Stillbirth in Iceland 1996-2021: causes and clinicopathological phenotypes

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Thesis for the degree of Philosophiae Doctor

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August 2026

School of Health Sciences
FACULTY OF MEDICINE
UNIVERSITY OF ICELAND

Andvanafæðingar á Íslandi 1996-2021: orsakir og svipgerðir

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Ágúst 2026

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Reykjavik, Iceland 2026

Ágrip

Markmið: Að rannsaka tíðni andvanafæðinga á Íslandi á árabilinu 1996-2021 og orsakir þeirra, meðal annars með því að endurskoða meinafræði fylgnanna.

Aðferðir: Klínískum upplýsingum var safnað úr sjúkraskrám mæðra sem höfðu fætt andvana barn eða börn á rannsóknartímanum (n=385) og barna þeirra (n=395). Börnunum var skipt í eftirfarandi hópa eftir meðgöngulengd þegar dauðsfallið greindist: ≥22 en <28 vikur (n=140), ≥28 en <37 vikur (n=130) and ≥37 vikur (n=125). Farið var yfir niðurstöður krufningar og lýsingu fylgju, belgja og naflastrengs og auk þess voru öll smásjárgler endurskoðuð og flokkuð samkvæmt Amsterdam samkomulaginu um fylgjumeinafræði (e. Amsterdam placental workshop consensus). Ákvörðuð var aðal (primary) og meðverkandi (associated) orsök dauðsfallsins samkvæmt Stokkhólms flokkun á andvanafæðingum (e. Stockholm classification of stillbirth). Tíðni andvanafæðinga, upplýsingum um mæður, nýbura og fylgjur þ.á.m. fylgjumeinafræði svo og orsakir andvanafæðinganna voru borin saman milli tveggja 13 ára tímabila (1996-2008 and 2009-2021), svo og milli þriggja meðgöngulengdarhópa. Beitt var kí-kvandrat prófi (Chi-square tests) og p-gildi 0.05 var talið tölfræðilega marktækt.

Niðurstöður: Tíðni andvanafæðinga lækkaði úr 4,10 í 2,88/1000 fæðingar (p=0,009) milli fyrri og seinni helminga rannsóknartímans vegna færri andvanafæðinga fyrir 37 vikna meðgöngu. Á seinni helmingi rannsóknartímans voru færri andvanafæðingar vegna sýkinga, fylgjuloss eða óútskýrðra orsaka. Algengustu aðalorsakir andvanafæðinga voru flæðistruflun um naflastreng (25,6%) og fylgjuþurrð (25,2%) og þessar orsakir voru báðar algengari eftir því sem meðgangan var lengri. Þrátt fyrir að ekki væri munur milli tímabila á hlutfalli andvanafæddra barna sem voru létt miðað við meðgöngulengd (undir 10. percentili) var marktækt hærra hlutfall fylgna léttar miðað við meðgöngulengd á seinni helmingi rannsóknartímans (30,3 vs 21,3%, p=0,002), þegar marktækt stærra hlutfall andvanafæðinga var rakið til fylgjuþurrðar (37,0 vs 17,0%, p=0,0002). Tíðni andvanafæðinga fullburða barna var 1,18/1000 börn fædd eftir 37 vikna meðgöngu og breyttist ekki yfir rannsóknartímann. Hjá andvanafæddum fullburða börnum var marktækt hærra hlutfall fylgna létt miðað við meðgöngulengd á seinni helmingi rannsóknartímans (43,5% vs. 31,7%, p<0.05), þegar langvinn bólga í fylgjutotum af óþekktum uppruna (e. chronic villitis of unknown etiology, VUE) greindist einnig marktækt oftar (40,3% vs. 12,7%, p<0,01). Algengustu orsakir andvanafæðinga fullburða barna voru flæðistruflun um naflastreng og fylgjuþurrð en 72% dauðsfall var rakin til annarrar þessara orsaka eða beggja. Marktækt hærra hlutfall andvanafæðinga fullburða barna var rakið til fylgjuþurrðar (með eða án

flæðistruflunar um naflastreng) á seinni hluta rannsóknartímans (56,5% vs 22,2%, p<0,001). Vefjasneiðar frá 96,4% af fylgjum andvanafæddra einbura voru endurskoðaðar og flokkaðar í fjóra meginhópa fylgjuskemmda (e. four major patterns of placental injury). Fylgjuskemmdin maternal vascular malperfusion (MVM) greindist í 19,0% af fylgjum, fetal vascular malperfusion (FVM) í 31,6%, acute chorioamnionitis (ACA) í 32,2% og VUE í 15,9%. Fleiri en einn meginhópur fylgjuskemmda fannst í 7,7% fylgna, oftast eftir fulla meðgöngu, og ekkert meginhópanna fjögurra í 27,9%. Svipað hlutfall af MVM fannst í fylgjunum óháð meðgöngulengd, FVM var algengara ≥28 vikur en ACA fannst oftast <28 vikur og VUE greindist oftast í fylgjum fullburða barna. Hærra hlutfall af einangruðu MVM fannst í fylgjum einbura með lága fæðingarþyngd en annarra andvana fæddra einbura (23,0 vs 6,1%), svo og hverra mæður höfðu verið með háþrýstingssjúkdóm á meðgöngu samanborið við fylgjur andvanafædda einbura hverra mæður höfðu ekki verið með háþrýsting (23,9 vs 11,8%). Naflastrengir flokkuðust í áhættu fyrir flæðistruflun hjá rúmlega helmingi (53,8%) andvanafæddra einbura og hlutfallið jókst með lengd meðgöngu (28,9% <28 viku, 56,0% ≥28 en <37 og 71,7% >37 vikur). Algengustu frábrigðin voru ofsnúnir, of langir og vafðir naflastrengir, sem oft fór saman. Fullburða andvana einburar með áhættunaflastrengi voru oft einnig með MVM og/eða VUE í fylgjunni.

Ályktanir: Tíðni andvanafæðinga lækkaði á síðari hluta rannsóknartímans vegna fækkunar á andvanafæðingum fyrirbura en tíðni andvanafæðinga fullburða barna breyttist ekki. Algengustu dánarorsakirnar voru flæðistruflun um naflastreng og fylgjuþurrð og báðar þessar orsakir voru algengari eftir því sem meðgangan var lengri. Hlutfall andvanafæðingum vegna fylgjuþurrðar jókst á seinni hluta tímans enda fækkaði andvanafæðingum fullburða barna ekki. Með lengri meðgöngu greindist oftar VUE eða FVM í fylgjum andvanafæddra barna svo og áhættunaflastrengir, oft eftir meðgöngu án þekktra áhættuþátta. Skilningur á meginhópum fylgjuskemmda og tengslum þeirra við klíníska áhættuþætti getur hjálpað við að útskýra hvers vegna barn dó fyrir fæðingu og við að leggja drög að eftirliti á næstu meðgöngu.

Lykilorð: Andvanafæðing, Amsterdam samkomulag um fylgjumeinafræði, Stokkhólmsflokkun andvanafæðinga, fylgjuþurrð, flæðistruflun um naflastreng.

Abstract

Aims: to explore the stillbirth rate (SBR) and examine the etiology of stillbirth in Iceland from 1996-2021 as well as review the placental histopathology.

Methods: Clinical information was obtained from medical records of mothers who had stillbirths and their infants (n=395). Infants were divided into groups according to gestational age (GA) at diagnosis of stillbirth: early preterm: ≥22 but < 28 weeks (n=140), late preterm: ≥28 but <37 weeks (n=130) and term: ≥ 37 weeks (n=125). Autopsy records and gross description of placenta were reviewed and microscopic slides re-evaluated and classified according to the Amsterdam placental workshop consensus into four major patterns of placental injury. Primary and associated causes of death were assigned according to the Stockholm classification of stillbirth. The SBR, maternal and fetoplacental characteristics, placental histopathology as well as cause of death were compared between two 13-year periods (1996-2008 and 2009-2021) and between GA groups. Chi-square tests were applied and p-level of 0.05 considered statistically significant.

Results: The SBR decreased from 4.10 to 2.88/1000 births (p=0.009) between the former and latter period, but the reduction was limited to stillbirths diagnosed before term. Fewer stillbirths in the latter period were attributed to causes such as infection and placental abruption as well as unknown/unexplained. The most common primary causes of stillbirth were reduced circulation in the umbilical cord (25.6%) and placental insufficiency (25.2%); both increased with advancing GA. Despite no difference in proportion of small for gestational age infants between the two periods, placental weight <10th percentile for GA was significantly more common in the latter period than the earlier (30.3% vs 21.3%, p= 0.002), when a larger proportion of stillbirths was attributed to placental insufficiency (37.0 vs 17.0%, p=0.0002). The stillbirth rate at term was 1.18/1000 term infants with no decrease between the two periods. In stillbirth at term, placentas weighing under the 10th percentile were more common in the latter (43.5 vs 31.7%, p<0.05). Chronic villitis of unknown etiology (VUE) was significantly more often diagnosed in the latter period (40.3 vs,12.7%, p<0.01. Cord complications and placental insufficiency were the most common causes of stillbirth at term as 72% (91/125) of deaths were attributed to these causes, either alone or together. Compared to the earlier period, stillbirth was significantly more often attributed to placental insufficiency (with or without cord complications) in the latter compared to the earlier (56.5% vs. 22.2%, p<0.001). Placental histologic slides were reviewed for 96.4% stillborn singletons and classified into four major patterns of placental injury. Maternal vascular malperfusion (MVM) was diagnosed in 19.0%, fetal vascular malperfusion

(FVM) in 31.6%, acute chorioamnionitis (ACA) in 32.2% and VUE in 15.9%. More than one pattern of placental injury was found in 7.7% and none of the major patterns in 27.9% of placentas. A similar proportion of MVM was seen in all GA groups, FVM was more common ≥28 weeks whereas ACA was most frequent <28 weeks and VUE most often diagnosed at term. A higher proportion of maternal vascular malperfusion 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 umbilical cord was classified as at risk in half (53.8%) of singleton stillbirths, the proportion increased with gestational age (28.9% <28 weeks, 56.0% ≥28 but <37 and 71.7% at term). Hypercoiled, excessively long and wrapped cords were most common. Term stillbirths with cord at risk often also had placental MVM and/or VUE.

Conclusions: The SBR decreased in the latter period due to a reduction in preterm stillbirth but the SBR at term was unchanged. Reduced circulation of the umbilical cord and placental insufficiency were the commonest causes of death, both increasing with gestational age. Stillbirth due to infection and placental abruption as well as unexplained stillbirths decreased during the study period whereas deaths attributed to placental insufficiency became more common, reflecting lack of reduction of stillbirth at term in the latter period. Stillbirths with VUE and FVM, as well as umbilical cord at risk, were more common with advancing GA and often without recognized risk factors. Understanding major patterns of placental injury and their correlation to clinical phenotypes of stillbirth is valuable when counselling after stillbirth and planning surveillance of a subsequent pregnancy.

Keywords:

Stillbirth, Amsterdam placental workshop consensus, Stockholm classification of stillbirth, placental insufficiency, umbilical cord complications.

Acknowledgements

First and foremost, I thank **Þóra Steffensen** for reviewing all available histopathology slides and classifying them according to the Amsterdam consensus. Thank you Þóra for increasing my insight into placental pathology, for the many fruitful discussions and for your friendship. Without your contribution, this study would not have been possible.

I would also like to thank pathologist **Nikos Papadogiannakis** for sharing his expertise as well as his encouragement and interest in the doctoral study.

Many thanks to my supervisors, **Jóhanna Gunnarsdóttir**, for all your time, great guidance and tireless patience in "teaching an old dog new tricks" and to **Karin Pettersson** for your valuable insight and illuminating comments and questions.

I thank my doctoral committee**, Unnur Anna Valdimarsdóttir** and **Kristjana Einarsdóttir** for their support and good comments, and especially my dear friend **Alexander K. Smárason** for the many excellent discussions throughout the doctoral study as well as critical reading and great comments and suggestions.

Reynir Tómas Geirsson I thank for introducing me to perinatal audit many years ago and **Þóra Steingrímsdóttir** for designating time for research in our department. Thanks to my friend and boss **Hulda Hjartardóttir** for releasing me from clinical duties to pursue Ph.D. studies and being a role model in doing this as a "mature student".

Many thanks to the Icelandic Centre for Research (Rannís) for a three-year Doctoral grant for the project *Stillbirth in Iceland 1996-2021: incidence, causes and consequences. Ref. nr: 239642-051.*

Last but not least, I thank my husband and best friend **Sveinn Yngvi Egilsson** for his patience and encouragement and our daughters, **Þorbjörg, Brynja and Hólmfríður** and grandchildren **Friðrik Yngvi, Baldur Ingi, Sveinn, Steingrímur, Þorvaldur** and **Lína Hind** for inspiring me.

The thesis is dedicated to all those affected by stillbirth and the lives that were not lived.

Contents

List of Abbreviations

- Acute chorioamnionitis (ACA)
- Artificial reproductive technology (ART)
- Chronic villitis of unknown etiology (VUE)
- Confidence interval (CI)
- Early neonatal death rate (ENDR)
- Fetal vascular malperfusion (FVM)
- Fetoplacental weight ratio (FPR)
- Gestational age (GA)
- High-income country (HIC)
- Hypertensive disorder of pregnancy (HDP)
- Intrauterine growth restriction (IUGR)
- Maternal vascular malperfusion (MVM)
- Perinatal mortality rate (PNMR)
- Small for gestational age (SGA)
- Stillbirth rate (SBR)

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List of Original Papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals.

I. **Stillbirth in Iceland 1996-2021: Incidence and etiology.** Ragnheidur I Bjarnadottir, Thora Steffensen, Alexander K Smarason, Karin Pettersson, Nikos Papadogiannakis, Kristjana Einarsdottir, Johanna Gunnarsdottir. Published in *Acta Obstetricia et Gynaecologica Scandinavica (AOGS)* 24th September 2025*

II. **Stillbirth at term in Iceland: Causes of death and patterns of placental injury.** Ragnheidur I Bjarnadottir, Thora Steffensen, Karin Pettersson, Nikos Papadogiannakis, Alexander K Smarason, Johanna Gunnarsdottir. Published in *Placenta* 25th March 2025*

III. **Clinicopathological phenotypes of singleton stillbirth: A retrospective cohort study.** Ragnheidur I Bjarnadottir, Thora Steffensen, Alexander K Smarason, Karin Pettersson, Nikos Papadogiannakis, Johanna Gunnarsdottir. Published in *Acta Obstetricia et Gynaecologica Scandinavica (AOGS)* 26th June 2026

Declaration of Contribution

The doctoral student, Ragnheiður Ingibjörg Bjarnadóttir (RIB), conceived the idea of the study and planned it in collaboration with the supervisors, Jóhanna Gunnarsdóttir (JG) and Karin Petterson (KP) with valuable input from Alexander Kristinn Smárason (AKS) and Þóra Steffensen (ÞS). RIB reviewed the medical records for all cases in the study, including antenatal and labour records as well as laboratory results and histopathology reports. ÞS reviewed all available pathological slides and classified the findings according to the Amsterdam Placental Workshop Group Consensus Statement. RIB developed a database for clinical and histopathological findings of each stillbirth. Based on this, RIB classified the cause of each death according to the Stockholm classification of stillbirth, which she modified according to the Amsterdam consensus in collaboration with ÞS. Cases that were challenging to classify were discussed with KP and Nikos Papadogiannakis (NP), who were among the authors of the Stockholm classification. RIB performed the statistical analysis and interpreted the results with input from JG, KP, AKS and ÞS. The three manuscripts were written by RIB and edited by co-authors JG, ÞS, KP, AKS, NK as well as Kristjana Einarsdóttir for the first paper. The thesis was written by RIB and revised by JG, KP and AKS. Artificial intelligence was neither used in writing the manuscripts nor the thesis.

1 Introduction

Jag har en liten kyrkogård i mitt bröst. *Den finns där hela tiden. Det är de små, små barnen som knappt fick börja livet som jag bär med mig. Det är oftast stilla och lugnt på kyrkogården i mitt bröst. Alla barnen sover djupt. Men så händer något som gör att det blir oroligt, de vrider sig mellan mina revben. Bilder, ljud och namn kommer till mig...Och den kommer att växa, den där kyrkogården. Den gör det för oss alla inom detta yrke. Att hålla riktningen och styrfarten där mellan de små gravarna, hur gör man det?*

I have a little cemetery in my chest. *It is always there. I carry with me the tiny babies that hardly got to begin life. Usually, it is quiet in the cemetery in my chest. All the babies are sound asleep. Then something disturbs their slumber, they become uneasy and kick between my ribs. Pictures, sounds and names come back... And the cemetery will grow larger. It does for all of us in this profession. But how to keep your aim and pace between the small graves?*

Dr. Ylva Strandberg, Obstetrician, Sahlgrenska Hospital, Gothenburg, Sweden.
Translation RIB

Stillbirth is one of the most devastating outcomes of pregnancy. Death of a baby before birth is a tragedy and there is no way to account for a life that was not lived (Dandona & Solberg, 2023). The loss is devastating for the parents (Höglund & Hildingsson, 2025) and clinicians may experience failure and even guilt (Cates et al., 2025). One of the first questions usually asked is why the baby died. The need for answers prompts investigations after stillbirth such as histopathological examination of the placenta and autopsy (Heazell et al., 2012). Clinicians strive to understand and explain what happened to facilitate coming to terms with the loss and eventually the grieving process (Heazell, 2022). Not least importantly, understanding the cause of death and risk of recurrence can help plan the mother´s antenatal care in subsequent pregnancies (Flenady et al., 2016). Furthermore, auditing causes of stillbirth may influence research and health policy and thus improve perinatal care which can ultimately reduce mortality (Kerber et al., 2015). Despite known maternal and fetal risk factors for stillbirth (Townsend et al., 2021; Yerlikaya et al., 2016), none of these are recognized in many cases. Although the stillbirth may have been unexpected, investigations after birth can provide explanations, especially placental pathology (Man et al., 2016). Due to progress in this field, the proportion of unexplained stillbirths has decreased in recent years (Thirumalaikumar L, 2019). Although histopathological changes in the placenta are not detected antenatally, correlation of obstetrical characteristics with placental

histopathology could improve the understanding needed to improve perinatal outcomes (Redline et al., 2023). Attributing cause of death can be complicated and often subjective. The fact that there are over 80 classification systems for stillbirth (International Stillbirth Alliance Collaborative for Improving Classification of Perinatal et al., 2017; Leisher et al., 2016a, 2016b) does not simplify this. Many classifications include all perinatal deaths but others only stillbirth, such as the Stockholm classification of stillbirth (Varli et al., 2008), which describes the chain of events leading to fetal death (primary cause) as well as contributing to it (associated cause). This classification was used in the first two papers in the doctoral study: "Stillbirth in Iceland 1996-2021; incidence and etiology" and "Stillbirth at term in Iceland: Causes of death and patterns of placental injury". The third paper, "Clinicopathological phenotypes of singleton stillbirth", correlates clinical features with histopathological findings in the placenta according to Amsterdam Placental Workshop Group Consensus Statement. Hopefully, these studies will enhance understanding needed to reduce stillbirth in the future. Indeed, research may help clinicians "keep their aim" in this important field.

1.1 Definition of stillbirth and perinatal mortality

Infants that are born without signs of life and cannot be resuscitated are termed stillbirths or intrauterine fetal deaths (IUFD). This includes deaths during pregnancy or antepartum stillbirths, and deaths of an infant during delivery or intrapartum stillbirths. Perinatal mortality is a term that includes stillbirths as well as death of infants in the first week after birth or early neonatal death (END). The stillbirth rate (SBR) is the number of stillbirths per 1000 births (live births and stillbirths), while the perinatal mortality rate (PNMR) is the number of stillbirths and early neonatal deaths per 1000 births.

As the gestational age (GA) when intrauterine fetal death is defined as stillbirth instead of a mid-trimester abortion or miscarriage varies widely, international comparisons can be difficult. In many high-income countries, fetal death is defined as stillbirth from 22 weeks of gestation or a birthweight of 500g if the GA is unknown. Pregnancies that end earlier are defined as mid-trimester abortions or miscarriages (International Stillbirth Alliance Collaborative for Improving Classification of Perinatal et al., 2017). In Iceland this definition has been used since 1994, but in many countries 28 completed gestational weeks is still used as a cut-off or a birthweight of 1000 g if the gestational age is not known. The World Health Organization (WHO) advises each country to use national definitions of stillbirth but to report all stillbirths both from 22 weeks and 28 weeks gestational weeks for international comparison (WHO, 2016).

1.2 Incidence of stillbirth

Globally, it is estimated that 2 million babies were stillborn after 28 weeks of gestation in 2019 and that 40% of these deaths were intrapartum. The global SBR is estimated to be 13.9 per 1000 births, but it differs almost ten-fold from 22.8 in West and Central Africa to 2.9 in Western Europe (Hug et al., 2021). Data is often missing from low-income countries with the most stillbirths (Cousens et al., 2011). The SBR of a country can be considered a marker of the quality of its perinatal care (Lawn et al., 2016). Not only is it important to register and count each death, but also to audit and classify them (Tollman et al., 2021). The incidence of intrapartum stillbirth is thought to reflect the quality of intrapartum care while antepartum stillbirth rather reflects accessibility and quality of antenatal care (WHO, 2016). Most intrapartum stillbirths, which are much more common in low-income countries, are caused by obstetrical emergencies, whereas conditions and diseases related to antepartum stillbirth can differ between low- and high-income countries (Lawn et al., 2011). In high-income countries (HICs), the stillbirth rate declined steeply for five decades preceding the 1990s (Kayode et al., 2022). This was mostly due to a reduction in intrapartum stillbirth, leading to the rate of antepartum stillbirth being up to ten times higher than of intrapartum stillbirth. In England and Wales, the stillbirth rate fell dramatically from 1940 to 1990 but subsequently increased slightly in the next two decades.

