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Stillbirth at term in Iceland: Causes of death and patterns of placental injury

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ABSTRACT

Background: Iceland is a high-income country with <400.000 inhabitants and low stillbirth rate (SBR). Increased antenatal risk assessment and interventions in high-risk pregnancies doubled the induction rate after 2008.
Objective: Estimate the SBR at term, comparing an earlier (1996–2008) and latter (2009–2021) 13-year period, and describe causes of death and patterns of placental injury of infants stillborn at term.
Study design: Stillbirth at term was defined as antepartum or intrapartum death of an infant that was diagnosed after ≥37 weeks of gestation. All cases (n = 125) had placental examination. Histopathological slides were reviewed, and pattern of placental injury classified according to the Amsterdam consensus. Medical records were found for all mothers who had stillbirth at term and cause of death assigned according to the Stockholm classification of stillbirth.
Results: No decrease in the SBR at term was found between periods. Majority of deaths (72 %) were caused by cord complications and/or placental insufficiency and deaths attributed to placental insufficiency increased in the latter period. Placentas weighing under the 10th percentile were more common in the latter period, 43.5 % vs. 30.2 % ($p < 0.05$) as was chronic villitis of unknown etiology (VUE), 40.3 % vs. 12.7 % ($p < 0.01$).
Conclusion: Stillbirth at term has not decreased in Iceland, despite increased antenatal surveillance and induction rate, with more deaths attributed to placental insufficiency and VUE increasingly found in the later period. Further research is needed on the correlation of patterns of placental injury with clinical phenotypes of mothers and infants.

1. Introduction

The grief of the parents whose infant is stillborn is profound and it is impossible to account for a life that was not lived [1]. Understanding why the infant died is important both for parents and clinicians and a basis for planning the mother's care in subsequent pregnancies [2]. Furthermore, auditing and classifying causes of stillbirth can influence health policy, clinical practice and research and may ultimately reduce mortality [3]. Over 80 classification systems have been described, some classify all perinatal death [4], while others only focus on stillbirth, such as the Stockholm classification of stillbirth [5].

Despite known risk factors for stillbirth [6,7], none are recognized for many mothers of stillborn infants. Although the stillbirth may have been unexpected, investigations after birth can provide explanations, especially placental pathology [8]. Due to progress in placental histopathology, the proportion of unexplained stillbirths has decreased in recent years [9]. However, pathological changes in the placenta are undetected before the stillbirth. Correlation of obstetrical characteristics with placental histopathology could improve the understanding needed to improve perinatal outcomes [10].

Abbreviations: Stillbirth rate, SBR; Gestational age, GA; Small for gestational age, SGA; Maternal vascular malperfusion, MVM; Fetal vascular malperfusion, FVM; Acute chorioamnionitis, ACA; Chronic villitis of unknown etiology, VUE.

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Iceland, a high-income country with under 400.000 inhabitants, has a stable and low caesarean section rate [11] and low stillbirth rate (SBR), as other Nordic countries [12]. Over the last decades, risk assessment was increased in antenatal care and guidelines implemented for surveillance of pregnancies considered high-risk with recommendation of low-dose acetylsalicylic acid, serial ultrasound scans and early-term induction of labor. The rate of induction of labor more than doubled in Iceland after 2008, to over 25 % of all deliveries [13,14]. This is due to induction of labor for prolonged pregnancy earlier than previously, as studies showed an increased risk of stillbirth with advancing gestation at term [15,16] as well as inducing labor after 37 weeks in hypertensive pregnancies after the HYPITAT study showed that this improved maternal outcome [17]. In addition, gestational diabetes became a more common indication for induction [14] due to changes in screening practices and higher body mass index (BMI) in the population [18]. Adverse neonatal outcome including intrapartum or early neonatal deaths decreased over time in Iceland [19] but change in the incidence or causes of antepartum stillbirth at term has not been studied in Iceland. The aims of the study were to estimate the SBR at term, comparing an earlier 13-year period (1996–2008) to a later (2009–2021) and describe causes of death and patterns of placental injury of infants stillborn at term.

