Fetal death
Population-based studies of pregnancies in Norway

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Norway 2014

Akershus University Hospital
ExtraStiftelsen Helse og Rehabilitering
LANDSFORENINGEN UVENTET BARNEDØD

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Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 1863

ISBN 978-82-8264-771-0

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Cover: Hanne Baadsgaard Utigard.
Printed in Norway: AIT Oslo AS.

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ACKNOWLEDGEMENTS

The present work was carried out at the Department of Obstetrics and Gynecology at Akershus University Hospital and The Institute of Clinical Medicine Faculty Division of Akershus University Hospital, University of Oslo with grants from the Norwegian Extrafoundation for Health and Rehabilitation, for which I am very grateful.

First of all I would like to thank my two wonderful and knowledgeable supervisors Professor Sven Ove Samuelsen and Professor Dr. Jeanette Magnus. I would like to express my deepest gratitude to Jeanette for stepping in as my supervisor, for guiding me, encouraging me and for believing in me. Your high scientific standards and professionalism are really admirable! I am so grateful to have had the chance to work with you.

I would also like to thank Professor Sven Ove Samuelsen, for his knowledge and genuine, continuous support throughout the years. I am really impressed by your knowledge; you always seem to have the answer to any complicated mathematical challenge. Thank you for always being available for questions and conversations, but not too early in the morning.

I would also like to thank former head of department Dr. Arne Urnes and Dr. Runar Eraker for having created a wonderful working place and for your support and conversations in difficult times. Thanks to Dr. Pernille Schjønsby and Dr. Hege Lundring who have taken over the baton of leadership and managed to preserve the unique milieu at KK. Dr. Renate Häger my clinical supervisor for sharing your clinical wisdom with me and being an inspiring role model. Thanks to all my colleagues at the Department of Gynecology and Obstetrics at Akershus University Hospital, for working so hard, almost never complaining and for creating the best working environment in the world. I also thank Professor Anne Eskild for her guidance when writing the papers.

All the cool researchers at the “Villa”, for good conversations and meetings and for being who you are. Especially Dr. Camilla Haavaldsen, my good friend and co-

author, it has been a pleasure to work and travel with you, and to share ups and downs with you. And I am looking forward to working in the clinic with you in the future.

My deep thanks Dr. Drude Fugelseth, Karin Vassbakk and Andrè Øyen of the Faculty of Medicine.

I have been privileged to have such excellent researchers as Dr. Fredrik Frøen Professor Leif Bakketeig and Dr. Vasilis Sitras reading my thesis and giving highly valued constructive comments.

The Medical Birth Registry of Norway for providing data for this work, and my thoughts goes out to all the women who lost their child.

My family and friends for supporting and helping me. Especially my parents for always believing in me and for being such good role models. My good friends “Verksted-jentene” your support, good spirit and excellent food has been invaluable during the years.

My children Mariam, Adam and Maria you mean everything to me and always remind me of what really matters in life. And finally my dear husband Tuqeer, thank you for your support, I could not have done this without your encouragement. Thank you for believing in me!

Lørenskog, October 2014
Ashi Sarfraz Ahmad

PAPERS INCLUDED IN THIS THESIS

Paper I.

Sarfraz AA, Samuelsen SO, Bruu AL, Jenum PA, Eskild A. **Maternal human parvovirus B19 infection and the risk of fetal death and low birthweight: a case-control study within 35 940 pregnant women.** *BJOG 2009;116:1492-1498.*

Paper II.

Sarfraz AA, Samuelsen SO, Eskild A. **Changes in fetal death risk during 40 years - different trends for different gestational ages: a population-based study in Norway.** *BJOG 2011;118:488-494.*

Paper III.

Haavaldsen C, **Sarfraz AA**, Samuelsen SO, Eskild A. **The impact of maternal age on fetal death: does length of gestation matter?** *Am J Obstet Gynecol 2010;203:554.e1-8.*

Paper IV.

Ahmad AS, Samuelsen SO. **Hypertensive disorders in pregnancy and fetal death at different gestational lengths: a population-based study of 2,121,371 pregnancies.** *BJOG 2012;119:1521-1528.*

DEFINITIONS AND ABBREVIATIONS

DEFINITIONS

Antepartum:	An event happening before labor.
Chronic hypertension:	Pre-pregnancy blood pressure of ≥140 mmHg systolic or ≥90 mmHg diastolic or increased blood pressure diagnosed before 20 weeks of gestation.
Early neonatal mortality:	Neonatal death within 7 days of birth.
Eclampsia:	Preeclampsia with seizures.
Fetal death, Papers I-III:	Birth of a dead fetus ≥16 weeks of gestation.
Fetal death, Paper IV:	Birth of a dead fetus ≥20 weeks of gestation.
Gestational hypertension:	Increase in maternal blood pressure to ≥140/90 mmHg after completed 20 weeks of gestation.
Intrapartum:	An event happening during labor.
Perinatal mortality rate, Papers II and IV:	Sum of infant deaths in pregnancies lasting ≥22 weeks (154 days) and within 7 days of birth, per 1000 births.
Pre-eclampsia:	Increase in maternal blood pressure of ≥140/90 mmHg combined with proteinuria after completed 20 weeks of gestation, measured on at least two occasions 6 hours apart.
Stillbirth, Paper II:	Birth of a dead fetus ≥22 weeks of gestation.

ABBREVIATIONS

BMI	Body mass index
CASP	Critical Appraisal Skills Programme
CI	Confidence interval
HR	Hazard ratio
ICD-10	International Classification of Diseases Revision 10
IgM	Immunoglobulin M
IgG	Immunoglobulin G
IUGR	Intrauterine growth restriction
LMP	Last menstrual period
MBRN	The Medical Birth Registry of Norway
OR	Odds ratio
PCR	Polymerase chain reaction
PVB	Human parvovirus B19
PMR	Perinatal mortality rate
RCT	Randomized controlled trial
RR	Relative risk (risk ratio in Paper IV)
SES	Socioeconomic status
SGA	Small for gestational age
SPSS	Statistical Package for the Social Sciences
T. gondii	Toxoplasma gondii
WHO	World Health Organization

1. INTRODUCTION

In Norway more than 200 infants ≥22 weeks of gestation are stillborn each year.[1] The global health impact of stillbirth is large, it is estimated that there are more than 2 million stillbirths annually. However, the true number is probably higher, as underreporting is common.[2;3] During the last 50 years stillbirth rates have declined in high-income countries, and the majority of cases (>98%) now happen in low- to middle-income countries.[4] This reduction can be attributed to improvements in public health, and in medical and antenatal care.

In Norway the late fetal mortality rate (≥28 weeks of gestation) dropped from around 40 per 1000 births in 1850 to 2 per 1000 births in 2012.[1;5] Most of this decline happened between 1950 and 1980, but recently it has slowed.[6;7] In high-income countries fetal mortality rates have stagnated, and sometimes risen,[8;9] though these phenomena seem to be region-specific. In some regions this may be due to an increased prevalence of certain risk factors (i.e. advanced maternal age, obesity, multiple pregnancies) for fetal death in women of childbearing age,[10] while in others the availability of prenatal diagnostics and induced termination of pregnancies may be the explanation.[11]

Causes of fetal death are complex and incompletely understood. Etiological studies reported that between 9% and 60% of fetal deaths are unexplained, that is, no maternal, fetal, placental or obstetric cause could be found.[12-17] Norwegian studies reported between 19% and 43% of stillbirths as unexplained.[16;18;19] Differences in the proportion of stillbirths classified as unexplained are due to variations in the extent of the investigations performed after fetal death, but are also dependent on the classification system applied.[10;20] In order to prevent fetal death, it is imperative to achieve a better understanding of its causes and risk factors. In order to inform preventive initiatives, caregivers and governments are reliant on relevant studies.

Nearly 30 years ago, Yudkin and colleagues reported that the risk of fetal death varied by gestational age, increasing gradually with increasing gestational age.[21] Recent studies have reported that the causes of fetal death also vary by gestational age.[13;22] As distribution of causes vary by gestational age, risk factors may also

contribute differently to risk of fetal death depending on gestational age. Interaction between certain risk factors for fetal death such as maternal age,[23] racial disparity,[24] and educational level[25] and gestational age has been implied, but needs to be further explored.

Furthermore, it is widely accepted that stillbirths may be prevented by selective, timely elective delivery of fetuses at risk of death, however, the outcome of this intervention is dependent on gestational age. This concept has contributed to a left-shift in the population distribution of gestational age at birth by increasing the number of iatrogenic premature births,[26] but at the same time decreasing the stillbirth rate. The timing of delivery in pregnancies with increased risk of stillbirth is thus challenged by the competing risks of neonatal morbidity (neurodevelopmental impairments, respiratory distress, and gastrointestinal complications) associated with preterm birth.[27]
In addition, studies of gestational-age-specific risk may guide clinicians on when to initiate antenatal care, and add to the knowledge on the pathological processes leading to stillbirth.

The overall aims of this thesis were to study how the fetal mortality rate varies across gestation and over time in the Norwegian population. The findings should advance the understanding of fetal death, and at the same time evaluate the Norwegian healthcare system.