According to data from the Icelandic Medical Birth Registry, the SBR in Iceland was on average 3.5 per 1000 born infants over the last quarter of a century but fluctuates markedly due to small numbers (Icelandic Medical Registry data 1996-2021). This SBR is similar to the other Nordic countries (Heino & Gissler, 2024) and among the lowest in Europe (Hug et al., 2021; Zeitlin et al., 2019). Although the SBR in HICs, including Iceland, is low in a global context, it has reduced little over the last decades, while the rate of early neonatal death (END) has declined much more. In fact, the SBR is twice as high as the rate of END in most HICs (Vicki Flenady et al., 2011; Flenady et al., 2016; Hauksdottir et al., 2018).

1.3 Risk factors for stillbirth

Risk factors can be defined as conditions or events that are associated with an increased rate of a disease. However, causality is not necessarily implied. Risk factors for stillbirth can be sociodemographic and/or medical. As many of these factors are common, risk stratification and prevention of stillbirth is difficult (Gandhi & Page, 2024).

The main maternal risk factors for stillbirth in HICs are nulliparity, advanced age, non-Caucasian race, socioeconomic deprivation, obesity, smoking, artificial reproductive technology (ART), multiple gestation, diabetes, hypertension, and previous adverse obstetrical outcome (V. Flenady et al., 2011; Gandhi & Page, 2024; Stillbirth Collaborative Research Network Writing, 2011; Yerlikaya et al., 2016). Furthermore,

many of these risk factors can be interrelated. An example of co-existing multifactorial risk factors could be a nulliparity, advanced maternal age and a pregnancy achieved with the help of ART. A mother with these risk factors might also be obese and develop gestational diabetes as well as hypertensive disorder in pregnancy (HDP), illustrating co-morbidity. Some risk factors, such as socioeconomic deprivation, obesity and smoking, may be modifiable. From a public health perspective, even maternal age could potentially be affected by social changes that make starting a family more feasible for young people.

Nulliparity as well as extremely high parity (grandmultiparity) has been shown to be a modest risk factor for stillbirth. While the latter is uncommon in HICs, the former is increasingly common with the global decline in fertility rates (Bhattacharjee et al., 2024).

Advanced maternal age, especially at first pregnancy, is also increasingly common in HICs. A large study from the United States showed that the relative risk of stillbirth was 1.32 (95% confidence interval (CI) 1.22-1.43) for mothers aged 35-39 and for mothers aged over 40 it was 1.88 (95% CI 1.64-2.16) when compared with mothers under the age of 35, after correcting for race, parity and medical disease (Reddy et al., 2006). The risk was highest for stillbirth at term. A more recent study that adjusted for pre-existing hypertension and diabetes also found an increased risk for mothers over the age of 40 compared to mothers 25-29 years of age. However, this was only significant for births after 39 weeks of gestation (Peneva & Finneran, 2024).

Obesity has increased globally and the association with stillbirth appears to be a "dose-response" relationship and is also most marked at term. Compared to mothers with a normal weight (body mass index (BMI) 18.5-24.9), the risk of stillbirth at 40 gestational weeks or more was twice as high for overweight mothers (BMI 25.0-29.0) and nearly four times as high for obese mothers (BMI >30.0) (Akselsson et al., 2023).

Furthermore, the stillbirth rate is strongly effected by socioeconomic deprivation (Harpur et al., 2021) and racial disparity (Silver & Reddy, 2024), which often co-exist. The risk is especially high for migrant women (Rasmussen et al., 2023) and highest for refugees (Yeshitila et al., 2024).

The association of smoking with adverse obstetric outcomes is well known and according to a meta-analysis of 34 studies (Marufu et al., 2015), the increased risk of stillbirth is 47% (OR 1.47, 95% CI 1.37-1.57).

Multiple gestation is a strong risk factor, as the risk of stillbirth for twins is more than double compared to singleton pregnancies, especially after 39 gestational weeks (Sairam et al., 2002). Studies have even found the adjusted stillbirth rate to be 4-5 times higher in multiple compared to singleton pregnancies (Stillbirth Collaborative Research Network Writing, 2011). However, chorionicity is important as stillbirth rates are significantly higher in monochorionic compared to dichorionic twins, 44.4 vs.

12.2/1000 births (RR 3.6, 95% CI 2.6-5.1), irrespective of gestational age (Glinianaia et al., 2011).

ART has been indicated as an independent risk factor for stillbirth. A large Nordic study comparing twins and singletons conceived after ART with those spontaneously conceived found a double risk of stillbirth before 28 weeks in ART singletons (AOR 2.08, 95% CI 1.55-2.78) but not at later gestations. Furthermore, no difference was found in the risk of stillbirth between twins conceived with ART and spontaneously.

Diabetes is a recognized risk factor for stillbirth, but this may not apply to gestational diabetes in all settings. A recent Australian study of over 100.000 pregnancies complicated by diabetes confirmed that pre-existing diabetes carried a 2-3 times increased risk of stillbirth (RR 2.68, 95% CI 2.01-3.56) across all gestational age and birthweight groups. However, the overall stillbirth risk in pregnancies with gestational diabetes was found to be lower than in pregnancies without diabetes (Gordon et al., 2025). This may be due to increased monitoring and early-term induction of labour, as mothers diagnosed with diabetes delivered earlier (median gestation 38.7 weeks vs. 39.4).

Hypertensive disorder in pregnancy (HDP) is a term that includes chronic or essential hypertension in pregnant mothers, pregnancy-induced hypertension and preeclampsia (Magee et al., 2022). It is estimated that 200.000 pregnancies affected by HDP end in stillbirth globally every year (de Bernis et al., 2016). In a large study based on data from the Norwegian birth registry from 1967-2006, the overall prevalence of HDP was found to be 4.7% and 9.2% of antepartum stillbirths occurred in hypertensive pregnancies (Ahmad & Samuelsen, 2012). The risk of stillbirth was highest for mothers diagnosed with preeclampsia (1.9%) and was almost as high for chronic hypertension (1.8%) but lower for gestational hypertension (1.2%). However, there was a 44% reduction in the stillbirth rate between the earlier 20 years of the study period compared to the latter. The SBR reduced by 80% for mothers with preeclampsia, while it declined by 57% for those with chronic hypertension, 49% for gestational hypertension, as well as 41% in normotensive pregnancies. This is almost certainly due to improvements in antenatal care for mothers classified as high risk due to preeclampsia.

Many other medical condition can increase the risk of stillbirth and can be chronic or underlying, such as a renal disease or an autoimmune one, such as systemic lupus erythematosus. Others are pregnancy-related, such as intrahepatic cholestasis of pregnancy. Moreover, obstetric antiphospholipid syndrome (APS) is a rare acquired autoimmune thrombophilia associated with stillbirth as well as recurrent miscarriage, placental insufficiency, pre-eclampsia and thrombosis in pregnancy (Arslan & Branch, 2020).

History of an adverse pregnancy outcome in a previous pregnancy is a risk factor for stillbirth. The risk is increased if there is a history of miscarriage, especially if it is recurrent or a late mid-trimester abortion. Previous caesarean delivery also appears to increase the risk of subsequent stillbirth. A recent study based on data on almost 2 million singleton births from the Swedish Birth Registry showed a 37% increased odds of stillbirth in mothers who had their first delivery by caesarean compared to vaginally (Al Khalaf et al., 2024). However, the risk is greatest when there were prior placental-related complications such as preeclampsia, intrauterine growth retardation (IUGR) and stillbirth. Together, the above complications are termed "the great obstetrical syndromes" and are associated with defective deep trophoblast implantation (Brosens et al., 2019; Burton et al., 2025).

Mothers who have previously delivered a stillborn infant have a markedly increased risk of recurrent stillbirth (RR 4.83, 95% CI 3.77-6.18), after adjustment for confounding factors, compared to mothers with no such history (Lamont et al., 2015). The absolute risk of stillbirth in a subsequent pregnancy has been estimated to be 2.5% for mothers whose first pregnancy resulted in stillbirth but 0.5% for mothers with one previous livebirth (Lamont et al., 2022). Although most mothers with a history of stillbirth later have livebirths, there is an increased risk of adverse perinatal outcomes, especially preeclampsia, placental abruption and IUGR in subsequent pregnancies (Black et al., 2008). However, the strongest clinical risk factors connected to stillbirth are obstetrical diseases in the index pregnancy such as antenatal bleeding and IUGR (Gardosi et al., 2013), both of which are strongly linked to hypertensive disease of pregnancy; especially pre-eclampsia (V. Flenady et al., 2011).

The risk of stillbirth increases with increasing severity of growth restriction (Pilliod et al., 2012). For example, the cumulative risk is estimated 1.5% for fetal weight under the 10th percentile for gestational age (GA) and gender (small for gestational age, SGA) and 2.5% at less than the 5th percentile (Getahun et al., 2007). These risk factors could also be considered causes but distinguishing between the two concepts can be difficult. It has been suggested that conditions that are common in stillbirths but uncommon in liveborn infants, that is have a high odds ratio, are likely to be considered causes, while conditions that are common in livebirths but even more common in stillbirths, that is have a lower odds ratio, are more likely to be considered risk factors (Silver & Reddy, 2024). However, it is unclear if a cut-off level of relative risk can be found that reliably distinguishes between a risk factor and a cause.

1.3.1. Changes in risk factors and obstetrical practice in Iceland

Iceland is a HIC with under 400.000 inhabitants, offering free antenatal, intrapartum and postnatal care. The caesarean section rate has been stable around 16-17% (Pyykonen et al., 2017; Rasmussen et al., 2023) over the last decades. As in most western countries, advanced maternal age, obesity (Jonsdottir et al., 2024) and HDP

have become more common in Iceland over the last decades (Swift et al., 2022). Furthermore, migration to Iceland more than tripled from 4.6% in 2006 to 14.1% in 2019. Almost half of the immigrant population (45%) are women, many of reproductive age (Guethmundsdottir et al., 2021). However, there has been a marked reduction in smoking in Iceland over the last decades, especially in pregnancy, making it one of the few risk factors for stillbirth becoming less common over time (2017).

There have also been marked changes in obstetrical practice during the 26-year study period (1996-2021) that the thesis covers. 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 labour. The rate of induction of labour more than doubled during the study period in Iceland (Gunnarsdottir et al., 2021). In fact, the induction rate increased from 12.3% of all deliveries in 1996 to over 28.3% in 2021, as illustrated in Fig.I below.

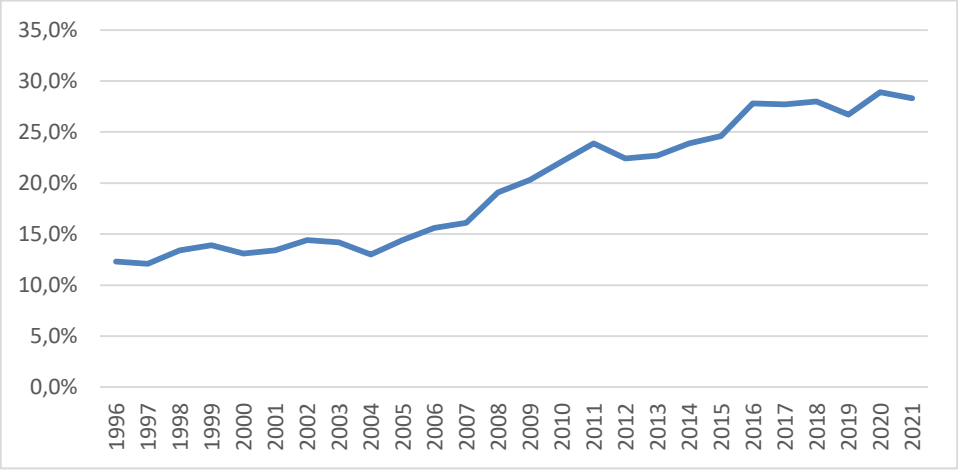

Figure 1 Induction rate in Iceland 1996-2021. Information from Icelandic Medical Birth Registry

This is partly due to induction of labour for prolonged pregnancy after 41 gestational weeks instead of 42 weeks previously (Swift et al., 2022), as studies showed increased risk of stillbirth with advancing gestation at term (Muglu et al., 2019; Wennerholm et al., 2019). Furthermore, induction of mothers diagnosed with pre-eclampsia was advised when 37 weeks´ gestation was reached, instead of expectant management until clinical deterioration, after the HYPITAT study showed this improved maternal outcome (Koopmans et al., 2009). In addition, gestational diabetes became a more common indication for induction (Swift et al., 2022) due to changes in screening practices and higher body mass index (BMI) in the population (Ontiveros et al., 2024). A recent Icelandic study (Gunnarsdottir et al., 2021) showed a decrease in adverse neonatal outcome, including intrapartum or early neonatal deaths, with an increased induction rate, but the possible effect of the increased rate of induction on the incidence of

antepartum stillbirth has not been studied in Iceland. With improved antenatal care and fetal surveillance, more high-risk pregnancies are recognised, which may reduce the incidence of stillbirth in these mothers. However, stillbirth is more difficult to prevent in pregnancies with no "warning signs".

1.4 Investigations after stillbirth

In addition to careful history taking and clinical examination when the fetal death is diagnosed, several laboratory tests are recommended to assess the mother´s health, which may be compromised due severe to disease, such as pre-eclampsia, sepsis or placental abruption. Furthermore, specific investigations are advised with the aim of determining the cause of death (Burden et al., 2025) as illustrated in Table I below. These investigations are included in the current protocol for investigations after stillbirth in Iceland. *Gæðahandbók LSH, LSH-910, september 2023*

A secondary analysis of investigations to determine the cause of 512 stillbirths in the Stillbirth Collaborative Research Network found the following usefulness of each test: placental pathology 64.6% (95% CI 57.9–72.0), autopsy 42.4% (95% CI 36.9–48.4), genetic testing 11.9% (95% CI 9.1–15.3), testing for antiphospholipid antibodies 11.1% (95% CI 8.4–14.4), Kleihauer test for fetomaternal haemorrhage 6.4% (95% CI 4.4–9.1), glucose screen 1.6% (95% CI 0.7–3.1), parvovirus 0.4% (95% CI 0.0–1.4) and syphilis 0.2% (95% CI 0.0–1.1). Placental pathology and fetal autopsy were considered most useful, followed by genetic testing and testing for antiphospholipid antibodies (Page et al., 2017). A cohort study from the USA found that clinical findings led to a probable cause of stillbirth in 24.3% of cases, 61.1% if placental pathology was added and 74. 3% when autopsy was included (Miller et al., 2016). Therefore, it is important to explain to parents that autopsy of the baby and a histopathological examination of placenta and umbilical cord are major components in the investigations recommended after stillbirth and a full work-up may find a possible or probable cause of death in up to ¾ of cases, providing key information for the management of a future pregnancy. However, grieving parents face making important decisions in a short time under difficult circumstances and may be reluctant to agree to various investigations, especially autopsy. It is therefore imperative that the discussion takes place in an unhurried manner and that bereaved parents receive compassionate and respectful counselling without any persuasion (Siassakos et al., 2018). If there is not consent for autopsy, it should be noted that gross and microscopic examination of placenta, umbilical cord and fetal membranes is considered the single most useful investigation to determine the cause of stillbirth (Miller et al., 2016).

Table 1 Recommended investigations after diagnosis of stillbirth

At diagnosis or admission: Maternal	**Indication**
Full blood count, creatinine, CRP, ALAT, LDH	Assess maternal health
Bile salts	Obstetric cholestasis
Blood group, antibodies	Immunization
APTT, PT, fibrinogen, FDP	Disseminated intravascular coagulation
Kleihauer	Fetomaternal haemorrhage
Bacteriology	Bacterial infection
Serology for toxoplasma, rubella, cytomegalovirus, herpes, syphilis, parvovirus B19,	Viral infection
Hb A1c	Undiagnosed diabetes
TSH, fT4, TPO	Undiagnosed thyroid disease
Anticardiolipin ab, lupus anticoagulant	Antiphospholipid syndrome
Blood for karyotyping (both parents)	Parental mosaicism or balanced translocation
After delivery: Fetoplacental	
Bacteriology, virology swabs	Bacterial or viral infection
Tissue for cytogenetics	Aneuploidy, single gene disorders
Autopsy	Malformation, signs of asphyxia
Histopathological examination of placenta and umbilical cord	Placental injury, umbilical cord at risk
Follow-up after delivery: Maternal	
Repeat anticardiolipin ab, lupus anticoagulant	Antiphospholipid syndrome
Other specific investigations	Suggested after postmortem

CRP: C-reactive protein, ALAT: Alanine aminotransferase, LDH: Lactate dehydrogenase
APTT: Activated partial prothrombin time, PT: Prothrombin time, FDP: Fibrin degradation products
HbA1c: Hemoglobin A1c. TSH: Thyroid stimulating hormone, fT4: free thyroxin, TPO: Thyroid peroxidase
Anticardiolipin ab: Anticardiolipin antibody

1.5 Determining cause of stillbirth

As previously mentioned, a risk factor is not inevitably a cause but distinguishing between the two concepts can be difficult. The concept and definition of cause has been debated by philosophers as well as epidemiologists, but it is commonly defined as an preceding condition or event that was necessary for a disease to occur (Rothman & Greenland, 2005). This means that without the determined cause, the disease would not have been presented at this time. However, this does not imply that the specific cause was sufficient to produce the disease although it is a necessary component. A classical way to distinguish between causal and noncausal associations of a condition or event to a disease is to consider the following: (1) strength, (2) consistency, (3) specificity, (4) temporality, (5) biological gradient, (6) plausibility, (7) coherence, (8)

experimental evidence, and (9) analogy of an association (Hill, 1965). Similar to risk factors, causes of stillbirth are often multiple and can be interrelated. Although a single cause is neither necessary nor sufficient for development of a disease, its removal could prevent it.

An example of coexisting causes could be an appropriately grown stillborn infant with a tightly wrapped nuchal cord, pointing to an umbilical cord accident. However, the placental weight is very low and histopathological examination reveals specific placental injury. Should the death be attributed to placental insufficiency? There are also signs of thrombosis in the umbilical cord and fetal vasculature of the placenta and autopsy shows signs of intermittent fetal asphyxia supporting reduced circulation in cord vessels. To which cause should the stillbirth be attributed? Could the infant have survived the placental injury if there had not also been reduced circulation in the cord or vice-versa? As this example illustrates, it is optimal to use a classification that accounts for probability of each cause as well as for multiple causes and the interaction between them.

1.6 Classification of stillbirth

Over 80 classification systems have been described, and many are modifications of pre-existing systems. Of these, at least 40 classify all perinatal mortality, both stillbirths and early neonatal deaths. Some systems are created for national use whereas others are used more widely, and the more recent ones are available in electronic format. However, at least 60 of the classification systems only record a single cause of death (Leisher et al., 2016b). Furthermore, not all classifications are based on histopathological findings. The first classifications of perinatal mortality were developed in Britain. Dugald Baird introduced the Aberdeen classification in the 1960s (Baird, 1969), which was based on clinical information on maternal factors. This was followed by the Hey system, which coded fetal and neonatal factors without requiring histopathological data (Hey et al., 1986) as well as a revised Aberdeen classification according to the current obstetric knowledge (Cole et al., 1986). However, as early as 1956 the British perinatal mortality survey had used autopsy data (Bound et al., 1956). In 1980, Wigglesworth described a pathophysiological approach based on autopsies to monitor perinatal mortality (Wigglesworth, 1980). The Wigglesworth criteria continue to be widely used, which define five groups: macerated normally formed stillbirths, congenital anomalies (stillbirth or neonatal death), neonatal death due to prematurity, fresh stillbirths presumed asphyxiated and lastly specific conditions such as toxoplasmosis.

During the last decades, several classification systems have been introduced that include information on maternal, fetal and placental/cord related factors associated with stillbirth in a hierarchical way. The Relevant Cause of Death (ReCoDe) classification was developed as the three older classification systems (Wigglesworth, Hey and

revised Aberdeen) consistently reported about 2/3 of stillbirths as being unexplained (Gardosi et al., 2005). The aim of this classification system was to identify the relevant condition at the time of fetal demise. It reduced the proportion of unexplained stillbirths by defining fetal growth restriction as an antecedent of stillbirth. Unlike the ReCoDe classification which is limited to stillbirth, the Tulip system classifies the cause and mechanism of perinatal mortality (Korteweg et al., 2006). This is a causal analysis based on clinical and pathological findings and the classification consists of six main causes with subclassifications: (1) congenital anomaly (chromosomal, syndrome and single- or multiple-organ system), (2) placenta (placental bed, placental pathology, umbilical cord complication and not otherwise specified [NOS]), (3) prematurity (preterm prelabour rupture of membranes, preterm labour, cervical dysfunction, iatrogenic and NOS), (4) infection (transplacental, ascending, neonatal and NOS), (5) other (fetal hydrops of unknown origin, maternal disease, trauma and out of the ordinary) and (6) unknown. The more intricate Cause of Death and Associated Conditions (CODAC) system also classifies the main cause of perinatal death, as well as up to two associated causes (Froen et al., 2009). This classification consists of ten main categories: infection, neonatal conditions or events, intrapartum events, congenital anomalies, fetal, cord, placental and maternal causes for stillbirth as well as unknown causes and finally termination of pregnancy. These ten categories can be classified further into 94 subcategories, that can be broken down into 577 categories and coded electronically. The Initial Causes of Fetal Death (INCODE) was developed by the researchers involved in the Stillbirth Collaborative Research Network (SCRN) (Dudley et al., 2010). This is a standardized method assigning probable and possible causes of stillbirth based on clinical, autopsy and placental pathology data. This classification consists of six broad categories of causes of stillbirth: maternal conditions, obstetric complications, maternal or fetal hematologic conditions, fetal genetic, structural and karyotypic abnormalities, placental and/or fetal infection and placental pathological findings. Neither chorioamnionitis with only maternal response nor SGA were considered causes of death according to INCODE.

However, when 81 classification systems were assessed for characteristics previously identified by experts as necessary for a system to be effective globally, none were found to be highly aligned with the necessary characteristics (Leisher et al., 2016a). Furthermore, none met criteria for "ease of use". There is therefore an unmet need for a globally effective classification system, especially one that is also "user-friendly ".

