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# Causes of death among full term stillbirths and early neonatal deaths in the Region of Southern Denmark

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**Abstract**

**Objective:** We examined the causes of death amongst full term stillbirths and early neonatal deaths.
**Methods:** Our cohort includes women in the Region of Southern Denmark, who gave birth at full term to a stillborn infant or a neonate who died within the first 7 days from 2010 through 2014. Demographic, biometric and clinical variables were analyzed to assess the causes of death using two classification systems: causes of death and associated conditions (CODAC) and a Danish system based on initial causes of fetal death (INCODE).
**Results:** A total of 95 maternal-infant cases were included. Using the CODAC and INCODE classification systems, we found that the causes of death were unknown in 59/95 (62.1%). The second most common cause of death in CODAC was congenital anomalies in 10/95 (10.5%), similar to INCODE with fetal, genetic, structural and karyotypic anomalies in 11/95 (11.6%). The majority of the mothers were healthy, primiparous, non-smokers, aged 20–34 years and with a normal body mass index (BMI).
**Conclusion:** Based on an unselected cohort from an entire region in Denmark, the cause of stillbirth and early neonatal deaths among full term infants remained unknown for the vast majority.

**Keywords:** Cause of death; CODAC; INCODE; neonatal death; perinatal mortality; stillbirth.

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## Introduction

In the last decade, perinatal mortality has come under new increased scrutiny. The *Lancet's* Stillbirth Series published a comprehensive review in 2011, in which the second part of the series compared national estimates on causes of death, including prevalence rates, occurrence of death and leading causes [1]. This series was intended to rally a global effort in reducing the rate of stillbirths. Based on these initiatives, we undertook this study to examine the possible causes of death amongst full term stillbirths and in the early neonatal period. Thus, we focused only on the causes of death in those infants that were expected to be born alive at term.

Previous studies have investigated maternal and fetal variables associated with stillbirths, and most included stillbirths from 22 gestational weeks [2–5]. In a 2011 meta-analysis investigating risk factors for stillbirths in high-income countries, maternal variables including overweight and obesity, advanced maternal age, smoking and primiparity were all significant risk factors for stillbirth [6]. In addition, small size for gestational age and abruption, as well as pre-existing diabetes and hypertension were significant contributors to stillbirths [6, 7]. A systematic review from 2014 indicated that the male sex may also be a contributing factor to stillbirths [8].

Our study focused on infants that are expected to have uncomplicated live births, and therefore, we excluded pre-term stillbirths. Our primary objective was to describe maternal and fetal factors associated with stillbirths and early neonatal deaths in an unselected cohort that could lead to hypotheses on cause of death. We aimed (1) to give descriptive characteristics according to maternal and fetal factors, (2) to examine the underlying cause of death according to two different classification systems and (3) to

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explore if unknown cause of death was related to the sex of the infant.

# Materials and methods

## Study population

The study cohort encompasses stillbirth cases of full term infants from 37 weeks of gestation and early neonatal deaths within 7 days of life in the Region of Southern Denmark in the period January 1, 2010–December 31, 2014. The mothers were identified based on the Danish Medical Birth Registry and the National Patient Registry. The Medical Birth Registry documents pregnancies and deliveries since 1973 with the purpose of monitoring the quality of obstetrical care and newborn health [9]. The National Patient Registry supplies further information on the discharge diagnosis, operations, investigations and treatments. A total of 97 mothers were identified and screened for our study, and two cases were excluded after medical chart review due to incorrect gestational age at the time of death.

## Definition of death and classification systems for causes of death

A stillbirth was defined as a fetal death at 22 weeks of gestation or later (based on the Danish Board of Health 2004 terminology), subdivided into antepartum and intrapartum periods. The fetal gestational age is determined by dates and verified by ultrasound measurement of the crown-rump length in the first trimester. An antepartum death occurred before the onset of labor, while an intrapartum death occurred during labor and birth. Early neonatal death was the death of a full term live birth within the first 7 days of life. Perinatal mortality included stillbirths and early neonatal deaths. Full term was defined as 37 weeks 0 days to 41 weeks 6 days gestation.

According to the guidelines outlined by the cooperative effort between the Danish Society of Obstetrics and Gynecology and the Danish Society of Pathology (2013), the recommended workup for fetal death after 22 weeks 0 days gestational age includes ultrasound confirmation of fetal death, chromosome analysis including array comparative genomic hybridization (CGH), microbiology investigations, TORCH titers, placental pathology, fetal/infant autopsy and maternal investigations including hematology, infection parameters, thrombophilia and preeclampsia blood samples. Specific investigations are ordered based on clinical history and indication.