In the following sections a definition of fetal death/stillbirth is given followed by a comprehensive review of the literature on certain risk factors for stillbirth and a brief overview of causes and consequences of stillbirth.

1.1 Definition of fetal death/stillbirth

The World Health Organization (WHO) in its International Classification of Diseases Revision 10 (ICD-10) defines fetal death as:
“Death prior to the complete expulsion or extraction from its mother of a product of conception, *irrespective of the duration of pregnancy*; the death is indicated by the

fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles".[28]

The WHO further distinguishes between *early fetal deaths/stillbirths* (death of a fetus with a birth weight ≥500 g, if birth weight not available gestational age ≥22 weeks or crown-heel length ≥25 cm) and *late fetal deaths/stillbirths* (death of a fetus with a birth weight ≥1000 g, if birth weight not available gestational age ≥28 weeks or crown-heel length ≥35 cm) (Figure 1).
In the United States and Canada fetal death are categorized into early fetal death (20-27 weeks of gestation) and late fetal death (≥28 weeks of gestation). Stillbirth categorization may also be based on timing of death in relation to labor; antepartum (prior to onset of labor) and intrapartum (during labor). The majority of stillbirths in high-income countries are antepartum.[29]

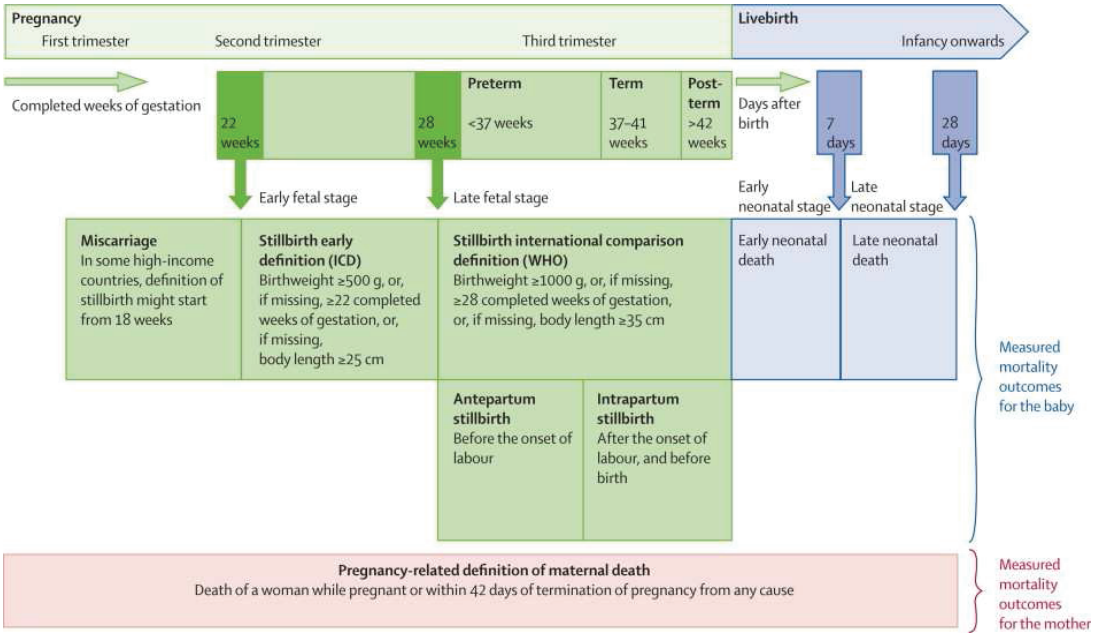

Figure 1. Defining stillbirths and associated pregnancy outcomes.
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Stillbirth is the informal term that covers both early and late fetal deaths.[30] The term "stillbirth" originates from the eighteenth century, and was applied to fetuses born without movement (still, but not necessarily lifeless). During the early twentieth century, the definition was further refined to "stillbirth is birth of a *viable* fetus born dead", and 28 weeks of gestation was set as the limit of viability.[31] The fetal period begins at 10 weeks of gestation, and therefore fetal deaths comprises some miscarriages as well, whereas the term stillbirth is more commonly applied to fetal death occurring at ≥22 weeks of gestation.[32]

The WHO recommends that late fetal deaths (≥28 weeks) should be reported to assure global comparability, as countries where most fetal deaths occur do not have reliable data on early fetal deaths, and the chance for survival prior to 30 weeks of gestation in these countries is very limited.[33;34] Whereas, in high-income countries the gestational age for neonatal survival has greatly decreased, as fetuses delivered as early as gestational week 22 may survive, and therefore in these countries early fetal deaths are more commonly registered.[35] However, as can be seen in Table 1, the gestational age threshold applied for reporting fetal death in high-income countries varies, making international comparison challenging.[36] The quality of the data in national vital registries also varies due to local legal definitions, and varying social, economic and cultural factors.[37]

In Norway, as per legal requirements passed in 1999, all fetal deaths occurring at ≥12 weeks of gestation are to be reported to the Medical Birth Registry of Norway (MBRN). The Norwegian Institute of Public Health publishes both early (gestational age 22-27 weeks) and late (gestational age ≥28 weeks) fetal death statistics.[1]
In the present thesis the terms fetal death and stillbirth will be applied interchangeably, and this thesis will only focus on fetal death ≥16 weeks of gestation.

Table 1. Reporting requirements for fetal death in different countries.[37-39]

Lower gestational week	Body length	Birthweight	Country	Year
≥28	≥35cm		League of Nations*	1925
≥28	≥35cm	≥1000 g	WHO	1950
≥28			United Kingdom	1926-1992
≥28			Sweden, Luxembourg Greece, Iceland Denmark	 -2003
≥26			Italy, Spain	
≥24			United Kingdom, Hungary Scotland, Portugal, Ireland	
≥22	≥25cm	≥500 g	ICD-9	1975
≥22		≥500 g	ICD-10 Denmark, Latvia, Lithuania, France Finland, Switzerland	1992 2004
≥20		≥350 g	United States** Canada	 1959
≥20		≥400 g	Australia New Zealand	
		≥500 g	Belgium, Germany, Poland, Austria, Slovenia	
≥16			Norway	1967-1998
≥12			Norway	1999

* Precursor to the United Nations 1919-1947.
** Most States
Abbreviations: ICD-9. International Classification of Diseases Revision 9: ICD-10. International Classification of Disease Revision 10

1.2 Scope of fetal death

The WHO reported global stillbirth (≥28 weeks) estimates of approximately 4.3 million in 1995 (stillbirth rate 29 per 1000 births).[40] A declining global trend has been reported with 3.3 million stillbirths in 2000 (stillbirth rate 24 per 1000 births), and 3 million in 2004 (stillbirth rate 22 per 1000).[41;42] Stanton and colleagues reported similar estimates for the year 2000 with 3.2 million (95% confidence interval [CI] 2.5-4.1) stillbirths at ≥28 weeks of gestation, corresponding to a stillbirth rate of 23.9 stillbirths per 1000 births (18.8-30.5).[4] The latest global estimate of 2.6 million stillbirths in 2009 (stillbirth rate 18.9 per 1000) shows that there has been a continuing gradual decline in the number of stillbirth.[2]

However, as can be seen in Figure 2, large global differences in the stillbirth rate prevail. Even across high-income countries the stillbirth rate (≥28 weeks of gestation) differs and has been reported to range between 1.7 per 1000 births in Slovak Republic to 4.9 per 1000 births in France in 2004,[43] and in 2009 between 1.5 per 1000 births in Czech Republic and 4.3 per 1000 in France.[44] When lower gestational age stillbirths (<28 weeks of gestation) are included in the estimates the inter-country differences increases from less than 4 to more than 8 stillbirths per 1000 births (some of the difference is due to registration of terminations of pregnancy as stillbirth in some countries). Also intra-country differences in stillbirth rates are reported and have been linked to accumulation of risk factors in deprived neighborhoods.[45] Although the stillbirth rate has declined the above described inequalities in the incidence indicates that further improvement is achievable.[14]