In Iceland, the Nordic-Baltic Perinatal Death Classification (Borch-Christensen et al., 1997) has been used since 1996. This classification was developed in 1995 by a group of Nordic paediatricians and obstetricians, including this author. The aim was to define deaths that were potentially avoidable by improved antenatal, intrapartum or neonatal care. The focus was therefore not on pathophysiological causes of perinatal death but on how to provide health care in different settings that can improve perinatal outcomes. This classification has been practical to use for perinatal audit in Iceland, as the

information needed is already collected when a birth is registered so all relevant data is available from the Icelandic Medical Birth Registry. Based on this classification, a study of perinatal mortality in Iceland 1994-2017 (Hauksdottir et al., 2018) showed a significant decrease in the perinatal mortality rate of infants born after 22 weeks of gestation. However, early neonatal deaths decreased more than stillbirths. The majority of perinatal deaths were stillbirths of non-growth-retarded singleton infants after 28 weeks of gestation and there was no reduction in stillbirth in this group. Causes of stillbirth in Iceland and changes in them over time have not been examined previously. As the Nordic-Baltic Perinatal Death Classification is not based on causes of death, another system was needed to explore the etiology of stillbirth in Iceland and changes in this over time. The Stockholm classification of stillbirth (Varli et al., 2008) was chosen. This system classifies stillbirth into 17 well-defined primary and associated causes, describing the chain of events leading to fetal death (primary cause) as well as contributing to it (associated cause), see appendix C. Furthermore, it grades the causes according to the strength of evidence into possible, probable and definite, taking into account both clinical and histopathological findings. The classification is based on and assumes extensive examination after a stillbirth. This includes clinical and laboratory investigations and a high rate of autopsy and placental examinations, as is the case in Iceland. Indeed, the Stockholm classification was chosen as it had been developed for a similar obstetrical population and perinatal healthcare system, including use of histopathology, as in Iceland. Moreover, two of the authors of the Stockholm classification, obstetrician Karin Pettersson and pathologist Nikos Papadogiannakis were willing to collaborate and share their expertise regarding the use of this classification.

1.7 Placental histopathology: Amsterdam placental workshop consensus

Attributing cause of death can be complicated and sometimes subjective. Despite known risk factors for stillbirth (Townsend et al., 2021; Yerlikaya et al., 2016), none are recognized in many pregnancies ending in fetal demise. However, investigations after the stillbirth, especially placental pathology, may provide explanations (Heazell & Martindale, 2009; Man et al., 2016). Specific histopathological lesions in the placenta cannot be diagnosed before delivery, although placental insufficiency may sometimes be suspected clinically. Therefore, the placenta can be compared to the "black box" that records events during a flight and can be used after a plane crash to understand events leading up to the disaster.

The Amsterdam consensus to standardize definitions of placental lesions was first published in 2016 (Khong et al., 2016) and its implementation further described in 2018 including "Four major patterns of placental injury" (Redline et al., 2021). Placental pathology can be divided into vascular and inflammatory categories (Redline,

2008). The vascular category is comprised of maternal vascular malperfusion (MVM) and fetal vascular malperfusion (FVM). MVM reflects failure of deep trophoblast implantation and spiral artery remodelling in early pregnancy. Formerly called uteroplacental insufficiency, it is linked to "the great obstetrical syndromes" which include pre-eclampsia, placental abruption, fetal growth restriction (FGR) as well as stillbirth (Brosens et al., 2019; Burton et al., 2025) and has a significant recurrence risk (OR = 1.6; 95% CI 1.3-1.9) (Christians & Huicochea Munoz, 2020). FVM reflects stasis leading to thrombosis in fetal vessels in the placenta. Usually caused by so-called umbilical cord accidents, it is associated with morphologic features of the umbilical cord, making it "at risk" of reduced vascular circulation (Redline & Ravishankar, 2018; Redline et al., 2021) but thrombophilia and endothelial damage can occasionally contribute. FVM is associated with stillbirth and central nervous system (CNS) injury in infants (Penn et al., 2021; Redline & Ravishankar, 2018), but is without a significant recurrence risk. Inflammatory lesions are divided into infectious and idiopathic subgroups. Acute chorioamnionitis (ACA) reflects histopathologic signs of bacterial, viral or fungal infections. The inflammatory response can be maternal and fetal and cause spontaneous preterm delivery and neonatal sepsis (Chisholm et al., 2018). Furthermore, severe inflammation of the vessels and tissues of the umbilical cord (necrotizing funisitis) are risk factors for stillbirth and neonatal complications (Redline, 2006). 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 (Himes & Simhan, 2008). Chronic villitis of unknown etiology (VUE) is considered to represent an immunological "host versus graft" response, causing inflammatory tissue damage (Redline, 2007). Low-grade VUE is common and considered of little significance. However, high-grade disease is associated with stillbirth and CNS injury (Derricott et al., 2016; Derricott et al., 2013) and a high recurrence risk of 25% to 50%, with the placental injury often being more advanced in subsequent pregnancies (A. A. Freedman et al., 2021). Although there is consensus on defining major patterns of placental injury, the clinical significance can be unclear. Certain placental lesions can be classified by extent or severity as low- or high-grade (Zhou et al., 2020). Furthermore, it is increasingly recognized that multiple types of placental lesions have a strong relation to adverse outcome (Marijnen et al., 2025).

In addition to major patterns of placental injury, the Amsterdam consensus defines the umbilical cord as "at risk" if 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 (Redline & Ravishankar, 2018; Redline et al., 2021).

It is challenging for clinicians to interpret findings of the pathology report, explain the relevance to parents and use to plan care in a subsequent pregnancy (Gallagher et al., 2023). A recent paper (Redline et al., 2023) called for studies correlating placental injury with clinical phenotypes of mothers and infants. Understanding this correlation can be a valuable when counselling after stillbirth and planning care in a future pregnancy (Heazell & Martindale, 2009).

2 Aims

The overall aim of the doctoral study is to explore the stillbirth rate (SBR) in Iceland over a quarter of a century, assess causes of stillbirth using the Stockholm classification of stillbirth and analyse clinicopathological phenotypes of stillbirth, including placental histopathological findings, according to the Amsterdam placental workshop consensus i.e. "four major patterns of placental injury".

Specific aims:

2.1 Mortality rate

Describe the perinatal mortality rate over the study period. Explore changes in SBR by comparing the earlier and latter half of the 26-year study period for all stillbirths and by gestational age (GA) groups at diagnosis of fetal demise: early preterm (before 28 weeks), late preterm (between 28 and 37 weeks) and term (37 weeks or more).

2.2 Characteristics and causes of stillbirth

Describe the maternal and fetoplacental characteristics as well as main causes of stillbirth according to GA groups. Compare these between the earlier and latter half of the study period.

2.3 Stillbirth at term

Explore causes and patterns of placental injury over the study period and compare them between SGA vs non-SGA as well as HDP vs non-HDP affected stillbirths at term.

2.4 Clinicopathological phenotypes of singleton stillbirth

Describe the patterns of placental injury and umbilical cord at risk in singleton stillbirth and correlate to clinical phenotypes in the three GA groups.

3 Materials and Methods

Stillbirth was defined as an infant born without signs of life who could not be resuscitated after 22 weeks of gestation or with a birthweight of at least 500g if the gestational age was unknown. This included both antepartum and intrapartum deaths. To define a stillbirth as intrapartum, fetal heart sounds must have been heard after labour started. Cases of fetal demise after termination of pregnancy were excluded, but these were very rare after 22 gestational weeks. Early neonatal deaths were defined as death of an infant within 7 days of birth. Gestational age (GA) was based on ultrasound examination before 22 weeks of gestation.

Personal identification numbers of mothers who had a stillbirth in Iceland from 1996-2021 (n=385) and the number of stillborn (n=395) and live born infants (n=113.094) during the same period was obtained from the Icelandic Medical Birth Registry. As perinatal mortality review was not formalized in Iceland until 1996, earlier stillbirths were not included.

Table 2 Overview of population and aims of the original papers

	Population	**Number**	**Aim**
Paper I	All stillbirths, singleton and multiple pregnancies	385 mothers 395 infants 381 placental examinations	2.1 2.2
Paper II	All stillbirths diagnosed after 37 gestational weeks of more, singleton and multiple pregnancies	125 mothers 125 infants 125 placental examinations	2.1 2.2 2.3
Paper III	Stillbirths after singleton pregnancy	338 mothers 338 infants 326 placental examinations	2.4

Clinical information was collected from medical records including results of all investigations of the mother and stillborn infant by the doctoral candidate (RIB), who is an experienced obstetrician. Infants were divided into groups according to GA at diagnosis of stillbirth: early preterm stillbirth <28 weeks (n=136), late preterm stillbirth ≥28 but <37 weeks (n=134) and term stillbirth ≥37 weeks (n=125). Over 40 variables

were recorded for each mother/infant pair as shown in Appendix A. The definition of small for gestational age (SGA) was birthweight under the 10th percentile of a newly published Swedish intrauterine growth curve.(Lindstrom et al., 2021; Lindstrom et al., 2023) Hypertensive disorder of pregnancy (HDP) was assigned according to the classification of the International Society for the Study of Hypertension in Pregnancy (ISSHP)(Magee et al., 2022). As a proxy for foreign origin, being non-Icelandic speaking was used instead of citizenship. Adverse outcome in previous pregnancy was defined as a history of HDP, delivering an SGA infant or having had a stillbirth prior to the index pregnancy. Maternal body mass index (BMI) was based on weight and height at the first antenatal visit.

The fetal autopsy records as well as the gross description of the placentas were reviewed. The trimmed weight of unfixed placental disc after removal of the membranes and umbilical cord was recorded. Placental weight under the 10th percentile and fetoplacental ratio (FPR) over the 90th percentile for the infant´s gestational age and sex was noted (Boyed T, 1999). A senior perinatal pathologist, Thora Steffensen (TS), re-evaluated archived microscopic slides and histological findings were documented in accordance with recommendations of the 2016 Amsterdam Placental Workshop Group Consensus on Sampling and Definitions of Placental Lesions (Khong et al., 2016), as described in Appendix B. The findings were classified into four major patterns of injury: maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), acute chorioamnionitis (ACA), and chronic villitis of unknown etiology (VUE) described by Redline et al (Redline et al., 2021). The umbilical cord was defined as at risk if any of the following features were found: excessive length (>70 cm), hypercoiling (>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 (Redline & Ravishankar, 2018; Redline et al., 2021). Moreover, information was recorded on cords with <1 coil /10 cm, as hypocoiled cords have been shown to be more susceptible to vascular occlusion (Georgiou et al., 2001).

The doctoral candidate discussed each case with the perinatal pathologist (TS) and assigned primary and associated cause of death according to the Stockholm classification of stillbirth (Varli et al., 2008). Cases that were challenging to evaluate were discussed with Karin Pettersson (KP) obstetrician, and Nikos Papadogiannakis (NP) pathologist, who are both authors of the Stockholm classification. An overview of 17 groups of the classification is shown in Table 3. The doctoral candidate and TS amended the Stockholm classification according to the terminology of the more recent Amsterdam consensus (Khong et al., 2016) and KP and NP took part in this modification. A detailed table with criteria for the probability of each group of the modified Stockholm classification is shown in Appendix C.

Table 3 Groups of Stockholm classification of stillbirth

Condition related to stillbirth
1. Malformation and chromosomal abnormalities
2. Infection 2.1 Bacterial 2.2 Virus 2.3 Other
3. Immunization 3.1 Erythrocyte immunization 3.2 Thrombocyte immunization
4. Feto-maternal transfusion
5. Twin-to-twin transfusion syndrome
6. Birth asphyxia
7. Placental insufficiency
8. Umbilical cord complication 8.1 Umbilical cord prolapse 8.2 Rupture of vessel in umbilical cord or membranes 8.3 Reduced circulation in the umbilical cord
9. Placental abruption
10. Preeclampsia
11. Diabetes mellitus
12. Intrahepatic cholestasis of pregnancy
13. Uterine complications
14. Coagulation disorders
15. Other
16. Unknown
17. Unexplained

Statistical analysis

RStudio and Excel were used to analyse the data.

3.1 Mortality rate

The perinatal mortality rate (PNMR) was calculated for each year of the study period, that is the stillbirths and early neonatal deaths with number of all infants, liveborn and stillborn, as the denominator. The overall SBR was calculated as the number of stillbirths per 1000 infants. Moreover, the number of stillbirths in each of the GA groups was calculated per 1000 infants at risk, which was the number of ongoing pregnancies at the beginning of each gestational age period. Relative risk (RR) of stillbirth and 95% confidence interval (CI) was calculated for each GA group.

3.2 Characteristics and causes of stillbirth

Numbers and proportions of maternal and fetoplacental characteristics, as well as causes of death, were compared between three GA groups as well as between two 13-year periods (1996-2008 and 2009-2021). This division into a former and a latter period was chosen due to stable induction rate in the former period and a sharply increased rate from 2009. Furthermore, the contribution of each primary cause of stillbirth according to the Stockholm classification was calculated per 1000 liveborn and stillborn infants, showing contribution of each group of the Stockholm classification to the average SBR for the earlier and latter period respectively. Moreover, the primary cause of stillbirth according to the Stockholm classification was stratified into three GA groups. Chi-square tests were applied and *p*-level of 0.05 considered statistically significant.

3.3 Stillbirth at term

Stillbirth at term was defined as a demise of an infant that was diagnosed at 37 weeks of gestation or later. Consequently, stillborn infants from a multiple pregnancy, whose intrauterine death had been diagnosed preterm but delivered at term with the liveborn twin, were excluded. When calculating the SBR at term, the number of infants born at term was used as the denominator. As before, the analysis was descriptive and presented as numbers and proportions of maternal and fetal characteristics, patterns of placental injury and cause of death. However, 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 the analysis was stratified for SGA infants and maternal HDP. Chi-square tests were applied and *p*-level of 0.05 considered statistically significant.

3.4 Clinicopathological phenotypes of singleton stillbirth

Multiple pregnancies were excluded so each stillbirth could be correlated with one placenta. As before, MVM was not graded. Both high- and low-grade FVM and VUE were documented in this study. Furthermore, all ACA was reported after staging by maternal and fetal inflammatory response. Analysis was descriptive and presented as numbers and proportions of maternal and fetal characteristics. Moreover, isolated as well as combined patterns of placental injury were compared between GA groups and correlated to clinical features. Different features of umbilical cords at risk were described and compared between GA groups. Chi-square tests were applied and *p*-level of 0.05 considered statistically significant.

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

4 Results

4.1 Mortality rate

Over the study period, 1996-2021, 113.094 infants were born in Iceland. During this time the perinatal mortality rate (PNMR) decreased, both the stillbirth rate (SBR) and early neonatal death rate (ENDR), although it fluctuated markedly from year to year (Fig.2.) (Paper I)

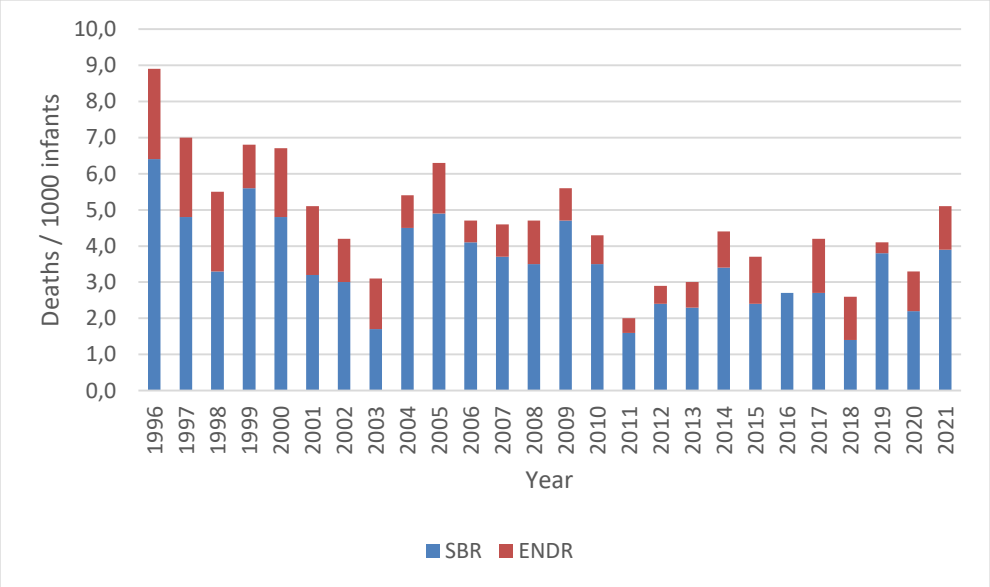

Figure 2 Perinatal mortality rate (PNMR): stillbirth rate (SBR) and early neonatal death rate (ENDR), in Iceland from 1996 to 2021.

A total of 395 infants were stillborn, giving a SBR of 3.49 per 1000 liveborn and stillborn infants for the study period. Table 4 shows a comparison of the SBR between the earlier (1996-2008) and latter (2009-2021) half of the study period. The overall SBR reduced significantly from 4.10 stillbirths per 1000 to 2.88 (RR=0.72; 95% CI=0.56-0.92, p-value=0.009). When the SBR was calculated for each of the three GA groups with the number of infants at risk as a denominator, it was found to have decreased in the latter period for stillbirths diagnosed before term.

Stillbirths diagnosed before 28 gestational weeks (early preterm) decreased from 1.50 to 0.98 per 1000 infants at risk (RR=0.67, 95% CI=0.41-1.06. p-value=0.09). Stillbirths diagnosed between 28 and 37 weeks reduced more markedly from 1.49 to 0.82 (RR= 0.56, 95% CI=0.38-0.84, p-value=0.004). However, no reduction was found in the SBR at term: 1.20 vs 1.15 per 1000 infants at risk (RR=0.98, 95% CI=0.69-1.40, p-value=0.9)(Bjarnadottir, Steffensen, Smarason, et al., 2025).

Table 4 Comparison between time periods of stillbirth rate* (SBR) in gestational age (GA) groups, calculated with infants at risk as denominator

GA groups	**1996-2008**		**2009-2021**			
	SB/n at risk	**SBR***	**SB/n at risk**	**SBR***	**RR (95% CI)**	**p-value**
Early preterm < 28 weeks	84 / 55853	1.50	56 / 57241	0.98	0.67 (0.41-1.06)	0.09
Late preterm 28 to 36+6 weeks	83 / 55601	1.49	47 / 57028	0.82	0.56 (0.38-0.84)	0.004
Term ≥ 37 weeks	63 / 52459	1.20	62 / 53721	1.15	0.98 (0.69-1.40)	0.9
All stillbirths	230 / 55853	4.10	165 / 57241	2.88	0.72 (0.56-0.92)	0.009

* Per 1000 infants at risk

4.2 Characteristics and causes of stillbirth

During the study period, 1996-2021, a total of 395 infants were stillborn to 385 mothers in Iceland. Most stillbirths were antepartum, as the death of 348 of 395 stillborn infants (88.1%) was confirmed before the start of labour but 47 infants died during delivery (intrapartum deaths) as illustrated in fig. 3. Most infants dying during delivery were extremely preterm as 35 of 47 infants had the GA of under 24 completed weeks. However, 4 of the 18 stillbirths ≥41 gestational weeks were intrapartum.

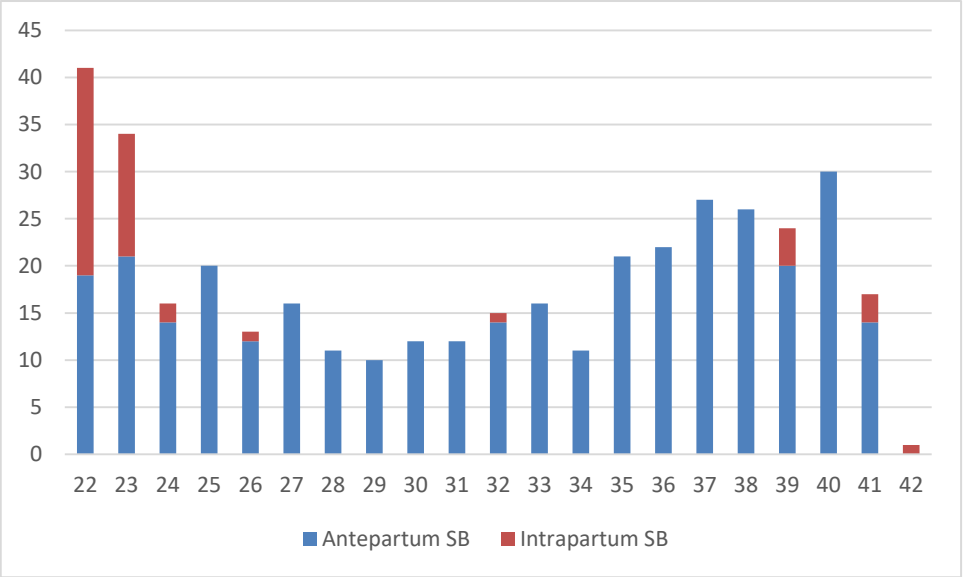

Figure 3 Number of antepartum and intrapartum stillbirths (SB) for each completed gestational week

Of the 385 pregnancies, 338 were singleton and 47 multiple gestations (Table 5). These were 46 twin pregnancies, in 36 one of the twins was born alive and in 10 both infants were stillborn. In addition, there was a triplet pregnancy with one stillborn infant. A comparison of maternal and fetoplacental characteristics of stillbirths between time periods is shown in Table 5. When the characteristics of women who had a stillbirth was compared between the former and latter half of the study period, no difference was found in the proportion that were aged 35 years or older at time of stillbirth (advanced maternal age). Similarly, there was not a difference in rates of obesity, defined as a BMI over 30, between the two periods. Furthermore, the difference between the two periods in the proportion of mothers diagnosed with HDP was negligible as was a previous history of an adverse outcome (HDP, SGA infant or stillbirth). A larger proportion of mothers in the latter period had not given birth before, 51.3% vs 42.7% although this did not reach statistical significance. A significantly smaller proportion of mothers having a stillbirth smoked in the latter period, 10.0% vs. 25.3%, p=0.001 and a significantly larger proportion was non-Icelandic speaking; 21.9% vs 10.2%, p=0.003. When comparing the gestational age of stillborn infants between the two periods, a significantly larger proportion was diagnosed at term in the latter: 37.6% vs. 27.4%, p-value=0.04. A negligible difference was found in the percentage of stillborn infants who were SGA, 46.7% in the latter period and 43.0% in the earlier, p-value=0.56. However, placental weight <10th percentile was significantly more common in the latter period than the earlier; 30.3% vs 21.3%, p-value= 0.002, as was elevated FPR; 24.2% vs, 15.7%, p-value= 0.005.

