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# Classification of stillbirths and risk factors by cause of death – a case-control study

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**Key words**
Classification, fetal death, risk factor, stillbirth, thrombophilia

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**Conflict of interest**
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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## Abstract

*Objective.* To investigate risk factors for stillbirths by cause, using the Causes of Death and Associated Conditions (CODAC) classification system for perinatal deaths. *Design.* Case-control study. *Setting.* Two university hospitals in Oslo, Norway, January 1990 through December 2003. *Sample.* Women with stillbirth after 22 gestational weeks (n = 377) and controls with live births (n = 1 215), and a subsample of 105 cases and 262 controls. *Methods.* Socio-demographic, clinical and thrombophilic risk factors for stillbirths were assessed by cause of death in univariate and multivariable logistic regression analyses. Stillbirths were classified according to CODAC based on information from medical records and validated placenta histology. *Main outcome measures.* Causes of stillbirths in percentages, prevalence, odds ratios and adjusted odds ratios for potential risk factors. *Results.* Approximately half of the women (n = 190) had placental and 19.4% (n = 73) unknown cause of stillbirth. Placental-associated conditions were registered in 18% (n = 68) of cases with a non-placental or an unknown cause. Smoking and small-for-gestational age were more prevalent in all causal groups, compared with controls, whereas twin pregnancy, hypertension and diabetes were more prevalent only among women with placental and unknown causes of stillbirth. The *F2rs179963* polymorphism and combined thrombophilia were significant risk factors for stillbirth with placental causes and antiphospholipid antibodies for stillbirth with non-placental causes. *Conclusions.* Two-thirds of all stillbirths (68%) were caused by or associated with placental pathology. Risk factors differed somewhat according to cause, apart from smoking and small-for-gestational age, which were significant risk factors across the causal groups.

**Abbreviations:** AC, associated conditions; aOR, adjusted odds ratio; CI, confidence interval; COD, cause of death; CODAC, Causes of Death and Associated Conditions classification for stillbirths and perinatal deaths; *F5 rs6025*, Factor V Leiden polymorphism; *F2 rs179963*, prothrombin G20210A polymorphism; IUFD, intrauterine fetal death; OR, odds ratio; SGA, small-for-gestational age; VIP, Venous Thromboembolism in Pregnancy study.

## Introduction

Frequently described risk factors for intrauterine fetal death (IUFD) are pre-pregnancy obesity, socio-economic factors, race, advanced maternal age and smoking. Other risk factors reported are advanced gestational age, multiple pregnancy and maternal diseases (1,2). In addition, both inherited and acquired thrombophilia have been reported to be associated with fetal death (3). Risk factors for unex-

## Key Message

Two-thirds of all stillbirths (68%) were caused by or associated with placental pathology according to the CODAC classification for stillbirths and perinatal deaths. Smoking and small-for-gestational age were significant risk factors across all causal groups. Other risk factors differed by cause.

plained stillbirths are frequently studied but data on risk factors according to specific causes of stillbirths are limited.

Classification of stillbirths is needed for the purpose of prevention, counseling and comparison of health care. Assigning a single cause of stillbirth can be challenging because of interaction between pathophysiological processes in the mother, placenta and fetus. Classification systems have been developed for the purpose of classifying stillbirths by cause. Ideally, classification systems for stillbirths should be able to capture both the direct cause of death (COD) and other clinical entities, as this can be important for deeper insight into the etiology. Suboptimal classification systems may lead to loss of information and a higher proportion of unexplained deaths. No single system is universally accepted, and this impedes comparison of stillbirth data. The recently developed CODAC (Causes of Death and Associated Conditions) classification system for perinatal death is designed to retain information on the main COD as well as up to two associated conditions (AC) (4). Placental histology can support or contradict suggested diagnoses, or provide new clues.

Our hypothesis was that risk factors vary according to COD, thus the aims of the study were to investigate risk factors for stillbirths by cause, using the CODAC classification system for perinatal deaths.

## Material and methods

The present study was a part of a larger hospital-based case-control study; the Venous Thromboembolism in Pregnancy study (VIP), and was registered as a clinical observational study at www.clinicaltrials.gov, with registration number NCT00856076 (5). Data on epidemiological, clinical (6) and biochemical risk factors for stillbirth (7,8) have already been published.