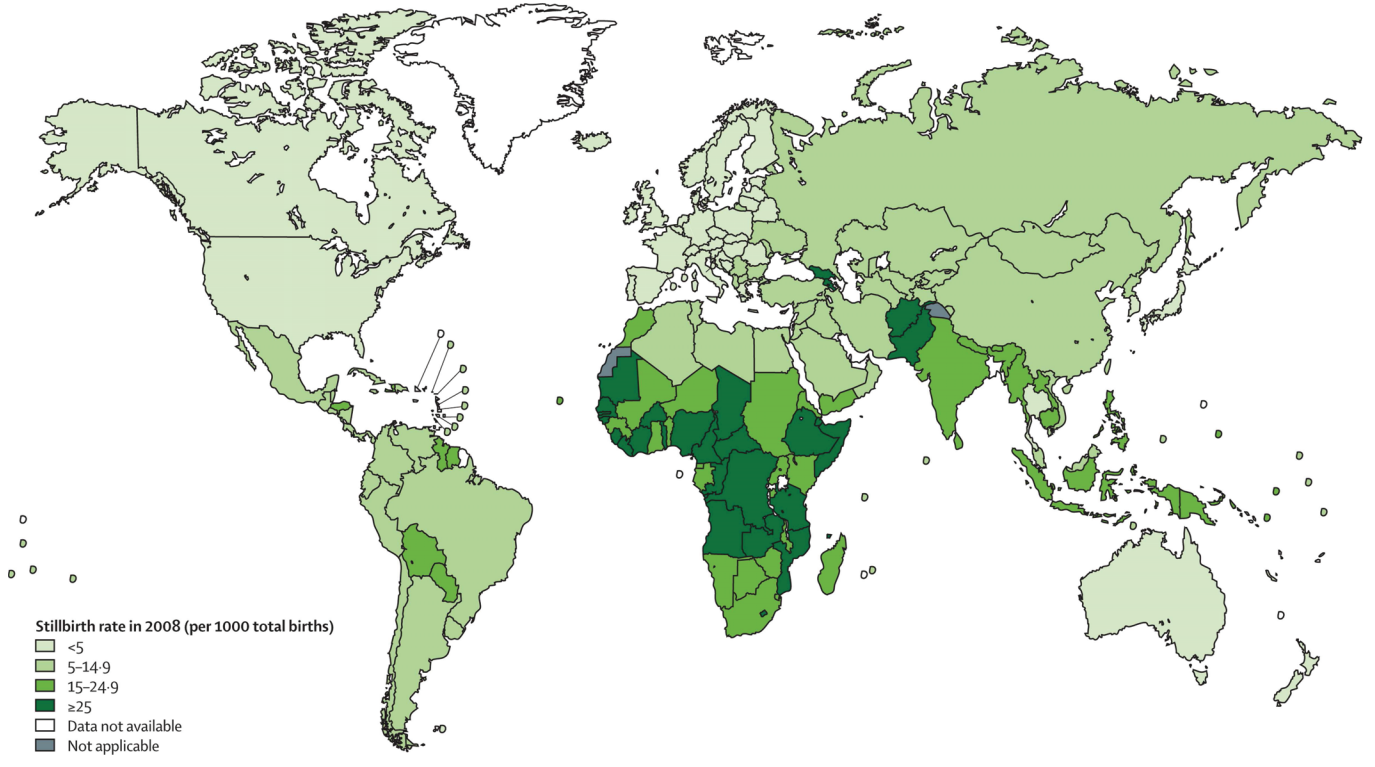

Figure 2. **Country variation in third trimester (≥28 weeks) stillbirth rates in 2008.**
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2. SYSTEMATIC REVIEW OF THE LITERATURE ON RISK FACTORS FOR STILLBIRTH

In this section a systematic review of observational studies was conducted, to explore the association between the most frequently reported risk factors in relation to stillbirth.

Literature search

Relevant studies were identified by a systematic search of the peer-reviewed literature covering the period January 1990 to December 2013. A literature search using Medline (Ovid and PubMed) was undertaken using the following terms: "*stillbirth*" or "*fetal death*" or "*fetal mortality*" or "*pregnancy outcome*", during the period 2003-2007, using a sensitive filter for the detection of etiological studies. For the period 1990-2002 and 2008-2013, a literature search using the Clinical Queries feature in PubMed for the terms "*stillbirth*" or "*fetal death*" was conducted, using a sensitive/broad filter for etiological studies. The reference lists of the obtained literature and current reviews were scrutinized for additional relevant publications.

Study inclusion and exclusion criteria

Studies that fulfilled the following requirements were included: the main focus of the study was stillbirth (≥20 weeks of gestation), at least one risk factor for stillbirth was assessed and the study was conducted in high-income countries (defined for the purpose of this review according to the Word Bank country classification: high-income members of the Organization for Economic Co-operation and Development).[46] The search was limited to publications in the English language and concerning human studies.

The review was limited to the following risk factors associated with stillbirth: *maternal demographic factors* (maternal age, parity, socioeconomic status (SES), race/ethnicity), *maternal lifestyle/behavioral factors* (maternal weight, smoking, alcohol and coffee consumption), *maternal medical disorders* (hypertensive disorders, diabetes), *pregnancy-related factors* (intrauterine growth restriction (IUGR), gestational age, previous stillbirth).

Studies were excluded if: a) stillbirth was not the main focus, b) the study only reported on intrapartum deaths, c) the study reported only perinatal deaths

and stillbirths were not reported separately, d) the study was assessed to have low quality. The quality of the papers was assessed by applying the Critical Appraisal Skills Programme (CASP) checklist for observational studies available at the CASP UK website.[47] The checklist is comprised of 12 questions enabling assessment of the methods used, validity of results, possible bias, confounding factors and generalizability.

Results

A total of 10,910 publications were initially identified (Figure 3). After the review a total of 150 papers met the inclusion criteria; 128 cohort studies (22 prospective and 106 retrospective), 19 case-control studies and three cross-sectional studies. In the following sections the results of the review is presented (Table 3).

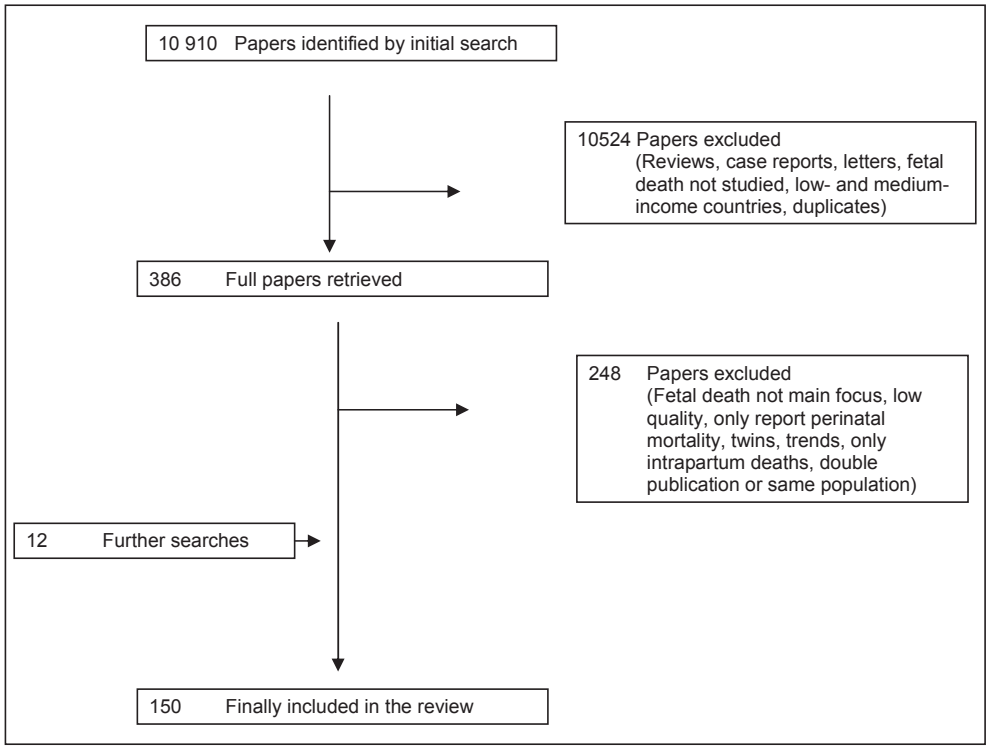

Figure 3. Inclusion and exclusion of studies for review.

2.1 Maternal age

The demographic distribution of pregnant women has increasingly shifted to the right in most high-income countries.[48] In Norway the proportion of childbearing women aged 35 years or older has increased from 5.6% in 1978 to 19.5% in 2012, accordingly in the United States the proportion changed from 4.5% to 14.9% during the same period.[1;23;49]

High maternal age at childbearing is consistently associated with an increased risk of fetal death and the risk increases more with advancing age above 35 years (35-39 years (odds ratio (OR) 1.3-2.0) and ≥40 years (OR 1.7-3.4)) as reported in the reviewed hospital-based[50-53] and large population-based cohort studies (Table 3).[23;54-69] However, the OR varies between studies, and some of the most recent studies do not report an increased risk among women aged 35-39 years.[53;69;70]

The cause of this increased risk remains unclear. Older women have a higher prevalence of medical conditions (hypertension, diabetes)[52;54;56;57;61] and of complications during pregnancy (preterm births, small for gestational age (SGA)[52;56;57;61] births). However, even after adjustment for these confounding factors the increased risk remains statistically significant,[54;56;60] indicating that increased maternal age is independently associated with increased risk of fetal death.
The incidence of fetal anomalies increases with maternal age,[71] however, detection and termination of anomalous fetuses have resulted in decreased impact of this cause in recent times.[51]
Contemporary older mothers have higher SES are more educated and have lower parity compared to older mothers a few decades ago, still the association with fetal death remains significant.[62]

Gestational age is an effect modifier of the relative risk (RR) of fetal death in older women,[23;60;64-66] as the risk of fetal death compared to younger women increases throughout pregnancy with the highest risk at term and post term.

