillbirth, with significant recurrence risk (OR = 1.6; 95% CI 1.3–1.9).[9] FVM reflects stasis leading to thrombosis in fetal vessels and subsequent downstream damage in the placenta. It is usually associated with features of the umbilical cord that make it at risk of reduced vascular circulation[7,10] but thrombophilia, endothelial damage, and fetal heart failure can occasionally contribute.[11] FVM is associated with stillbirth and central nervous system (CNS) injury in infants but considered without a significant recurrence risk.[10,12] Inflammatory lesions are divided into infectious and idiopathic subgroups. Acute chorioamnionitis (ACA) reflects bacterial or fungal infections. The response can be maternal and fetal and cause spontaneous preterm delivery and neonatal sepsis.[13] Furthermore, inflammation of the vessels and stroma of the umbilical cord with necrosis are known risk factors for stillbirth and neonatal complications.[14] There is a considerable risk of recurrence (OR = 2.4; 95% CI, 1.2–4.7), often due to maternal factors such as cervical insufficiency.[15] Chronic villitis of unknown etiology (VUE) is considered to represent an immunological "host versus graft" response causing inflammatory tissue damage.[16] Although low-grade VUE is considered of little significance, high-grade disease is associated with stillbirth and CNS injury,[17,18] with a high recurrence risk of 25%–50%.[19] Certain placental lesions are classified by extent or severity as low or high grade,[20] and combinations of different patterns of placental injury are also strongly related to adverse outcome.[21] Although there is consensus on defining major patterns of placental injury, their clinical significance can be unclear.

Key message

Understanding patterns of placental injury, their clinical correlation, and risk of recurrence can help plan care after stillbirth. Stillbirths with maternal vascular malperfusion often had clinical signs of high-risk pregnancy, unlike stillbirths with villitis of unknown etiology and fetal vascular malperfusion and/or umbilical cord at risk.

It can be challenging for obstetricians to interpret the pathology report, correlate with clinical features, and apply to planning care in a subsequent pregnancy. The aim of this study was to describe major patterns of placental injury in singleton stillbirth in Iceland and correlate with clinical phenotypes in gestational age groups. It was inspired by a paper by Redline et al.,[11] calling for studies correlating placental injury with phenotypes of mothers and infants to increase understanding needed to improve perinatal outcomes.

2 | MATERIAL AND METHODS

This descriptive retrospective cohort study included all singleton stillbirths in Iceland during the study period 1996–2021. Iceland, a high-income country with a population of <400 000, offers free antenatal, intrapartum, and postpartum care. Of the 113,094 infants born in Iceland during the study period, 395 were stillborn, giving a stillbirth rate (SBR) of 3.5 per 1000 infants. Personal identification numbers of mothers who delivered stillborn infants were obtained from the Icelandic Medical Birth Registry. Stillbirth was defined as a birth of an infant without signs of life that cannot be resuscitated after 22

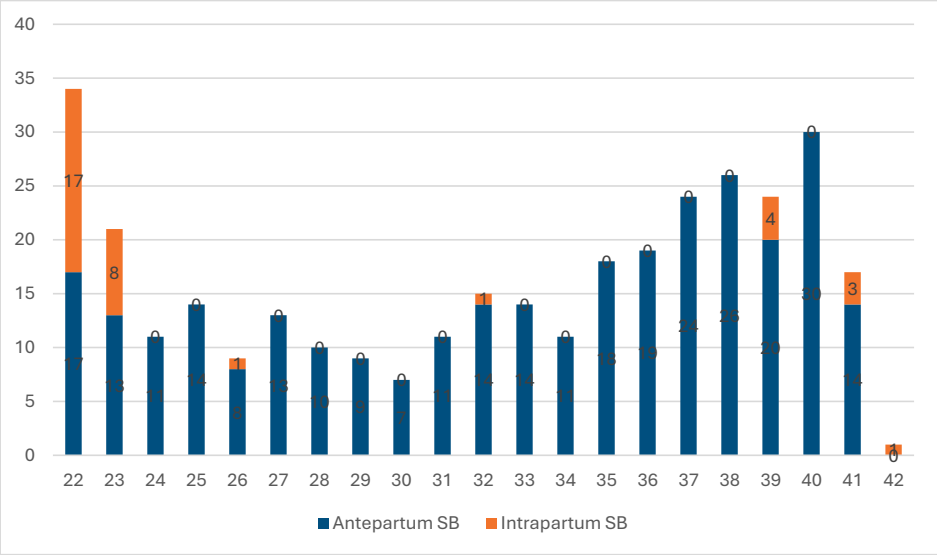

FIGURE 1 Number of stillbirths (SB) for each completed gestational week.

gestational weeks, including antepartum and intrapartum deaths. Stillbirths before 1996 were not included, as perinatal mortality review was not formalized in Iceland until then. To correlate each stillbirth with one placenta, multiple pregnancies were excluded. Gestational age (GA) was based on ultrasound estimation during the first half of pregnancy and stillbirths were grouped according to GA at diagnosis of fetal demise into three groups; <28 weeks, ≥28 but <37 weeks, and ≥37 weeks.