The autopsy rate was 80% and placental examination was performed in over 96% of stillbirths with no difference over the study period (Bjarnadottir, Steffensen, Smarason, et al., 2025).

Table 5 Comparison of maternal and fetoplacental characteristics between time periods

	1996-2008	2009-2021	
Mothers of SB infants (n=385)	**n=225**	**n=160**	
	n (%)	n (%)	**p-value**
Advanced maternal age (>=35 y)	60 (26.7)	40 (25.0)	0.80
Obese (BMI>30)	51 (22.7)	34 (21.3)	0.94
Nullipara	96 (42.7)	82 (51.3)	0.12
Smoker	57 (25.3)	16 (10.0)	0.001
Non-Icelandic speaking	23 (10.2)	35 (21.9)	0.003
Hypertensive Disease of Pregnancy	25 (11.1)	21 (13.1)	0.66
Adverse outcome in previous pregnancy	22 (9.8)	17 (10.6)	0.92
Multiple pregnancy	30 (13.3)	17 (10.6)	0.55
SB infants, n=395	**n=230**	**n=165**	
	n (%)	n (%)	**p-value**
Early preterm (GA < 28 weeks)	84 (36.5)	56 (33.9)	0.67
Late preterm (GA 28 to 36+6 weeks)	83 (36.1)	47 (28.5)	0.14
Term (GA ≥ 37 weeks)	63 (27.4)	62 (37.6)	0.04
Birthweight < 10th percentile*	99 (43.0)	77 (46.7)	0.56
Birthweight > 90th percentile*	20 (8.7)	7 (4.2)	0.15
Placental weight < 10th percentile*	49 (21.3)	50 (30.3)	0.002
Fetoplacental ratio > 90th percentile*	36 (15.7)	40 (24.2)	0.005
Autopsy	185 (80.4)	132 (80.0)	1.0
Placental examination	222 (96.5)	159 (96.4)	1.0

*For gestational age and gender

The contribution of each primary cause of stillbirth according to the Stockholm classification to the SBR is shown in Table 6. The number of stillbirths for each cause is calculated per 1000 liveborn and stillborn infants, showing contribution of each group of the Stockholm classification to the average SBR for the earlier and latter period respectively. Placental insufficiency and reduced flow in the umbilical cord were the two main contributors to the SBR in both periods. Placental insufficiency was considered the primary cause of death in 0.70 per 1000 delivered infants in the earlier period, when almost 1/5 of the SBR was attributed to this. In the latter period, placental insufficiency was an even more frequent primary cause of stillbirth or 1.07 per 1000 infants and more than 1/3 of the SBR was primarily attributed to this in the latter period. Reduced flow in the umbilical cord was considered the primary cause of stillbirth in 1.00 per 1000 infants in the earlier half of the study period or almost 1/4 of the SBR. In the latter period, 0.79 stillbirths per 1000 were primarily attributed to cord complications or nearly 1/3 of the SBR. In the earlier period, 1.70 stillbirths per 1000 infants were attributed to either placental insufficiency or reduced circulation in the umbilical cord and 1.86 per 1000 in the latter. Infection was considered the primary cause of 0.57/1000 infants in the earlier period, but this was less common in the latter, 0.23/1000. In the earlier period, 0.45 stillbirths per 1000 infants was attributed to placental abruption but this cause contributed less to the SBR in the latter period, 0.25/1000. All other primary causes were uncommon but more so in the latter period. Unexplained or unknown causes of stillbirth also became less common, 0.59/1000 in the earlier period and 0.16/1000 in the latter(Bjarnadottir, Steffensen, Smarason, et al., 2025).

Table 6 Contribution of each primary cause of death according to Stockholm classification to the stillbirth rate (SBR) of the two time periods

	1996-2008	**2009-2021**
	n SB=230	n SB=165
	Total infants n=55853	Total infants n=57028
Stockholm classification	n /1000 infants	n /1000 infants
Malformation	0.09	0.16
Infection	0.57	0.23
Immunisation	0.04	0
Fetomaternal transfusion	0.04	0.07
Twin-to-twin transfusion syndrome	0.16	0.05
Birth asphyxia	0.05	0
Placental insufficiency	0.70	1.07
Cord prolapse	0.07	0.02
Reduced circulation in umbilical cord	1.00	0.79
Placental abruption	0.45	0.25
Preeclampsia	0.11	0.05
Diabetes mellitus	0.07	0.02
Intrahepatic cholestasis of pregnancy	0.04	0.02
Uterine rupture	0.04	0
Other causes	0.11	0.02
Unexplained/unknown	0.59	0.16
Average stillbirth rate	4.10	2.88

Table 7 shows the primary cause of stillbirth according to the Stockholm classification stratified into three GA groups. Over half of all stillbirths irrespective of GA were primarily attributed to either reduced circulation in the umbilical cord (25.6%) or placental insufficiency (25.3%). Primary causes following in frequency were infection (11.9%) and placental abruption (9.9%) as well as unknown or unexplained (10.6%). Other primary causes of death were rare as each accounted for less than 4% of all stillbirths. The proportion of each primary cause of death differed between GA groups. Placental insufficiency was considered the primary cause of death in 14.3% of early preterm stillbirths (n=20), 29.2% of late preterm stillbirths (n=38) and 33.6% of stillbirths at term (n=42). Similarly, reduced circulation of the umbilical cord was considered the primary cause of death in 12.9% of early preterm stillbirths (n=18), 26.9% of late preterm stillbirths (n=35) and 33.6% of stillbirths at term (n=35). In fact, 72% of stillbirths at term (90/125, 72%) was attributed to either of these two major causes. However, over ¼ of stillbirths before 28 weeks were attributed to infection, which was rarely considered a primary cause of stillbirth at term. Furthermore, placental abruption was more common in stillbirth before term, and the few stillbirths (n=12) due to twin-to-twin transfusion syndrome were all diagnosed before 28 gestational weeks. Only 9 stillbirths (2.3%) were primarily attributed to preeclampsia, one at term and 6 of 9 cases were in the early preterm GA group (Bjarnadottir, Steffensen, Smarason, et al., 2025).

Table 7 Primary cause of death according to Stockholm classification by GA groups

	All	**Early preterm < 28 weeks**	**Late preterm 28–36+6 weeks**	**Term ≥ 37 weeks**
Stillborn infants	**n=395**	**n=140**	**n=130**	**n=125**
Stockholm classification	n (%)	n (%)	n (%)	n (%)
Malformation	14 (3.5)	5 (3.6)	8 (6.2)	1 (0.8)
Infection	45 (11.4)	37 (26.4)	6 (4.6)	2 (1.6)
Immunisation	2 (0.5)	0 (0)	2 (1.5)	0 (0)
Fetomaternal transfusion	6 (1.5)	0 (0)	3 (2.3)	3 (2.4)
Twin-to-twin transfusion syndrome	12 (3.0)	12 (8.6)	0 (0)	0 (0)
Birth asphyxia	3 (0.8)	0 (0)	0 (0)	3 (2.4)
Placental insufficiency	100 (25.3)	20 (14.3)	38 (29.2)	42 (33.6)
Cord prolapse	5 (1.3)	3 (2.1)	1 (0.8)	1 (0.8)
Reduced circulation in umbilical cord	101 (25.6)	18 (12.9)	35 (26.9)	48 (38.4)
Placental abruption	39 (9.9)	21 (15.0)	11 (8.5)	7 (5.6)
Preeclampsia	9 (2.3)	6 (4.3)	2 (1.5)	1 (0.8)
Diabetes mellitus	5 (1.3)	2 (1.4)	2 (1.5)	1 (0.8)
Intrahepatic cholestasis of pregnancy	3 (0.8)	0 (0)	1 (0.8)	2 (1.6)
Uterine rupture	2 (0.5)	0 (0)	0 (0)	2 (1.6)
Other causes	7 (1.8)	5 (3.6)	2 (1.5)	0 (0)
Unexplained/unknown	42 (10.6)	11 (7.9)	19 (14.6)	12 (9.6)

Table 8 illustrates clinicopathological findings in the stillbirths primarily attributed to the commonest causes of death: placental Insufficiency and reduced circulation in the umbilical cord. When placental insufficiency was considered the primary cause, the proportion of SGA was 70.8%, low placental weight was 59.4% and elevated fetoplacental ratio was 40.6%. Furthermore, MVM was detected in 44.8% of the placentas, high-grade VUE in 33.3% and high-grade FVM in 25.0%. Over half of stillbirths primarily attributed to placental insufficiency had an umbilical cord at risk, while this applied to all deaths attributed to reduced circulation in umbilical cord. Placental FVM was diagnosed in 46.9% of stillbirths primarily attributed to reduced cord circulation but MVM and high-grade VUE was rare in this group (7.3% each).

Table 8 Clinicopathological characteristics of stillbirths primarily attributed to placental insufficiency and reduced circulation in umbilical cord

	Placental insufficiency n=96	**Reduced circulation in umbilical cord n=96**
Birthweight <10th percentile for GA	68 (70.8)	28 (29.2)
Placental weight <10th percentile for GA	57 (59.4)	15 (15.6)
Fetoplacental ratio >90th percentile for GA	39 (40.6)	14 (14.6)
Maternal Vascular Malperfusion*	43 (44.8)	7 (7.3)
Fetal Vasculat Malperfusion, high-grade	24 (25.0)	30 (31.3)
Fetal Vascular Malperfusion, low-grade	8 (8.3)	15 (15.6)
Villitis of Unknown Etiology, diffuse**	14 (14.6)	0
Villitis of Unknown Etiology, patchy**	17 (18.7)	7 (7.3)
Umbilical cord at risk	54 (56.2)	96 (100.0)

*Not graded

**High grade

4.3 Stillbirth at term

Table 9 shows a comparison of primary causes of stillbirth according to the Stockholm classification between the earlier and latter period for preterm stillbirths as well as for stillbirths diagnosed at term. A larger proportion of preterm stillbirths was attributed to placental insufficiency in the latter period (26.2%) than in the earlier (18.0%). However, the difference was more pronounced for term stillbirths, 58.4% in the latter period and 14.3% in the earlier. The proportion of preterm stillbirths attributed to reduced cord circulation also increased in the latter period (27.2 % vs 15.0%). However, this proportion decreased in the latter period for term stillbirths. Deaths attributed to infection decreased in the latter period and this cause was very rare at term. There was no difference in the proportion of preterm stillbirths due to placental abruption. However, the proportion of stillbirths at term due to abruption reduced by two-thirds as it was 9.5% in the earlier period and 3.2% in the latter. Stillbirths attributed to other acute intrapartum events such as birth asphyxia, cord prolapse, and uterine rupture were uncommon but even rarer in the latter period. The reduction was even more evident at term. Finally, the proportion of stillbirths with an unknown or unexplained cause decreased in the latter period compared to the earlier, both for preterm stillbirths (4.8% vs.16.2%) and term (6.5% vs. 9.5%) (Bjarnadottir, Steffensen, Pettersson, et al., 2025).

When analysing primary as well as associated causes of stillbirth at term; placental insufficiency (PI) and/or reduced circulation in the umbilical cord (RCC) were found alone or together in almost ¾ (92/125), as shown in fig. 4. There were 22 cases of isolated placental insufficiency (PI only) but in addition 28 also had reduced circulation in the umbilical cord contributing to the death, giving a total of 50 cases with placental insufficiency (PI all). In 70 cases, RCC was either the primary or associated cause of death (RCC all), in 42 without signs of PI (RCC only)(Bjarnadottir, Steffensen, Pettersson, et al., 2025).

Table 9 Primary cause of death according to Stockholm classification by time periods

	Preterm stillbirths		Term stillbirths	
	1996-2008	**2009-2021**	**1996-2008**	**2009-2021**
	n=167	n=103	n=63	n=62
	n (%)	n (%)	n (%)	n (%)
Stockholm classification				
Malformation	5 (3.0)	8 (7.8)	0 (0)	1 (1.6)
Infection	30 (18.0)	13 (12.6)	2 (3.2)	0 (0)
Immunisation	2 (1.2)	0 (0)	0 (0)	0 (0)
Fetomaternal transfusion	0 (0)	3 (2.9)	2 (3.2)	1 (1.6)
Twin-to-twin transfusion syndrome	9 (5.4)	3 (2.9)	0 (0)	0 (0)
Birth asphyxia	0 (0)	0 (0)	3 (4.8)	0 (0)
Placental insufficiency	30 (18.0)	27 (26.2)	9 (14.3)	34 (54.8)
Cord prolapse	4 (1.7)	0(0)	0 (0)	1 (1.6)
Reduced circulation in umbilical cord	25 (15.0)	28 (27.2)	31 (49.2)	17 (27.4)
Placental abruption	19 (11.3)	12 (11.7)	6 (9.5)	2 (3.2)
Preeclampsia	6 (2.6)	2 (1.9)	0 (0)	1 (1.6)
Diabetes mellitus	3 (1.8)	1 (0.6)	1 (1.6)	0 (0)
ICP*	1 (0.6)	0 (0)	1 (1.6)	1 (1.6)
Uterine rupture	0 (0)	0 (0)	2 (3.2)	0 (0)
Other causes	6 (2.6)	1 (0.6)	0 (0)	0 (0)
Unexplained/unknown	27 (16.2)	5 (4.8)	6 (9.5)	4 (6.5)

*Intrahepatic cholestasis of pregnancy

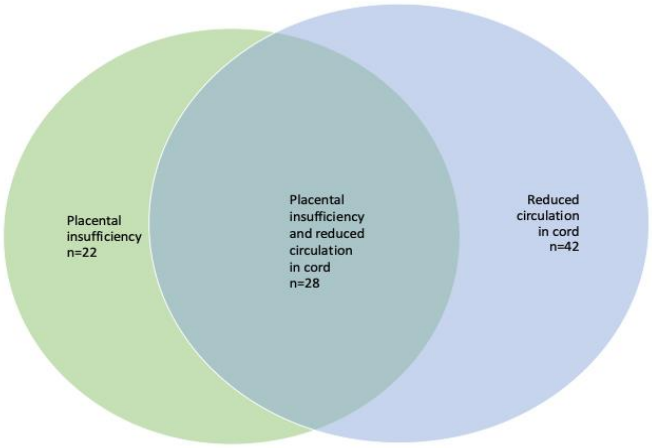

Figure 4 Placental insufficiency (PI) and/or reduced circulation in umbilical cord (RCC) as cause of stillbirth at term

In Table 10, clinicopathological phenotypes of stillbirth at term were compared between two time periods. No differences were found between periods in parity, age, BMI or HDP in the index pregnancy. As seen for all stillbirths irrespective of GA, smoking was less common among mothers of stillborn term infants in the latter period (11.3%) compared with the earlier (22.2%) and more were non-Icelandic speaking in the latter period (14.3% vs 25.8%), but neither reached statistical significance. Comparison of Icelandic speaking and non-Icelandic speaking mothers showed no difference in clinicopathological characteristics, shown in Table 11. Although there was no difference in gestational age (GA) between the two periods, the mean birthweight was 3420 g in the earlier period and 3230 g in the latter (Table 10). The proportion of term stillborn infants with a fetoplacental weight ratio (FPR) over the 90th percentile was 30.3% in the earlier and 37.1% in the latter half of the study period, p=0.07. Furthermore, the placental weight was under the 10th percentile in 30.2 % of stillbirths at term in the earlier period and 43.5% in the latter, p<0.05. When the four major patterns of placental injury were compared 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 20.6% of slides from the earlier period and 51.5% of slides in the latter, p<0.001 whereas VUE was seen in review in 12.7% of placental slides from term stillbirths in the earlier and 40.3% in the latter half, p<0.01. However, no difference was found between period in the proportion of placentas with MVM or ACA on review of placental slides (Bjarnadottir, Steffensen, Pettersson, et al., 2025).

Table 10 Clinicopathological phenotypes of stillbirth at term by periods

	1996-2008 n=63	**2009-2021 n=62**	**p-value**
Stillbirth rate (/1000 term infants)	1.19	1.15	0.89
Maternal characteristics:			
Mean age (SD)	30.5 (5.51)	31.1 (6.27)	0.48
Mean BMI (SD)	26.8 (6.59)	27.5 (5.63)	0.55
Nullipara, n (%)	22 (34.9)	27 (43.5)	0.42
Smoker, n (%)	14 (22.2)	7 (11.3)	0.26
Language other, n (%)	9 (14.3)	16 (25.8)	0.17
HDP, n (%)	8 (12.7)	11 (17.7)	0.59
Fetoplacental characteristics:			
Mean GA in days (SD)	275 (10.1)	275 (9.75)	0.66
Mean birthweight in g (SD)	3420 (590)	3230 (613)	0.09
Birthweight <10th percentile, n (%)	14 (22.2)	21 (33.9)	0.21
Placental weight <10th percentile, n (%)	20 (31.7)	27 (43.5)	<0.05
Fetoplacental ratio >90th percentile, n (%)	19 (30.2)	23 (37.1)	0.07
Umbilical cord at risk	40 (63.5)	41 (66.1)	0.90
Autopsy performed, n (%)	48 (76.2)	52 (83.0)	0.40
Median n of histologic slides (range)	8.3	14	
Maternal vascular malperfusion, n (%)	14 (22.2)	19 (30.6)	0.23
Fetal vascular malperfusion, n (%)	13 (20.6)	32 (51.5)	<0.001
Chronic villitis of unknown etiology, n (%)	8 (12.7)	25 (40.3)	<0.001
Acute chorioamnionitis (all), n (%)	18 (28.6)	17 (27.4)	0.50
Maternal floor infarct, n (%)	5 (7.9)	1 (1.6)	0.22

Table 11 Clinicopathological characteristics of non-Icelandic speaking compared with Icelandic speaking mothers of infants stillborn at term

	Non- Icelandic speaking n=25	**Icelandic speaking n=100**	**All mothers n=125**
Birthweight < 10th percentile, n (%)	8 (32.0)	23 (23.0)	31 (24.8)
Placental weight < 10th percentile, n (%)	7 (28.0)	39 (39.0)	46 (36.8)
Fetoplacental ratio >90th percentile, n (%)	7 (28.0)	35 (35.0)	42 (33.6)
PI all, n (%)	10 (40.0)	42 (42.0)	52 (41.6)
RCC only, n (%)	9 (36.0)	32 (32.0)	41 (32.8)
Unexplained, n (%)	2 (8.0)	9 (9.0)	11 (8.8)
MVM, n (%)	4 (16.0)	22 (24.0)	28 (22.4)
VUE, n (%)	6 (24.0)	27 (27.0)	33 (26.4)
FVM, n (%)	13 (52.0)	32 (32.0)	45 (36.0)
ACA*, n (%)	0 (0.0)	2 (2.0)	2 (1.6)

PI all: placental insufficiency all
RCC only: reduced circulation in umbilical cord only
MVM: maternal vascular malperfusion
VUE: chronic villitis of unknown etiology, high-grade
FVM: fetal vascular malperfusion, high-grade
ACA*: acute chorioamnionitis with stage 3 fetal inflammatory response.

Of infants stillborn at term, 28% (35/125) were SGA and their placentas were significantly more often under the 10th percentile or 62% vs 26.7% of non-SGA stillbirths, p<0.001. However, no difference was found in any of the 4 major patterns of placental injury between SGA and non-SGA infants. Of mothers with stillbirth at term, 19 had been diagnosed with HPD and MVM was found in 52.6% of their placentas. However, the proportion was 21.7% in mothers not diagnosed with HDP, p=0.07. (Table 12) (Bjarnadottir, Steffensen, Pettersson, et al., 2025).

Table 12 Clinicopathological phenotypes of term stillbirth associated with SGA or HDP

	All 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 (%)	41 (32.8)	4 (11.4)	37 (41.1)	0.012	4 (21.1)	37 (34.9)	0.36
FPR>90th perc., n (%)	42 (33.6)	9 (25.7)	33 (36.7)	0.65	8 (42.1)	34 (32.1)	0.62
Placenta<10th perc.,n (%)	46 (36.8)	22 (62.9)	24 (26.7)	<0.001	8 (42.1)	38 (35.8)	0.57
MVM, n (%)	33 (26.4)	9 (23.1)	24 (26.7)	0.64	10 (52.6)	23 (21.7)	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>90th perc.: Fetoplacental ratio over 90th percentile for gestational age
Placenta<10th perc.: placental weight under 10th percentile for gestational age
MVM: maternal vascular malperfusion
VUE: chronic villitis of unknown etiology
FVM: fetal vascular malperfusion

4.4 Clinicopathological phenotypes of singleton stillbirth

As illustrated in figure 5, half of singleton infants stillborn before term (107/216, 49.5%) had a birthweight <10th percentile (SGA), but this applied to only about 1 in 4 stillborn infants at term. In contrast, singletons stillborn at term were twice as likely to have low placental weight, compared to preterm stillborn infants (36.1% vs 19.0%). Furthermore, elevated FPR 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 (Paper III).