Studies of young maternal age (<19 years) and fetal death are inconsistent, reporting both an increased risk,[54;58;67;72-74] and no increased risk.[55;75;76] Large population-based studies, most from the United States, display higher fetal mortality rates in

women aged <19 years compared to older women, with an OR varying between 1.05 and 1.76.[54;55;58;59;72] However, when analyses are adjusted for sociodemographic factors,[55;59] and preterm birth,[72] the OR is no longer significantly increased in most studies. In the largest study of teenage pregnancies to-date (5.8 million births to girls aged 15-19 years), Salihu and colleagues reported that the OR of fetal death in girls aged 15-19 years became insignificant relative to women aged 20-24 years, only when preterm birth was included in the multivariable model.[72] Hence, the mechanism involved in fetal death in teenage pregnancies may be different than that among older women, involving higher occurrence of unfavorable socioeconomic characteristics,[59] and biological immaturity.[77]

2.2 Parity

Increased risk of fetal death in nulliparas (women with no previous births) is reported in several studies; case-control,[78-80] hospital-based[50] and population-based retrospective cohort studies[23;59;60;66;68;81-85] (OR 1.2-1.9). Some of the risk may be explained by increased prevalence of hypertensive disorders (namely pre-eclampsia) and IUGR.[60] Multiparity ($\geq$3 pervious births) has also been reported to increase the risk of fetal death (OR 1.7-2.9).[23;50;59;70;80] and may partly be explained by selective fertility (replacement of a infant loss by new pregnancy).[86]

2.3 Maternal weight

The proportion of overweight (25 kg/m^2 $\leq$ body mass index (BMI)<30 kg/m^2) and obese (BMI $\geq$30 kg/m^2) pregnant women is increasing in high-income countries. In the United States, reports from the National Health and Nutritional Survey estimated that 35% of women aged $\geq$20 years were obese in 2009-2010 (compared to 15% in 1960).[87;88] A large population-based cohort study in Norway during 2000-2007 reported that approximately 30% of pregnant women (total cohort of 58 383) had a pre-pregnancy BMI $\geq$25 kg/m.[89]

The first study to report an increased risk of fetal death in women with high pre-pregnancy BMI was a case-control study by Little and colleagues, using data from the 1980 United States National Natality and Fetal Mortality Survey.[79] Even though the study only included married women, and had to rely on information collected by mail-in questionnaire, their results are in accordance with the results of several large

population-based prospective[90-92] and retrospective cohort studies[68;70;82;83;93-97] and two case-control study[69;98] included in this review. All studies but one reported an increased risk of fetal death in overweight and obese women, however, varying BMI reference groups were applied and hence the results were not directly comparable. A dose-dependent relationship was proposed, as the risk of fetal death progressively increased with increasing BMI (overweight: OR 1.1-2.5 and obese: OR 1.4-3.2). The retrospective cohort study by Kashan and colleagues did not find any significant association between maternal BMI and stillbirth; however, the study missed information on BMI for a large proportion of the women (37%).[99]
Weight gain during pregnancy was not associated with fetal death,[92;98] whereas weight gain between pregnancies was reported to increase the risk.[96;100] The Swedish study by Villamor and colleagues reported on changes in BMI between first and second pregnancies, and demonstrated that the risk of fetal death increased linearly with weight gain, and a weight gain of 3 BMI units increased the risk by 60% (OR 1.63, 95% CI 1.20-2.21).[100] Overweight and obese women have a higher prevalence of hypertensive disorders, diabetes and, lower SES, but adjusting for these potential confounders did not change the risk estimates significantly.[91;92;94;98]

The association between low BMI/underweight has been less extensively studied, as most early studies applied women in the lowest BMI category as reference group.[83;90;98] Studies assessing risk of fetal death in women with low BMI did not find any significant result.[82;91;92;95;97]

Two Danish studies reported causes of fetal death in overweight and obese women, and showed higher proportions of unexplained death (OR 3.6, 95% CI 1.8-7.6) and placental dysfunction (IUGR, placental infarctions and placental abruption) (OR 5.2, 95% CI 2.5-10.9) in obese women compared to normal weight women.[91;92]

Furthermore one study reported that the risk of fetal death in overweight and obese women was modified by gestational age.[92] Nohr and colleagues noted that the increased risk of fetal death in overweight women at 37-40 weeks (hazard ratio (HR) 1.7, 95% CI 0.9-3.0) compared to normal weight women, increased more as pregnancy advanced past 40 weeks (HR 2.9, 95% CI 1.1-7.7).[92] However, a more recent study could not confirm the interaction between BMI and gestational age.[97]

An association between maternal overweight and obesity and fetal death has clearly been made, however, the biological pathway remains unclear. The proposed mechanisms are: a) increased availability of nutrients causing expanded growth in the fetus, but inability of the placenta to supply oxygen to the fetus leading to hypoxia and death,[91] b) hyperlipidemia resulting in lower levels of prostacycline and higher levels of thromboxane production increasing the risk of placental thrombosis,[94] c) higher risk of congenital anomalies in the offspring and medical disorders as diabetes and hypertensive disorders in the mother,[97] d) impaired ability to detect decreased fetal movements.[97]

2.4 Medical conditions

Maternal medical conditions associated with fetal death are presented in Table 2. In the following section, the most prevalent disorders in pregnant women are further discussed: a) hypertensive disorders and b) diabetes.

The prevalence of hypertensive disorders in the pregnant women varies across studies (depending on data source and population characteristics),[55;101-106] Studies on hypertensive disorders and fetal death were very heterogeneous and therefore not easily comparable as different fetal death definitions(20-28 weeks) and reference groups (normotensive women, low-risk pregnancies) were applied.
Hypertensive disorders in pregnancy are associated with increased risk of fetal death, most consistently demonstrated for chronic hypertension with a two to three-fold increase in risk.[53;55;66;68;101;105;107-112] The Australian study by Heard and colleagues did not report significant increased risk of stillbirth among women with chronic hypertension relative to normotensive women during 1998-2001, however, the risk was significantly elevated in an earlier time period 1991-1997 (RR 3.4).[103] Increased risk of fetal death is also reported among women with preeclampsia and pregnancy induced hypertension,[55;66;101;102;105;113-116] however, in the most recent studies low risk and even lack of risk is reported possibly due to closer monitoring and timely delivery of the compromised fetuses.[22;102;103;110;114;117] Gestational hypertension is categorized with preeclampsia in most studies from the United States (as pregnancy induced hypertension), however, when separately studied it was not associated with any increased risk of fetal death.[103;104;117]

The risk of fetal death in women with hypertension is modified by gestational age. The risk of fetal death among women with chronic hypertension is increased but stable between week 36-38 and increases steadily thereafter.[108] Among women with preeclampsia higher risk of fetal death was reported in early preeclampsia compared to late preeclampsia.[115] The exact mechanism linking fetal death and hypertension is not clear, however, women with hypertension are more likely to give birth to low birth weight infants,[101;103;104] most likely due to reduced uteroplacental blood flow.[118]

Pregnancy in women with diabetes is associated with an increased risk of fetal death, and the incidence of this disorder is increasing.[55;68;119;120]
Studies included in the review reported a 3 to 4-fold increased risk of fetal death in women with diabetes type 1,[119;121-127] and a 2 to 3-fold increased risk among women with diabetes type 2 or pregestational diabetes,[53;55;68-70;111;120;128-131] but higher risk in women requiring adjunctive insulin treatment.[132;133]

One of the largest studies on diabetes type 1 was a multi-center study conducted in Denmark in 1993-1999 (n=1218),[127] identifying suboptimal glycemic control as the main contributing factor in this study. The increased risk among women with diabetes type 2 may pertain to higher prevalence of other risk factors as high maternal age, high BMI, ethnical diversity and social deprivation.[124]
Factors contributing to the increased risk of fetal death in diabetic pregnancies are congenital anomalies (especially cardiac anomalies),[121-124;127;129-131] pre-term births[123;127;130] and fetal macrosomia.[121;127;133] Diabetic women also have a three- to six-fold increased risk of hypertensive disorders.[123;127;130]

Gestational diabetes is more prevalent than other types of diabetes; however, the association between this disorder and fetal death is uncertain. Two studies reported increased risk of fetal death,[98;134] whereas three studies did not report any increased risk of fetal death,[66;126;135] but reported higher risk of preeclampsia, caesarean section, macrosomia, preterm deliveres.[135] Lack of an association between gestational diabetes and stillbirth may be due inability to diagnose all affected women, leading to high number of affected women in the control group resulting in attenuated estimates. Wood and colleagues conducted a nested case-control study

and reported higher stilllbirth rates in pre-diabetic women (who were later diagnosed with diabetes) compared to non-diabetic controls (OR 4.7).[128] The authors suggested that the unexpected increased risk could be related to undiagnosed gestational diabetes or insulin resistance

Several mechanisms have been proposed that may lead to fetal death in diabetic women: a) uncontrolled hyperglycemia and ketoacidoses,[122] b) utero-placental impairment caused by microangiopathy, in particular among women with long duration type 1 or type 2 diabetes,[133] c) fetal hyperglycemia leading to hyperinsulinemia, which further increases anaerobic metabolism and eventually hypoxia and acidosis.[136]