2. Methods

The Icelandic Medical Birth Registry provided personal identification numbers of all mothers who delivered stillborn infants in Iceland from 1996 to 2021 and the number of stillborn and live born infants during the same period. As perinatal mortality review was formalized in Iceland in 1996 with improved documentation, earlier stillbirths were not included. Stillbirth was defined as an infant born without signs of life that cannot be resuscitated, including both antepartum and intrapartum deaths. Term stillbirths were defined as infants whose death was diagnosed at or after 37 weeks of gestation. Therefore, stillbirths where the intrauterine death of a twin had been diagnosed before 37 weeks of gestation but was delivered at term with the liveborn twin, were excluded. Gestational age was based on ultrasound examination before 22 weeks of gestation.

The 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 over the 90th percentile for the infant's gestational age and sex was noted [20]. 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 less than 0.5 cm), marginal-, membranous- or furcate insertion site, thin cord (less than 0.8 cm in diameter), tethered cord (amnionic web) and potentially obstructing clinical conditions including cord entanglements and cord prolapse [21,22]. All placental slides from term stillbirths (n = 125) were reviewed. Archived microscopic slides were re-evaluated by the same pathologist (TS) and histologic findings documented in accordance with recommendations of the 2016 Amsterdam Consensus conference [23]. The histologic findings were classified into four major patterns of injury, described by Redline et al. [21]: 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. Definitions of the histopathologic findings as per the Amsterdam consensus conference can be viewed in Supplement I [24]. In accordance with the Amsterdam consensus, MVM was not graded, as explained in Supplement I. However, as grading of MVM has recently been described [25], an analysis of high-grade MVM according to this was carried out. FVM and VUE were graded according to the Amsterdam consensus [21] and only included if high-grade. ACA was not graded but classified according to maternal/fetal response as shown in Supplement I.

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, see Supplement II, Table S1. The definition of small for gestational age (SGA) was birthweight under the 10th percentile of a newly published Swedish intrauterine growth curve [26]. Hypertensive disorder of pregnancy (HDP) was assigned according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) classification [27]. Each case was discussed with the pathologist (TS), and based on re-evaluation of the placental and autopsy gross description and slides as well as clinical review, the primary and associated cause of death assigned according to the Stockholm classification of stillbirth [5], which was modified slightly according to the terminology of the Amsterdam consensus [23], see Supplement II, Table S2.

Placental insufficiency was considered a primary cause of death if histopathological examination of the placenta showed >30 % parenchymal loss, such as infarction or villitis, or the infant had IUGR verified by ultrasound or post mortem examination and histopathological examination of the placenta suggested placental insufficiency (15–30 % parenchymal loss or small placenta <10th percentile for GA, maturation defect, chronic villitis or fetal thrombotic vasculopathy.Reduced circulation in the umbilical cord was considered the primary cause of the death if the umbilical cord was defined as "at risk" and 2 of 4 following signs were found: histopathological signs of stasis at the site of a knot, segmental cord discoloration, autopsy of the fetus showing signs of asphyxia or findings of thrombosis in umbilical cord or chorionic plate. Other primary and associated causes of death, with a definite, probable or possible association to stillbirth, are described in Table S2 in Supplement II.

Cases that were difficult to evaluate were discussed with (KP) and (NP), both authors of the Stockholm classification.

The SBR at term was calculated, using the number of infants born at term as the denominator. Analysis was mainly descriptive and presented as numbers and proportions of maternal and fetal characteristics, patterns of placental injury and cause of death. To account for major primary and associated causes of stillbirth of term infants, analysis was performed for composite groups of placental insufficiency (PI) and/or reduced circulation in the umbilical cord (RCC). Two 13-year periods (1996–2008 and 2009–2021) were compared, and analysis further stratified for SGA infants and mothers diagnosed with HDP. As a sensitivity analysis, primary cause of death was examined in cases with autopsy. Also, the comparison of placental injury between periods was repeated, stratified according to number of slides examined per placenta. Chi-square tests were applied and *p*-level of 0.05 considered statistically significant. RStudio and Excel were used to analyze data. The study was approved by the Icelandic National Bioethics Committee on February 22, 2022 (reference VSNb2022020010/03.01).

3. Results

During the study period 106.180 infants were born at or after 37 weeks of gestation and 125 were stillborn, 122 singletons and 3 infants were one of a pair of twins. There was no multiple pregnancy with more than one stillborn infant during the study period. Of term stillbirths, 77 infants died before 40 weeks (37 + 0 to 39 + 6 weeks of gestation) and 46 infants after 40 weeks (40 + 0 to 42 + 1). Intrapartum stillbirth was rare (n = 6). Overall, the SBR at term was 1.18/1000 term infants with much fluctuation between years (Fig. 1). There was no decrease in the SBR at term between the earlier (63/52459 term infants) and later (n = 62/53721 term infants) 13-year period, 1.19 vs. 1.15/1000 term infants, p = 0.89 (Table 1).