All fetal autopsy records and gross description of placenta were reviewed. The recorded placental weight was trimmed weight of unfixed placental disc after removal of the membranes and umbilical cord. Placental weight under the 10th percentile and fetoplacental weight ratio (FPR) over the 90th percentile for the infant's gestational age and sex was noted.[22] The umbilical cord was defined "at risk" if any of the following features were found: excessive length (over 70 cm); hyper-coiling (more than 3 coils/10 cm); true knot; stricture (cord diameter <0.5 cm); marginal, membranous, or furcate insertion site; thin cord (<0.8 cm in diameter); tethered cord (amnionic web); and potentially obstructing clinical conditions including cord entanglements and cord prolapse.[7,10] Furthermore, information was recorded on cords with <1 coil/10 cm, as "hypocoiled" cords have been shown to be more susceptible to occlusion.[23] All available placental slides from singleton stillbirths were reviewed and archived microscopic slides re-evaluated by the same pathologist (TS) in accordance with recommendations of the 2016 Amsterdam Consensus conference.[6] The histopathologic findings were classified into four major patterns of placental injury as described by Redline et al.[7]: maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), chronic villitis of unknown etiology (VUE), and acute chorioamnionitis (ACA). More than one pattern of placental injury could be seen in the same placenta. Further definitions of the histopathologic findings according to the Amsterdam consensus conference[24] can be seen in Appendix S1. MVM was not graded but FVM and VUE were graded, and both low- and high-grade findings documented. ACA was staged according to inflammatory response into (a) maternal inflammatory response only, (b) fetal inflammatory response with only involvement of the umbilical vein (stage 1), and (c) fetal inflammatory response with involvement of umbilical vein and one or more umbilical arteries (stage 2) or necrotizing funisitis (stage 3).

Clinical information was collected by the same obstetrician (RIB) from medical records including results of all investigations of the mother and stillborn infant. Over 40 variables were recorded for each mother/infant pair, as shown in Table S1 in Supplements. However, some of variables were not used, as they were rare or not considered relevant to this study of clinicopathological phenotypes of singleton stillbirth in Iceland. The subset of variables chosen to represent risk factors were nulliparity, maternal age, body mass index (BMI), non-Icelandic origin, smoking, hypertensive disorder of pregnancy (HDP), small for gestational age (SGA) infants, and a history of obstetrical complications are marked * and defined in Supporting Information S1. Although risk factors are defined as conditions associated with an increased rate of a disease, causality is not necessarily implied.

Hypertensive disorder of pregnancy (HDP) was assigned according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) classification.[25] The definition of SGA was birthweight under the 10th percentile for gestational age and gender according to a recently published Swedish intrauterine growth curve.[26] If medical records confirmed a history of HDP, SGA, or stillbirth in a previous pregnancy, this was noted as "previous complications." Instead of citizenship, "non-Icelandic speaking" was used as a proxy for non-Icelandic origin.

Analysis was descriptive and presented as numbers and proportions of maternal and fetal characteristics and patterns of placental injury, alone and in combinations. Chi-square tests were applied, and *p*-level of 0.05 considered statistically significant. Data were analyzed with RStudio and Excel.

TABLE 1 Clinical phenotypes by gestational age (GA) groups.

	All ($n=338$)	<28 w ($n=102$)	28–36^{+6} w ($n=114$)	≥37 w ($n=122$)
Antepartum stillbirth, *n* (%)	303 (89.6)	76 (74.5)	113 (99.1)	114 (93.4)
Intrapartum stillbirth, *n* (%)	35 (10.4)	26 (25.5)	1 (0.9)	8 (6.6)
Maternal characteristics				
Age >35 years, *n* (%)	85 (25.1)	29 (28.4)	23 (20.2)	33 (27.0)
BMI >30, *n* (%)	75 (22.2)	21 (20.6)	21 (18.4)	33 (27.0)
Primipara, *n* (%)	155 (45.9)	54 (52.9)	53 (46.5)	48 (39.3)
Smoker, *n* (%)	65 (19.2)	24 (23.5)	20 (17.5)	21 (17.2)
Non-Icelandic speaking, *n* (%)	55 (16.3)	15 (14.7)	16 (14.0)	24 (19.7)
HDP, *n* (%)	46 (13.6)	12 (11.8)	14 (12.3)	20 (16.4)
Previous complication[a]	36 (10.7)	8 (7.8)	13 (11.4)	15 (12.3)
Fetoplacental characteristics				
Birthweight <10th perc., *n* (%)	139 (41.1)	50 (49.0)	57 (50.0)	32 (26.2)
Placental weight <10th perc, *n* (%)	85 (25.1)	19 (18.6)	22 (19.3)	44 (36.1)
Fetoplacental ratio >90th perc., *n* (%)	67 (19.8)	9 (8.8)	18 (15.8)	40 (32.8)
Umbilical cord at risk, *n* %	175 (51.8)	28 (27.4)	61 (53.5)	86 (70.5)

[a]History of pre-eclampsia, fetal growth restriction, or stillbirth in previous pregnancy.

3 | RESULTS

During the study period, 395 infants were stillborn in Iceland, 338 of these after a singleton pregnancy. The number of singleton stillbirths, both antepartum and intrapartum, in each completed gestational week is shown in Figure 1. Almost 90% of the stillbirths were antepartum ($n=303$), and the few intrapartum deaths mostly occurred before 24 completed weeks of gestation (25/35). In fact, almost half of stillbirths before 24 weeks were intrapartum (25/55).

Although maternal characteristics were similar irrespective of gestational age (Table 1), this was not true for fetoplacental characteristics. While almost half (107/216, 49.5%) of singleton infants stillborn before term had a birthweight <10th percentile (SGA), this applied to only about 1/4 of those stillborn at term. By contrast, singletons stillborn at term were twice as likely to have low placenta weight (under the 10th percentile for gestational age and gender) compared with preterm stillborn infants (36.1% vs. 19.0%). Also, fetoplacental weight ratio (FPR) over the 90th percentile was increasingly common in higher GA groups; 8.8% before 28 weeks, 15.8% between 28 and 37 weeks, and 32.8% of stillbirths at term. The umbilical cord was defined as "at risk" in over half of all stillbirths (53.0%) but more commonly with increasing GA, 27.4% before 28 weeks, 53.5% between 28 and 37 weeks, and 70.5% at term (Table 1).