All women with a diagnosis of stillbirth, from 1 January 1990 through 31 December 2003, at Oslo University Hospital Ullevål, Oslo, and Akershus University Hospital, Nordbyhagen, both in Norway, were identified retrospectively by a search for selected codes of the WHO International Classification of Diseases (ICD) versions 9 or 10, using the patient administrative system of the respective hospitals. We identified 434 possible cases of stillbirth, defined as IUFD in singleton or duplex pregnancies after 22 completed gestational weeks or birthweight $\geq$ 500 g. After reviewing the medical records, we excluded 49 cases wrongly diagnosed and eight with non-retrievable records, leaving 377 women with a verified diagnosis of stillbirth. The expected date of delivery was estimated by routine ultrasound examination at 16–18 gestational weeks for 73% of the women. In the absence of ultrasound data, gestational age was determined by the first day of the last menstrual period. The time of fetal death was determined by the gestational age at diagnosis.

For both arms of the VIP study, 1229 controls were selected among women delivering at Oslo University Hospital Ullevål in the study period. For each case of venous thrombosis in pregnancy or the postpartum period, four women, giving birth at the same time, were selected from the Medical Birth Registry of Norway as possible controls. The two women first listed served as controls, but if one or both of their medical records were not retrievable, the third and/or fourth women were selected as control(s). After exclusion of five women under the age of 16 or over 44 years (none of the cases was in these age groups) and nine women with a stillbirth, the control group comprised 1215 women with live singleton or duplex births at Oslo University Hospital Ullevål in the study period.

The cases and controls were identified at the participating hospitals, and medical records were retrieved and reviewed for validation of the diagnosis of stillbirth and other relevant information. Individual data were transferred to a case report form which contained data on demographics, general health, obstetrical history, details of the index pregnancy and delivery, postmortem examination of the infant, and laboratory data including histological examination of the placenta. The case report forms were scanned, consistency analysis run and invalid data entries corrected after a second review of relevant medical records. Risk factors assessed were maternal age, parity, marital status, assisted reproductive therapy, smoking habits, twin pregnancy, thyroid disease, preexisting diabetes mellitus, gestational diabetes, hypertensive disorders, small-for-gestational age (SGA), placental abruption and placenta previa. Validated population-based growth charts (9) were used to determine whether the fetus was SGA, which was defined as birthweight below the 2.5$^{th}$ percentile for gestational age.

In 2006–2008 the cases and controls were invited to participate in the second part of the study to answer a questionnaire and to donate a blood sample. Women who had emigrated, were foreign citizens, dead or had an invalid or unknown address, were excluded. A letter of invitation was sent to 346 women with a history of IUFD. After two reminders, 105 women agreed to participate (Figure 1). The controls were approached by two invitations. In 2006, 353 of 1092 invited controls (10) agreed to participate and donate a blood sample. In this subset, 326 of 353 responders were invited in 2008 to answer an IUFD-related questionnaire by postal mail. After two reminders, the questionnaire was returned by 262 women (Figure 1).

Lupus anticoagulant was analyzed with two validated in-house lupus ratio tests (11), based on activated partial thromboplastin time and Russell's viper venom time. Anticardiolipin IgM and IgG antibodies were analyzed

with in-house enzyme-linked immunosorbent assay (ELISA) tests and anti-$\beta_2$ glycoprotein 1 IgG and IgM antibodies with commercial ELISA kits (QUANTALite $\beta_2$GP1, INOVA Diagnostics Inc., San Diego, CA, USA). The cut-off values for a positive test were defined by the 99$^{th}$ percentile of the values of the control group. Antithrombin and protein C activities and free protein S were determined using commercial kits Coamatic® Antithrombin, Coamatic® Protein C and HemosIL Free Protein S reagent kits, respectively (Instrumentation Laboratory Inc., Bedford, MA, USA). Women with antithrombin activity <80%, protein C activity <70% and protein S two standard deviations below the mean of the controls were defined as deficient. The polymorphisms *F5 rs6025* (factor V Leiden) and *F2 rs179963* (prothrombin gene G20210A) were detected with commercial detection kits (Roche Diagnostics, Basel, Switzerland). Two women reported use of warfarin medication at the time of blood sampling and were therefore excluded from analyses of inherited thrombophilia.

The results of the original histological examinations of the placentas were reviewed. The placentas had been evaluated by general pathologists but no standardized protocols for macro- and microscopic evaluation or sampling of placental tissue were in use in the study period. In most cases, sections had been sampled from the umbilical cord, the membranes and a minimum of two sections from placental tissue from areas with and without focal parenchymal pathology. The tissue sections had routinely been fixed in formalin, processed and embedded in paraffin blocks, and 3.5μm sections stained with hematoxylin-eosin.