Full autopsy was carried out in 80 % of the 125 infants stillborn at term (n = 100) and all placentas had histopathological examination. The primary cause of death according to the Stockholm classification of stillbirth appeared similar whether infants had autopsy or not (Table S3).

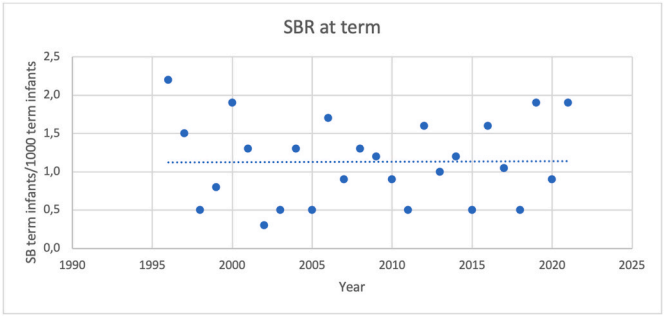

Fig. 1. Stillbirth rate at term in Iceland.

Table 1
Clinicopathological phenotypes of stillbirth at term by periods.

	1996–2021	1996–2008	2009–2021	p-value
Number of infants born at term	106180	52459	53721	
Number of stillborn infants at term	125	63	62	
Stillbirth rate (/1000 term infants)	1.18	1.19	1.15	0.89
Maternal characteristics:				
Mean age (SD)	30.9 (5.88)	30.5 (5.51)	31.1 (6.27)	0.48
Mean BMI (SD)	27.1 (6.12)	26.8 (6.59)	27.5 (5.63)	0.55
Nullipara, n (%)	49 (39.2)	22 (34.9)	27 (43.5)	0.42
Smoker, n (%)	21 (16.8)	14 (22.2)	7 (11.3)	0.26
Language other, n (%)	25 (20.0)	9 (14.3)	16 (25.8)	0.17
HDP, n (%)	19 (15.2)	8 (12.7)	11 (17.7)	0.59
Fetoplacental characteristics:				
Mean GA in days (SD)	275 (9.69)	275 (10.1)	275 (9.75)	0.66
Mean birthweight in g (SD)	3330 (600)	3420 (590)	3230 (613)	0.09
Birthweight <10 th percentile, n (%)	35 (28.0)	14 (22.2)	21 (33.9)	0.21
Placental weight <10 th percentile, n (%)	46 (36.8)	19 (30.2)	27 (43.5)	**<0.05**
Fetoplacental ratio >90 th percentile, n (%)	42 (33.6)	19 (30.2)	23 (37.1)	0.07
Umbilical cord at risk	81 (64.8)	40 (63.5)	41 (66.1)	0.90
Pattern of placenta injury:				
Autopsy performed, n (%)	100 (80)	48 (76.2)	52 (83.0)	0.40
Median n of histologic slides (range)	11.3 (4–29)	8.3	14.5	**<0.001**
Maternal vascular malperfusion, n (%)	28 (22.4)	12 (19.0)	16 (25.8)	0.26
Fetal vascular malperfusion, n (%)[a]	45 (36.0)	13 (20.6)	32 (51.5)	**<0.001**
Chronic villitis of unknown etiology, n (%)[a]	33 (26.4)	8 (12.7)	25 (40.3)	**<0.001**
Acute chorioamnionitis (all), n (%)	35 (28.0)	18 (28.6)	17 (27.4)	0.50
Maternal floor infarct, n (%)	6 (4.8)	5 (7.9)	1 (1.6)	0.22

[a] High-grade only.

The average number of slides per placenta was 11.2 (range 4–29), 8.3 in the earlier period (1996–2008) and 14.0 in the later (2009–2021). In the earlier period there were five or more in over 95 % of cases (60/63) and over 10 in 36.5 % (23/63). In the later period the number of slides per placenta was never under five and over 10 in 75.8 % of cases (47/62). (Table S4).

Table 1 shows clinicopathological phenotypes of stillbirth at term with comparison between two time periods. There were no differences between periods in parity, age, BMI or HDP in the index pregnancy. Smoking was less common among mothers of stillborn term infants in the later period (11.3 %) compared with the earlier (22.2 %) and more were non-Icelandic speaking in the later period (14.3 % vs 25.8 %), but these differences were not statistically significant. A comparison of Icelandic speaking and non-Icelandic speaking mothers showed no difference in clinicopathological characteristics (Table S5).