Placental examination had been carried out in the vast majority of singleton stillbirths (326/338, 96.4%) and could thus be reviewed and classified into four major patterns of placental injury according to the Amsterdam classification. Overall, MVM was diagnosed in 62 placentas (19.0%), FVM in 103 (31.6%), ACA in 105 (32.2%), and VUE in 52 (15.9%). However, none of the above four major patterns of placental injury were found in 91 (27.9%) of the placentas. Maternal floor infarct was diagnosed in 10 of these cases, and in 41, the umbilical cord was defined as at risk, most often at term. Furthermore, over 1/4 of the stillbirths without major patterns of placental injury were affected by an acute adverse obstetrical event, most often placental abruption. An additional few cases had fetal malformation or no specific positive findings.

Table 2 shows the number of placentas with the four major patterns of placental injury in each of the three GA groups, with grading of FVM and VUE into high and low grade and staging of ACA according to the inflammatory response. In addition, isolated patterns of placental injury "only" as well as their combinations are depicted for each GA group. A similar proportion of MVM was seen in all GA groups; however, FVM was more common after 28 gestational weeks and VUE was most often diagnosed in stillbirth at term. ACA was most often diagnosed in stillbirths before 28 gestational weeks, even more so when there was advanced fetal inflammatory response. There was no difference between GA groups in the proportion of placentas without any of the 4 major patterns of placental injury. In 25 stillbirths (7.7%), more than one pattern of placental injury was found in the same placenta. The majority of these placentas with combined patterns of placental injury were from term stillbirths (20/25, 80%). The combination of ACA with other major patterns of placental injury shows that signs of infection were found in association with other placental injury in 14.4% of all stillbirths, and this was more common after 28 weeks. In Table 3, combinations of more than one pattern of placental injury were excluded and clinical phenotypes shown for isolated patterns of placental injury. ACA was the most frequent isolated injury in intrapartum stillbirth and was found in almost a third of those placentas, but the majority had maternal inflammatory response only.

Most maternal characteristics were similar between the four groups. However, 26% of cases with isolated MVM had

TABLE 2 Four major patterns of placental injury by gestational age groups: Single and/or combinations.

	All	<28 weeks	28 + 0–36 + 6	≥37 weeks
	n = 326	*n* = 98	*n* = 109	*n* = 120
	n (%)	*n* (%)	*n* (%)	*n* (%)
Placental injury, single or combined				
Maternal vascular malperfusion (MVM)[a]	**62 (19.0)**	**17 (17.3)**	**18 (16.5)**	**27 (22.5)**
Fetal vascular malperfusion (FVM)	**103 (31.6)**	**19 (19.4)**	**39 (35.8)**	**45 (37.5)**
FVM high-grade	69 (21.2)	14 (14.3)	33 (30.3)	22 (18.3)
FVM low-grade	34 (10.4)	5 (5.1)	6 (5.5)	23 (19.2)
Villitis of unknown etiology (VUE)	**52 (15.9)**	**3 (3.1)**	**12 (11.0)**	**37 (30.8)**
VUE high-grade	47 (14.4)	3 (3.1)	10 (9.2)	34 (28.3)
VUE low-grade	5 (1.5)	0	2 (1.8)	3 (2.5)
Acute chorioamnionitis (ACA)	**105 (32.2)**	**41 (41.8)**	**27 (24.8)**	**37 (30.8)**
Acute chorioamnionitis[b]	59 (18.1)	17 (17.3)	19 (17.4)	23 (19.2)
Acute chorioamnionitis[c]	27 (8.3)	10 (10.2)	6 (5.5)	11 (9.2)
Acute chorioamnionitis[d]	19 (5.8)	14 (14.3)	2 (1.8)	3 (2.5)
None of the 4 major patterns	**91 (27.9)**	**28 (28.6)**	**33 (30.3)**	**30 (25.0)**
Maternal floor infarct	10 (3.1)	3 (3.1)	5 (4.6)	2 (1.7)
Cord at risk without 4 major patterns	41 (12.6)	8 (8.2)	12 (11.0)	21 (17.5)
Single type of placental injury				
Maternal vascular malperfusion (MVM)[a]	**44 (13.5)**	**15 (15.3)**	**17 (15.6)**	**12 (10.0)**
Fetal vascular malperfusion (FVM)	**75 (23.0)**	**16 (16.3)**	**36 (33.0)**	**22 (18.3)**
FVM high-grade only	*62 (19.0)*	*12 (12.2)*	*34 (31.2)*	*16 (13.3)*
Villitis of unknown etiology (VUE)	**29 (8.9)**	**3 (3.1)**	**9 (8.3)**	**17 (14.2)**
VUE high-grade only	*29 (8.9)*	*3 (3.1)*	*9 (8.3)*	*17 (14.2)*
Acute chorioamnionitis (ACA)	**58 (17.8)**	**33 (33.7)**	**13 (11.9)**	**12 (10.0)**
Combined placental injury				
MVM and FVM	**12 (3.7)**	**2 (2.0)**	**1 (0.9)**	**9 (7.5)**
MVM and VUE	**6 (1.8)**	**0**	**0**	**6 (5.0)**
VUE and FVM	**16 (4.9)**	**1 (1.0)**	**2 (1.8)**	**13 (10.8)**
MVM and VUE and FVM	**1 (0.3)**	**0**	**0**	**1 (0.8)**
ACA and/or MVM and/or FVM and/or VUE	**47 (14.4)**	**8 (8.2)**	**14 (12.8)**	**25 (20.8)**

[a]Not graded.