The primary cause of death was coded according to the causes of death and associated conditions (CODAC) classification system using version 2 (2009), in addition to a Danish pathology coding guidelines under the Danish Association of Obstetrics and Gynecology, a slightly modified version based on the initial causes of fetal death (INCODE) research tool [10, 11]. CODAC is a classification system that codes a primary cause of death in addition to two associated conditions. It registers the presence of supplementary information including autopsy, placental pathology, chromosome analysis and infection investigations; CODAC received high ratings in terms of ease of use, retention of essential information and high inter-observer reliability based on an international audit [10, 12]. Only primary cause of death was considered in our study. INCODE is a classification system developed by the Stillbirth Collaborative Research Network. It is a self-integrated research tool that allows the user to assign a cause of death from objective findings and pre-determined definitions based on evidence-based medicine and to categorize these findings as present, possible or probable cause of death [11]. The level of evidence needed is stringent because one or more pre-defined associated findings must be present in addition to the main pathology in order to fulfill the criteria as a possible or probable cause of death. The authors utilized INCODE's standardized method to assign primary cause of death in the CODAC system for ambiguous cases.

## Data collection of clinical details

We retrospectively reviewed the mothers' medical charts including laboratory results, placenta pathology and infant autopsy reports. The data were obtained from paper medical charts or the electronic journal system, including scanned pregnancy surveys and journals. The extracted data were entered into a secure online database. All data were reviewed and categorized by one author (MNB), a physician specialized in general pediatrics. Ambiguous cases were reviewed by a team of authors with expertise in the fields of perinatal pathology, obstetrics, pediatrics and internal medicine, and the primary cause of death was decided by a consensus of experts' opinions.

## Data on maternal, fetal, autopsy and placental factors

The data were divided into maternal, fetal/infant, autopsy and placental categories. Maternal variables included age, parity, history of earlier stillbirths, abortions and miscarriages, prenatal exposures (smoking and alcohol use, infections during the pregnancy), biometrical data (height, weight), as well as past medical history. Fetal/infant variables included date of birth, gestational age, sex, birth weight, as well as obstetrical history (time of death, mode of delivery, obstetrical complications). The autopsy variables included biometrical measurements (weight, crown-rump, crown-heel, foot plate length), assessment of the infant's weight in relation to the gestational age, histological findings, and malformations from both external and internal investigations. Placenta variables included measurements, umbilical cord analysis, and macroscopic and histological analysis of the membranes and placenta, including fetal and maternal surfaces.

## Statistics

Descriptive statistics were used to analyze the data. Maternal characteristics were given according to antepartum, intrapartum or neonatal periods of fetal death. Descriptive characteristics were given according to fetal demographics and biometrics, overall and stratified by known and unknown causes of death; and main causes of death were given by the CODAC and the INCODE-based classification system. Fisher's exact test was used to evaluate the association between the sex of the infant and unknown cause of death.

The project was approved by the Danish Board of Health (J.nr. 3-3013-189/1) and the Danish Data Protection Agency (J.nr. 2012-41-0856).

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## Results

A total of 95 maternal-infant cases were included. Within this total, 64 (67.4%) of the deaths occurred in the antepartum period, 10 (10.5%) in the intrapartum period and 21 (22.1%) in the neonatal period. Placental reports were available in 74 cases (78.0%). Autopsies were performed in 61 cases (64.0%) and 98.0% of these were performed at the specialized regional hospital, Odense University Hospital, by perinatal pathologists using a standardized template for the investigations.

The maternal characteristics according to stillbirths and early neonatal deaths are given in Table 1. The majority of the mothers were healthy, primiparous, non-smokers, aged 20–34 years and with a normal body mass index (BMI). Maternal pre-pregnancy BMI over 25 was present in 38 (40.0%) cases. The mothers were healthy without prior medical history in 61 (64.2%) of the cases.

The fetal demographics and biometrics, overall and stratified by known and unknown causes of death based on the CODAC classification system are displayed in Table 2. The majority of the infants had an appropriate weight for the gestational age (62.1%). Among the infants that underwent autopsies, 71.2% of these cases were concluded with an unknown cause of death.