Although there was no difference in gestational age (GA) between the two periods, there was a trend for lower mean birthweight and a fetoplacental weight ratio (FPR) over the 90th percentile for gestational age, but this did not reach statistical significance (Table 1). However, more stillborn term infants had a placental weight under the 10th percentile for GA in the later period (43.5 % vs. 30.2 %, $p < 0.05$). When comparing patterns of placental injury between periods, significantly more high-grade FVM and VUE was found in revision of the histopathological slides from the latter period. FVM was found in 51.5 % of slides (32/62) from the latter period and 20.6 % (13/63) from the earlier, $p < 0.001$ whereas VUE was seen in 40.3 % (25/62) vs. 12.7 % (8/63) of slides on review, $p < 0.01$. No difference was found between the periods in MVM nor ACA. However, when high-grade MVM was analyzed, there was a trend for increase in the latter period, 24.2 % (15/62) vs. 9.5 % (6/63), $p = 0.05$ (Table S6).

The primary cause of stillbirth at term according to the Stockholm classification is shown in Table 2, with comparison between the earlier and latter periods. Due to the small population, numbers were very low for most causes of death as defined by the Stockholm classification. Although acute chorioamnionitis was often seen as maternal response with or without fetal response (Table S8), infection was only considered the main cause of stillbirth in two cases with signs of necrotizing umbilical vasculitis, as there were no cases of fetal pneumonia or maternal sepsis. The cause of death was unexplained (positive findings but no definite association to stillbirth) or unknown (no positive findings) in 10 cases (8 %), with a reduction over time. The most common primary causes of stillbirth at term were cord complications with signs of reduced circulation in the umbilical cord (RCC) in 48 cases (38.4 %) and placental insufficiency (PI), which 43 stillbirths were primarily attributed to, that is 34.4 % of all term stillbirth. Comparing the time periods, the primary cause of death was significantly less often attributed to cord complication in the latter (27.4 vs. 49.2 %. $p = 0.02$), when it was significantly more often attributed to placental insufficiency (54.8 vs 14.3 %, $p < 0.001$).

When accounting for primary as well as associated causes of death; placental insufficiency (PI) and/or reduced circulation in the umbilical cord (RCC) were found alone or together in almost ¾ of stillbirths at term (92/125), (Fig. 2, Table 3). In 28 term stillbirths, there were signs of both PI and RCC, and additionally 22 cases of PI without signs of cord complications (PI only): a total of 50 cases with placental insufficiency

Table 2
Primary cause of term stillbirth according to Stockholm classification by periods.

	1996–2021	1996–2008	2009–2021	p-value
Primary cause of death	n = 125	n = 63	n = 62	
Malformation, n (%)	1 (0.8)	0	1 (1.6)	
Infection, n (%)	2 (1.6)	2 (3.2)	0	
Immunization, n (%)	0	0	0	
Fetomaternal transfusion, n (%)	3 (2.4)	2 (3.2)	1 (1.6)	
Twin-to-twin transfusion syndrome, n (%)	0	0	0	
Birth asphyxia, n (%)	3 (2.4)	3 (4.8)	0	
Placental insufficiency, n (%)	**43 (34.4)**	**9 (14.3)**	**34 (54.8)**	**<0.001**
Cord prolapse, n (%)	1 (0.8)	0	1 (1.6)	
Reduced circulation in umbilical cord, n (%)	**48 (38.4)**	**31 (49.2)**	**17 (27.4)**	**0.02**
Placental abruption, n (%)	8 (6.4)	6 (9.5)	2 (3.2)	0.28
Preeclampsia, n (%)	1 (0.8)	0	1 (1.6)	
Diabetes mellitus, n (%)	1 (0.8)	1 (1.6)	0	
Intrahepatic cholestasis of pregnancy, n (%)	2 (1.6)	1 (1.6)	1 (1.6)	
Uterine rupture, n (%)	2 (1.6)	2 (3.2)	0	
Other causes, n (%)	0	0	0	
Unexplained/unknown n (%)	10 (8.0)	6 (9.5)	4 (6.5)	0.76