[b]Maternal inflammatory response only.

[c]Stage 1 fetal inflammatory response.

[d]Stage 2–3 fetal inflammatory response.

hypertensive disorder in the index pregnancy while the proportion was 17.6% in isolated VUE and lower in other groups. The proportion of SGA differed in placentas with isolated patterns of placental injury: 72.7% of stillborn singletons with MVM, <50% of those with high-grade FVM or VUE, and 37.5% of those with ACA. Low placental weight and high FPR were most common in stillbirths with placentas with isolated MVM (61.4% and 52.3%, respectively), less so in isolated VUE (31.0% and 17.2%), and relatively rarely in the others. The umbilical cord was "at risk" in the majority of stillbirths with isolated FVM (79.0%). Table 4 illustrates the association of SGA and HPD with patterns of placental injury. A larger proportion of SGA stillbirths, compared to those with

TABLE 3 Isolated major patterns of placental injury and clinical phenotypes of singleton stillbirth.

Reviewed placentas		MVM only	FVM[a] only	VUE[a] only	ACA only
n = 326		*n* = 44	*n* = 62	*n* = 29	*n* = 56
	n	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Intrapartum death	34	2 (4.5)	3 (4.8)	1 (3.4)	18 (32.1)
Maternal characteristics					
Age >35 years	85	11 (25.0)	16 (25.8)	8 (27.6)	19 (33.9)
Primipara	151	26 (59.1)	27 (43.5)	14 (48.3)	28 (50.0)
Body mass index >30	72	7 (15.9)	14 (22.6)	8 (27.6)	10 (17.9)
Smoker	64	13 (29.5)	6 (9.7)	5 (17.2)	17 (30.3)
Non-Icelandic	53	6 (13.6)	12 (19.4)	4 (13.8)	13 (23.2)
Hypertensive disorder	46	11 (25.0)	5 (8.1)	5 (17.2)	4 (7.1)
Previous complication	35	7 (15.9)	7 (11.3)	4 (13.8)	1 (1.8)
GA <28 weeks	97	15 (34.1)	12 (19.4)	3 (10.3)	32 (57.1)
GA 28–36 + 6 weeks	109	17 (38.6)	34 (54.8)	9 (31.0)	12 (21.4)
GA ≥37 weeks	120	12 (27.3)	16 (25.8)	17 (58.6)	12 (21.4)
Fetoplacental characteristics					
Birthweight <10th perc.	136	32 (72.7)	28 (45.1)	14 (48.3)	21 (37.5)
Placental weight <10th perc.	84	27 (61.4)	8 (12.9)	9 (31.0)	6 (10.7)
Fetoplacental ratio >90th perc.	66	23 (52.3)	6 (9.7)	5 (17.2)	3 (5.4)
Umbilical cord at risk	175	20 (45.4)	49 (79.0)	14 (48.3)	19 (33.9)

[a]High-grade.

birthweight over the 10th percentile, had a placenta with isolated MVM (23.0% vs. 6.1%), but the difference was less marked for isolated high-grade FVM (20.1% vs. 17.2%) and isolated high-grade VUE (10.1% vs. 7.6%), and there was a negative association for placentas with isolated ACA (15.1% vs. 18.7%). Stillbirths with maternal HDP were also associated with isolated MVM (23.9% vs. 11.8%) but not with high-grade FVM nor VUE.

Types of umbilical cords at risk by gestational age groups are shown in Table 5. The cord was defined as at risk in over half (53.7%) of singleton stillbirths, increasing with gestational age from 28.9% of stillbirths diagnosed before 28 weeks to 56.0% between 28 and 37 weeks and 71.7% of term stillbirths. The abnormalities most commonly found were hypercoiled, excessively long, and wrapped cords, and all of these were most frequent at term. Furthermore, these abnormalities were often found together as excessively long cords were both significantly more often hypercoiled and wrapped (Table S3). Hypocoiling, aberrant cord insertion, and particularly true knots and strictures were less common. Almost 2/3 of singleton stillbirths with an umbilical cord at risk had no signs of MVM or VUE (Table S4). However, it was more common with advancing gestational age to have placental MVM or VUE, as well as umbilical cord at risk. In over half of cases with umbilical cord at risk, FVM was found in the placenta. The proportion of FVM, both low and high grade, according to different types of umbilical cord at risk is illustrated in Table 6. High-grade FVM was more frequently detected than low-grade, especially when the cord was hypercoiled, excessively long or with stricture. However, low-grade FVM was more common when the cord was hypocoiled, with a true knot, amniotic web, or cord prolapse. Table 6, which includes all FVM, low and high-grade including non-isolated, illustrated that umbilical cord was at risk in almost 90% of stillbirths with FVM of some type (92/103).

4 | DISCUSSION

Like the "black box" after an airplane crash, the placenta can help explain why an infant was stillborn,[3] especially if major patterns of placental injury and their correlations with clinical features are understood.[27] Placental examination was performed in over 96% of singleton stillbirths in Iceland, and the four major patterns of placental injury, alone or in combination, were detected in almost ¾ of cases (72.1%). None of the four major patterns were found in 27.9% of placentas. In over half of these cases, the umbilical cord was defined as at risk and few had a defined placental pathology such as maternal floor infarct. However, over 1 in 4 stillbirths with none of the major patterns in the placenta were affected by an adverse obstetrical event resulting in sudden fetal demise. The causes of stillbirth are outside the scope of this study, but the research group has recently published a paper on the etiology of stillbirth in Iceland 1996–2021.[28] This showed that the stillbirth rate in Iceland decreased significantly

from 4.10 stillbirths per 1000 births in the earlier half of the study period to 2.88 in the latter ($p=0.009$), due to a reduction in preterm stillbirths. However, no reduction was found in stillbirth at term, which was most often attributed to reduced circulation in the umbilical cord and placental insufficiency.