Table 2. Prevalence of maternal medical conditions associated with fetal death.[10;32;101;103-105;112;113;121-124;127-133;137-141]

	Prevalence	Fetal mortality rate (per 1000 births)
Hypertensive disorders	3.7-10%	
Preeclampsia	1.1-4.2%	7-26
Gestational hypertension	2.1-4.3%	4-6
Chronic hypertension	0.5-2.1%	8-16
Diabetes	2.5-12%	
Type 1 or type 2 diabetes	0.5-2%	10-34
Gestational diabetes	2-10%	5-10
Thrombophilia	1-5%	18-40
Renal disease	<1%	15-200
Systemic lupus erythematosus	<1%	40-150
Thyroid disease	0.2-2%	12-20
Cholestasis of pregnancy	<0.1%	12-30

2.5 Smoking

Maternal smoking is associated with an increased risk of fetal death (OR 1.2-2.0), and it has been argued that a causal relationship has been revealed.[16;53;60;66;68-70;79;83;142-148] There is a linear relationship between increasing risk of fetal death and increasing quantity of tobacco used.[79;83;142;143;145] Pregnant women that quit smoking prior to 16 weeks of gestation have the same risk of fetal death as non-smokers.[143] Women, who smoked during their first pregnancy, but not their second pregnancy, have the same risk in the second pregnancy as non-smokers.[142] Maternal tobacco

exposure in utero is not associated with increased risk of stillbirth in the daughters of mothers that smoked during pregnancy.[149]

The retrospective cohort study by Gray and colleagues reported that 38% of the inequality in stillbirth occurrence in Scotland could be attributed to smoking.[147] A population-based retrospective cohort study (n=638,242) from Sweden reported an increased risk of stillbirth among smokers compared to non-smokers (OR 1.4, 95% CI 1.3-1.6), and demonstrated that after controlling for IUGR and placental complications (placental abruption, placenta previa and antepartum hemorrhage) the risk was no longer increased (RR 1.0, 95% CI 0.9-1.1).[60] This finding supports the proposed mechanism involved in fetal death associated with smoking: a) smoking causes diffusion of nicotine and carbon monoxide across the placenta which inhibits fetal oxygen transport and increases vascular resistance, b) the placenta of smokers exhibits characteristic pathological features (decidual necrosis and infarcts), which are likely caused by smoking.

Even though the rate of daily smokers among the pregnant population in Norway has declined (from 34% in 1987 to 11% in 2004 and 9.5% in 2012) the numbers are still quite high.[1;150;151]

2.6 Alcohol and coffee consumption

There are few studies of the association between alcohol consumption and the risk of fetal death.[68;79;152-157] Two case-control studies have been conducted in the United States, one did not report any increased risk of fetal death among women reporting alcohol consumption during pregnancy,[79] whereas the other study reported that each additional drink per week increased the risk by 1%.[152] The increased risk of fetal death among abstainers reported by Little and colleagues may be due to “healthy drinker effect”, as women with previous adverse outcome may abstain from alcohol in later pregnancies.[79] Two studies reported that the risk was only significantly increased at early gestation (<16 weeks and <28 weeks, respectively), with no significant risk in late pregnancy.[156;157] Kesmodel and colleagues conducted a prospective cohort study (n=24,768 women), and reported an increased risk of stillbirth in women who consumed $\geq$5 drinks per week, compared to women consuming $\leq$1 drink per week (RR 3.0, 95% CI 1.4-6.4).[153]

The proposed mechanisms that may lead to fetal death in women with high alcohol consumption are: a) fetoplacental dysfunction, b) increased production of prostaglandins, c) hypoglycemia.[153]

Coffee consumption during pregnancy has been associated with increased risk of fetal death, however, only when moderate to high amounts are consumed; ≥3 cups of coffee per day (RR 1.7, 95% CI 1.0-2.8),[153] ≥5 cups of coffee per day (OR 1.4, 95% CI 1.0-1.8),[79] ≥8 cups of coffee per day (OR 3.0, 95% CI 1.5-1.9).[158] Bech and colleagues conducted a prospective cohort study in Denmark and reported an increased risk of fetal death at 20-27 weeks of gestation in women consuming ≥4 cups of coffee per day, whereas the risk was not significantly increased at gestational age ≥28 weeks.[159]

The proposed mechanisms that may lead to fetal death in women with high coffee consumption are: a) increased levels of catecholamines in the maternal circulation that may cause vasoconstriction, b) placental dysfunction.[159]

2.7 Social disparity and race/ethnicity

Pregnant women reporting low SES or belonging to a racial/ethnic minority face a nearly two-fold increased risk of fetal death.[24;25;68-70;147;148;160-185] In modern urban settings, many risk factors often coexist (low SES, racial/ethnic minority, smoking, teenage pregnancies) making the contribution of each risk factor difficult to disentangle. Women with low SES are more often smokers, have a higher BMI, and are more often unmarried, but even after adjusting for these risk factors the risk of fetal death is increased compared to women with high SES,[164;166;168] especially for antepartum fetal deaths.[163;168] Stephansson and colleagues found that even after controlling for an extensive number of maternal and pregnancy-related risk factors (maternal age, height, BMI, smoking, country of birth, number of antenatal care visits, involuntary childlessness) and excluding pregnant women with medical conditions (diabetes, pre-eclampsia and eclampsia) the increased risk related to low SES remained.[168]

Social inequality in stillbirth may be explained by an increased frequency of negative life events, low level of education and more emotional problems (stress, anxiety and

depression), whereas the contribution of health risk behaviors (smoking, obesity) is small.[148;168] Educational inequality in stillbirth is reported by several studies, and appears to persist over time.[170;171] In addition, social disparity is more strongly associated with specific causes of stillbirth (unexplained,[25;172] SGA,[25;172] diabetes[25]), and stillbirth at preterm gestation.[25]

Substantial racial and ethnical disparity in stillbirth risk has recently been reported by several studies in high-income countries.[24;160;162;165;167;169;173;174;176-186] Most studies regarding race are from the United States, and report an increased risk of fetal death among Black women compared to White women (OR 1.6-3.1),[24;160;162;165;176;177;181] and a higher incidence of IUGR and pre-term births.[162;165;181] The risk of stillbirth among Black women is reported to be greatest at 20-23 weeks of gestation and at 41 weeks compared to White women.[24] A Canadian study reported highest risk at late gestation (>37 weeks) among Aboriginal Canadian compared to non-Aboriginal Canadian.[186]

Ethnical inequality in stillbirth has been reported by studies comparing outcome among native-born and immigrant populations throughout Europe.[173;174;179;180;183-185] Populations studied are heterogeneous and reason for the observed disparity remains uncertain.

Proposed mechanisms to explain inequality in stillbirth risk among minorities are low SES,[177;183] higher prevalence of maternal diseases,[185;186] teenage pregnancies, and late start of prenatal care,[179] consanguinity and congenital anomalies.[186] Other studies did not confirm these associations.[174;179;180]

Two Norwegian studies reported a higher risk for antepartum fetal death among ethnic Somali women (OR 2.5, 95% CI 1.7-3.7) and non-Western women (OR 2.2, 95% CI 1.3-3.8), compared to women of Norwegian and Western origin, respectively.[167;169] The author hypothesized that sub-optimal care (defined as failure to act on non-reassuring fetal status or incorrect assessment of labor progression) may be an important contributing factor.[167] The racial/ethnic disparity in pregnancy outcome may also be due to cultural differences concerning nutrition, self-care and compliance with medical recommendations, miscommunication and reduced effectiveness or access to health care.

2.8 Intrauterine growth restriction

IUGR, in most studies defined as SGA with weight below the 10th percentile for a specific gestational age, is associated with increased risk of fetal death.[8;70;80;84;187-195] SGA is often used in studies to indicate IUGR although not all SGA fetuses are pathological small. The magnitude of the risk also depends on whether population-based birth weight (based on birth weights of infants born at particular gestational ages including both normal and abnormal outcome), population-based intrauterine fetal weights (assessed by ultrasound) or customized birth weight percentiles have been employed (based on ultrasound assessed intrauterine weights adjusted for maternal height, weight, parity and ethnic group, with the purpose to differentiate between constitutional and pathological smallness).[80;188;190;192]

Of thirteen reviewed studies, nine retrospective cohort studies[70;84;187-189;191-193;195] and four case-control studies,[8;80;190;194] all reported increased risk of fetal death among fetuses that were SGA, and with accelerated risk as pregnancy advances. In the case-control study by Frøen and colleagues, among 76 validated unexplained fetal deaths (antepartum deaths that had undergone thorough post-mortem investigations) 52% were SGA (birth weight <10th percentile of standard adjusted for gestational age, maternal weight, height, ethnicity and parity, and sex of the baby).[190] The authors concluded that IUGR is one of the strongest risk factors for fetal death particularly among smokers and overweight and obese women.