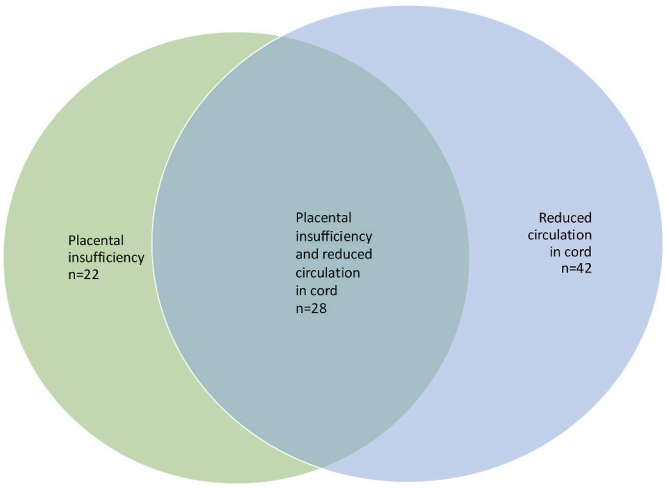

Fig. 2. The two main primary and associated causes of stillbirth at term in Iceland (n = 93).

Table 3
Primary and associated cause of death: Placental insufficiency and/or reduced circulation in the umbilical cord by periods.

	All term SB n = 125	1996–2008 n = 63	2009–2021 n = 62	p-value
Placental insufficiency all, n (%)	50 (40.0)	14 (22.2)	36 (58.1)	**<0.001**
Placental insufficiency & reduced cord circulation, n (%)	28 (22.4)	10 (15.9)	18 (29.0)	0.12
Reduced cord circulation only, n (%)	42 (33.6)	26 (41.3)	16 (25.8)	0.10
Reduced cord circulation all	70 (56.0)	36 (57.1)	34 (54.8)	0.94

(PI all). Placental insufficiency, with or without signs of reduced circulation in umbilical cord (PI all), was significantly more often the cause of death in the later period, 36 (58.1 %) vs. 14 cases (22.2 %) in the earlier, $p < 0.001$. In 70 cases the death was attributed to RCC (RCC all), 42 of these without signs of PI (RCC only), with no significant difference over time (Table 3).

More than one pattern of placental injury was often found in the same placenta. As seen in Table 4, MVM and VUE were more common in placentas where the stillbirth was attributed to placental insufficiency, either as primary or associated cause (PI all) than RCC only. This applied whether MVM was classified as high-grade or not (Table S7). As expected, umbilical cord at risk was most common in stillbirth attributed only to RCC (Table 4).

Table 4
Patterns of placental injury and umbilical cord at risk for primary causes of term stillbirth.

	All term SB (n = 125)	Placental insufficiency all (n = 50)	Reduced cord circulation only (n = 42)
MVM, n (%)	28 (22.4)	20 (40.0)	4 (9.5)
VUE, n (%) *	33 (26.4)	23 (46.0)	6 (14.3)
FVM, n (%) *	45 (36.0)	22 (44.0)	14 (33.3)
Umbilical cord at risk	81 (64.8)	30 (60.0)	38 (90.5)

Each case may have more than one type of placental injury and/or umbilical cord at risk.
MVM, maternal vascular malperfusion, VUE, chronic villitis of unknown etiology, FVM, fetal vascular malperfusion.
* High-grade only.

Although 28 % (35/125) of term stillborn infants were found to be SGA, no difference could be demonstrated in any of the patterns of placental injury between SGA and non-SGA infants. However, the placentas of the SGA infants were significantly more often under the 10th percentile for GA. Only 19 mothers experiencing stillbirth at term had been diagnosed with HPD, and the difference in patterns of placental injury between them and normotensive mothers was not found to be statistically significant (Table 5).

4. Discussion

The SBR at term did not decrease in Iceland over the study period. Almost ¾ of term stillbirths were due to placental insufficiency and/or umbilical cord complications as co-existing conditions contributing together to fetal demise, although having different pathophysiological origins. More deaths were attributed to placental insufficiency in the later period (2009–2021) than the earlier (1996–2008). Placentas weighing under the 10th percentile for gestational age were more common in the later period and VUE more often diagnosed on review of histopathological slides from the later period. No association was found between VUE and stillborn infants at term that were SGA or whose mothers had HDP.

The SBR at term is relatively low in Iceland; 1.18/1000 term infants. In comparison, a meta-analysis of 13 cohort studies based on 15 million term pregnancies in high-income countries showed the rate of stillbirth at term to vary from 1.1 to 3.2 per 1.000 term pregnancies [16]. A study from Denmark showed a reduction in stillbirth at term from April 2, 1000 in 2000 to April 1, 1000 in 2012 after the induction rate doubled [28], however their baseline SBR was higher than in Iceland.