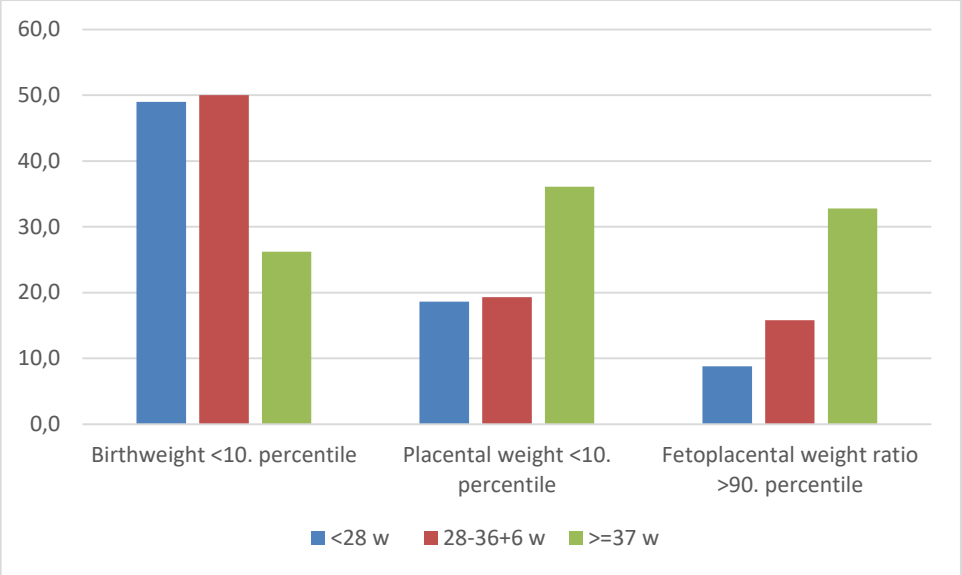

Figure 5 Fetoplacental characteristics of stillborn singletons by gestational age groups

The four major patterns of placental injury found in revised slides from stillborn singleton stratified into three GA groups are shown in Table 13. MVM is not graded but FVM and VUE is graded into high and low-grade, and ACA was staged according to the maternal and fetal inflammatory response. Additionally, both 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 at term. ACA was most often diagnosed in stillbirths before 28 gestational weeks, and this was most evident in cases with advanced fetal inflammatory response. There was no difference between GA groups in the proportion of placentas where none of the 4 major patterns of placental injury was diagnosed. More than one pattern of placental injury was found in same placenta in 25 singleton stillbirths (7.7%). Most placentas with combined patterns of placental injury were from stillbirths at term (20/25, 80%). The combination of ACA with other major patterns of placental injury showed that signs of infection were found in association with other placental injury in 14.4% of all stillbirths, more

commonly after 28 weeks (Paper III). As illustrated in Table 14, the umbilical cord was defined as at risk in over half of all stillbirths (53.0%) but this was more common with increasing GA: 27.4% before 28 weeks, 53.5% between 28 and 37 weeks and 70.5% at term.

Table 13 Patterns of placental injury in singleton stillbirth by gestational age groups

	All n=326	**<28 weeks n=98**	**28+0 - 36+6 n=109**	**≥37 weeks n=120**
Placental injury, single or combined	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Maternal vascular malperfusion (MVM) -not graded	**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[1]	59 (18.1)	17 (17.3)	19 (17.4)	23 (19.2)
Acute Chorioamnionitis[2]	27 (8.3)	10 (10.2)	6 (5.5)	11 (9.2)
Acute Chorioamnionitis[3]	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)**
Single type of placental injury				
Maternal vascular malperfusion (MVM)*	**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 MVM or FVM or VUE	47 (14.4)	8 (8.2)	14 (12.8)	25 (20.8)
Umbilical cord at risk	**175 (53.8)**	**28 (28.9)**	**61 (56.0)**	**86 (71.7)**
Cord at risk without 4 major patterns	41 (12.6)	8 (8.2)	12 (11.0)	21 (17.5)

[1] Maternal inflammatory response only

[2] Stage 1 fetal inflammatory response

[3] Stage 2-3 fetal inflammatory response

Clinical phenotypes for isolated patterns of placental injury are shown in Table 14. ACA was the most frequent isolated injury in intrapartum stillbirth, being found in almost a third of placentas (18/34, 32.1%). Most maternal characteristics were similar between the 4 patters. However, 26% of cases with isolated MVM had hypertensive disorder in the index pregnancy while the proportion was 17.6% in isolated VUE and lower in other patterns. The proportion of SGA differed with isolated patterns of placental injury. The majority (72.7%) of stillborn singletons with placental MVM were SGA, less than half those with high-grade FVM and VUE, and about a third (37.5%) of stillborn singletons with ACA. Low placental weight and high FPR was most common in singleton stillbirths with isolated placental MVM (61.4 vs 52.3%), less with VUE (31.0 vs 17.2%) and relatively rarely in others. The umbilical cord was at risk in most stillbirths with isolated FVM (79.0%)

Table 14 Isolated major patterns of placental injury and clinical phenotypes of singleton stillbirth

Reviewed placentas n=326		**MVM only n=44**	**FVM* only n=62**	**VUE* only n=29**	**ACA only 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 percentile	136	32 (72.7)	28 (45.1)	14 (48.3)	21 (37.5)
Placental weight <10th percentile	84	27 (61.4)	8 (12.9)	9 (31.0)	6 (10.7)
Fetoplacental ratio >90th percentile	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)

*High grade

Types of umbilical cords at risk found in different GA groups are shown in Table 15. In over half (53.8%) of singleton stillbirths, the umbilical cord was defined as at risk. The proportion increased with gestational age from 28.9% of stillbirths diagnosed before 28 weeks to 56.0% between 28 and 37 weeks and 71.7% of stillbirths at term. Hypercoiled, excessive long and wrapped cords were the most common aberrations and all 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 16). Hypocoiling, aberrant cord insertion and particularly true knots and strictures were less common.

Table 15 Type of umbilical cord at risk in stillborn singletons by gestational age groups

	All n=325	<28 weeks n=97	28+0 - 36+6 n=109	≥37 weeks n=120
Umbilical cord at risk	**175 (53.8)**	**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 16 Association of length of umbilical cord and other aberrations

Umbilical cord at risk	Excessively long umbilical cord, n= 54	Normal or short umbilical cord, n= 271	p-value
Hypercoiled cord, n=60	23 (42.6)	37 (13.7)	<0.001
Hypocoiled cord, n=22	3 (5.6)	19 (7.0)	
True knot in cord, n=15	3 (5.6)	12 (4.4)	
Wrapped cord, n=42	11 (20.4)	31 (11.4)	<0.001
Cord prolapse, n=4	2 (2.7)	2 (0.70)	

Placental FVM was found in ½ of singleton stillbirths with umbilical cord at risk, as shown in Table 17, which illustrates the proportion of FVM (low- and high-grade) in stillborn singletons with different types of umbilical cord at risk. Almost 90% of stillbirths with placental FVM have some type of umbilical cord at risk (92/103). High-grade FVM was more frequently detected than low-grade, especially when the cord was hypercoiled, excessively long or with stricture. However, FVM was more often low-grade than high-grade in cases with a true knot in the cord and especially in cord prolapse. About 2/3 of singleton stillbirths with umbilical cord at risk had neither signs of MVM or VUE. However, the combination of umbilical cord at risk and placental MVM or VUE was more common with advancing gestational age.

Table 17 Proportion of stillborn singletons with FVM by type of umbilical cord at risk

		High-grade FVM n=69	Low-grade FVM n=34	All FVM n=103
	n	n (%)	n (%)	n (%)
Umbilical 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 *	116	37 (31.9)	18 (15.5)	55 (47.4)

*Without MVM or VUE in placenta

5 Discussion

Main results:

The SBR in Iceland decreased significantly over the study period, due to fewer preterm stillbirths. However, there was no change in the SBR at term. The commonest causes of death were reduced circulation of the umbilical cord and placental insufficiency and both increased with GA. Stillbirth due to infection and placental abruption, as well as unexplained deaths, decreased during the study period whereas deaths attributed to placental insufficiency became more common. Stillbirths with placental FVM and VUE, as well as umbilical cord at risk, were more common with advancing GA and often without recognised risk factors.

5.1 Mortality rate

The total SBR in Iceland decreased significantly over the study period from 4.10 stillbirths per 1000 births in the earlier half (1996-2008) to 2.88 in the latter (2009-2021) (p=0.009). However, when the SBR was calculated for GA groups with number of infants at risk as denominator, the reduction was only found for preterm stillbirths, with no difference in the SBR at term. This contrasts with a review of MBRRACE-UK data from the United Kingdom, which found a 20% reduction in the SBR from 2013 to 2019, mainly due to a reduction in the rate of term stillbirths by one-fifth (Burden et al., 2025), although decreasing from a higher initial rate. Finding no reduction in the rate of stillbirth at term in Iceland was perplexing, as antenatal risk assessment had increased during the study period with implementation of guidelines for surveillance of high-risk pregnancies and an escalation of the rate of induction of labour (Swift et al., 2022; Swift et al., 2018). This called for an analysis of maternal and fetoplacental characteristics of stillbirths over the study period, stratified for GA groups, as well as of causes of death.

5.2 Characteristics and causes of stillbirth

Recent studies have shown that advanced maternal age, obesity and HDP have become more common in Iceland over the last decades (Swift et al., 2018). However, for mothers who had stillbirths, the proportion with these characteristics did not increase significantly between the two time periods. Furthermore, there was no difference in the proportion with a history of adverse outcome in a previous pregnancy. Indeed, this may be due to increased antenatal surveillance in high-risk pregnancies leading to interventions which reduce the risk of stillbirth. The negligible increase in the proportion of stillborn SGA infants over time can support this, as these pregnancies

were more likely to be detected antenatally. However, low placental weight was more common in the latter half of the study period, both absolutely and also relatively to birthweight as high FPR. Stillbirth is strongly associated with SGA (Gardosi & Hugh, 2023; Heazell et al., 2019) as well as low placental weight (Hutcheon et al., 2012) and high FPR for GA (Haavaldsen et al., 2013). Nonetheless, it is important to note that SGA infants are not necessarily growth restricted (Wilcox & Basso, 2023). Furthermore, stillbirth due to placental insufficiency can be independent of fetal growth restriction (FGR) (Freedman et al., 2019). When detected, FGR may lead to elective delivery, especially at term, and prevent some stillbirths. However, small placentas or high FPR is rarely detected antenatally. Although placental volume estimation with three-dimensional ultrasound has been described (Azpurua et al., 2010), it has proven difficult to validate and the correlation with magnetic resonance imaging is poor (Sagberg et al., 2021). If improved imaging methods could be developed to estimate placental weight, screening for small placentas, absolutely or in relation to the estimated fetal weight, could be a better predictor for risk of stillbirth due to placental insufficiency than screening for SGA.

The commonest causes of stillbirth were reduced circulation in the umbilical cord and placental insufficiency. A fourth of all stillbirths was attributed to each of these two causes according to the Stockholm classification. A larger proportion of stillbirth was attributed to umbilical cord complications with higher GA groups, which is in line with other studies (Hayes et al., 2020) (Hammad et al., 2020). With advancing GA, a larger proportion of stillbirth was also attributed to placental insufficiency, which is recognized as one of the major causes of stillbirth, especially in advanced gestations (Man et al., 2016) (Pinar et al., 2014). Furthermore, a larger percentage of stillbirths was attributed to placental insufficiency in the latter period, when a larger proportion of stillborn infants were diagnosed at term. However, in the latter period, fewer deaths were attributed to causes such as infection and placental abruption, that were more common in stillbirth before term. Infection is an important cause of stillbirth globally, especially in low- and middle-income settings (Goldenberg et al., 2010; McClure et al., 2022) but is a less common cause in high income countries (HICs). Finding fewer stillbirths due to placental abruption corresponds to a study of the rate of placental abruption in several HICs, including Norway, Sweden, Finland, Canada and United States, which showed a reduction in the European countries after 2000 and was partially explained by less smoking (Ananth et al., 2015). However, the rate of abruption did not reduce in the US, where it has in fact increased from 1.2% of deliveries in 2000 to 1.6% in 2020 (Wright et al., 2025). The strong association between placental abruption with obstetrical risk factors, especially pre-eclampsia, is well known (Wright et al., 2025) and the reduction found in abruption-related stillbirth in Iceland may by due to less smoking and as well as improvements in antenatal care. This is supported by a study of singleton livebirths in Iceland 1997-2018 that showed a significant reduction in placental abruption (Gunnarsdottir et al., 2021).

One in ten deaths over the study period were unexplained, which corresponds to a recent study showing that a probable cause could be found for over 85% of stillbirths based on clinical review and placental histopathological examination (Odendaal et al., 2022). There were fewer unexplained stillbirths in the latter half of the study period, which probably reflects advances in placental histopathology.

5.3. Stillbirth at term

Fewer stillbirths were attributed to acute adverse obstetrical events such as placental abruption, birth asphyxia, uterine rupture and cord prolapse in the latter half of the study period, especially at term. Although these deaths were relatively uncommon in Iceland throughout the study period, they become even rarer with time. This may be partly due to changes in the obstetrical care in Iceland, which has been increasingly centralized with fewer rural birth places with limited service in obstetrical emergencies. This is supported by a recent study showing a reduction of adverse maternal and neonatal outcomes in Iceland over the last two decades (Gunnarsdottir et al., 2021). However, stillbirth at term did not decrease over the study period. Although the number of stillborn infants did not increase between the earlier and latter period, the proportion of stillbirths diagnosed at term increased from 27.4 to 37.6 %. This is similar to the UK, where a third of stillborn babies were born at term and previously considered to be healthy (Muglu et al., 2019)

Stillbirth at term was most often attributed to reduced flow in the umbilical cord which was frequently found in association with placental insufficiency. Placental insufficiency was the second most common cause, and significantly more deaths were attributed to this in the latter half of the study period. Almost 3 out of 4 stillbirths at term were antenatal deaths caused by umbilical cord complications and/or placental insufficiency.

These findings contrast with a study of term stillbirth in Stockholm using the same classification, where infection was found to be a frequent cause of death along with placental insufficiency (Amark et al., 2021). This may be due to differences in attributing the main cause of death to infection in cases of ACA without severe fetal response, as well as dissimilarities in the obstetrical populations of Iceland and Sweden. However, these findings are in agreement with a recent Italian study on stillbirth at term using the ReCoDe classification, which found the two major causes to be placental and umbilical cord disorders (Salerno et al., 2023). Finding no decrease in stillbirth at term between the two time periods and actually more deaths attributed to placental insufficiency in the latter period is perplexing, especially in view of the increased antenatal surveillance for high-risk pregnancies and doubling of the rate of induction of labour (Swift et al., 2022). This raises the question of whether the SBR at term would have increased without these interventions. Although there was an increase in maternal age, BMI and HDP in the general obstetrical population in Iceland (Swift et al., 2018), no difference in these risk factors were found among the mothers who had

stillbirths at term. It is possible that increased surveillance and interventions prevented cases of stillbirth at term for mothers with clinical risk-factors. In Iceland, as in other HICs with comprehensive antenatal care, women considered high-risk of adverse outcome are less likely to carry pregnancies past term than low-risk mothers. This may apply even more in the latter period with increased rate of induction of labour.

In stillbirth at term, placentas weighing under the 10th percentile were significantly more common in the latter period compared with the earlier although there was no increase in the proportion of SGA infants. Placental MVM was found to have a significant association with HDP in stillbirth diagnosed at term. This relationship was expected as other studies have shown an association, especially with pre-eclampsia (Brosens et al., 2019). However, the proportion of MVM in stillbirth at term did not increase between periods. This may be due to the increased antenatal surveillance and early-term induction of labour when mothers were diagnosed with hypertension. On the other hand, no significant association was found between VUE and HDP, although admittedly the cases were few. This chronic inflammation was significantly more often diagnosed in placentas of term stillbirths in the latter period. VUE is a T-cell mediated placental inflammation (Mekinian et al., 2021) that is poorly understood although considered to have an immunological etiology (Derricott et al., 2016), perhaps triggered by a viral infection (Ernst et al., 2021). However, VUE is still an enigma and research is needed on its correlation with clinicopathological phenotypes of mothers and infants (Redline et al., 2023). Although VUE has previously been associated with FGR (Derricott et al., 2013), no significant relationship was found in this study. As discussed above, SGA is not synonymous to FGR (Coutinho et al., 2020; Wilcox & Basso, 2023). In fact, this study found no relationship between term stillborn SGA infants and any major pattern of placental injury. This suggests that surveillance of fetal growth by serial ultrasound may not be an appropriate method to detect placental dysfunction at term. In fact, recent studies show that screening for fetal growth does not reduce the stillbirth rate at term as the association between FGR and fetal demise weakens with advancing gestation (Coutinho et al., 2020; Halimeh et al., 2019). However, recent studies suggest that placental biomarkers may increase the detection of placental insufficiency (King et al., 2022). This could enable surveillance and interventions to prevent term stillbirth.

5.4 Clinicopathological phenotypes of singleton stillbirth

Although infants stillborn before term were twice as often SGA compared to term stillbirths, low placental weight and high FPR for GA was more often found in stillbirth at term than before (Paper III). This difference in fetoplacental weight between preterm and term stillbirth has not been described previously.

Like the "black box" after an airplane crash, the placenta can help explain why an infant was stillborn (Graham & Heazell, 2020), especially if major patterns of placental injury

and their correlations with clinical features are understood (Ravishankar & Redline, 2020). Placental examination was performed in over 96% of singleton stillbirths in Iceland and the 4 major patterns of placental injury, alone or in combination, was detected in almost ¾ of cases (72.1%). None of the 4 major patterns were found in over 1 in 4 placentas and only few of these had a defined other placental pathology such as Maternal floor infarct. In many of these cases, there had been an adverse obstetrical event that led to sudden death, such as acute placental abruption, uterine rupture or fetomaternal transfusion (Paper III) although a few deaths were unexplained.

When comparing the 4 major patterns of placental injury in singleton stillbirths between GA groups, the proportion of MVM was similar, whereas FVM was more common after 28 gestational weeks. ACA was most often diagnosed in stillbirths before 28 gestational weeks, especially with advanced fetal inflammatory response and VUE was most often diagnosed at term (Paper III). Several studies have compared pathological phenotypes according to GA for all examined placentas i.e. not solely stillbirths. They have found VUE and FVM to be most common in term and late preterm pregnancies, MVM in early and late preterm and ACA in early preterm pregnancies which are often previable (Redline & Ravishankar, 2018; Redline et al., 2021; Stanek, 2014).

Although detecting more than one pattern of placental injury was relatively uncommon in singleton stillbirth in Iceland, 80% of combined lesions were found at term (Paper III). Such multiplicity of lesions has been correlated to worse perinatal outcome than isolated lesions (Alexa A Freedman et al., 2021; Marijnen et al., 2025; Stanek & Funk, 2025).

In this study, MVM was frequently seen in stillbirths with HDP in the index pregnancy as well as a history of HDP, SGA and stillbirth in a previous pregnancy. This is consistent with the known association of defective deep trophoblast implantation with the "Great Obstetrical Syndromes" (Brosens et al., 2011; Burton et al., 2009), including 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 (Burton & Jauniaux, 2018; Kulkarni et al., 2021). 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 (Redline & Ravishankar, 2018). Finding SGA in stillbirths with high-grade FVM is not unexpected, as the association of FVM with fetal growth restriction has been described (Redline & Ravishankar, 2018). However, neither low placental weight nor high FPR was frequent in stillbirths with high-grade FVM. This is in agreement with previous studies that suggested the low birthweight can be associated with abnormal cord insertion such as marginal-, membranous- or furcate insertion site or a thin cord (Redline & Ravishankar, 2018; Redline et al., 2021). ACA was more often seen in stillbirth before 28 weeks, when the death was more often intrapartum, especially in extremely premature infants, as has been previously described (Chisholm et al., 2018; McClure et al., 2022). In fact,

the median gestational age for intrapartum stillbirth in this material was 23 weeks (Paper III). Other studies have shown high-grade VUE to be frequently found in stillbirths with low placental weight and high FPR for GA (Mekinian et al., 2021; Redline, 2007). However, this study did not find the proportion of high-grade VUE to be as high as MVM in stillbirths with absolutely or relatively small placentas. Moreover, neither SGA nor HDP was as frequent in stillbirths with high-grade VUE as in those with MVM. 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". Furthermore, VUE is more often found with higher GA and most common in stillbirth at term (Mekinian et al., 2021).

Information on placental histological lesions after uncomplicated pregnancies is limited in the literature. In a large study from 2011, which recruited over 1100 mothers from an unselected obstetrical population, no pathological findings were found in 72.1% of placentas (Pathak et al., 2011). However, as the study was done prior to the Amsterdam consensus, the positive pathological findings can be difficult to interpret. Another study from 2018 of placental lesions after 944 singleton term pregnancies with normal outcome found ACA with maternal inflammatory response in >42% of placentas (Romero et al., 2018). Maternal and fetal malperfusion was detected 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. Again, the criteria of the Amsterdam consensus were not applied in this study, although a similar classification of the Society for Pediatric Pathology was used. More prospective studies on patterns of placental pathology in placentas from unselected pregnancies are therefore needed to bridge the knowledge gap and aid clinicians further in interpreting the significance of the pathology report after adverse outcomes of pregnancy.

The umbilical cord was defined as at risk according to the Amsterdam consensus (Redline & Ravishankar, 2018; Redline et al., 2021) in over half of singleton stillbirths in Iceland. The proportion increased with advancing GA to over 70% of stillbirths at term. The most common abnormalities were hypercoiled, excessively long and wrapped cords. All of these were most frequent at term and were moreover often found together. However, as the aim and scope of Paper III was to describe clinicopathological phenotypes of singleton stillbirth without determining cause of death, it should not be assumed that these stillbirths were necessarily caused by umbilical cord complications. In fact, 1 in 3 stillborn singletons with umbilical cord at risk also had placental MVM or VUE, more often at term, suggesting multifactorial causes of death.

The proportion of stillbirth attributed to umbilical cord complications range widely, dependent on classification system for cause of stillbirth as well as definitions of cord

complications. According to the Stockholm classification of stillbirth, over 25% of all stillbirths in Iceland were attributed to reduced circulation in the umbilical cord and the proportion increased with gestational age (Bjarnadottir, Steffensen, Smarason, et al., 2025). An American study of 496 stillbirths using the INCODE classification associated 19% of deaths (95% CI 16-23%) with an umbilical cord abnormality (Hammad et al., 2020).