Interestingly an interaction between IUGR and certain risk factors such smoking and hypertensive disorders have recently been demonstrated. Gardosi and colleagues demonstrated that women in West Midlands who smoked during pregnancy but did not have a growth restricted fetus had the same risk of fetal death as non-smokers, whereas the risk increased when the fetus was growth restricted, but the highest risk was observed in non-smokers with IUGR.[70] Likewise Helgadottir and colleagues in Norway observed that women with hypertensive disorders in pregnancy did not have an increased risk of fetal death without IUGR, whereas the risk increased when the fetus was growth restricted, and was highest among normotensive women with IUGR.[53] Gardosi and colleagues concluded that women without recognized risk factors such as smoking may be considered low risk and therefore are less likely to have IUGR detected antenatally.

IUGR may be caused by maternal, placental, uterine or fetal causes; however, the majority of cases are associated with placental insufficiency.[196]

2.9 Gestational age

Several studies have reported increased risk of fetal death as pregnancy continues past term.[85;189;197-202] The fetal mortality rate increases two- to three-fold at 42 weeks (1.6-3.7 per 1000 ongoing pregnancies) compared to 40 weeks (0.3-1.1 per 1000 ongoing pregnancies).[85;189;197;199] Some of the reported variation in fetal mortality is likely caused by the different methods of estimating gestational age (last menstrual period (LMP), or ultrasound), the local policy regarding expectant management or routine induction of labor at 41 weeks, and the period studied. The presumed mechanism is placental insufficiency, and this is supported by histological examinations of post-term placentas that revealed calcifications, infarcts, perivillous fibrin deposits and arterial thrombosis.[189]

The most recent studies report comparative estimates of gestational-age-specific fetal and neonatal mortality in high- and low risk pregnancies in an effort to deliver data regarding the optimal time for delivery.[201;202]

The association between stillbirth and certain risk factors such as maternal age $\geq$35 years, BMI $\geq$25, SGA, educational attainment and race is modified by gestational age.[23-25;60;85;92;105;189] Reddy and colleagues reported that the RR of fetal death at 41 weeks was 300% higher in women $\geq$40 years of age (RR 3.13, 95% CI 2.02-4.85) compared to women <35 years, whereas it was 85% higher at gestational age 39-40 weeks (RR 1.85, 95% CI 1.43-2.39).[23]

2.10 Previous stillbirth

Increased risk of recurrent fetal death among women with a previous fetal death has been reported in two case-control studies (OR 10.2 and HR 5.8),[203;204] and two population-based cohort studies.[205;206] Samueloff and colleagues reported higher incidence of diabetes, hypertensive disorders and low birth weight infants among women with recurrent fetal death.[203] Other previous adverse outcomes of the first pregnancy, such as preterm birth, giving birth to a SGA infant and developing pre-eclampsia has also been associated with increased risk of fetal death in the subsequent pregnancy.[207-210]

Table 3. Studies of risk factors for fetal death.

Paper	Outcome fetal death	Country and study period	Sample size	Study design	Independent variable	Findings
*Raymond E.G. et al. 1994[60]	≥28 weeks	Sweden 1986-1989	638 242	Retrospective cohort	Maternal age Parity Smoking	Increased risk of FD for women aged ≥35 years (OR 1.4), after exclusion of women with hypertension, diabetes, placental complications and IUGR. Increased risk of FD in nulliparas (OR 1.2), women smoking (OR 1.4), with higher risk >32 weeks
Fretts R.C. et al. 1995[50]	≥500 g	Canada 1961-1974 and 1978-1993	94 346	Retrospective cohort	Maternal age Parity	Increased risk of FD for women aged 35-39 years (OR 1.9), ≥40 years (OR 2.4) during 1978-1993 nulliparas (OR 1.9), high parity (>3 children) (OR 1.7) in 1961-1974. In 1978-1993 high parity (OR 1.8)
Fretts R.C. et al. 1997[51]	≥500 g	Canada 1961-1974 and 1978-1995	101 640	Retrospective cohort	Maternal age	Increased risk of FD in women ≥35 years in both time periods: 1961-1974 (OR 1.5) and 1978-1995 (OR 1.8).
Nybo-Andersen A. et al. 2000[58]	≥28 weeks	Denmark 1978-1992	634 272	Prospective cohort	Maternal age	Increased risk of FD for women aged ≤19 or ≥35 years
Jolly M. et al. 2000[76]	≥24 weeks	United Kingdom 1988-1997	341 708	Retrospective cohort	Maternal age	No increased risk of FD in women <18 years, after adjusting for ethnicity, parity, BMI, hypertension, diabetes, smoking
Jolly M. et al. 2000[57]	≥24 weeks	United Kingdom 1988-1997	385 120	Retrospective cohort	Maternal age	Increased risk of FD in women aged 35-40 years (OR 1.4), >40 years (OR 1.8), adjusted for GD, PE,smoking
Salihu H.M. et al. 2003[61]	≥20 weeks	United States 1997-1999	12 066 854	Retrospective cohort	Maternal age	Increased risk of FD in women aged 30-39 years (OR 1.1), 40-49 years (OR 1.9) and >50 years (OR 2.2), after adjusting of parity, marital status, education, smoking, drinking, year and prenatal care
Canterino J.C. et al. 2004[55]	≥24 weeks	United States 1995-2000	21 610 873	Retrospective cohort	Maternal age CH, PIH, Any diabetes (GD + PD)	Increased risk of FD for women aged 35-39 years (RR 1.3), 40-44 years (RR 1.7) and 45-49 years (RR 2.4), no increased risk among women aged 15-19 years, CH (RR 2.4) and PIH (RR 1.5), diabetes (RR 1.9) after adjustment for parity, race, marital status, prenatal care, education, smoking, placental abruption

Jacobsson B. et al. 2004[56]	≥28 weeks	Sweden 1987-2001	1 566 313	Retrospective cohort	Maternal age	Increased risk of FD in women aged 40-44 years (OR 2.1) and ≥45 years (OR 3.8), after adjusting for parity, marital status, malformations, smoking, disease and multiple pregnancy
Bateman B.T. et al. 2006[54]	≥22 weeks	United States 1995-2000	5 874 203	Retrospective cohort	Maternal age	Increased risk of FD in women aged ≤19 years (OR 1.1), 35-39 years (OR 1.3) and ≥40 years (OR 1.7), after adjusting for maternal, placental and fetal risk factors
*Reddy U.M. et al. 2006[23]	≥20 weeks	United States 2001-2002	5 458 735	Retrospective cohort	Maternal age Parity	Increased risk of FD at 37 to 41 weeks for women aged 35-39 years (RR 1.3) and >40 years (RR 1.9), even after adjusting for disease, parity and race/ethnicity Nulliparas had 2-3 fold increased risk of FD in all maternal age groups
Salihu H.M. et al. 2006[72]	≥20 weeks	United States 1989-2000	17 842 467	Retrospective cohort	Maternal age	Increased risk of FD in girls aged 10-14 years (OR 1.6) and 15-19 years (OR 1.1), pre-term birth accounted for the excess risk
O'Leary C.M. et al. 2007[59]	≥20 weeks	Australia 1984-2003	499 595	Retrospective cohort	Maternal age Parity	Risk of FD in women aged 35-39 years (OR 1.6 in 1984-1993 vs. 1.5 in 1994-2003). Adjustment for year, parity and sociodemographic factors. High FD rate in nulliparas (8/1000 births) and high parity (>4 children) (12/1000) compared to uniparas (6 /1000)
Hoffman M.C. et al. 2007[52]	≥20 weeks	United States 1989-2004	126 402	Retrospective cohort	Maternal age	After adjustment for race/ethnicity, parity, hypertension and diabetes an increased risk of FD at gestational week 40-41 among women aged ≥40 years (OR 2.3)
Haldre K. et al. 2007[75]	≥500 g	Estonia 1992-2002	51 890	Retrospective cohort	Maternal age	Women aged ≤17 or 18-19 years did not have increased risk of FD relative to women aged 20-24 years
Salihu H.M. et al. 2008[63]	≥20 weeks	United States 1978-1997	1 235 307	Retrospective cohort	Maternal age	Increased adjusted HR of FD among women aged 30-34 years (1.4), 35-39 (2.0) and >40 years (3.4) relative to women aged 20-24 years.
De Vienne C.M. et al. 2009[73]	≥22 weeks	France 1994-2001	8 514	Retrospective cohort	Maternal age	Increased risk of FD among teenagers (RR 1.4-1.2) compared to women aged 20 years.
Reddy U.M. et al. 2010[68]	≥23 weeks	United States 2002-2008	174 809	Retrospective cohort	Maternal age, race, parity, BMI(18.5-24.9), PD, CH, smoking, alcohol	Increased risk of FD among women aged 35-39 (HR1.4), >40 (HR 1.6), nulliparas (HR 1.2), Black race (HR 2.0), Hispanic (HR 1.5), BMI>30 (HR 1.3), PD (HR 2.7), CH (HR 2.0), smoking (HR 1.6), Alcohol during pregnancy (HR 1.7)