For the purpose of a more accurate classification of causality, the original placenta specimens were retrieved and reassessed, when available. Placental tissue from 268 stillbirths was reassessed by two experienced pathologists (G.T. and B.R.) with a special interest in placental pathology, blinded to the clinical details of the stillbirth. Placentas with microscopic signs of acute or chronic villitis and/or intervillositis were immunostained with a standard panel of antibodies to T-cell- and histiocytic markers. When the placenta specimens were not available for reassessment, the original histological descriptions (n = 99) were used. Histological descriptions of the placenta were available for 367/377 (97.3%) of the women. In addition to the placental histology, other relevant information

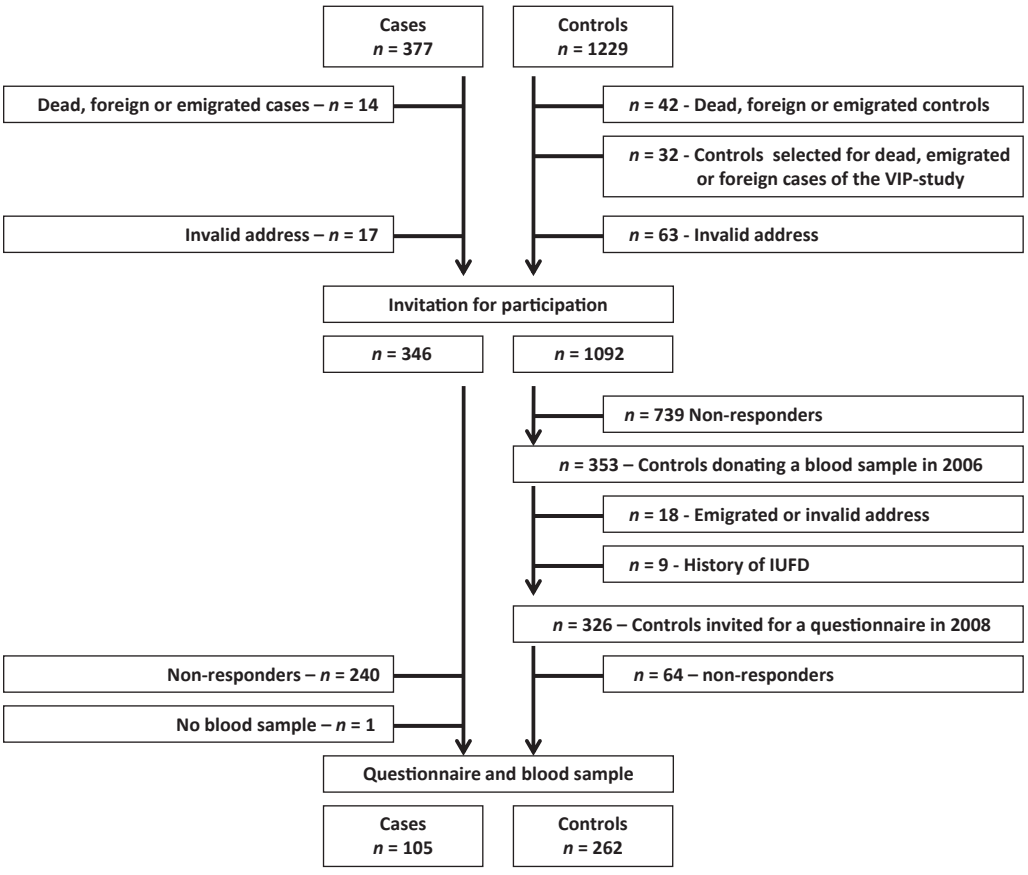


**Figure 1.** Selection of the study population. IUFD, intrauterine fetal death; VIP, Venous Thromboembolism in Pregnancy.

from the medical records was used to classify the stillbirths according to cause, including information on maternal factors, laboratory reports and the autopsy reports (available among 70% of the cases).