But how common is an umbilical cord at risk and which characteristics increase the risk of stillbirth? Certainly, nuchal cords are common in uncomplicated births, being found in up to 30% at 40 weeks without increased risk of adverse perinatal outcome (Cohain, 2010). However, the association of certain aberrations of the umbilical cord with stillbirth have been described (Hammad et al., 2020; Hayes et al., 2020). 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%. Although no association was seen between stillbirth and any nuchal cord (OR 1.11, 95% CI 0.62-1.98), multiple loops of nuchal cord compared to single or no loop had an OR of 2.36 (95% CI 0.99-5.62) and the risk was significantly higher with a true knot (OR 4.65, 95% CI 2.09-10.37)(Hayes et al., 2020). However, data was lacking on cord length and coiling as well as cord insertion in the 145 studies analysed. Furthermore, there was no data on the combined effects of multiple cord abnormalities. However, a study from the Medical Birth registry of Norway of over 600.000 births found a prevalence of velamentous cord insertion of 1.5% and marginal insertion of 6.3% in singletons, while 6% of twins had velamentous and 10.9% marginal insertion (Ebbing et al., 2013). Both velamentous and marginal insertions were associated with adverse perinatal outcome but the risk was higher for velamentous, being associated with a threefold higher risk of perinatal death at term compared to normal cord insertion (OR=3.3, 95% CI 2.5-4.3).

More research on umbilical cord variations and their effect on adverse perinatal outcome is needed. Causality between umbilical cord at risk and adverse outcome should be assigned with caution and with possible multifactorial interaction in mind.

5.5 Advantages and limitations

One of the strengths of this study is that medical records were available for all the mothers and their stillborn infants and were reviewed by the doctoral candidate, an obstetrician who is experienced in perinatal audit. Furthermore, all available histopathological slides were re-evaluated by the same experienced perinatal pathologist (TS). The obstetrician and the pathologist discussed each case after reviewing the clinical and histopathological findings and assigned the primary and associated cause of death according to the Stockholm classification of stillbirth. This interdisciplinary collaboration was strengthened with discussions of challenging cases with authors of the Stockholm classification (KP, NP), who had a long experience of using this system.

5.5.1 Data from the Icelandic Medical Birth Registry

Information on all births from Iceland has been collected in the Icelandic Birth Registry since 1972. The data is electronic from 1982 but is unfortunately incomplete. Information about maternal smoking was missing until 2021, but part of the reduction in stillbirths may be explained by reduced smoking in the population of Iceland (Statistics Iceland, 2017), especially fever deaths caused by placental abruption. Moreover, data on maternal BMI was only available for the last years of the study period. Furthermore, information on ART is lacking completely from the registry. Due to unavailability of relevant background information on the obstetrical population in Iceland over the study period, it was not possible to correct for maternal risk factors such as obesity and smoking. The long study period, which covered more than a quarter of a century, can both be considered a strength and a limitation. Diagnostic criteria for obstetrical diseases, such as HDP and gestational diabetes, changed during this time and therefore their registration in the Icelandic Medical Birth Registry. However, changes in the obstetrical population and clinical practice over the last decades may have influenced the incidence and etiology of stillbirth. The 26-year study period was divided into a former (1996-2008) and latter period (2009-2021) which were compared throughout the study. The induction rate doubled between these periods in Iceland. Although changes in perinatal practice may generally happen gradually, in the small society of Iceland changes in guidelines for antenatal care tended to be implemented promptly due to centralized antenatal care.

5.5.2 Stockholm classification of stillbirth

The Stockholm classification of stillbirth (Varli et al., 2008) consists of 17 groups (Appendix C) but due to the small population of Iceland, there are extremely few cases in the less common ones. One of the strengths of this system is the clear criteria for each group, which also classify the association of the relevant conditions to the death as definite, probable or possible, based on clinical findings and results of investigations before and after the stillbirth. In view of the chain of events, most stillbirths of extremely immature infants (often intrapartum deaths) were attributed to infection as this was considered to have led to the extremely preterm delivery. However, in most cases these infections were without fetal response and would have been unlikely to lead to the death of more mature infants. Therefore, other classifications might have attributed these deaths to extreme prematurity. Furthermore, the Stockholm classification is based on a chain of events leading up to the death either principally (primary cause) or by contributing to it (associated cause). The possibility of attributing stillbirth to more than one cause is an important advantage of the Stockholm classification. However, when two conditions co-exist and interact, determining which one led primarily to a stillbirth and which was contributary can be challenging. When developing the Stockholm classification, it was decided to prioritise placental insufficiency over reduced circulation in umbilical cord when both conditions co-existed. The combination of these

two conditions became increasingly common over the study period, especially at term. Because of this ranking, more deaths were primarily attributed to placental insufficiency in the latter period while those primary attributed to reduced circulation in the umbilical cord decreased.

5.5.3 Histopathological review of placental slides

Placenta examination was performed for over 96% of stillborn infants in Iceland during the study period, which must be considered a major strength. Importantly, this means that the results of placenta histopathology was not affected by selection bias. Moreover, all histopathological slides were re-evaluated in view of changes in criteria through the study period and classified according to the Amsterdam consensus (Khong et al., 2016) by the same perinatal pathologist (TS). There was a significant increase of VUE in placentas of stillborn infants in the later period as well as more findings of FVM. The increase in FVM in the later period can at least partially be explained by changes in sampling practices, as more samples were taken from chorionic plate vessels after the Amsterdam Consensus 2016 (Redline & Ravishankar, 2018). Although there were more slides per placenta in the later period, it does not fully explain the marked increase in VUE. More slides could admittedly increase the diagnosis of focal VUE, but hardly diffuse VUE, affecting by definition at least 30% of the placenta so it would be unlikely to be missed when the average number of slides was 8.3.

Another limiting factor is the lack in the literature of robust data on the prevalence of placental pathology and umbilical cord at risk in uncomplicated livebirths. Placentas are generally not sent for histopathological examination without defined clinical indications, which is often an adverse outcome. In the United States, it is estimated that 20-25% of placentas have a histopathological examination currently and the proportion has gradually increased from 10-15% in the 1990s (Redline et al., 2023).

Finally, the main limitation of the study is the small numbers. Stillbirth is fortunately an uncommon occurrence in the sparsely populated, high-income country of Iceland. Nonetheless, although Iceland's SBR can be considered low, it is almost three times higher than its infant mortality rate, which is among the lowest in Europe, being 1.1 per 1000 liveborn infants in 2019 (ref. Hagstofan). This is also the case in other HICs, such as the United States, with little reduction in the SBR over the last two decades, in spite of significant decrease in infant mortality (Gregory et al., 2021; Hug et al., 2021). As pointed out in a recent clinical review article in JAMA (Kern-Goldberger et al., 2026), efforts to reduce stillbirth are currently hampered by difficulty in identifying the pregnancies at risk. Indeed, stillbirth often occurs in pregnancies where no risk factors were recognized, especially at term (Bjarnadottir, Steffensen, Pettersson, et al., 2025).

6 Conclusions

The aims of this doctoral study, to explore the SBR and causes of stillbirth in Iceland over a quarter of a century, were met. Although the SBR decreased over the study period, no reduction was found in the rate of stillbirth at term. This was unexpected and led to further analysis of causes of death and patterns of placental injury in term stillbirth. Moreover, the clinicopathological phenotypes of singleton stillbirth were described for GA groups with emphasis on patterns of placental injury, i.e. the four major patterns of placental injury as well as umbilical cord at risk. This work resulted in three original papers that this thesis is based on.

The Stockholm classification, which was amended here according to the more recent Amsterdam placental workshop consensus, proved comprehensive and user-friendly and illuminated the causes of stillbirth in Iceland during the study period. The classification assumes a high level of investigations after a stillbirth, including autopsy and placental examination, as is the case in Iceland, and was therefore very well suited to analyse and classify causes of stillbirth in this setting.

In the latter half of the study period, fewer deaths were attributed to causes that were more common in preterm stillbirths, such as infection and placental abruption. This could to some extent be due to a lower threshold for treatment and intervention in very preterm pregnancies which may have led to liveborn delivery. Furthermore, deaths due to acute intrapartum events such as birth asphyxia, uterine rupture and cord prolapse, although rare throughout the study period, were even fewer it the latter half. This may be due to improved intrapartum surveillance and management of obstetrical emergencies over time. However, placental insufficiency and reduced flow in the umbilical cord were the main causes of stillbirth in Iceland, both increasing with gestational age. Finding that a larger proportion of stillbirths was diagnosed at term in the latter period, despite increased antenatal surveillance and a doubled induction rate, was perplexing. More term stillbirths were attributed to placental insufficiency in the latter period, when more placental VUE was seen on review of histopathological slides. Many of these stillborn infants were delivered after a pregnancy which had been considered "low risk". As had previously been described (Burton & Jauniaux, 2018), placental MVM was frequently found in stillbirths with low birthweight or placental weight (absolutely or relatively to birthweight) as well as with HDP in the index pregnancy. In contrast, stillbirths with VUE, FVM and umbilical cord at risk were often term and without recognised risk factors. Preventing these stillbirths is a major challenge for antenatal care.

Auditing and classifying stillbirth is an important step in preventing the future loss of a "life that was not lived" (Dandona & Solberg, 2023; Flenady et al., 2016), be it on a global, national, institutional or individual basis. The role of the obstetrician in counselling parents that have lost their baby is an extremely important and difficult one. The bereavement is usually unexpected, and it is important that clinicians can explain why the baby died as well as the risk of recurrence.

One of the advantages of the Amsterdam consensus is objective criteria to classify most placental pathology into four major patterns of placental injury, with different clinical phenotypes and risks of recurrence. Understanding the major patterns of placental injury and their recurrence risk can therefore be a valuable tool when counselling after stillbirth and planning surveillance of a subsequent pregnancy. However, as background data on the prevalence of placental pathology and umbilical cord at risk in uncomplicated livebirths is lacking, a prospective study is planned on the prevalence of placental injury in an unselected obstetrical population in Iceland. Another study on the outcomes of a subsequent pregnancy in mothers with a history of stillbirth in also underway. That study will focus on perinatal outcomes by patterns of placental pathology at the time of the previous stillbirth and is based on the findings of this thesis.

Hopefully, this doctoral study can improve the understanding of the causes and clinicopathological phenotypes of stillbirth which may lead to new and better ways to save babies in the future.

"Hope is the thing with feathers that perches in the soul – and sings the tunes without the words – and never stops at all." Emily Dickinson

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Original Publications

Paper I

Stillbirth in Iceland 1996-2021: Incidence and etiology. Ragnheidur I Bjarnadottir, Thora Steffensen, Alexander K Smarason, Karin Pettersson, Nikos Papadogiannakis, Kristjana Einarsdottir, Johanna Gunnarsdottir. Published in *Acta Obstetricia et Gynaecologica Scandinavica (AOGS)* 24th September 2025

Received: 28 May 2025 | Revised: 4 September 2025 | Accepted: 10 September 2025

DOI: 10.1111/aogs.70058

ORIGINAL RESEARCH

Stillbirth in Iceland 1996–2021: Incidence and etiology

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Abstract

Introduction: This study describes the stillbirth rate (SBR) in Iceland 1996–2021 and the causes of stillbirth according to the Stockholm classification of stillbirth, comparing time periods and gestational age (GA) groups.

Material and Methods: Clinical information was obtained from medical records of mothers who had stillbirths and their infants ($n=395$). Infants were divided into groups according to GA at diagnosis of stillbirth: early preterm: ≥22 but <28 weeks ($n=140$), late preterm: ≥28 but <37 weeks ($n=130$), and term: ≥37 weeks ($n=125$). Autopsy records and gross descriptions of the placenta were reviewed, and microscopic slides were reevaluated, and findings classified according to the Amsterdam Consensus. Primary and associated causes of death were assigned according to the Stockholm classification of stillbirth. The SBR, maternal and fetoplacental characteristics, and causes of death were compared between two 13-year periods (1996–2008 and 2009–2021) and between GA groups.

Results: The SBR decreased from 4.10 to 2.88/1000 births ($p=0.009$) between the two periods, but this decrease was limited to stillbirths diagnosed before term. Fewer stillbirths in the latter period were attributed to causes such as infection and placental abruption, and unexplained stillbirths reduced (0.59 vs. 0.16/1000, $p<0.05$). The most common primary causes of stillbirth were reduced circulation in the umbilical cord (25.6%) and placental insufficiency (25.2%); both increased in incidence with more advanced gestation. Despite no difference in small-for-gestational-age infants, a larger percentage of stillbirths had low placental weight (21.3% vs. 30.3%, $p=0.002$) and high fetoplacental ratio for GA (15.7% vs. 24.2%, $p=0.005$) in the latter period, when a larger proportion of stillbirths were attributed to placental insufficiency (17.0% vs. 37.0%, $p=0.0002$).

Conclusions: The SBR decreased in the latter period due to a reduction in preterm stillbirth, whereas the SBR at term was unchanged. Reduced circulation of the umbilical

Abbreviations: FPR, fetoplacental ratio; GA, gestational age; HDP, hypertensive disorder of pregnancy; SBR, stillbirth rate; SGA, small for gestational age.

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Funding information
Icelandic Centre for Research, Grant/Award Number: 239642-051

cord and placental insufficiency were the commonest causes, and both increased with GA. Stillbirth due to infection and placental abruption, as well as unexplained stillbirths, decreased during the study period, whereas deaths attributed to placental insufficiency became more common, reflecting a lack of reduction of stillbirth at term in the latter period.

KEYWORDS
Amsterdam consensus, placental histopathology, placental insufficiency, Stockholm classification of stillbirth, umbilical cord complications

1 | INTRODUCTION

Stillbirth is one of the most devastating outcomes of pregnancy. The stillbirth rate (SBR) of a country is considered a marker of the quality of its antenatal and intrapartum care. Globally, it is estimated that 2 million babies were stillborn after 28 weeks of gestation in 2019, with an SBR of 13.9 per 1000 births, differing almost 10-fold from 22.8 in West and Central Africa to 2.9 in Western Europe.[1] In addition to registering[2] stillborn infants, auditing causes of stillbirth can influence health policy, clinical practice, research, and ultimately reduce mortality. Over 80 classification systems have been described,[3] many include all deaths in the perinatal period while others focus only on stillbirth. The Nordic-Baltic Perinatal Death Classification,[4] used in Iceland since 1996, was developed to define deaths that were potentially avoidable by improved antenatal, intrapartum, or neonatal care. This classification has been practical for perinatal audit in Iceland, as the information needed is available from the Icelandic Medical Birth Registry. A study of perinatal mortality in Iceland 1994–2017,[5] based on the above classification, showed a significant decrease in the perinatal mortality rate of infants born after 22 weeks of gestation. However, early neonatal deaths decreased more than stillbirths. The largest group of perinatal deaths was stillbirths of non-growth-restricted singleton infants after 28 weeks of gestation, with no reduction in this group. However, as this classification is not based on causes of death, another system is needed to explore changes in causes over time. The Stockholm classification of stillbirth,[6] with 17 well-defined primary and associated causes of fetal death, describes the chain of events leading to fetal death (primary cause) as well as contributing to it (associated cause) and grades causes into possible, probable, and definite. It is important for parents and clinicians to understand why an infant died before birth, not least as it can influence the mother's care in subsequent pregnancies. Although various risk factors for stillbirth have been described,[7,8] it often occurs in pregnancies without recognized risk factors.[8] However, investigations after stillbirth often provide explanations, especially placental pathology.[9]

Iceland has a low SBR and caesarean section rate[10] similarly to other Nordic countries.[11] The induction rate increased markedly in Iceland after 2008,[12,13] due to inducing labor earlier for prolonged pregnancy as well as for pregnancies with hypertensive disorder after the HYPITAT study.[14] A recent study showed that adverse neonatal outcomes decreased over time in Iceland, but it included only live births.[15] Causes of stillbirth in Iceland have not been examined previously. The study aimed to explore the changes in the SBR and compare the main causes of stillbirth between two periods: 1996–2008 and 2009–2021, and according to three gestational age (GA) groups. The Stockholm classification of stillbirth was used to assign the cause of death, and the placental pathology was reviewed according to current classification.

Key message

The stillbirth rate decreased due to a reduction in preterm stillbirth, with fewer cases attributed to infection and placental abruption. The most common causes were cord complications and placental insufficiency, both increasing with gestational age.

2 | MATERIAL AND METHODS

The Icelandic Medical Birth Registry provided personal identification numbers of mothers who had a stillbirth in Iceland from 1996 to 2021 and the number of stillborn and live born infants during the same period. Stillbirth was defined as an infant born without signs of life who could not be resuscitated after 22 weeks of gestation or with a birthweight of at least 500 g if the GA was unknown. This included both antepartum and intrapartum deaths. Early neonatal deaths were defined as the death of an infant within 7 days of birth. As perinatal mortality review was not formalized in Iceland until 1996, earlier stillbirths were not included. GA was based on ultrasound examination before 22 weeks of gestation. Infants were divided into groups according to GA at diagnosis of stillbirth: early preterm stillbirth <28 weeks ($n = 136$), late preterm stillbirth ≥28 but <37 weeks ($n = 134$), and term stillbirth ≥37 weeks ($n = 125$).

The fetal autopsy records were reviewed as well as the gross description of the placenta. The recorded placental weight was the trimmed weight of the unfixed placental disc after removal of the membranes and umbilical cord. Cases with placental weight under the 10th percentile and/or fetoplacental ratio (FPR) over the 90th percentile for the infant's GA and sex were noted.[16] Archived microscopic slides were re-evaluated by a senior pathologist (TS) and histological findings documented in accordance with recommendations of the 2016 Amsterdam consensus conference,[17] as described in Appendix S1. The findings were classified into four major patterns of injury: maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), acute chorioamnionitis (ACA), and chronic villitis of unknown etiology (VUE) described by Redline et al.[18] More than one pattern of placental injury could be seen in the same placenta.

Clinical information was collected by a senior 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 (Table S1). The definition of small for gestational age (SGA) was birthweight under the 10th percentile of a newly published Swedish intrauterine growth curve.[19,20] Hypertensive disorder of pregnancy (HDP) was assigned according to the classification of the International Society for the Study of Hypertension in Pregnancy (ISSHP).[21] Instead of citizenship, being non-Icelandic speaking was used as a proxy for foreign origin. A history of HDP, delivering an SGA infant, or having a stillbirth prior to the index pregnancy, was defined as an adverse outcome in a previous pregnancy. Body Mass Index (BMI) is based on maternal weight at the first antenatal visit and self-reported height.

Each case was discussed by the obstetrician (RB) and the pathologist (TS), and the primary and associated causes of death were assigned according to the Stockholm classification of stillbirth,[6] which was modified according to the terminology of the Amsterdam consensus,[17] as is detailed in Table S2. Placental insufficiency is defined according to the Stockholm classification as (a) histopathological examination of the placenta showing at least 15% parenchymal loss or (b) SGA and postmortem examination suggesting asymmetric fetal growth or (c) small placenta <10th percentile or elevated fetoplacental weight ratio >90th percentile or (d) delayed villus maturation. Further details with grading into possible, probable, and definite causes are shown in Table S2. Reduced circulation in the umbilical cord is defined as (a) umbilical cord with stricture or large vessel thrombosis without other findings or (b) umbilical cord at risk (i.e. true knot, wrapped cord, stricture, deviant length, deviant coiling, or deviant insertion) and one of the following: histopathological examination of the umbilical cord showing signs of stasis or segmental cord discoloration or postmortem of the fetus showing signs of asphyxia or (c) ultrasound showing reduced blood flow; see Table S2. Cases that were challenging to evaluate were discussed with (KP) and (NP), both authors of the Stockholm classification.

2.1 | Statistical analysis

The perinatal mortality rate was calculated as stillbirths or early neonatal deaths with liveborn and stillborn infants as the denominator. The overall SBR was calculated as the number of stillbirths per 1000 infants. The number of stillbirths in each of the GA groups was calculated per 1000 infants at risk, which was the number of ongoing pregnancies at the beginning of each GA period. Numbers and proportions of maternal and fetal characteristics as well as causes of death were compared between two 13-year periods (1996–2008 and 2009–2021). This division into a former and a latter period was chosen due to a stable induction rate in the former period but a sharply increased rate from 2009.

In addition, causes of death according to the Stockholm classification were compared between three GA groups. Chi-squared tests

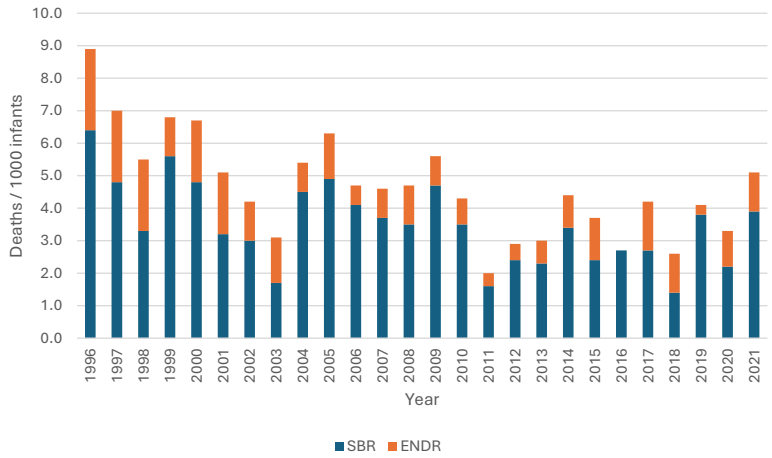

FIGURE 1 Perinatal mortality rate (PNMR): Stillbirth rate (SBR) and early neonatal death rate (ENDR), in Iceland from 1996 to 2021.

were applied, and a *p*-level of 0.05 was considered statistically significant. RStudio and Excel were used to analyze the data.

3 | RESULTS

Over the study period, 395 infants were stillborn to 385 mothers. These were 338 singleton pregnancies and 47 multiple pregnancies: 46 twin pregnancies, 10 where both infants died, and a triplet pregnancy where one infant was stillborn. Although the perinatal mortality rate, comprising of the early neonatal death rate and the SBR, fluctuated greatly, it decreased in general during the study period (Figure 1). Comparing earlier and latter 13-year periods, the total SBR decreased significantly from 4.10 stillbirths per 1000 births to 2.88 (RR = 0.72; 95% CI = 0.56 to 0.92) (Table 1). The SBR in each GA group, using the number of infants at risk as a denominator, was compared between the two time periods as shown in Table 1. It decreased for both early and late preterm stillbirths, from 1.50 to 0.98/1000 infants at risk (RR = 0.67, 95% CI = 0.41 to 1.06) before 28 weeks and 1.49–0.82 (RR = 0.56, 95% CI = 0.38 to 0.84) between 28 and 37 weeks. However, the SBR at term did not decrease: 1.20 versus 1.15/1000 infants at risk (RR = 0.98, 95% CI = 0.69 to 1.40).