The association between stillbirth at term and low placental weight for GA is well known [29], but finding more placentas weighing under the 10th percentile for GA over time was unexpected.

Placental insufficiency and cord complications were found to be the major causes of stillbirth at term with a significant increase in the former between the two time periods. A recent Italian study on stillbirth at term using the Classification of stillbirth by relevant condition at death (ReCoDe) [30] also found the two major causes to be placental and umbilical cord disorders [31]. In our study, cord complications with signs of reduced circulation were more frequent than found by the Stillbirth Collaborative Research Network, where 19 % of stillbirths were attributed to cord complications [32]. However, those stillbirths were not exclusively term, and a different classification system (Initial Causes of Fetal Death classification system) was used.

A recent Swedish study of stillbirth at term using the Stockholm classification of stillbirths found infection to be the most frequent cause of death along with placental insufficiency [33]. This may be due to differences in attributing infection as the main cause of death in cases of ACA without severe fetal response, as well as dissimilarities in the obstetrical populations of Iceland and Sweden.

Finding no decrease in the SBR at term between the two time periods and in fact more deaths attributed to placental insufficiency in the later period is perplexing, especially in view of the increased antenatal surveillance for high-risk pregnancies and doubling of the rate of induction of labor. However, a recent study from the Netherlands found that 909 inductions at 41 weeks and 2–3 days instead of 42 weeks were needed to prevent one perinatal death [34]. Therefore, our study may lack power to detect a potential impact on the SBR from inducing slightly earlier at term. The increase in antenatal surveillance and induction rate in Iceland over the last decades may have had other benefits, as a recent study showed a decrease in adverse maternal and neonatal outcomes in 1997–2019 [19].

In Iceland, as in other high-income countries with accessible antenatal care, women considered to have the highest risk of adverse outcome are less likely than “low risk” mothers to carry their

Table 5
Clinicopathological phenotypes of term stillbirth in pregnancies with SGA or HDP.

	All term SB n = 125	SGA n = 35	Not SGA n = 90	p-value	HDP n = 19	Not HDP n = 106	p-value
PI all, n (%)	52 (41.6)	20 (57.1)	32 (35.5)	**0.005**	12 (63.2)	40 (37.7)	0.07
RCC only, n (%)	42 (33.6)	4 (11.4)	38 (42.2)	0.012	4 (21.1)	38 (35.8)	0.36
FPR >90 th perc., n (%)	42 (33.6)	9 (25.7)	33 (36.7)	0.65	8 (42.1)	34 (32.1)	0.62
Placenta <10 th perc., n (%)	46 (36.8)	22 (62.9)	24 (26.7)	**<0.001**	8 (42.1)	38 (35.8)	0.57
MVM, n (%)	28 (22.4)	8 (22.9)	20 (22.2)	0.46	8 (42.1)	20 (18.9)	0.07
VUE, n (%)*	33 (26.4)	10 (28.6)	23 (25.6)	0.54	8 (42.4)	25 (23.6)	0.16
FVM, n (%)*	45 (36.0)	11 (31.4)	34 (37.8)	1.0	8 (42.4)	37 (34.9)	0.73

SGA: Small for gestational age i.e. birthweight under the 10th percentile for gestation age, *HDP*: Hypertensive disease of pregnancy.
PI all: placental insufficiency all; *RCC only*: reduced circulation in umbilical cord only; *FPR > 90*th *perc.*: Fetoplacental ratio over 90th percentile for gestational age; *Placenta < 10*th *perc.*: placental weight under 10th percentile for gestational age.
MVM: maternal vascular malperfusion, *VUE*: chronic villitis of unknown etiology, *FVM*: fetal vascular malperfusion.
* High-grade only.

pregnancies past term, especially in the later period with increased rate of induction of labor. Although there was an increase in maternal age, BMI and HDP in the general obstetrical population in Iceland [13], no difference in these risk factors were found among the mothers who had stillbirths at term. This raises the question of whether there would have been an increase in the term SBR without the increased interventions.