CODAC is a classification system for perinatal deaths, recently developed by an international collaborative group of investigators (4). To classify the case in CODAC, only minimum of information is mandatory but more detailed information usually generates a more accurate classification. The main focus is the COD, with the possibility of coding for two additional "associated conditions" (ACs) to obtain more detailed information. For each case, CODAC thus allows up to three codes with three digits each (xxx xxx xxx), although only one code (xxx) is necessary. The first (or single) code represents the main COD. The second code can represent a secondary COD (if the first condition is not thought to be sufficient to fulfill the criteria of a solitary COD) or an AC, and the third code represents an AC. The first digit in each code represents "Level I" or the main categories of the COD or the AC (Supporting Information Tables S1 and S2). The second and third digits, in each code, represent Levels II and III, each level representing more detailed information. Each Level I category comprises several Level II categories which, in turn, comprise several Level III categories. Ten coding rules have been defined for CODAC (4). To be a COD the condition should be expected to be mortal in a significant proportion of cases (at least 5%) and to be an AC the condition should contribute significantly in explaining the circumstances of death. The system includes 10 main groups (Level I), 94 sub-groups (Level II) and 577 sub-sub-groups (Level III). Two of the main groups were not relevant for coding in this study (group 9: termination and group 1: neonatal death). The group of unknown cause (group 8) has subgroups according to how much information is available on the case. When all available information on each case had been reviewed it was assigned the most appropriate code(s) according to the CODAC classification system by one of the authors (L.B.H.).

For detection of potential variations in risk factors according to cause, risk factors were analyzed by comparing prevalences in different main causal groups with prevalences in the control group. The eight original causal groups of the CODAC system were combined into three study groups: placental causes (n = 190), unknown causes (n = 73) and "other causes" (the remaining six causal groups: infections, intrapartum deaths, congenital anomalies, fetal, cord and maternal causes) (n = 114). In the multivariable analysis the "other" and unknown causes were combined into one group named non-placental causes (n = 187). Risk factors were analyzed by chi-squared tests or Fisher's exact tests and multivariable logistic regression analysis. The relevant variables were analyzed in three models: one including all variables, one excluding smoking and the third excluding SGA. Missing values for socio-demographic and clinical variables were denoted the reference group. Variables included in the multivariable models were chosen based on the significance of each variable in the univariate analyses ($p$-value <0.15). The results are presented as percentages, odds ratios (OR) and adjusted (aOR) with 95% confidence intervals (CI). Significance level was set at $p < 0.05$. Interactions between significant factors were tested at a 95% significance level ($p < 0.05$). All data was analyzed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

The Regional Committee for Medical Research Ethics, Region East, Norway, approved the study (Project #163-04014). Authorization for the use of information from medical records for research purposes was obtained from the Norwegian Ministry of Health and Social Affairs. The Norwegian Data Inspectorate approved the use of data containing sensitive personal health information, and the merging of clinical and register-data by using the unique 11-digit personal identification number given to all Norwegian citizens at birth or immigration. All participants that donated a blood sample signed a written informed consent form.

## Results

The main COD (Level I) according to the CODAC classification system is displayed in Table 1. Placental causes were the most frequent COD, accounting for 50.4% of all stillbirths, whereas unknown COD was second in line with 19.4% of the cases. Subclassification (Level II) revealed that two-thirds (67.4%) of the placental causes were due to placental abruption/retroplacental hematoma or infarctions/thrombi. These two entities were responsible for 34% of all stillbirths and placental abruption/retroplacental hematoma alone was the cause of 16% of all stillbirths (Supporting Information Table S3).

An AC was coded for 273/377 (72%) of all cases. Among the cases classified as having an unknown COD, 59/73 (81%) had ACs: 26 (36%) a placental condition, 10 (14%) a cord condition, 10 (14%) a perinatal condition, five (7%) a maternal condition and five (7%) an associated maternal condition. A placental AC was assigned to 68/187 (36%) of cases with a non-placental COD or 18% of all cases. Thus 258/377 (68%) of all cases had either a placental COD or a placental AC.

Prevalences of demographic and clinical characteristics among women with stillbirths and the controls are displayed in Table 2. Smoking and SGA were more prevalent in all causal groups compared to the controls while other

**Table 1.** Causes of Death and Associated Conditions classification (CODAC): Causes of stillbirth (COD) – level I.

| CODAC COD – level I | Cases (n = 377) % | n |
|---|---|---|
| 0 – Infection | 12.2 | 46 |
| 2 – Intrapartum | 0.5 | 2 |
| 3 – Congenital anomaly | 6.1 | 23 |
| 4 – Fetal | 2.1 | 8 |
| 5 – Cord | 8.0 | 30 |
| 6 – Placenta | 50.4 | 190 |
| 7 – Maternal | 1.3 | 5 |
| 8 – Unknown | 19.4 | 73 |

risk factors differed by causal group. The aORs of the risk factor analyses are presented in Table 3.