Comparing characteristics of mothers who had a stillbirth between the two periods, a slightly larger proportion were nulliparous in the

TABLE 1 Comparison between time periods of stillbirth rate[a] (SBR) at different gestational age (GA) groups, calculated with infants at risk as the denominator.

	1996–2008		2009–2021			
GA groups	**SB/*n* at risk**	**SBR[a]**	**SB/*n* at risk**	**SBR[a]**	**RR (95% CI)**	***p*-Value**
Early preterm <28 weeks	84/55 853	1.50	56/57 241	0.98	0.67 (0.41 to 1,06)	0.09
Late preterm 28 to 36 + 6 weeks	83/55 601	1.49	47/57 028	0.82	0.56 (0.38 to 0.84)	0.004
Term ≥37 weeks	63/52 459	1.20	62/53 721	1.15	0.98 (0.69 to 1.40)	0.9
All stillbirths	230/55 853	4.10	165/57 241	2.88	0.72 (0.56 to 0.92)	0.009

[a]Per 1000 pregnancies at risk.

TABLE 2 Comparison of maternal and fetoplacental characteristics between time periods.

	1996–2008	**2009–2021**	
	***n* = 225**	***n* = 160**	
Mothers of SB infants (*n* = 385)	***n* (%)**	***n* (%)**	***p*-Value**
Advanced maternal age (≥35 years)	60 (26.7)	40 (25.0)	0.80
Obese (BMI >30)	51 (22.7)	34 (21.3)	0.94
Nullipara	96 (42.7)	82 (51.3)	0.12
Smoker	57 (25.3)	16 (10.0)	0.001
Non-Icelandic speaking	23 (10.2)	35 (21.9)	0.003
Hypertensive disease of pregnancy	25 (11.1)	21 (13.1)	0.66
Adverse outcome in previous pregnancy	22 (9.8)	17 (10.6)	0.92
Multiple pregnancy	30 (13.3)	17 (10.6)	0.55
	***n* = 230**	***n* = 165**	
SB infants, *n* = 395	***n* (%)**	***n* (%)**	***p*-Value**
Early preterm (gestational age [GA] <28 weeks)	84 (36.5)	56 (33.9)	0.67
Late preterm (GA 28 to 36 + 6 weeks)	83 (36.1)	47 (28.5)	0.14
Term (GA ≥37 weeks)	63 (27.4)	62 (37.6)	0.04
Birthweight <10th percentile for GA	99 (43.0)	77 (46.7)	0.56
Birthweight >90th percentile for GA	20 (8.7)	7 (4.2)	0.15
Placental weight <10th percentile for GA	49 (21.3)	50 (30.3)	0.002
Fetoplacental ratio >90th percentile for GA	36 (15.7)	40 (24.2)	0.005
Autopsy	185 (80.4)	132 (80.0)	1.0
Placental examination	222 (96.5)	159 (96.4)	1.0

Abbreviations: SB, stillborn.

latter period (42.7% vs. 53.1%), but no difference was found in obesity (BMI <35) or advanced age (>35 years), as shown in Table 2. However, fewer of the mothers smoked: 25.3% versus 10.0%, and more did not speak Icelandic: 10.2% versus 21.9% in the latter period. There was no difference in the proportion of mothers suffering stillbirth who were diagnosed with HDP or who had an adverse outcome in a previous pregnancy. A significantly larger proportion of all stillbirths were diagnosed at term in the latter period: 27.4% versus 37.6%. Although little difference was found between periods in the percentage of stillborn infants who were SGA, 43.0% versus 46.7%, more placentas were <10th percentile for GA (21.3% vs. 30.3%) in the latter period and FPR >90th percentile for GA was more common (15.7% vs. 24.2%). The autopsy rate was 80% and placental examination was performed in over 96% of stillbirths during the study period.

Table 3 shows the histological findings of the placentas that had been examined after stillbirth ($n=381$), which are classified into four major patterns of placental injury according to the Amsterdam consensus, with a comparison between time periods. More than one pattern of placental injury could be found in the same placenta. MVM was in found in 74 (19.4%) of the placentas examined during the study period, high-grade FVM was found in 75 placentas (19.7%), and low-grade FVM was found in an additional 35 (9.2%). High-grade chronic VUE was detected in of 52 placentas (13.6%); this was more often patchy than diffuse (36% vs. 16%). ACA was found in 121 of the 381 placentas examined, or 31.8%. However, 67 (17.6%) showed maternal inflammatory response only, 31 (8.1%) had grade 1, and 23 (6.0%) had a grade 2 or 3 fetal inflammatory response. Additionally, Maternal floor infarct (MFI) was diagnosed in 11 placentas (2.9%). Finally, the umbilical cord was found to be "at risk" in 205 of the stillbirths having placental examination or 53.8%. In the latter period, a larger proportion of placentas was diagnosed with FVM (17.2% vs. 45.3%) and high-grade VUE (8.5% vs. 20.8%) as well as umbilical cord at risk (45.0% vs. 66.0%). However, less increase was found in the proportion of placentas with MVM (17.6% vs. 22.0%), and none in MFI (3.1% vs. 2.5%).

TABLE 3 Comparison of histological findings in reviewed placentas between time periods.

	All $n=381$	1996–2008 $n=222$	2009–2021 $n=159$
Maternal vascular malperfusion[a]	74 (19.4)	39 (17.6)	35 (22.0)
Fetal vascular malperfusion, high grade	75 (19.7)	25 (11.3)	50 (31.4)
Fetal vascular malperfusion low grade	35 (9.2)	13 (5.9)	22 (13.8)
Villitis of unknown etiology,[b] diffuse	16 (4.2)	7 (3.1)	9 (5.7)
Villitis of unknown etiology,[b] patchy	36 (9.4)	12 (5.4)	24 (15.1)
Maternal floor infarct	11 (2.9)	7 (3.1)	4 (2.5)
Acute chorioamnionitis[c]	67 (17.6)	35 (15.8)	32 (20.1)
Acute chorioamnionitis[d]	31 (8.1)	13 (5.9)	18 (11.3)
Acute chorioamnionitis[e]	23 (6.0)	19 (8.6)	4 (2.5)
Umbilical cord at risk	205 (53.8)	100 (45.0)	105 (66.0)

[a]Not graded.
[b]High-grade.
[c]Maternal inflammatory response only.
[d]Stage 1 fetal inflammatory response with involvement of the umbilical vein.
[e]Stages 2–3 fetal inflammatory response with involvement of umbilical vein and one or more umbilical arteries (stage 2) or necrotizing funisitis (stage 3).

The primary cause of stillbirth according to the Stockholm classification and the four major patterns of placental injury detected in each group is shown in Table 4. It illustrates that many of the Stockholm groups are small, with very few cases where placental injury was found, as the cause of death was based on clinical findings.

The clinicopathological findings in stillbirths primarily attributed to placental insufficiency and reduced circulation in the umbilical cord are shown in Table 5. Of stillbirths primarily attributed to placental insufficiency, 70.8% were SGA infants, 59.4% low placental weight for GA, and 40.6% an elevated fetoplacental weight ratio. The most common placental injury found in this group was MVM or 44.8%, but high-grade VUE has been diagnosed in 33.3% and high-grade FVM in 25.0%. Over half of stillbirths attributed to placental insufficiency fulfilled criteria for umbilical cord at risk (56.2%), as did all stillbirths attributed to reduced circulation in the umbilical cord. Almost half (46.9%) of stillbirths primarily attributed to reduced cord circulation were diagnosed with FVM, 31.3% high grade, and 15.6% low grade, but MVM and high-grade VUE were rarely found in this group (7.3% each).

Table 6 illustrates the primary causes of stillbirth according to the Stockholm classification, with stratification into GA groups. Overall, the two commonest primary causes were reduced circulation in the umbilical cord (25.6%) and placental insufficiency (25.3%), with over half of all stillbirths being attributed to one or the other. The primary causes following in frequency were infection (11.9%) and placental abruption (9.9%) as well as unknown or unexplained (10.6%). Other primary causes of death were rare, each cause accounting for less than 4% of all stillbirths. Both placental insufficiency and reduced circulation in the cord were more often the primary causes of death in higher GA groups. Placental insufficiency was considered the primary cause of death in 20 early preterm stillbirths (14.3%), 38 late preterm (29.2%), and 42 term stillbirths (33.6%). Similarly, 18 early preterm stillbirths were primarily attributed to reduced circulation in the umbilical cord (12.9%), 35 of late preterm (26.9%), and 35 of stillbirths diagnosed at term (33.6%). In fact, almost ¾ of stillbirths at term (90/125, 72%) were attributed to either of these two causes. More than ¼ of stillbirths before 28 weeks were attributed to infection, which was rarely a primary cause of stillbirth at term. Placental abruption was also more common in stillbirths diagnosed before term, and the few stillbirths ($n=12$) due to twin-to-twin transfusion syndrome were all diagnosed before 28 gestational weeks. Few stillbirths were primarily attributed to preeclampsia, one at term, and 6 out of 9 cases were in the early preterm GA group.

TABLE 4 Patterns of placental injury and primary cause of death according to the Stockholm classification in stillbirths with placental examination, *n* = 381.

		Four major patterns of placental injury			
		MVM[a] *n* = 74	FVM[b] *n* = 75	VUE[b] *n* = 52	ACA[c] *n* = 54
Stockholm classification	***n***	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Malformation	13	0	4	3	0
Infection	47	2	1	0	38 (70.4)
Immunization	2	1	0	1	0
Fetomaternal transfusion	6	0	0	2	0
Twin-to-twin transfusion syndrome	12	0	1	0	1
Birth asphyxia	3	1	1	1	2
Placental insufficiency	96	43 (58.1)	24 (32.0)	31 (59.6)	7 (13.0)
Cord prolapse	5	1 (1.3)	0	0	1 (1.8)
Reduced circulation in umbilical cord	96	7 (9.5)	30 (40.0)	7 (13.5)	2 (3.7)
Placental abruption	38	6 (8.1)	3 (4.0)	2 (3.8)	1 (1.8)
Preeclampsia	9	8 (10.8)	1 (1.3)	0	0
Diabetes mellitus	5	2 (2.7)	1 (1.3)	0	0
Intrahepatic cholestasis of pregnancy	3	0	0	1 (1.9)	0
Uterine rupture	2	0	0	0	1 (1.8)
Other causes	7	0	0	0	0
Unexplained/unknown	40	3 (4.0)	9 (12.0)	4 (7.7)	1 (1.8)

Abbreviations: ACA, acute chorioamnionitis; FVM, fetal vascular malperfusion; MVM, maternal vascular malperfusion; VUE, chronic villitis of unknown etiology.

[a]Not graded.

[b]High grade.

[c]With fetal response.

TABLE 5 Clinicopathological characteristics of stillbirths primarily attributed to placental insufficiency and reduced circulation in umbilical cord.

	Placental insufficiency, *n* = 96	Reduced circulation in umbilical cord, *n* = 96
Birthweight <10th percentile for gestational age (GA)	68 (70.8)	28 (29.2)
Placental weight <10th percentile for GA	57 (59.4)	15 (15.6)
Fetoplacental ratio >90th percentile for GA	39 (40.6)	14 (14.6)
Maternal vascular malperfusion[a]	43 (44.8)	7 (7.3)
Fetal vascular malperfusion, high-grade	24 (25.0)	30 (31.3)
Fetal vascular malperfusion, low-grade	8 (8.3)	15 (15.6)
Villitis of unknown etiology,[b] diffuse	14 (14.6)	0
Villitis of unknown etiology,[b] patchy	17 (18.7)	7 (7.3)
Maternal floor infarct	7 (7.3)	0
Umbilical cord at risk	54 (56.2)	96 (100.0)

[a]Not graded.

[b]High grade.

In Table 7, the primary cause of stillbirth according to the Stockholm classification is compared between periods. It showed that a larger proportion of stillbirths was attributed to placental insufficiency (17.0% vs. 37.0%) in the latter period, whereas there was little change in the proportion of stillbirths attributed to reduced cord circulation (24.3% vs. 27.3%). However, unknown or unexplained stillbirths became less common (14.3% vs. 5.5%), and deaths due to most other causes, such as infection and placental abruption, decreased in the latter period. Although very rare, stillbirths attributed to acute intrapartum events such as asphyxia,

TABLE 6 Primary cause of death according to Stockholm classification by gestational age groups.

	All stillbirths	Early preterm <28 weeks	Late preterm 28–36 + 6 weeks	Term ≥37 weeks
	n = 395	*n* = 140	*n* = 130	*n* = 125
Number of stillbirths	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Stockholm classification				
Malformation	14 (3.5)	5 (3.6)	8 (6.2)	1 (0.8)
Infection	45 (11.4)	37 (26.4)	6 (4.6)	2 (1.6)
Immunization	2 (0.5)	0 (0)	2 (1.5)	0 (0)
Fetomaternal transfusion	6 (1.5)	0 (0)	3 (2.3)	3 (2.4)
Twin-to-twin transfusion syndrome	12 (3.0)	12 (8.6)	0 (0)	0 (0)
Birth asphyxia	3 (0.8)	0 (0)	0 (0)	3 (2.4)
Placental insufficiency	100 (25.3)	20 (14.3)	38 (29.2)	42 (33.6)
Cord prolapse	5 (1.3)	3 (2.1)	1 (0.8)	1 (0.8)
Reduced circulation in umbilical cord	101 (25.6)	18 (12.9)	35 (26.9)	48 (38.4)
Placental abruption	39 (9.9)	21 (15.0)	11 (8.5)	7 (5.6)
Preeclampsia	9 (2.3)	6 (4.3)	2 (1.5)	1 (0.8)
Diabetes mellitus	5 (1.3)	2 (1.4)	2 (1.5)	1 (0.8)
Intrahepatic cholestasis of pregnancy	3 (0.8)	0 (0)	1 (0.8)	2 (1.6)
Uterine rupture	2 (0.5)	0 (0)	0 (0)	2 (1.6)
Other causes	7 (1.8)	5 (3.6)	2 (1.5)	0 (0)
Unexplained/unknown	42 (10.6)	11 (7.9)	19 (14.6)	12 (9.6)

cord prolapse, and uterine rupture were even fewer in the latter period. This table also illustrates the number of stillbirths per 1000 liveborn and stillborn infants for each cause, showing the contribution of each group of the Stockholm classification to the total SBR for the earlier and latter period. Placental insufficiency and reduced flow in the umbilical cord were the main contributors to the SBR in both periods.

4 | DISCUSSION

The SBR in Iceland decreased significantly from 4.10 stillbirths per 1000 births to 2.88 ($p = 0.009$) between two 13-year periods due to a reduction in preterm stillbirths. This reduction appeared to be due to fewer deaths attributed to causes that were more common before term, such as infection and placental abruption.

Infection was considered a primary cause of stillbirth in cases where maternal or fetal sepsis, pneumonia, or severe chorioamnionitis with necrotizing funisitis was seen. In addition, stillbirths were attributed to infection if this started a chain of events causing preterm labor with the intrauterine death of a previable fetus. Thus, over ¼ of early preterm stillbirths were attributed to infection, making this the most common primary cause of stillbirth before 28 weeks of gestation. Although the reason is unclear, stillbirths attributed to infection were less common in the latter period, corresponding to a recent study showing a reduction of spontaneous preterm deliveries in Iceland.[22] Placental abruption was also a more common cause of death in stillbirths under 28 weeks than later in pregnancy, as caesarean section leading to fetal salvage was more likely to be performed in cases of placental abruption after 28 weeks. Placental abruption appeared to be a less common cause of death in the latter period, and a significant reduction in placental abruption has previously been described among live births in Iceland over a similar study period.[15] Although very rare, stillbirths attributed to acute intrapartum events such as asphyxia, cord prolapse, and uterine rupture were even fewer in the latter period.

Only 1/10 of the deaths over the study period were unexplained, which is in accordance with a recent study showing that a probable cause could be found for over 85% of stillbirths based on clinical review and placental histopathological examination.[23] Unexplained stillbirth was much less common in the latter half of the study period, probably reflecting advances in placental histopathology.

No reduction was found in the SBR at term over the study period. Stillbirth was more often attributed to umbilical cord complications with signs of reduced circulation with advancing GA, which is in accordance with other studies.[24,25] As pregnancy advanced, stillbirth was more often attributed to placental insufficiency, which is recognized as one of the major causes of stillbirth, especially with advancing GA.[9,26] A larger percentage of stillbirths was attributed to placental insufficiency in the latter period, when a

TABLE 7 Primary cause of death according to Stockholm classification by time periods.

	1996–2008 Stillbirths *n* = 230 *n* (% of SB)	2009–2021 Stillbirths *n* = 165 *n* (% of SB)	1996–2008 Total infants *n* = 55 853 *n*/1000 infants	2009–2021 Total infants *n* = 57 028 *n*/1000 infants
Stockholm classification			SBR 4.10	SBR 2.88
Malformation	5 (2.2)	9 (5.5)	0.09	0.16
Infection	32 (13.9)	13 (7.9)	0.57	0.23
Immunization	2 (0.9)	0 (0)	0.04	0
Fetomaternal transfusion	2 (0.9)	4 (2.4)	0.04	0.07
Twin-to-twin transfusion syndrome	9 (3.9)	3 (1.8)	0.16	0.05
Birth asphyxia	3 (1.3)	0 (0)	0.05	0
Placental insufficiency	39 (17.0)	61 (37.0)	0.70	1.07
Cord prolapse	4 (1.7)	1 (0.6)	0.07	0.02
Reduced circulation in umbilical cord	56 (24.3)	45 (27.3)	1.00	0.79
Placental abruption	25 (10.9)	14 (8.5)	0.45	0.25
Preeclampsia	6 (2.6)	3 (1.8)	0.11	0.05
Diabetes mellitus	4 (1.7)	1 (0.6)	0.07	0.02
Intrahepatic cholestasis of pregnancy	2 (0.9)	1 (0.6)	0.04	0.02
Uterine rupture	2 (0.9)	0 (0)	0.04	0
Other causes	6 (2.6)	1 (0.6)	0.11	0.02
Unexplained/unknown	33 (14.3)	9 (5.5)	0.59	0.16

larger proportion of stillborn infants were diagnosed at term. We have recently published a study of stillbirths at term in Iceland that showed that the cause of death was significantly more often attributed to placental insufficiency over time, as was placental weight <10th percentile.[27] This was unexpected, as guidelines had been implemented for antenatal risk assessment in Iceland in the latter period, with recommendation of low-dose acetylsalicylic acid, serial ultrasound scans, and early-term induction of labor for pregnancies considered high risk. In fact, the induction rate has more than doubled in Iceland since 2008.[12,13]

Preeclampsia was considered a cause of death in the Stockholm classification, whereas HDP is described in the results as a risk factor. Despite studies showing that advanced maternal age, obesity, and HDP have become more common in Iceland over the last decades,[12] no difference was seen in these characteristics, nor in adverse outcomes in a previous pregnancies, in mothers who had stillbirths between the two time periods. This may be due to increased antenatal surveillance of mothers with known risk factors, leading to interventions that can have reduced the risk of stillbirth. Finding little increase in the proportion of placentas with MVM or SGA infants can support this.

In this study, there was no difference over time in the proportion of stillborn infants that were SGA, although small placentas, either absolutely or relatively to birthweight, were more common in the latter period. SGA,[28] low placental weight,[29] and high FPR for GA[30] are all known to have a strong association with stillbirth. Although it is important to note that a SGA infants are not necessarily growth restricted,[31] it has also been demonstrated that stillbirth due to placental insufficiency can be independent of fetal growth restriction.[32] Detecting growth restriction may lead to elective delivery, especially at term, and thus prevent some stillbirths, whereas small placentas or high FPR are seldom detected antenatally. Estimating placental volume with three-dimensional ultrasound has been described[33] but has proven difficult to validate, and the correlation with magnetic resonance imaging is poor.[34] If imaging methods to estimate placental weight were improved, screening for small placentas or small in relation to the estimated fetal weight might be a better predictor for the risk of stillbirth at term due to placental insufficiency than screening for SGA.

The strength of this study is that all available histopathological slides were re-evaluated by the same experienced perinatal pathologist (TS), medical records were available for all mothers and their stillborn infants, and reviewed by the same senior obstetrician (RIB), and both collaborated closely in assigning the cause of death. This interdisciplinary collaboration was strengthened with case discussions with authors of the Stockholm classification of stillbirth (KP, NP), who also collaborated in revising the Stockholm classification according to the terminology of the more recent Amsterdam Consensus.[17]

The main limitation of this study is low numbers due to the small population of Iceland. Due to this, there are extremely few cases in the less common groups of the Stockholm classification of stillbirth, which consists of 17 primary and associated causes. Another limitation is that data from the Icelandic Medical Birth Registry is incomplete. There was no information about maternal smoking in general, but part of the reduction in stillbirths may be explained by reduced smoking in the population of Iceland,[35] especially fever deaths caused by placental abruption. Furthermore, data on maternal BMI was only available for the last years of the study period. As the relevant background information on the obstetrical population in Iceland over the study period was not available, correcting for maternal risk factors such as HDP, gestational diabetes, obesity, and smoking was not possible.

Another challenge was the long study period, covering more than a quarter of a century, although this may also be considered a strength. During this time, there were changes in diagnostic criteria for obstetrical diseases and their registration in the Icelandic Medical Birth Registry, as well as actual changes in the obstetrical population and practice, which can certainly influence the incidence and etiology of stillbirth. The 26-year study period was divided into a former (1996–2008) and latter period (2009–2021), which were compared throughout the study. Although changes in perinatal practice usually happen gradually, in Iceland, the induction rate doubled between these periods, and changes in guidelines for antenatal care tend to be implemented promptly due to centralized antenatal care in a very small society.