Saade G.R. et al. 2011[69]	≥20 weeks	United States 2006-2008	2430	Case-control	Maternal age, race, PD, smoking, BMI (18.5-24.9), recurrence	Factors associated with FD, maternal age≥40 years (OR 2.4), Black race (OR 2.1), PD (OR 2.5), BMI 25-29.9 (OR 1.4), BMI 30-34 (OR 1.7), BMI≥35 (1.7), smoking (OR 1.6), previous FD (OR 5.9)
Helgadottir L.B. et al. 2011[53]	≥23 weeks or ≥500g	Norway 2004-2008	88 987	Case-control	Maternal age, PD, CH, smoking,	Factors associated with FD maternal age ≥40 years (OR 2.5), CH (OR 2.1), PD(OR 4.8), smoking (OR 2.6)
Balayla J. et al. 2011[67]	≥24 weeks	United States 1995-2004	37 504 230	Retrospective cohort	Maternal age	Women <15 years had increased risk of FD (OR 1.3), 35-40 year (OR 1.3), 40-45 years (OR 1.6), and >45 years (OR 2.2) compared to women aged 25-30 years.
Kenny L.C. et al. 2013[62]	≥24 weeks	United Kingdom 2004-2008	274 563	Retrospective cohort	Maternal age	Increased risk of FD among women aged 30-34 years (adjusted RR 1.2), 35-39 years (1.4), ≥40 years (1.8) compared to women aged 20-29 years
*Gordon A. et al. 2013[66]	≥22 weeks	Australia 2002-2006	327 690	Retrospective cohort	Maternal age Parity PD, GD CH,PE Smoking	Increased risk of FD in women 35-39 years (adjusted HR 1.4), and ≥40 years (HR 2.4). Nullipara (HR 1.2), PD (HR 2.7),GD (HR 0.7), CH (HR 2.8), PE (HR 1.1), Smoking (HR 1.8)
*Lisonkova S. et al. 2013[65]	≥22 weeks	United States 2003-2005	6 846 695	Retrospective cohort	Maternal age	Increased risk of FD among women ≥35 years compared to women aged 20-29 years in early gestation (weeks 22-33, OR 1.4) and late gestation (weeks ≥34, OR 1.7)
*Page J.M. et al. 2013[64]	≥37 weeks	United States 2005	2 961 382	Retrospective cohort	Maternal age	Increased risk of FD with increasing gestation at term especially among older mothers
Warshak C.R. et al. 2013[74]	≥20 weeks	United States 1998-2005	529 445	Retrospective cohort	Maternal age	Women aged <18 years increased risk of FD (adjusted RR 1.2) compared to women 18-35 years.
Gardosi J. et al. 2013[70]	≥24 weeks	United Kingdom 2009-2011	92 218	Retrospective cohort	Maternal age, parity, ethnicity, BMI (18.5-24.9), smoking, PD, IUGR	No increased risk of FD among women ≥35 years. Increased risk of FD among nulliparas (RR 1.8), parity≥3 (RR 1.6), African (RR 2.4), African-Caribbean (2.3), Indian (RR 2.1), Pakistani (RR 3.0), BMI≥35 (RR 1.6), PD (RR 3.9), Smoking (RR 2.5), IUGR ((7.8)
Little R.E. et al. 1993[79]	≥28 weeks or ≥1000 g	United States 1980	4 667	Case-control	Parity BMI (reference <18.2) Smoking Alcohol Coffee/tea	Increased risk of FD in nulliparas (OR 1.3), BMI 22.2-26.1 (OR 1.5), BMI 26.2-30.1 (OR 1.6) and BMI>30.1 (OR 2.2), smoking 1-19 cigarettes/day (OR 1.3), 20-29 cigarettes/day (OR 1.4), abstinence from alcohol associated with intrapartum FD, >5 cups of coffee/tea /day (OR 1.4)

Cnattingius S. et al. 1998[84]	≥28 weeks	Sweden 1983-1992	1 026 249	Retrospective cohort	Parity BW/IUGR	Increased risk of FD in nulliparas (OR 1.4), in pregnancies with IUGR, mild IUGR (RR 2.7) and extreme IUGR (RR 22.2). Risk modified by maternal age, height, smoking and hypertensive disorder
Cnattingius S. et al 1998[83]	≥28 weeks	Sweden 1992-1993	167 750	Retrospective cohort	Parity BMI (<20) Smoking	Increased risk of FD in nulliparas (OR 1.2), BMI 25-29.9 (OR 1.7), BMI >30 (OR 2.7), smoking 1-9 cigarettes/day (OR 1.3) or >10 cigarettes per day (OR 1.7), adjusted for age, parity, education, smoking, height, cohabitation
Aliyu M.H. et al. 2005[81]	≥20 weeks	United States 1989-2000	27 069 385	Retrospective cohort	Parity	Fetal mortality increased with increasing parity among women with 5-9 (OR 1.1), 10-14 (OR 2.0) and >15 (OR 2.3) prior live births
Jacquemyn Y. et al. 2006[78]	≥20 weeks or ≥500 g	Belgium 2003	59 253	Case-control	Parity	Women with 5-9 prior births had an increased risk of FD compared to women with 2-4 prior births
Hilder L. et al. 2007[85]	≥37 weeks	United Kingdom 1989-1991	145 695	Retrospective cohort	Parity Post-term	Higher risk of FD post-term (>42 weeks) among nulliparas relative to uniparas or multiparas (RR 3.0) Increased risk of FD as pregnancy progresses (for nulliparas) 41 weeks (1.4 per 1000 ongoing pregnancies) and >42 weeks (3,0 per 1000)
McCowan L.M.E. et al. 2007[80]	≥20 weeks or ≥400 g	New Zealand 1993-2000	437	Case-control	Parity BW/IUGR	Increased risk of FD in nulliparas (OR 1.3) and women with high parity (>3 children) (OR 1.5), 46% of FD >24 weeks were IUGR according to customized standards and 34% were IUGR according to population standards
Sebire N.J. et al. 2001[94]	≥24 weeks	United Kingdom 1989-1997	287 213	Retrospective cohort	BMI (20-25)	Increased risk of FD in women with BMI 25-30 (OR 1.1) and BMI >30 (OR 1.4), after adjusting for diabetes, pre-eclampsia and smoking
Stephansson O. et al. 2001[98]	≥28 weeks	Sweden 1987-1996	1 339	Case-control	BMI (<19.9) GD, PD	Increased risk of FD with increasing BMI, BMI 20-24.9 (OR 1.2), BMI 25-29.9 (OR 1.9), BMI >30 (OR 2.1), Higher prevalence of gestational diabetes among cases (12.8%) than among controls (9.1%)
Cedergren M.I. et al. 2004[90]	≥28 weeks	Sweden 1992-2001	805 275	Prospective cohort	BMI (19.8-26)	Increased risk of FD in women BMI 29.1-35 (OR 1.8), BMI 35.1-40 (OR 2.0) and BMI >40 (OR 2.8), after adjusting for maternal age, parity, year of birth, smoking
Kristensen J. et al. 2005[91]	≥28 weeks	Denmark 1989-1996	24 505	Prospective cohort	BMI (18.5-24.9)	Increased risk of FD in women with BMI >30 (OR 2.8), but not in women with BMI <30

Nohr E.A. et al. 2005[92]	≥28 weeks	Denmark 1998-2001	54 505	Prospective cohort	BMI (18.5-24.9)	Increased risk of FD in women with BMI >30 with advancing gestation: weeks 37-39 (HR 3.5) and weeks >40 (HR 4.6), after adjusting for age, parity, height, socioоccupational status, exercise, smoking, alcohol consumption, coffee consumption.
Villamor E. et al. 2006[100]	≥28 weeks	Sweden 1990-1998	151 025	Prospective cohort	BMI	Women whose BMI rose >3 units between the first and second pregnancy had increased risk of FD (OR 1.6)
Salihu H.M. et al. 2007[93]	≥20 weeks	United States 1978-1997	1 413 953	Retrospective cohort	BMI (18.5-24.9)	Increased risk of FD in women BMI 30-34.9 (HR 1.3), BMI 35-39.9 (HR 1.4) and BMI >40 (HR 1.9), after adjusting for race, age, education, marital status, smoking, prenatal care, fetal gender, year of birth
Bhattacharya S. et al. 2007[82]	≥24 weeks	United Kingdom 1976-2005	24 241	Retrospective cohort	BMI (20-24.9)	Increased risk of FD in women with BMI 30-34.9 (OR 1.8)
Khashan A.S. et al. 2009[99]	≥24 weeks	United Kingdom 2004-2006	99 403	Retrospective cohort	BMI (18.5-24.9)	High or low BMI not significantly associated with increased risk of FD, adjustment for infant sex, maternal age, SES, parity and ethnicity
Tennant P.W.G. et al. 2011[97]	≥20 weeks	United Kingdom 2003-2005	29 856	Retrospective cohort	BMI (18.5-24.9)	Increased risk of FD among obese women (BMI ≥30) (OR 2.2) adjusted for age, ethnicity, smoking, SES
Whiteman V.E. et al. 2011[96]	≥20 weeks	United States 1978-2005	218 389	Retrospective cohort	BMI (18.5-24.9)	Interpregnancy change in BMI increases risk of FD, highest HR when overweight women get obese (HR 1.4)
Scott-Pillai R. et al. 2013[95]	≥24 weeks	United Kingdom 2004-2011	30 298	Retrospective cohort	BMI (18.5-24.9)	Increased risk of FD among women with BMI>40 (RR 3.0) adjusted for age, parity, SES, parity, year
Fretts R.C. et al. 1992[22]	≥500 g	Canada 1961-1988	88 651	Retrospective cohort	Any hypertension	Increased risk of FD in women with hypertension during 1961-1969 (RR 2.4) but not significantly increased 1980-1988
Ananth C.V. et al. 1995[101]	≥20 weeks	United States 1988-1991	387 655	Retrospective cohort	CH, PIH, eclampsia	Increased risk of FD >28 weeks of gestation in women with CH (OR 3.3) and PIH (OR 1.4)
*Smulian J.C. et al. 2002[105]	≥24 weeks	United States 1995-1997	10 614 679	Retrospective cohort	CH, PIH, eclampsia	Increased risk of FD in women with CH (RR 2.7) and PIH (RR 1.4), after adjusting for gestational age, anemia, fever, age, parity, race/ethnicity, marital status. Highest risk past gestational week 38
Allen V.M. et al. 2004[113]	≥20 weeks and ≥500 g	Canada 1988-2000	135 466	Retrospective cohort	CH, PIH, SuPE	Women with any hypertensive disorder during pregnancy had increased risk of FD (RR 1.4)
Heard A.R. et al. 2004[103]	≥400 g or ≥20 weeks	Australia 1991-2001	70 386	Retrospective cohort	CH, PIH, SuPE	No significant increased risk of FD in women with hypertension during 1998-2001