The 105 women who donated blood-samples for the biomarker study were distributed equally among the main COD groups as the whole study population; 48% had placental causes and 20% an unknown cause. The prevalences of thrombophilia in different groups of COD and the ORs for the association of thrombophilia and stillbirth are displayed in Table 4. The *F2 rs179963* prothrombin gene polymorphism was more prevalent among women with placental COD compared with the controls (OR 5.7; 95% CI: 1.4–23.8), while being positive for any one of the antiphospholipid antibodies was associated with a history of stillbirth from non-placental causes (OR 2.8; 95% CI: 1.1–7.4).

## Discussion

In an unselected population of women, we found that approximately two-thirds of all stillbirths were caused by or associated with placental conditions (68.4%). This is in line with the findings of two recently published studies (1,12). Korteweg et al. (12) reported 64.9% of deaths to be caused by placental pathology and stated that classifications without or with minimal subdivision of a placental group were not useful in modern perinatal audit. The

**Table 2.** Prevalence of demographic and clinical characteristics among women with intrauterine fetal death by main Cause of Death (COD) of the Causes of Death and Associated Conditions classification (CODAC) and controls.

| | All (n = 377) | | COD Placenta (n = 190) | | COD Unknown (n = 73) | | COD Other (n = 114)[a] | | COD Non-placental (n = 187)[b] | | Controls (n = 1215) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | % | *p* | % | *p* | % | *p* | % | *p* | % | *p* | % |
| Age (years) | | | | | | | | | | | |
| <30 | 44.6 | 1.0 | 42.6 | 0.5 | 49.3 | 0.6 | 44.7 | 0.6 | 46.5 | 0.5 | 43.6 |
| 30–34 | 32.9 | Ref | 35.3 | Ref | 31.5 | Ref | 29.8 | Ref | 30.5 | Ref | 32.4 |
| ≥35 | 22.5 | 0.6 | 22.1 | 0.4 | 19.2 | 0.6 | 25.4 | 0.6 | 23.0 | 0.9 | 24.0 |
| Parity | | | | | | | | | | | |
| 0 | 51.5 | 0.3 | 53.2 | 0.2 | 49.3 | 0.9 | 50.0 | 0.8 | 49.7 | 0.7 | 48.5 |
| ≥1 | 48.5 | Ref | 46.8 | Ref | 50.7 | Ref | 50.0 | Ref | 50.3 | Ref | 51.5 |
| Civil status | | | | | | | | | | | |
| Married/cohabiting | 86.2 | Ref | 85.8 | Ref | 95.9 | Ref | 80.7 | Ref | 86.6 | Ref | 92.0 |
| Not married/cohabiting | 13.8 | **0.001** | 14.2 | **0.005** | 4.1 | 0.4 | 19.3 | **<0.0001** | 13.4 | **0.02** | 8.0 |
| Assisted reproduction | 1.9 | 0.9 | 2.6 | 0.4 | 2.7 | 0.4 | 0 | - | 1.1 | 0.8 | 1.7 |
| Twin pregnancy | 5.8 | **<0.0001** | 7.4 | **<0.0001** | 6.8 | **0.008** | 2.6 | 0.7 | 4.3 | 0.06 | 2.1 |
| Hypertensive disorders | 15.7 | | 18.4 | | 17.8 | | 9.7 | | 12.8 | | 9.2 |
| Pre-eclampsia | 7.2 | **0.047** | 9.5 | **0.006** | 5.5 | 0.7 | 4.4 | 0.7 | 4.8 | 0.9 | 4.8 |
| Hypertension | 8.5 | **0.002** | 8.9 | 0.005 | 12.3 | **0.004** | 5.3 | 0.9 | 8.0 | **0.04** | 4.4 |
| Diabetes | 3.4 | **0.01** | 2.1 | 0.5 | 8.2 | **<0.0001** | 2.6 | 0.2 | 4.8 | **0.001** | 1.4 |
| Diabetes type 1 or 2 | 1.9 | **0.009** | 1.1 | 0.3 | 4.1 | **0.001** | 1.8 | 0.08 | 2.7 | **0.003** | 0.4 |
| Gestational diabetes | 1.6 | 0.3 | 1.1 | 0.9 | 4.1 | **0.02** | 0.9 | 0.9 | 2.1 | 0.2 | 1.0 |
| Placental abruption | 11.7 | **<0.0001** | 22.6 | **<0.0001** | 0 | - | 0.9 | 1.0 | 0.5 | 1.0 | 0.8 |
| Placenta previa | 1.3 | 0.2 | 2.1 | 0.07 | 0 | - | 0.9 | 0.6 | 0.5 | 1.0 | 0.7 |
| Smoking (at first visit) | 35.8 | **<0.0001** | 37.9 | **<0.0001** | 32.9 | **<0.0001** | 34.2 | **<0.0001** | 33.7 | **<0.0001** | 13.4 |
| Small-for-gestational-age | 35.8 | **<0.0001** | 41.1 | **<0.0001** | 23.3 | **<0.0001** | 35.1 | **<0.0001** | 30.5 | **<0.0001** | 1.8 |
| Thyroid disease | 4.2 | **<0.0001** | 4.7 | **<0.0001** | 2.7 | 0.2 | 4.4 | **0.02** | 3.7 | **0.004** | 1.1 |