The main causes of death classified by the CODAC and the INCODE-based Danish system are summarized in

**Table 1:** Maternal variables associated with perinatal infant deaths, 2010–2014.

| Maternal characteristics | Total n (%) | Antepartum n (%) | Intrapartum n (%) | Neonatal n (%) |
|---|---|---|---|---|
| | 95 (100.0) | 64 (67.4) | 10 (10.5) | 21 (22.1) |
| Maternal age at delivery (years) | | | | |
| <20 | 2 (2.1) | 2 (3.1) | – | – |
| 20–34 | 72 (75.8) | 48 (75.0) | 8 (80.0) | 16 (76.2) |
| 35–39 | 15 (15.8) | 8 (12.5) | 2 (20.0) | 5 (23.8) |
| ≥40 | 6 (6.3) | 6 (9.4) | – | – |
| Pre-pregnancy BMI (kg/m$^2$) | | | | |
| <18.5 | 3 (3.2) | 3 (4.7) | – | – |
| 18.5–24.9 | 52 (54.7) | 35 (54.7) | 4 (40.0) | 13 (61.9) |
| 25–29.9 | 24 (25.3) | 17 (26.6) | – | 7 (33.3) |
| 30–34.9 | 5 (5.3) | 2 (3.1) | 2 (20.0) | 1 (4.8) |
| ≥35 | 9 (9.5) | 6 (9.4) | 3 (30.0) | – |
| (missing data) | 2 (2.1) | 1 (1.6) | 1 (10.0) | – |
| Parity | | | | |
| Primiparous | 51 (53.7) | 38 (59.4) | 4 (40.0) | 9 (42.9) |
| Multiparous | 44 (46.3) | 26 (40.6) | 6 (60.0) | 12 (57.1) |
| Gestational age (weeks) | | | | |
| 37 | 22 (23.2) | 13 (20.3) | 4 (40.0) | 5 (23.8) |
| 38 | 22 (23.2) | 13 (20.3) | 3 (30.0) | 6 (28.6) |
| 39 | 20 (21.1) | 15 (23.4) | 2 (20.0) | 3 (14.3) |
| 40 | 17 (17.9) | 11 (17.2) | 1 (10.0) | 5 (23.8) |
| 41 | 14 (14.7) | 12 (18.8) | – | 2 (9.5) |
| Medical conditions | | | | |
| None | 61 (64.2) | 49 (76.6) | 2 (20.0) | 10 (47.6) |
| Diabetes | 1 (1.1) | – | – | 1 (4.8) |
| Preeclampsia | 6 (6.3) | 2 (3.1) | 3 (30.0) | 1 (4.8) |
| Hypertension | 2 (2.1) | – | 2 (20.0) | – |
| Autoimmune disease | 1 (1.1) | 1 (1.6) | – | – |
| Anti-cardiolipin antibodies | 2 (2.1) | 1 (1.6) | – | 1 (4.8) |
| Thyroid disorder | 2 (2.1) | 2 (2.3) | – | – |
| Psychiatric disorder | 11 (11.6) | 6 (9.4) | 1 (10.0) | 4 (19.0) |
| Other | 11 (11.6) | 6 (9.4) | 3 (30.0) | 2 (9.5) |
| (missing data) | 6 (6.3) | 1 (1.6) | 2 (20.0) | 3 (14.3) |
| Prenatal smoking | | | | |
| Non-smoker | 75 (78.9) | 54 (84.4) | 6 (60.0) | 15 (71.4) |
| Smoker | 19 (20.0) | 10 (15.6) | 4 (40.0) | 5 (23.8) |
| (missing data) | 1 (1.1) | – | – | 1 (4.8) |

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**Table 2:** Fetal/infant variables associated with perinatal infant deaths, overall and stratified by known and unknown cases based on the CODAC classification system.