In the present study, MVM was frequently seen in stillbirths with hypertensive disorder in the index pregnancy as well as those with a history of HDP, SGA, and stillbirth in a prior pregnancy. This is consistent with the known association of defective deep trophoblast implantation with the "Great Obstetrical Syndromes",[29,30] which include pre-eclampsia, fetal growth restriction, and stillbirth. Furthermore, stillbirths with placental MVM most often had low birthweight and placental weight, as well as high FPR, as expected.[31,32]

The umbilical cord was most often at risk in stillbirths with high-grade FVM, which is consistent with reduced circulation in the cord causing stasis leading to fetal vascular thrombosis,[10] and the association of certain characteristics of the umbilical cord with stillbirth is well recognized.[33,34] Finding SGA in stillbirths with high-grade FVM is not unexpected, as the association of FVM with fetal growth restriction has been described.[10] However, neither low placental weight nor high FPR was frequent in stillbirths with high-grade FVM. This is consistent with previous studies, which suggested that low birthweight was associated with abnormal cord insertion, such as marginal, membranous, or furcate insertion site, or a thin cord.[7,10]

Placental ACA with severe fetal inflammatory response (stage 2–3) was most common in stillbirth before 28 weeks in this study. These deaths were often intrapartum, especially in extremely premature infants, as has been previously described.[13,35] In fact, the median gestational age for intrapartum stillbirth in our material was 23 weeks. However, the majority of ACA found in placentas of stillbirths after 28 weeks showed only maternal inflammatory response, which is also a common finding after live births. A study of placental lesions after uncomplicated term pregnancies found ACA in 42.3%, but the majority had only maternal inflammatory response (36.1%) and severe fetal inflammatory response was rare (<5%).[36]

Studies have shown high-grade VUE to be frequently found in stillbirths with low placental weight and high FPR for GA,[16,37] but this study did not find this association to be as strong as for MVM. Moreover, neither SGA nor HDP was as frequent in stillbirths with high-grade VUE as in those with MVM. Although it is important to acknowledge that SGA is not synonymous with fetal growth restriction,[38] this may suggest that stillbirths with VUE are less likely than those with MVM to have clinical signs that indicate an increased risk of fetal demise. In other words, stillbirths with VUE seem more likely to occur in pregnancies that had been considered "low risk."

TABLE 4 Association between Small for Gestational Age (SGA) <10th percentile and Hypertensive disorders in pregnancy (HDP) with isolated major patterns of placental injury.

	n	SGA	Not SGA
Reviewed placentas	326	*n* = 139	*n* = 187
MVM only	44	32 (23.0%)	12 (6.1%)
FVM[a] only	62	28 (20.1%)	34 (17.2%)
VUE[a] only	29	14 (10.1%)	15 (7.6%)
ACA only	56	21 (15.1%)	35 (18.7%)
None of the four major patterns	91	23 (16.5%)	68 (34.3%)
		HDP	**Not HDP**
Reviewed placentas	326	*n* = 46	*n* = 280
MVM only	44	11 (23.9%)	33 (11.8%)
FVM[a] only	62	5 (10.9%)	57 (19.5%)
VUE[a] only	29	5 (10.9%)	24 (8.2%)
ACA only	56	4 (8.7%)	52 (18.6%)
None of the four major patterns	91	9 (19.6%)	82 (28.1%)

[a]High-grade.

TABLE 5 Types of umbilical cord at risk in singleton stillbirth by gestational age groups.

	All	<28 weeks	28 + 0–36 + 6	≥37 weeks
	n = 326	*n* = 97	*n* = 109	*n* = 120
Umbilical cord at risk	175 (53.7)	28 (28.9)	61 (56.0)	86 (71.7)
Hypercoiled cord	60	13	20	27
Hypocoiled cord	22	1	5	16
Excessive cord length	54	13	16	25
True knot in cord	15	1	3	11
Stricture of cord	16	3	8	5
Velamentous insertion	14	1	5	8
Marginal insertion	18	6	5	7
Furcate insertion	7	0	2	5
Amniotic web	13	2	2	9
Wrapped cord	42	2	14	26
Cord prolapse	4	2	1	1

TABLE 6 Proportion of stillborn singletons with FVM by types of umbilical cord at risk.

		High-grade FVM	Low-grade FVM	FVM (all)
		n = 69	*n* = 34	*n* = 103
	n	*n* (%)	*n* (%)	*n* (%)
Cord at risk	175	65 (37.1)	27 (15.4)	92 (52.6)
Hypercoiled cord	60	27 (45.0)	8 (13.3)	35 (58.3)
Hypocoiled cord	22	4 (18.2)	5 (22.7)	9 (40.9)
Excessive cord length	54	19 (35.2)	8 (14.8)	27 (50.0)
True knot in cord	15	1 (6.7)	2 (13.3)	3 (20.0)
Stricture of cord	16	5 (31.3)	2 (12.5)	7 (43.8)
Velamentous insertion	14	5 (35.7)	3 (21.4)	8 (57.1)
Marginal insertion	18	3 (16.7)	2 (11.1)	5 (27.8)
Furcate insertion	7	2 (28.6)	2 (28.6)	4 (57.1)
Amniotic web	13	2 (15.4)	3 (23.1)	5 (38.5)
Wrapped cord	42	8 (11.6)	7 (16.7)	15 (35.7)
Cord prolapse	4	0 (0)	1 (25.0)	1 (25.0)
Isolated cord at risk[a]	116	37 (31.9)	18 (15.5)	55 (47.4)

[a]Umbilical cord at risk without MVM or VUE in placenta.