[a]Other = infections, intrapartum deaths, congenital anomalies, fetal, cord and maternal causes.

[b]Non-placental = unknown and other causes combined in one group.

*p*-values represent results of comparison between cases and controls in univariate analyses.

Bold figures are statistically significant. Ref = reference group.

**Table 3.** Risk factors for stillbirths by cause of death (COD) compared with controls. Adjusted odds ratios (aOR) with 95% confidence intervals (CI). Columns 1 and 4: adjusted for all the variables in the table and age. Columns 2 and 5: adjusted for the same variables except "smoking". Columns 3 and 6: adjusted for the same variables except "small-for-gestational-age".

| | COD | | | | | |
|---|---|---|---|---|---|---|
| Variable | Placenta (n = 190) aOR 95% CI | Placenta (n = 190) aOR 95% CI | Placenta (n = 190) aOR 95% CI | Non-placental (n = 187)[a] aOR 95% CI | Non-placental (n = 187)[a] aOR 95% CI | Non-placental (n = 187)[a] aOR 95% CI |
| Age (years) | | | | | | |
| <30 | 0.8 | 0.8 | 0.8 | 1.0 | 1.1 | 1.0 |
| | 0.5–1.3 | 0.5–1.4 | 0.5–1.1 | 0.7–1.5 | 0.7–1.6 | 0.7–1.4 |
| 30–34 | Ref | Ref | Ref | Ref | Ref | Ref |
| ≥ 35 | 1.1 | 1.2 | 0.9 | 0.9 | 0.9 | 0.9 |
| | 0.6–1.8 | 0.7–2.0 | 0.6–1.5 | 0.5–1.5 | 0.6–1.5 | 0.6–1.4 |
| Civil status | | | | | | |
| Not married/cohabiting | 1.4 | 1.7 | 1.4 | 1.2 | 1.7 | 1.3 |
| | 0.7–2.6 | 0.9–3.1 | 0.8–2.4 | 0.7–.2.2 | 1.0–2.9 | 0.8–2.2 |
| Twin pregnancy | 3.7 | 3.6 | 5.1 | 2.9 | 2.6 | 2.7 |
| | 1.4–9.9 | 1.4–9.2 | 2.5–10.6 | 1.1–7.6 | 1.1–6.5 | 1.2–6.4 |
| Preeclampsia/eclampsia | 0.5 | 0.4 | 1.8 | **0.3** | **0.3** | 1.0 |
| | 0.2–1.1 | 0.2–1.0 | 0.9–3.5 | **0.1–0.9** | **0.1–0.8** | 0.5–2.1 |
| Hypertension | 2.3 | 2.1 | 2.7 | 1.9 | 1.8 | 1.8 |
| | 1.0–4.9 | 1.0–4.6 | 1.4–5.0 | 0.9–3.7 | 0.9–3.5 | 0.9–3.3 |
| Diabetes | 3.2 | 3.5 | 1.8 | 5.0 | 5.2 | 3.2 |
| | 1.0–10.6 | 1.1–11.2 | 0.6–5.8 | 2.1–12.2 | 2.2–12.2 | 1.3–7.7 |
| Placental abruption | 42.3 | 50.6 | 29.8 | 0.7 | 0.8 | 0.5 |
| | 19.4–92.1 | 23.5–109.2 | 14.2–62.2 | 0.1–6.0 | 0.1–6.6 | 0.1–3.9 |
| Smoking (at first visit) | 2.4 | | 3.4 | 3.0 | | 3.2 |
| | 1.5–3.9 | | 2.3–5.0 | 2.0–4.5 | | 2.2–4.6 |
| Small-for-gestational-age | 48.6 | 54.7 | | 29.8 | 30.8 | |
| | 26.9–87.7 | 30.5–98.3 | | 16.6–53.3 | 17.4–54.6 | |
| Thyroid disease | 5.3 | 6.6 | 3.0 | 5.0 | 5.3 | 3.7 |
| | 1.9–15.1 | 2.4–18.1 | 1.0–8.5 | 1.8–13.9 | 2.0–14.4 | 1.4–9.7 |

[a]Non-placental = infections, intrapartum deaths, congenital anomalies, fetal, cord, maternal, and unknown causes.

distribution of women in other causal groups was also in agreement with other recent reports (1,13).