Stillbirth at term was most often primarily attributed to reduced flow in the umbilical cord in this study, although less often in the latter time period. Placental insufficiency was the second most common primary cause and significantly more deaths attributed to this in the latter period. Cord complications were frequently found in association with placental insufficiency and the primary cause of death was attributed to the placental insufficiency if both conditions co-existed in the same case. This is due to the hierarchy in the Stockholm classification system, so when both signs of placental insufficiency and reduced circulation in the umbilical cord were found in the same case, the primary cause of death was attributed to placental insufficiency. Therefore, the apparent reduction in cord complications as the primary cause of death in the latter period is undoubtedly explained by the increase in placental insufficiency.

MVM did not increase significantly between periods, although a trend was seen for high-grade MVM. This study did not have the power to detect a significant association between MVM and HDP although other studies have shown an association, especially with pre-eclampsia [35]. The increase in FVM in the latter period can partially be explained by changes in sampling practices, as more slides were taken from chorionic plate vessels after FVM was first described in 2006 [22]. Unexpectedly, VUE was significantly more often diagnosed in the later period. VUE is still an enigma, and research is needed on its correlation with clinicopathological phenotypes of mothers and infants [10]. It is characterized by infiltration of maternal T-cells into the chorionic villi and thought to represent a reaction similar to transplant allograft rejection [36–38]. Another theory is that the chronic inflammation may be triggered by a viral infection [39]. Admittedly the cases were very few, but no significant relationship was found between VUE and HPD nor SGA in this study. VUE has been associated with fetal growth restriction [40], but it is important to acknowledge that SGA is not synonymous to fetal growth restriction [41,42].

In this study, no relationship was found between SGA and any major pattern of placental injury for stillbirth at term. This suggests that surveillance of fetal growth by serial ultrasound may not be an appropriate method to detect placental insufficiency in term infants. In fact, recent studies show that screening for fetal growth does not reduce the stillbirth rate at term as the association between growth restriction and fetal demise weakens with advancing gestational age [41,43]. Estimating placental volume with ultrasound has been described [44] and recent studies suggest that placental biomarkers may increase the detection of placental insufficiency [45], which could enable increased surveillance and interventions to prevent term stillbirth.

The main strength of the study was that placental examination was performed in all stillbirths at term in Iceland during the study period, preventing selection bias of the histopathology results. Furthermore, all histopathological slides were re-evaluated in view of changes in criteria during the study period and classified according to the Amsterdam consensus [23] by the same perinatal pathologist (TS). Another strength is that medical records were found for all mothers who had stillbirths at term, and reviewed by same obstetrician (RIB), who collaborated closely with the pathologist in assigning cause of death according to the Stockholm classification. This interdisciplinary collaboration was strengthened with case discussions with authors of the Stockholm classification of stillbirth (KP, NP). However, the fact that there was only one pathologist reviewing the slides and one obstetrician reviewing the clinical notes can be considered a weakness [46], although both worked according to clear criteria stated in the paper.

The unequal number of slides in the earlier and latter period may be a bias in the study, but it reflects changes in histopathological practice over the study period. It was standard practice to take four slides per placenta from 1997 to 2016, when the standard number of slides was increased to five after the publication of the Amsterdam consensus [23]. In addition, extra slides would be taken from macroscopic placental lesions. In this study, the number of slides per placenta were more than five in over 97.5 % of all cases over the study period. Interestingly, the increased diagnosis in the latter period compared with the earlier was only found when >10 slides were examined. This suggests that taking more than the recommended five slides per placenta when investigating stillbirth may increase the detection of placental injury. However, the main limitation of this study is low numbers, as stillbirth at term is a rare occurrence in the small population of Iceland.

5. Conclusion

Stillbirth at term has not decreased in Iceland over the last quarter of a century, despite increased antenatal surveillance and a doubled induction rate. More deaths were attributed to placental insufficiency in the latter period as well as more VUE on review of histopathological slides from placentas of stillborn term infants. Further research is needed on major patterns of placental injury, their clinical phenotypes and association with genotypes and biomarkers [47].

CRediT authorship contribution statement

Ragnheidur I. Bjarnadottir: Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Thora Steffensen:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. **Karin Pettersson:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Nikos Papadogiannakis:** Writing – review & editing, Methodology, Conceptualization. **Alexander K. Smarason:** Writing – review & editing, Resources, Methodology, Conceptualization. **Johanna Gunnarsdottir:** Writing – review &

editing, Visualization, Supervision, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ragnheidur Ingibjorg Bjarnadottir reports financial support was provided by The Icelandic Centre for Research. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2025.02.007.

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