| Fetal/infant characteristics | Total (%) | Known causes (%) | Unknown causes (%) |
|---|---|---|---|
| | 95 (100.0) | 36 (100.0) | 59 (100.0) |
| Sex | | | |
| Male | 48 (50.5) | 17 (47.2) | 31 (52.5) |
| Female | 47 (49.5) | 19 (52.8) | 28 (47.5) |
| Mean birthweight (±SD) | 3083 (762) | 2941 (1000) | 3164 (581) |
| Weight for gestational age | | | |
| Small for gestational age (SGA)[a] | 12 (12.6) | 10 (27.8) | 2 (3.4) |
| Appropriate for gestational age | 59 (62.1) | 14 (38.9) | 45 (76.3) |
| Large for gestational age | 3 (3.2) | 3 (8.3) | – |
| (missing data) | 21 (22.1) | 9 (25.0) | 12 (20.3) |
| Autopsy (yes) | 61 (64.2) | 19 (52.8) | 42 (71.2) |
| Time of death | | | |
| Antepartum | 64 (67.4) | 13 (36.1) | 51 (86.4) |
| Intrapartum | 10 (10.5) | 8 (22.2) | 2 (3.4) |
| Neonatal | 21 (22.1) | 15 (41.7) | 6 (10.2) |

[a]SGA definition based on <2 SD corresponding to <22%.

**Table 3:** Causes of death according to the CODAC and INCODE-based classification systems.

| | Total n (%) | Antepartum n (%) | Intrapartum n (%) | Neonatal n (%) |
|---|---|---|---|---|
| | 95 | 64 (67.4) | 10 (10.5) | 21 (22.1) |
| CODAC | | | | |
| 0) Infection | 1 (1.1) | 1 (1.6) | – | – |
| 1) Neonatal | 5 (5.3) | – | – | 5 (23.8) |
| 2) Intrapartum | 4 (4.2) | – | 2 (20.0) | 2 (9.5) |
| 3) Congenital anomaly | 10 (10.5) | 1 (1.6) | 3 (30.0) | 6 (28.6) |
| 4) Fetal | – | – | – | – |
| 5) Cord | 2 (2.1) | 1 (1.6) | 1 (10.0) | – |
| 6) Placenta | 5 (5.3) | 3 (4.7) | 1 (10.0) | 1 (4.8) |
| 7) Maternal | 9 (9.5) | 7 (10.9) | 1 (10.0) | 1 (4.8) |
| 8) Unknown | 59 (62.1) | 51 (79.7) | 2 (20.0) | 6 (28.6) |
| INCODE-based | | | | |
| 1) Maternal medical conditions | 5 (5.3) | 4 (6.3) | 1 (10.0) | – |
| 2) Obstetric complications | 9 (9.5) | 4 (6.3) | 2 (20.0) | 3 (14.3) |
| 3) Maternal or fetal hematological conditions | 3 (3.2) | 2 (3.1) | – | 1 (4.8) |
| 4) Fetal genetic, structural and karyotypic abnormalities | 11 (11.6) | 1 (1.6) | 3 (30.0) | 7 (33.3) |
| 5) Placenta and/or fetal infection | – | – | – | – |
| 6) Pathological placenta conditions | 2 (2.1) | 2 (3.1) | – | – |
| 6) Complications at premature delivery | – | – | – | – |
| 7) Other pertinent condition not specified | 6 (6.3) | – | 2 (20.0) | 4 (19.0) |
| 8) Unknown | 59 (62.1) | 51 (79.7) | 2 (20.0) | 6 (28.6) |

Table 3. Unknown cause of death was the highest attributor in both classification systems, comprising 62.1% of all perinatal deaths. In both systems, the occurrence of death in the antepartum period comprised 67.4% of all perinatal mortality. Deaths due to maternal factors occurred mainly in the antepartum period. In the CODAC system, the second and third most common causes of death were attributed to congenital anomalies (10.5%) and maternal causes including preeclampsia, thrombophilias and autoimmune disorders (9.5%). Among deaths due to congenital anomalies, six of 10 (60.0%) occurred in the early neonatal period. In the INCODE-based system, fetal genetic, structural and karyotypic abnormalities, including congenital diaphragmatic hernias, cardiac anomalies and lung hypoplasia (11.6%) were the second most common causes of death followed by obstetric complications (9.5%). Cord

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and placental complications comprised a small percentage of the causes of death (6.0% or less) in both classification systems.

Known causes of intrapartum and neonatal deaths in non-anomalous infants were attributed to placenta abruption (three cases), umbilical cord prolapse and fetal dystocia (two cases). There were single cases due to maternal antiphospholipid syndrome, maternal preeclampsia with severe placenta infarction, difficult and prolonged labor, meconium aspiration syndrome, intestinal ileus, intestinal necrosis and complications from intubation.

The male to female ratio was 1:1 in a crude subdivision of all perinatal deaths. The odds ratio (OR) for an unknown cause of death for females was 0.81 [95% confidence interval (CI) (0.32–2.01)] compared to males.