The cause was unknown in 20% of the cases. A recent study of stillbirths in six high-income countries reported 30% with unknown causes and claimed the main reason to be inadequately investigated cases (1). The reported numbers of unexplained stillbirths ranges from 9 to 71% (14,15) depending on the sources of information available and the classification system used (16,17). Systems capable of retaining detailed information have a lower proportion of unexplained deaths (18,19). CODAC has recently been evaluated and compared with five other classification systems (14). It received the highest score regarding the ability to retain important information and for ease of use. It had the lowest proportion of unexplained stillbirths and good inter-observer agreement (14). The importance of placental histology has been demonstrated in several reports (14,16,20) and may lead to lower proportions of unexplained stillbirths (16).

Smoking was equally frequent in all causal groups. Placenta pathology has been suggested as a pathway for the association of smoking and stillbirth (21). If the mode of effect of smoking on fetal death were entirely through placental pathology one would expect the risk of IUFD associated with smoking to vanish when adjusting for SGA. We could not confirm this in our study. We registered smoking habits at first antenatal visit only, but smoking habits could have changed later in pregnancy, which might have affected the results. Studies suggest that women who reduce or quit smoking in the first trimester have a comparable risk of stillbirth as non-smokers (22). Smoking might also be an expression of other confounders such as social deprivation, something we do not have data on and thus have not adjusted for. Stillborn infants were more often SGA compared with live-born infants, unrelated to the cause of death. Fetal growth restriction is reported to be the factor most often associated with stillbirths and is probably a sign of a variety of conditions that may lead to fetal death (15,16). Whether it is a marker of placental insufficiency or causally associated with the mechanism of death is unclear (2).

**Table 4.** Prevalences of acquired and inherited thrombophilia among women with intrauterine fetal death by cause of death (COD) and controls. Odds ratios (OR) and 95% confidence interval (CI) for intrauterine fetal death compared with controls.

| COD | All n = 105 [a]n = 103 | | Placenta n = 50 [a]n = 49 | | [b]Non-placental n = 55 [a]n = 54 | | Controls n = 262 |
|---|---|---|---|---|---|---|---|
| Variable[a] | n | OR 95% CI | n | OR 95% CI | n | OR 95% CI | n |
| *F5 rs6025* | 11 | 1.4 0.7–3.1 | 7 | 2.0 0.8–5.1 | 4 | 1.0 0.3–3.0 | 20 |
| *F2 rs1799963* | 6 | **4.0 1.1–14.4** | 4 | **5.7 1.4–23.8** | 2 | 2.5 0.4–13.9 | 4 |
| AT, PC or PS | 3 | 0.8 0.2–3.2 | 1 | 0.6 0.1–4.7 | 2 | 1.1 0.2–5.2 | 9 |
| Any inherited thrombophilia | 19 | 1.7 0.9–3.1 | 11 | **2.2 1.0–4.7** | 8 | 1.3 0.6–3.0 | 31 |
| APA | 10 | 2.0 0.9–4.8 | 3 | 1.2 0.3–4.5 | 7 | **2.8 1.1–7.4** | 13 |
| Any thrombophilia | 28 | **1.9 1.1–3.3** | 14 | **2.0 1.0–4.1** | 14 | 1.8 0.9–3.6 | 43 |

[a]Two women reported use of warfarin and were therefore excluded from all analyses of inherited thrombophilias.
[b]Non-placental = infections, intrapartum deaths, congenital anomalies, fetal, cord, maternal, and unknown causes.
APA, antiphospholipid antibodies; AT, antithrombin deficiency; *F2 rs179963*, prothrombin gene G20210A polymorphism; *F5 rs6025*, factor V Leiden polymorphism; PC, protein C deficiency; PS, protein S deficiency.
Bold figures are statistically significant.