5 | CONCLUSION

The overall SBR in Iceland decreased over the study period due to a reduction in stillbirths that were diagnosed before term. In the latter half of the study period, fewer deaths were attributed to causes that were more common in preterm stillbirths, such as infection and placental abruption. While the results cannot fully explain this decrease, it could partially be due to a lower threshold for treatment and interventions leading to liveborn delivery, especially in very preterm pregnancies. Placental insufficiency and reduced flow in the umbilical cord were the main contributors to the SBR in Iceland, and over half of stillbirths were attributed to one or the other. The fact that a larger proportion of stillbirths was diagnosed at term in the latter period may explain that the cause of death was more often primarily attributed to placental insufficiency in this period. Further research into causes of stillbirth and placental histopathology is needed.

AUTHOR CONTRIBUTIONS

Ragnheidur I. Bjarnadottir: Conceptualization, methodology, investigation, data curation, resources, formal analysis, visualization, funding acquisition, project administration, writing—original draft. **Thora Steffensen**: Conceptualization, methodology, investigation, resources, writing—reviewing and editing. **Karin Pettersson**: Conceptualization, supervision, writing—reviewing and editing. **Nikos Papadogiannakis**: Conceptualization, writing—reviewing and editing. **Alexander K. Smarason**: Conceptualization, methodology, resources, visualization, writing—reviewing and editing. **Kristjana Einarsdottir**: Methodology, writing—reviewing and editing. **Johanna Gunnarsdottir**: Conceptualization, methodology, data curation, visualization, funding acquisition, project administration, supervision, writing—reviewing and editing.

ACKNOWLEDGMENTS

Many thanks to the staff at the Department of Pathology at Landspitali for finding histopathological slides.

FUNDING INFORMATION

RIB received a grant from the Icelandic Centre for Research for the project Stillbirth in Iceland 1996–2021: incidence, causes, and consequences. Ref. no.: 239642-051.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

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

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SUPPORTING INFORMATION

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

How to cite this article: Bjarnadottir RI, Steffensen T, Smarason AK, et al. Stillbirth in Iceland 1996–2021: Incidence and etiology. *Acta Obstet Gynecol Scand*. 2025;104:2155-2164. doi:10.1111/aogs.70058

Paper II

Stillbirth at term in Iceland: Causes of death and patterns of placental injury.
Ragnheidur I Bjarnadottir, Thora Steffensen, Karin Pettersson, Nikos Papadogiannakis, Alexander K Smarason, Johanna Gunnarsdottir. Published in *Placenta* 25th March 2025

Placenta 162 (2025) 14–19

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

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

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ARTICLE INFO

Keywords:
Stillbirth
Amsterdam placental workshop consensus
Maternal vascular malperfusion (MVM)
Fetal vascular malperfusion (FVM)
Acute chorioamnionitis (ACA)
Chronic villitis of unknown etiology (VUE)

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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https://doi.org/10.1016/j.placenta.2025.02.007
Received 9 September 2024; Received in revised form 23 January 2025; Accepted 11 February 2025
Available online 11 February 2025

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).

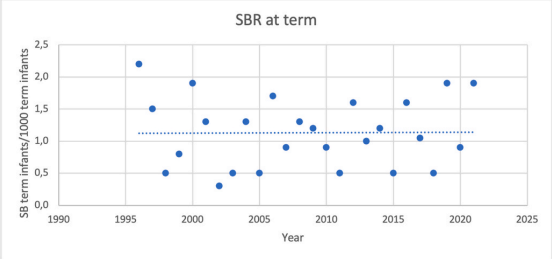

Fig. 1. Stillbirth rate at term in Iceland.

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

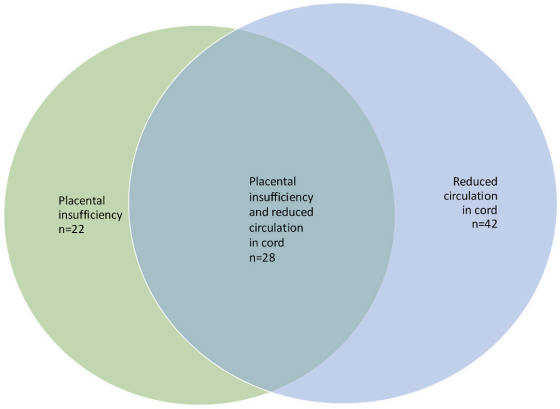

Fig. 2. The two main primary and associated causes of stillbirth at term in Iceland (n = 93).

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.

Financial support

RIB received a grant from the Icelandic Centre for Research for the project Stillbirth in Iceland 1996–2021: incidence, causes and consequences. Ref. nr: 239642-051.

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.

Acknowledgements

Thanks to the Pathology staff at Landspitali for finding histopathological slides.

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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Paper III

Clinicopathological phenotypes of singleton stillbirth: A retrospective cohort study. Ragnheidur I Bjarnadottir, Thora Steffensen, Alexander K Smarason, Karin Pettersson, Nikos Papadogiannakis, Johanna Gunnarsdottir. Published in *Acta Obstetricia et Gynaecologica Scandinavica (AOGS)* 26th June 2026

Received: 2 April 2026 | Revised: 25 May 2026 | Accepted: 8 June 2026

DOI: 10.1111/aogs.70294

ORIGINAL RESEARCH

Clinicopathological phenotypes of singleton stillbirth: A retrospective cohort study

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Funding information
Icelandic Centre for Research, Grant/Award Number: Ref. nr: 239642-051

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

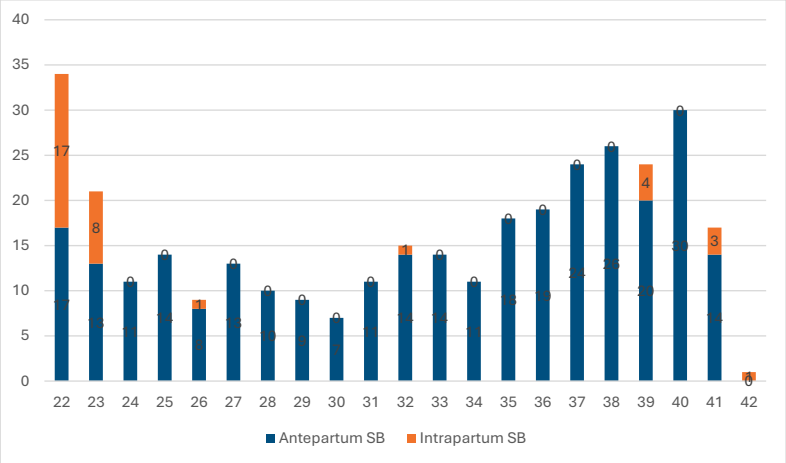

FIGURE 1 Number of stillbirths (SB) for each completed gestational week.

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 *n* = 326	<28 weeks *n* = 97	28 + 0–36 + 6 *n* = 109	≥37 weeks *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.

ACKNOWLEDGMENTS

Many thanks to the Pathology staff at Landspitali for finding the histopathological slides.

FUNDING INFORMATION

RIB received a grant from the Icelandic Centre for Research for the project Stillbirth in Iceland 1996–2021: incidence, causes, and consequences. Ref. nr: 239642-051.

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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SUPPORTING INFORMATION

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

How to cite this article: Bjarnadottir RI, Steffensen TS, Smarason AK, Pettersson K, Papadogiannakis N, Gunnarsdottir J. Clinicopathological phenotypes of singleton stillbirth: A retrospective cohort study. *Acta Obstet Gynecol Scand*. 2026;00:1-11. doi:10.1111/aogs.70294

Appendix A

Clinical information collected from hospital medical records

Variable	Definition	Value
Maternal age	Maternal age at delivery of SB	Years
Parity	Previous deliveries at >= 22 weeks	Number
Gestational age	Gestational age in days by ultrasound at SB dx	Days
No of infants	Single or multiple pregnancy, no of infants	Number
Birthweight	Birthweight of SB infant at delivery in grams	Grams
Gender	Gender of SB infant	(1) female, (2) male
Birthplace	Hospital where SB infant was born	Name
BMI	Weight at 1. antenatal visit, self-reported height	Kg/m^2
Smoking	Self-reported at 1. antenatal visit	(0) no, (1) yes
Medication	Name of medication taken during pregnancy	Name
Language	Speaks other native language than Icelandic	(0) no, (1) yes
Prior adverse	HDP, SGA or stillbirth in previous pregnancy	(0) no, (1) HDP, (2) SGA, (3) SB
Previous CS	CS in previous pregnancy	(0) no, (1) yes
Previous Ab	Previous history of miscarriage	(0) no, (1) yes <3, (2) yes ≥3, (3) yes >12 weeks
HDP	Hypertensive disorder of pregnancy	(0) no, (1) essential hypertension (2) gestational hypertension, 3) preeclampsia /eclampsia
DM	Diabetes mellitus in pregnancy	(0) no, (1) pre-gestational DM, (2) GDM

Cholestasis	Intrahepatic cholestasis in pregnancy	0=no, 1=bile acids≤70 mmol/L, 2= bile acids>70 mmol/L
Abruption	Clinical signs of placental abruption	0=no, 1= chronic, 2=partial, 3=total abruption
IPD	Intrapartum death	0=no, 1=yes
DFM	Decreased fetal movements (DFM)	0=no, 1=yes, did not seek help, 2=yes, sought help
Presented	How mother presented at diagnosis of SB	(1) Planned antenatal visit, (2) DFM, (3) Labour/ROM, (4) Induction of labour, (5) Other
Medical dx	ICD 10 non-obstetrical diagnoses	ICD codes
Obstetrical dx	ICD 10 obstetrical diagnoses	ICD codes
Fetal growth	Ultrasound estimation of fetal growth	(0) not done, (1) normal, (2) SGA, (3) LGA
Doppler flows	Ultrasound doppler flows	(0) not done, (1) normal, (2) abnormal
Infection	Signs of maternal infection	Description of clinical signs
Bacteria	Bacterial culture	Description of positive culture
Virus, TORCH	Serology	Description of serological findings
DIC	Disseminated intravascular coagulation	(0) no, (1) abnormal coagulation tests but not DIC, (2) clinical DIC
FMT	Fetomaternal transfusion	(0) <1% (1) 1-40% (2) > 40%
Isoimmunisation	Erythrocyte immunisation	(0) no immunization (1) antibodies, no clin signs (2) antibodies, clin signs
APS	Antiphospholipid syndrome	(0) No (1) Borderline values (2) APS confirmed
Karyotype	Karyotype of fetal or placental tissue	(0) Not done (1) Normal (2) Uncertain relevance, (3) Clin relevant abnormality (9) No growth
Microarray	Microarray of fetal or parental tissue	(0) Not done (1) Normal (2) Uncertain relevance, (3) Clin relevant abnormality
Autopsy	Autopsy of SB infant	(0) Not done (1) Performed
Weight of infant	Weight of SB infant at autopsy	Grams
Placental weight	Trimmed weight of placenta at autopsy	Grams
Malformation	Malformation diagnosed found at autopsy	Description

Asphyxia	Signs of asphyxia found at autopsy	Description
Infection	Signs of infection of placenta, cord or fetus found at autopsy	Description
Anaemia	Signs of fetal anaemia found at autopsy	Description
Placental pathology	Pattern of placental injury according to Amsterdam consensus	Description
Primary cause of death	Primary cause of death according to Stockholm classification	Groups 1-17
Probability	Probability of primary cause	Definite/ probable/possible
Associated cause	Associated cause of death according to Stockholm classification	Groups 1-17

Appendix B

Amsterdam consensus on placental injury

The histologic findings were classified into four major patterns of placental injury as described by Redline et al(Redline et al., 2021): maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), chronic villitis of unknown etiology (VUE) and acute chorioamnionitis (ACA). Advanced villous maturation is the histological "sine qua non" of MVM in preterm placentas. However, in term placentas this is represented histologically by alternating pattern of villous paucity and crowding, with foci of large dense syncytial knots, intervillous fibrin, and villous agglutination, often adjacent to stem villi.(Redline et al., 2021) Therefore, other findings were relied on for diagnosis of MVM in the term placentas, such as placental weight <10th percentile for gestational age with villous infarcts involving at least 20% of the placental parenchyma or a clinical history of abruption or fetal placental weight ratio >90th percentile for gestational age without villous damage other than infarcts. Decidual arteriopathy and superficial implantation site was also noted. MVM was not graded.

For fetal vascular malperfusion (FVM), umbilical cord "at risk "was identified in the gross description if any of the following features were found: excessive length (>70 cm), hyper-coiling (>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.(Redline & Ravishankar, 2018; Redline et al., 2021). FVM is defined by the presence of avascular villi or villous stromal/vascular karyorrhexis. Minimal criteria (Redline et al., 2021) are two or more intermediate to large foci of AV/VSK or three or more foci of small-intermediate sized AV/VSK. If only small foci are identified, either umbilical cord at risk (see below) or large fetal vessel lesions is also required. High grade FVM is defined as 2 or more large vessel thrombi (mural or occlusive) or total number of affected villi exceeding 15/slide or one focus over 45 villi.(Redline et al., 2021) The Amsterdam consensus conference defined small foci (2-4 terminal villi), intermediate foci (5-10 villi) and large foci (>10 villi).(Khong et al., 2016) Large fetal vessels include umbilical cord vessels, chorionic plate vessels, and stem villous vessels (*Pathology of the Placenta. A practical guide.* , 2018).

Staging of maternal and fetal inflammatory response in ascending intrauterine infection was as follows (Khong et al., 2016): Maternal inflammatory response stage 1: acute subchorionitis or chorionitis, stage 2: acute chorioamnionitis: polymorphonuclear leukocytes extend into fibrous chorion and/or amnion and stage 3: necrotizing

chorioamnionitis: karyorrhexis of polymorphonuclear leukocytes, amniocyte necrosis and/or amnion basement membrane hypereosinophilia. Fetal inflammatory response stage 1: chorionic vasculitis or umbilical phlebitis, stage 2: involvement of the umbilical vein and one or more umbilical arteries and stage 3: necrotizing funisitis.

Chronic villitis of unknown etiology (VUE) was applied to the histologic diagnosis of lymphohistiocytic villitis with absence of histologic findings of infection and after review of clinical records excluded congenital infection. High grade-patchy has multiple foci and at least one with >10 contiguous villi, whereas high grade-diffuse has >10 villi per focus and > 30% total villi affected.

Maternal floor infarct was diagnosed when there was fibrinoid material involving at least 3mm of parenchyma adjacent to the diagnosed maternal floor on a single slide (*Pathology of the Placenta. A practical guide.* , 2018).

Appendix C

*Stockholm classification modified according to the Amsterdam consensus (terminology changes in **bold**)*

Conditions related to stillbirth	Definite association	Probable association	Possible association
1. Malformation and chromosomal abnormalities		Chromosomal abnormality in the placenta, combined with significant placental pathology that may cause stillbirth	Chromosomal abnormality in the placenta that may cause stillbirth *or* clinically significant malformation that according to the literature may cause stillbirth
2. Infection 2.1 Bacterial	Signs of infection in the fetus (e.g. pneumonia) *or* positive culture of heart blood or amnion or maternal blood, combined with signs of infection on the placenta, i.e. subchorionitis /chorioamnionitis **or chorionic plate vasculitis/ umbilical phlebitis/ umbilical arteritis**	Clinical signs of chorioamnionitis in the mother, plus histopathological examination of the placenta showing subchorionitis/ chorioamnionitis **or chorionic plate vasculitis/ umbilical phlebitis/ umbilical arteritis** *or* positive culture from sites other than heart blood, amnion or maternal blood, plus histopathological examination of the placenta showing signs of subchorionitis/ chorioamnionitis **or chorionic plate vasculitis/ umbilical**	Subchorionitis/ chorioamnionitis **or chorionic plate vasculitis/ umbilical phlebitis/ umbilical arteritis** in the placenta, without positive cultures *or* clinical signs only of chorioamnionitis *or* positive culture of heart blood or amnion only (possible contamination taken into account)

		phlebitis/ umbilical arteritis *or* histopathological examination of the placenta showing signs of subchorionitis/ chorioamnionitis **or chorionic plate vasculitis/ umbilical phlebitis/ umbilical arteritis**	
2.2 Virus	Positive PCR (for selected virus) in the placenta or fetal tissue, plus signs of viral infection in the fetus *or* histopathological examination of the placenta showing signs of viral infection (e.g. viral inclusions or villitis)	Signs of viral infection in the fetus or in the placenta without positive PCR (for selected virus) *or* positive PCR (for selected virus) in fetal tissues	Positive PCR (for selected virus) in the placenta only
2.3 Other	Parasites (e.g. malaria, toxoplasma), fungi, etc. where a probability assessment is carried out individually		
3. Immunization 3.1 Erythrocyte immunization	Signs of severe immunization in the mother, plus signs of anaemia in the fetus		
3.2 Thrombocyte immunization	Postmortem of the fetus showing massive hemorrhage, plus positive findings of thrombocyte antibodies in the parents making immunization	Postmortem of the fetus showing hemorrhages, plus positive findings of thrombocyte antibodies making	

	possible	immunization possible, in the parents	
4. Feto-maternal transfusion	Findings suggesting massive feto-maternal transfusion, exceeding 40% of the fetal blood volume *or* findings suggesting feto-maternal transfusion, with a fetal Hb>1% and signs of anaemia in the fetus (e.g. pallor or a sinusoidal cardiotocograph (CTG))	Positive fetal Hb (>1%) but corresponding to less than 40% of the fetal blood volume, plus findings in the placenta (e.g. increased erythropoiesis or oedema)	Positive fetal Hb (>1%) but corresponding to less than 40% of the fetal blood volume
5. Twin-to-twin transfusion syndrome	Monochorionic twin with ultrasound or clinical signs compatible with transfusion syndrome, plus histopathological examination of the placenta showing anastomosis with possibility for transfusion syndrome	Monochorionic twin with ultrasound or clinical signs of transfusion syndrome, where perfusion study of the placenta has not been performed	
6. Birth **asphyxia**	Shoulder dystocia, malpresentation or other severe birth trauma *or* biochemical or electronic fetal monitoring suggesting fetal **asphyxia/hypoxia**		
7. Placental insufficiency	Histopathological examination of the placenta showing >30% parenchymal loss, such as infarction or villitis *or* **involvement of >30% of the intervillous space by MPFD or CHI** *or*	SGA plus histopathological examination of the placenta suggesting placental insufficiency (see definite)	Histopathological examination of the placenta suggesting placental insufficiency (see definite) with a normal weight baby *or* **SGA and postmortem examination suggests**

	SGA and postmortem examination suggesting asymmetric fetal growth, plus histopathological examination of the **placenta showing 15-30%** parenchymal loss**/ intervillous space involvement** or al placenta <10th percentile or **delayed villus maturation**		**asymmetric fetal growth with**out placenta pathology *or* **elevated fetoplacental weight ratio >90th percentile**
8. Umbilical cord complication 8.1 Umbilical cord prolapse	Clinical signs of umbilical cord prolapse		
8.2 Rupture of a vessel in the umbilical cord or membranes	Ruptured vessel in the membranes *or* the umbilical cord plus signs of fetal **anaemia**, such as pallor or sinusoidal CTG		
8.3 Reduced circulation in the umbilical cord Umbilical cord at risk: True knot Wrapped cord Stricture Deviant length Deviant coiling Deviant insertion	**Umbilical cord at risk plus 2/4 signs:** Histopathological examination of the umbilical cord showing signs of stasis at the site of a knot *or* segmental cord discoloration *or* postmortem of the fetus showing signs of **asphyxia** *or* findings of thrombosis in umbilical cord or chorionic plate **or stem villous vessels** (**i.e. large vessel thrombosis**) *or* ultrasound showing decreased blood flow	Umbilical cord at risk plus 1/4 signs (see definite)	**Umbilical cord with stricture without other findings** *or* **large vessel thrombosis without other findings**

9. Placental abruption	Clinical signs of a large abruption	Histopathological examination of the placenta showing extensive signs of abruption (>30%) *or* clinical signs suggesting placental abruption	Histopathological examination of the placenta showing signs of abruption
10. Preeclampsia	Eclampsia *or* preeclampsia and placental abruption *or* preeclampsia and IUGR		
11. Diabetes mellitus	Previously known (or clinically diagnosed at birth) type 1 diabetes and signs of intrauterine or intrapartum asphyxia *or* previously known (or clinically diagnosed at birth) type 1 diabetes and LGA or SGA *or* previously known (or clinically diagnosed at birth) type 1 diabetes and severe malformation	Type 2 diabetes or gestational diabetes and signs of intrauterine or intrapartum asphyxia *or* Type 2 diabetes or gestational diabetes and LGA *or* Type 2 diabetes or gestational diabetes plus histopathological placenta findings suggesting diabetes *or* Type 1 diabetes with no other findings	Type 2 diabetes or gestational diabetes with no other findings
12. Intrahepatic cholestasis of pregnancy	Raised bile acid levels (> 70 mmol/L), plus history of typical pruritus		Raised bile acid levels (40- 70 mmol/L), plus history of pruritus
13. Uterine complications	Clinical signs of obstructed circulation due to uterine rupture or torsion		
14. Coagulation disorders	Antiphospholipid syndrome diagnosed in the mother, plus histopathological examination of the	Histopathological examination of the placenta showing infarction (15-30%) or thrombosis in	Diagnosed thrombophilia other than antiphospholipid syndrome plus histopathological

	placenta showing >30% infarction or thrombosis in fetal placental vessels *or* antiphospholipid syndrome diagnosed in the mother and postmortem of the fetus showing thrombosis	fetal placental vessels plus raised levels of cardiolipin antibodies *or* diagnosed antiphospholipid syndrome *or* histopathological examination of the placenta showing >30% infarction, plus antithrombin deficiency or homozygous factor V mutation	examination of the placenta showing >15% infarction or thrombosis in fetal placental vessels *or* medium raised levels of cardiolipin antibodies
15. Other causes related to stillbirth * Trauma *Asystole in the mother *Malignancy in fetus or placenta *AV block with SS-A and SS-B antibodies in the mother *Storage disease in the placenta, e.g. glycogenosis *Tumor in the placenta *Premature labour in extreme prematurity			
16. Unknown Obvious findings, e.g. hydrops, asphyxia and oligohydramnios, but no definite association to stillbirth			
17. Unexplained No positive findings in the investigation			

MPFD – massive perivillous fibrin deposition
CHI – chronic histiocytic intervillositis