Furthermore, VUE is more often found with higher GA, being most common in stillbirth at term, as is recognized.[37] Interestingly, we have found that although infants stillborn before term were twice as often SGA compared with term stillbirths, low placental weight and high FPR for GA were more often found in stillbirth at term. This aligns with recent studies, which indicate that screening for fetal growth does not reduce the stillbirth rate at term.[38,39] Although placental volume estimation with ultrasound has been described,[40] its reproducibility has been questioned. Placental biomarkers may predict placental injury, mainly MVM.[41] If biomarkers for VUE could be found, they might help reduce stillbirth in term pregnancies without recognized risk factors.

In over half of cases in this study, the umbilical cord was defined as at risk. This was most common in stillbirths at term (71.7%). However, more term stillbirths with umbilical cord at risk also had MVM and/or VUE compared with stillbirths before term. Indeed, in our recent study of causes of stillbirth at term in Iceland,[42] using the Stockholm classification of stillbirth,[43] the most common cause of death was reduced flow in the umbilical cord, which was frequently in association with placental insufficiency. The commonest cord abnormalities were excessively long, hypercoiled, and/or wrapped cords. All of these were most frequently found at term and were furthermore often found together. About half of these cases had placental FVM which was most often high-grade. The majority of singleton stillbirths with isolated high-grade FVM had an umbilical cord at risk, the proportion was almost 90% when low-grade and non-isolated FVM was included. This is in contrast with a recent Italian study of antepartum singleton stillbirth affected with FVM,[44] as less than half of those umbilical cords (48/103) showed gross abnormalities. However, the incidence of cord abnormalities in all singleton stillbirths was not reported, which could affect the results. The overall prevalence of umbilical cord at risk in stillbirth in the literature ranges widely, dependent on classification system for cause of stillbirth as well as definitions of cord complications. According to a previous study of causes of stillbirth in Iceland by this group,[28] using the Stockholm classification of stillbirth,[43] over 25% of stillbirths were attributed to reduced circulation in the umbilical cord and the proportion increased with gestational age. A study using the INCODE (Initial Causes of Fetal Death) classification system[34] found that 19% of deaths (95% CI 16–23%) were associated with umbilical cord abnormalities. But how common is an umbilical cord at risk and which characteristics increase the risk of stillbirth? Nuchal cords are common in uncomplicated births, being found in up to 30% at 40 weeks without increased risk of adverse perinatal outcome.[45] A systemic review and meta-analysis of 145 studies found nuchal cords in 22% of all births, multiple loops of cord in 4%, and true knots in the cord in 1%. No association was seen between stillbirth and any nuchal cord (OR 1.11, 95% CI 0.62–1.98), but the risk of stillbirth doubled if loops of nuchal cord were multiple compared with single or no loop (OR 2.36, 95% CI 0.99–5.62) and was four times higher with a true knot (OR 4.65, 95% CI 2.09–10.37).[33] In the 145 studies analyzed, data were lacking on cord length, coiling, and cord insertion. However, a study of over 600 000 births from the Medical Birth Registry of Norway found a prevalence of 1.5% for velamentous cord insertion and 6.3% for marginal cord insertion in singletons. Although both were associated with adverse perinatal outcome, the risk was higher for velamentous insertion, which was associated with a threefold higher risk of perinatal death at term compared with normal cord insertion (OR = 3.3, 95% CI 2.5–4.3).[46]

However, the aim of this study is to describe clinicopathological phenotypes of singleton stillbirth without determining cause of death, and it should not be assumed that the stillbirths with umbilical cord at

risk were caused by umbilical cord complications. Causality between umbilical cord at risk and adverse outcome should be assigned with caution and with possible multifactorial interaction in mind. In fact, 1 in 3 stillborn singletons with umbilical cord at risk also had placental MVM or VUE, suggesting multifactorial causes of death, and the proportion was higher at term. More research on umbilical cord variations and their effect on adverse perinatal outcome is needed.

The main strength of the study was to cover an entire nation with the high rate of placental examination (96.4%). Furthermore, that all histopathological slides were re-evaluated and classified according to the Amsterdam consensus[7] by the same perinatal pathologist (TS). Another strength is that medical records were found for all stillbirths and reviewed by the same obstetrician (RIB). However, the fact that a single pathologist reviewed the slides and a single obstetrician reviewed the clinical notes could also be considered a weakness,[47] although both worked according to clear criteria stated in the paper. The main limitation of this study is low numbers, due to the small population of Iceland.

Another limitation is the lack of an unselected control group of placentas from live births. Indeed, information on patterns of placental injury after uncomplicated pregnancies is limited in the literature. In a large study from 2011,[48] which recruited over 1100 mothers from an unselected obstetrical population, no pathological findings were found in 72.1% of placentas from uncomplicated pregnancies. However, the positive pathological findings can be difficult to interpret as the study was performed prior to the Amsterdam consensus. Another study from 2018 of placental lesions in 944 term pregnancies with normal outcome,[36] detected maternal and fetal malperfusion in 36.7% and 19.7% of placentas, respectively, but only 7.4% and 0.7% of these had multiple lesions and were considered "high burden." VUE was found in 18.5% of the placentas, and 2.4% was classified as high-grade VUE. Although a similar classification of the Society for Pediatric Pathology was used in this study, the criteria of the Amsterdam consensus were not applied.