Diabetes and twin pregnancy were risk factors for stillbirths with both placental and non-placental causes. The mechanism of fetal death in diabetes is unknown but alterations in fetal carbohydrate metabolism and uteroplacental insufficiency secondary to vascular disease are possible explanations (23). Fetal and maternal complications are generally more frequent in twin pregnancies, especially monozygotic twins, in addition to unique placental complications such as twin–twin transfusion syndrome (24,25). Hypertension was a significant risk factor among stillbirths with placental causes. This concurs with placenta pathology most likely being the origin of pregnancy-related hypertensive disorders (26).

Our data provide new information regarding risk factors for stillbirth with placental causes. In the other causal groups, risk factors could not be studied separately because of small sample size. The control group was for practical reasons selected from only one of the study hospitals. This might have caused a selection bias, as the delivering populations at each of the hospitals may differ. We have reported earlier that the women in our control group were on average older than the general delivery population (6). Comparing all women giving birth at each of the study hospitals revealed that the women at Oslo University Hospital Ullevål more often had hypertension, pre-eclampsia and gestational diabetes. This may have affected the risk estimates associated with these variables towards "null", finding a weaker association than actually exists.

Inherited thrombophilia combined and *F2 rs179963* alone were significantly associated with stillbirth from placental causes. The association of *F2 rs179963* and stillbirth is consistent with the results of a meta-analysis of case-control studies (3). The prevalence of *F5 rs6025* was double among women with placental COD compared with the controls, although this did not reach statistical significance. The literature is not consistent regarding the association between factor V Leiden and IUFD. A recent meta-analysis of prospective cohort studies suggested an association between factor V Leiden and pregnancy loss, but the results included pregnancy loss in all trimesters and few numbers of fetal deaths after 20 weeks of gestation (27). The main pathogenesis of thrombophilia-related stillbirth is assumed to be through abnormalities in placental vasculature (28), which our findings support. Korteweg et al. (18) did not find significant differences in the prevalence of thrombophilic defects, but they compared women in different causal groups internally and not with live-birth controls. Whether coagulation abnormalities are the causes of abnormal placentation or just exert an effect on an already compromised placenta is not known. In a study of thrombophilia and placental pathology, no specific placental lesions were found among women with thrombophilia (29). Similar findings at delivery might simply represent a final common pathway for different underlying abnormalities. We did not compare placental findings in different causal groups or in

stillbirths and live birth, as this was not within the scope of the study. The small sample size in the analyses of thrombophilic risk factors limits the conclusions. In particular, the study was underpowered to detect any differences regarding the very low prevalent conditions of antithrombin, protein C and protein S deficiencies.

Limitations of our study are the collection of blood samples at a single time point only and the long time elapsing after the index pregnancy. However, one of the rationales for repeated testing is to avoid false positive tests due to transiently elevated antiphospholipid antibodies, which is not a concern in the present study where the samples were collected 3–18 years after the index pregnancy. Moreover, it may be possible that some women have become either negative or positive for antiphospholipid antibodies after the index pregnancy, but there is no reason to believe that this would differ between cases and controls.

In the CODAC classification the assigned cause of death is a matter of expert opinion. The cases were all classified by one author (L.B.H.) and it is possible that another coder would not have agreed in all cases. A kappa of 0.82–0.94 has been reported for CODAC when the coding rules are extensively followed (4). L.B.H. is an experienced obstetrician and the placenta histological examinations were performed by experienced pathologists (G.T. and B.R.). We do not believe the coding to be a source of large bias. Supportive of our findings is that the distribution in causal groups was in agreement with the distribution reported in six other high-income countries (1).

Early diagnosis of placental dysfunction is a major clinical challenge. Screening tests in low-risk groups have been demonstrated to be poor predictors of complications such as pre-eclampsia and fetal growth restriction (30,31). However, the use of a "placental profile" by three separate tests – maternal serum screening, second trimester uterine artery Doppler and placental morphologic condition – has been proposed among women in high-risk groups for evaluating the risk of complications, with somewhat promising results (32).

In conclusion, two-thirds of all stillbirths (68%) were caused by or associated with placental pathology. Risk factors differed somewhat according to cause, apart from smoking and SGA, which were significant risk factors across all causal groups.

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## Supporting information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** The Causes of Death and Associated Conditions (CODAC) classification system. Cause of death (COD).

**Table S2.** The Causes of Death and Associated Conditions (CODAC) classification system. Associated conditions (AC).

**Table S3.** Cause of death (COD) – Level II for placental causes (subgroups).