## Discussion

We examined the causes of death in full term stillbirths and early neonatal deaths occurring in an unselected cohort of infants in the Region of Southern Denmark from 2010 through 2014. The basic characteristics according to maternal and fetal variables showed that the vast majority of deaths occurred in the antepartum period, in infants that were an appropriate size for gestational age, born to healthy and primiparous women who were non-smokers, aged 20–34 years and with a normal BMI. Using two different classification systems, we found that the vast majority of cases were ascribed to unknown causes of death (62.1%). As expected, these proportions were the same in both systems, as the INCODE-based guidelines were applied to the CODAC system to classify ambiguous cases.

The strength of our study is the complete and unselected cohort of full term stillbirths and early neonatal deaths, as well as access to medical journals and pathology reports, allowing for evaluation of causes of death against different classification systems. Our study also has limitations; it is descriptive in its nature and the data review was completed by mainly one reviewer.

The prevalence of an unknown cause of death was 62.1% in our study. Previous studies have reported proportions of unknown causes of death in the range of 12–66% [2–5, 13]. Many of these studies investigated stillbirths from 22 gestational weeks. One study examined causes of death in full term infants and found that the proportion of unknown causes of death was 14.5% in term/post term stillbirths compared with 10.7% in preterm stillbirths using the Stockholm classification of stillbirth [5]. The large discrepancy compared with our study could be explained by the different classification systems and level of evidence needed to establish a diagnosis. Additionally, the classification systems were used retrospectively in our review and not at the time of death and examination. Findings necessary to meet the criteria for a conclusive cause of death could thus have been overlooked. Another study that examined causes of death in full term stillbirths was conducted by the Stillbirth Collaborative Research Network [3]. This was a prospective multi-center cohort study that used the INCODE classification system and found a possible or probable cause of death in 60 of 84 cases (71.4%) and an unknown cause in 28.6%. Due to their inclusion criteria, autopsy and placenta investigations were performed in 100% of the cases with chromosome analysis in 96.5% of the cases. The reason for the discrepancy from our study could be that our cohort is based on an unselected cohort and we had a lower percentage of autopsy and placenta investigations.

Our study provides descriptive analyses of maternal and fetal variables. Due to the lack in control group, we do not investigate the risk factors for infant death. However, there is a high correlation when we compare the maternal and fetal variables from our cohort with the proportions observed in the published medical literature. Prenatal smoking and high pre-pregnancy BMI has been correlated with an increased risk of stillbirth [14]. The proportion of smokers and overweight and obese mothers in our study were comparable to those in five other high income countries (Australia, Canada, USA, UK and the Netherlands) [6].

We also explored the associated risk of fetal sex in relation to cause of death. The results of one systematic review and meta-analysis indicated that male sex may be a contributing factor to perinatal mortality and male babies are at a 10% higher risk of stillbirth across all regions [8]. This may be due to factors such as X-linked conditions, increased preterm labor and poor fetal growth, or newer theories involving the immunogenicity of molecules encoded by the Y chromosome [15]. We found that the odds of an "unknown" cause of death was reduced (OR = 0.81) for females as compared to males, though not statistically significant. These lower odds for female fetuses can implicate unknown contributory factors in the death of male fetuses as discussed above. This is new data that is generally lacking in previous cohort studies. A larger prospective study which clearly delineates and evaluates the cause of death and associated conditions between the sexes could clarify some of the unknown factors associated with higher perinatal mortality in the male sex. This could lead to better insight into some of the unknown cases.

In summary, using two different classification systems, we found that 62.1% of our cases were due

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to unknown causes with females having lower odds for an unknown cause of death compared with males. The majority of the cases occurred in the antepartum period of mothers who were healthy, primiparous, non-smokers, aged 20–34 years and had a normal BMI. The identification of a known cause of death might be improved by a concerted effort to complete a standard and uniform investigation in all perinatal death cases, including chromosome analysis as well as autopsy and placental investigations performed by a perinatal pathologist.

**Author's statement**

**Conflict of interest:** Authors state no conflict of interest.

**Material and methods:** Informed consent: Consent has been obtained from the appropriate authorities according to Danish law from the Danish Board of Health (J.nr. 3-3013-189/1) and the Danish Data Protection Agency (J.nr. 2012-41-0856).

**Ethical approval:** The research related to human subject use has complied with all the relevant national regulations, and institutional policies, and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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