Prospective studies on patterns of placental pathology in placentas from unselected pregnancies are needed to bridge the knowledge gap and aid clinicians further in interpreting the significance of the pathology report after adverse outcomes of pregnancy.

5 | CONCLUSION

The placenta can be considered a "black box," providing information after a stillbirth. Understanding the major patterns of placental injury and their correlation with clinical phenotypes can be a valuable tool to counsel parents after a stillbirth, advise on recurrence risk, and plan surveillance of a subsequent pregnancy. Stillbirths, where MVM was found in the placenta after delivery, often had clinical signs of a "high-risk" pregnancy, such as hypertensive disorder or SGA. This was less common in stillbirths with placental VUE and FVM, which were often associated with umbilical cord at risk. Furthermore, these deaths were more frequent at term. Methods to identify these pregnancies before birth may help reduce stillbirth in the future.

AUTHOR CONTRIBUTIONS

Ragnheidur I. Bjarnadottir: Conceptualization, Methodology, Investigation, Data curation, Resources, Formal analysis, Visualization, Funding acquisition, Project administration, Writing—Original draft. **Thora S. Steffensen:** Conceptualization, Methodology, Investigation, Data curation, Resources, Writing—Reviewing and Editing. **Alexander K. Smarason:** Conceptualization, Methodology, Resources, Writing—Reviewing and Editing. **Karin Pettersson:** Conceptualization, Supervision, Writing—Reviewing and Editing. **Nikos Papadogiannakis:** Conceptualization, Writing—Reviewing and Editing. **Johanna Gunnarsdottir:** Conceptualization, Methodology, Data curation, Visualization, Funding acquisition, Project administration, Supervision, Writing—Reviewing and Editing.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the Icelandic National Bioethics Committee on February 22, 2022 (reference VSNb2022020010/03.01).

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REFERENCES

1. Heazell AE, McLaughlin MJ, Schmidt EB, et al. A difficult conversation? The views and experiences of parents and professionals on the consent process for perinatal postmortem after stillbirth. *BJOG*. 2012;119(8):987-997.
2. Heazell AEP. Managing stillbirth: taking care to investigate the cause and provide care for bereaved families. *J Perinat Med*. 2022;50(6):642-644.
3. Graham N, Heazell AEP. When the fetus goes still and the birth is tragic: the role of the placenta in stillbirths. *Obstet Gynecol Clin North Am*. 2020;47(1):183-196.
4. Leisher SH, Teoh Z, Reinebrant H, et al. Classification systems for causes of stillbirth and neonatal death, 2009–2014: an assessment

of alignment with characteristics for an effective global system. *BMC Pregnancy Childbirth*. 2016;16:269.
5. International Stillbirth Alliance Collaborative for Improving Classification of Perinatal D, Flenady V, Wojcieszek AM, et al. Classification of causes and associated conditions for stillbirths and neonatal deaths. *Semin Fetal Neonatal Med*. 2017;22(3):176-185.
6. Khong TY, Mooney EE, Ariel I, et al. Sampling and definitions of placental lesions: Amsterdam placental workshop group consensus Statement. *Arch Pathol Lab Med*. 2016;140(7):698-713.
7. Redline RW, Ravishankar S, Bagby CM, Saab ST, Zarei S. Four major patterns of placental injury: a stepwise guide for understanding and implementing the 2016 Amsterdam consensus. *Mod Pathol*. 2021;34(6):1074-1092.
8. Redline RW. Placental pathology: a systematic approach with clinical correlations. *Placenta*. 2008;29 Suppl A:S86-S91.
9. Christians JK, Huicochea Munoz MF. Pregnancy complications recur independently of maternal vascular malperfusion lesions. *PLoS One*. 2020;15(2):e0228664.
10. Redline RW, Ravishankar S. Fetal vascular malperfusion, an update. *APMIS*. 2018;126(7):561-569.
11. Redline RW, Roberts DJ, Parast MM, et al. Placental pathology is necessary to understand common pregnancy complications and achieve an improved taxonomy of obstetrical disease. *Am J Obstet Gynecol*. 2023;228(2):187-202.
12. Penn AA, Wintermark P, Chalak LF, et al. Placental contribution to neonatal encephalopathy. *Semin Fetal Neonatal Med*. 2021;26(4):101276.
13. Chisholm KM, Norton ME, Penn AA, Heerema-McKenney A. Classification of preterm birth with placental correlates. *Pediatr Dev Pathol*. 2018;21(6):548-560.
14. Redline RW. Inflammatory responses in the placenta and umbilical cord. *Semin Fetal Neonatal Med*. 2006;11(5):296-301.
15. Himes KP, Simhan HN. Risk of recurrent preterm birth and placental pathology. *Obstet Gynecol*. 2008;112(1):121-126.
16. Redline RW. Villitis of unknown etiology: noninfectious chronic villitis in the placenta. *Hum Pathol*. 2007;38(10):1439-1446.
17. Derricott H, Jones RL, Heazell AE. Investigating the association of villitis of unknown etiology with stillbirth and fetal growth restriction – a systematic review. *Placenta*. 2013;34(10):856-862.
18. Derricott H, Jones RL, Greenwood SL, Batra G, Evans MJ, Heazell AE. Characterizing villitis of unknown etiology and inflammation in stillbirth. *Am J Pathol*. 2016;186(4):952-961.
19. Freedman AA, Miller GE, Ernst LM. Chronic villitis: refining the risk ratio of recurrence using a large placental pathology sample. *Placenta*. 2021;112:135-140.
20. Zhou YY, Ravishankar S, Luo G, Redline RW. Predictors of high grade and other clinically significant placental findings by indication for submission in singleton placentas from term births. *Pediatr Dev Pathol*. 2020;23(4):274-284.
21. Freedman AA, Keenan-Devlin LS, Borders A, Miller GE, Ernst LM. Formulating a meaningful and comprehensive placental phenotypic classification. *Pediatr Dev Pathol*. 2021;24(4):337-350.
22. Boyed TGD, Lis G, McCall J, Juozokas A, Pflueger S. Normative values for placental weights. *Mod Pathol*. 1999;12:1P.
23. Georgiou HM, Rice GE, Walker SP, Wein P, Gude NM, Permezel M. The effect of vascular coiling on venous perfusion during experimental umbilical cord encirclement. *Am J Obstet Gynecol*. 2001;184(4):673-678.
24. Khong TY, Mooney EE, Ariel I, et al. Sampling and definitions of placental lesions: Amsterdam placental workshop group consensus statement. *Arch Pathol Lab Med*. 2016;140(7):698-713.
25. Magee LA, Brown MA, Hall DR, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens*. 2022;27:148-169.
26. Lindstrom L, Cnattingius S, Axelsson O, Granfors M. Accuracy and precision of sonographic fetal weight estimation in Sweden. *Acta Obstet Gynecol Scand*. 2023;102(6):699-707.
27. Ravishankar S, Redline RW. What obstetricians need to know about placental pathology. *Obstet Gynecol Clin North Am*. 2020;47(1):29-48.
28. Bjarnadottir RI, Steffensen T, Smarason AK, et al. Stillbirth in Iceland 1996-2021: incidence and etiology. *Acta Obstet Gynecol Scand*. 2025;104:2155-2164.
29. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. *Am J Obstet Gynecol*. 2011;204(3):193-201.
30. Burton GJ, Woods AW, Jauniaux E, Kingdom JC. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. *Placenta*. 2009;30(6):473-482.
31. Kulkarni VG, Sunilkumar KB, Nagaraj TS, et al. Maternal and fetal vascular lesions of malperfusion in the placentas associated with fetal and neonatal death: results of a prospective observational study. *Am J Obstet Gynecol*. 2021;225(6):660 e1–e12.
32. Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. *Am J Obstet Gynecol*. 2018;218(2S):S745-S761.
33. Hayes DJL, Warland J, Parast MM, et al. Umbilical cord characteristics and their association with adverse pregnancy outcomes: a systematic review and meta-analysis. *PLoS One*. 2020;15(9):e0239630.
34. Hammad IA, Blue NR, Allshouse AA, et al. Umbilical cord abnormalities and stillbirth. *Obstet Gynecol*. 2020;135(3):644-652.
35. McClure EM, Silver RM, Kim J, et al. Maternal infection and stillbirth: a review. *J Matern Fetal Neonatal Med*. 2022;35(23):4442-4450.
36. Romero R, Kim YM, Pacora P, et al. The frequency and type of placental histologic lesions in term pregnancies with normal outcome. *J Perinat Med*. 2018;46(6):613-630.
37. Mekinian A, Kolanska K, Cheloufi M, et al. Chronic Villitis of unknown etiology (VUE): obstetrical features, outcome and treatment. *J Reprod Immunol*. 2021;148:103438.
38. Coutinho CM, Melchiorre K, Thilaganathan B. Stillbirth at term: does size really matter? *Int J Gynaecol Obstet*. 2020;150(3):299-305.
39. Halimeh R, Melchiorre K, Thilaganathan B. Preventing term stillbirth: benefits and limitations of using fetal growth reference charts. *Curr Opin Obstet Gynecol*. 2019;31(6):365-374.
40. Azpurua H, Funai EF, Coraluzzi LM, et al. Determination of placental weight using two-dimensional sonography and volumetric mathematic modeling. *Am J Perinatol*. 2010;27(2):151-155.
41. King VJ, Bennet L, Stone PR, Clark A, Gunn AJ, Dhillon SK. Fetal growth restriction and stillbirth: biomarkers for identifying at risk fetuses. *Front Physiol*. 2022;13:959750.
42. Bjarnadottir RI, Steffensen T, Pettersson K, Papadogiannakis N, Smarason AK, Gunnarsdottir J. Stillbirth at term in Iceland: causes of death and patterns of placental injury. *Placenta*. 2025;162:14-19.
43. Varli IH, Petersson K, Bottinga R, et al. The Stockholm classification of stillbirth. *Acta Obstet Gynecol Scand*. 2008;87(11):1202-1212.
44. Avagliano L, Monari F, Melis B, Facchinetti F, Bulfamante G. The invisible killer: fetal vascular malperfusion in stillbirths without macroscopic cord abnormalities. *Pathologica*. 2025;117(1):18-27.
45. Cohain JS. Nuchal cords are necklaces, not nooses. *Midwifery Today Int Midwife*. 2010;93:46-48. 67–8.
46. Ebbing C, Kiserud T, Johnsen SL, Albrechtsen S, Rasmussen S. Prevalence, risk factors and outcomes of velamentous and marginal cord insertions: a population-based study of 634,741 pregnancies. *PLoS One*. 2013;8(7):e70380.
47. Redline RW, Vik T, Heerema-McKenney A, et al. Interobserver reliability for identifying specific patterns of placental injury as defined by the Amsterdam classification. *Arch Pathol Lab Med*. 2022;146(3):372-378.

48. Pathak S, Lees CC, Hackett G, Jessop F, Sebire NJ. Frequency and clinical significance of placental histological lesions in an unselected population at or near term. *Virchows Arch*. 2011;459(6):565-572.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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