Roberts C.L. et al. 2005[104]	≥400 g or ≥20 weeks	Australia 2000-2002	250 173	Cross-sectional	CH, PE, GH, SuPE	Increased risk of FD in women with CH (OR 3.5)
Basso O. et al. 2006[102]	≥24 weeks	Norway 1967-2003	804 448	Retrospective cohort	PE	The risk of FD in women with PE decreased from 1967-78 (OR 4.2) to 1991-2003 (OR 1.3)
Aagaard-Tillery K.M. et al. 2006[107]	≥400 g or ≥20 weeks	United States 1992-2002	4 286	Case-control	CH, PE, eclampsia	Increased risk of FD in women with CH (HR 2.2)
Gilbert W.M. et al. 2007[112]	≥22 weeks	United States 1991-2001	29 842	Retrospective cohort	CH	Increased risk of FD in women with CH (OR 2.4)
Zetterström K. et al. 2008[109]	≥28 weeks	Sweden 1992-2004	866 188	Prospective cohort	CH	Increased risk of FD among women with CH (OR 2.0) adjusted for age, parity, smoking and BMI
*Hutcheon J.A. et al. 2010[108]	≥36 weeks	United States 1995-2005	171 669	Retrospective cohort	CH	Increased risk of FD among women with CH and risk increases steadily from week 38 to week 41
Ananth C.V. et al. 2010[116]	≥24 weeks	United States 1990-1991 and 2003-2004	57 208 959	Retrospective cohort	PIH	Increased risk of FD among women with PIH in both periods, higher risk among multipara and Black women
Tuuli M.G. et al. 2011[110]	≥20 weeks	United States 1990-2008	62 841	Retrospective cohort	CH, PE, SuPE	Increased risk of FD in women with CH (OR 1.9), not PE or SuPE, adjusted for smoking, diabetes, race, BMI,
Cruz M.O. et al. 2011[117]	>23 weeks	United States 2002-2008	27 944	Retrospective cohort	GH, mild PE, mild CH	Hypertensive disorders not associated with increased risk of FD
Yanit K.E. et al. 2012[111]		United States 2006	532 088	Retrospective cohort	CH PD	Increased risk of FD among women with CH (OR 2.5), PD (OR 3.2) CH+PD (OR 7.1), adjusted for parity, age, renal disease, care, insurance, education, obesity
Klungsøyr K. et al. 2012[114]	≥500 g or ≥22 weeks	Norway 1967-2008	2 416 501	Retrospective cohort	PE	Increased risk of FD among women with PE, large reduction in risk during study period (RR 4.5 – RR 1.3)
*Lisonkova S. et al. 2013[115]	≥20 weeks	United States 2003-2008	456 668	Retrospective cohort	PE	Increased risk of FD in early-onset PE (OR 5.8) and not significant increased among late-onset PE (OR 1.3), adjusted for race, age, parity, education, sex, marital status, infertility treatment, CH, diabetes, anomalies
Cnattingius S. et al. 1994[131]	≥28 weeks	Sweden 1983-1986	4 914	Prospective cohort	PD	Increased risk of FD in women with type 1 and type 2 diabetes (RR 3.3)
Casson I.F. et al. 1997[132]	≥24 weeks	United Kingdom 1990-1994	462	Retrospective cohort	Insulin dependent PD	Increased risk of FD in women with type 1 and type 2 insulin-dependent diabetes (RR 5.0)
Wood S.L. et al. 2003[128]	≥20 weeks or ≥500 g	United Kingdom 1988-1999	13 953	Retrospective cohort and case-control	PD	Increased risk of FD in prediabetic pregnancies (pregnancy prior to onset of diabetes) (OR 4.7), and in pregnancies with diabetes (OR 4.4)

Penney G.C. et al. 2003[121]	≥24 weeks	Scotland 1998-1999	273	Prospective cohort	Dia1	Increased FD rate in women with Dia1 (18.5 per 1000 births) compared to all Scottish births (5.2 per 1000)
Lauenborg J. et al. 2003[122]	≥24 weeks	Denmark 1990-2000	1 361	Retrospective cohort	Dia1	FD rate in women with Dia1 was 18 per 1000 births
Dunne F. et al. 2003[129]	≥24 weeks	United Kingdom 1990-2002	182	Retrospective cohort	Dia2	Increased FD rate in women with Dia2 (12.2 per 1000 births)
Evers I.M. et al. 2004[123]	≥24 weeks	Netherlands 1999-2000	323	Prospective cohort	Dia1	Fetal mortality rate in women with Dia1 was 18.5 per 1000 births
Jensen D.M. et al. 2004[127]	≥24 weeks	Denmark 1993-1999	1 218	Prospective cohort	Dia1	Increased risk of FD in women with Dia1 (RR 4.7)
*Silva I.S. et al. 2005[133]	≥24 weeks	United Kingdom 1979-1995	1 112	Prospective cohort	Insulin-treated PD	Increased risk of FD in women with insulin-treated pregestational diabetes (RR 4.7), the risk was highest ≥37 weeks of gestation (RR 6.4)
Yang J. et al. 2006[130]	≥20 weeks	Canada 1988-2002	151 105	Prospective cohort	PD	Increased risk of FD in women with PD (RR 2.5)
Macintosh M.C.M. et al. 2006[124]	≥24 weeks	United Kingdom 2002-2003	2 359	Retrospective cohort	Dia1 and Dia2	Increased risk of FD in women with Dia1 (RR 4.5) and Dia2 (RR 5.1)
Pettica P. et al. 2009[126]	≥20 weeks	Canada 2005-2006	120 604	Retrospective cohort	GD, PD	Increased risk of FD in women with PD (RR 2.3), but no increased risk in GD
Persson M. et al. 2009[125]	≥28 weeks	Sweden 1991-2003	1 265 296	Retrospective cohort	Dia1	Increased risk of FD in Dia1 (OR 3.3) adjusted for age, parity, BMI, CH. Smoking, ethnicity
Fadl H.E. et al.2010[135]	≥28 weeks	Sweden 1991-2003	1 260 297	Retrospective cohort	GD	No increased risk of FD
Beyerlein A. et al. 2010[120]	≥500 g	Germany 1987-2007	2 292 053	Retrospective cohort	PD	Increased risk of FD in PD but declining trend over time
Eidem I. et al. 2011[119]	≥22 weeks	Norway 1985-2004	1 162 399	Retrospective cohort	Dia1	Increased risk of FD in Dia1 (OR 3.8), adjusted for age, parity, year, sex, education, ethnicity and marital status. Declining trend with time. Increased risk at term.
*Rosenstein M.G. et al 2012[134]	≥36 weeks	United States 1997-2006	4 190 953	Retrospective cohort	GD	Increased risk of FD in GD (RR 1.3), and risk increased from 36 week to 42 weeks
Wisborg K. et al. 2001[143]	>28 weeks	Denmark 1989-1996	25 102	Prospective cohort	Smoking	Increased risk of FD among women smoking during pregnancy (OR 2.0). If women stopped smoking in 1st trimester no increased risk
Frøen J.F. et al. 2001[16]	≥22 weeks	Norway 1986-1995	873	Case-control	Smoking	Higher prevalence of women smoking >10 cigarettes per day among women with FD (OR 3.6)

Högberg L. et al. 2007[142]	≥28 weeks	Sweden 1983-2001	526 691	Prospective cohort	Smoking	Increased risk of FD in women smoking 1-9 (OR 1.2) or >10 (OR 1.5) cigarettes/day. Women smoking in 2nd pregnancy (OR 1.6), but no increased risk if they quit
Salihu H.M. et al. 2008[144]	≥20 weeks	United States 1978-1997	1 235 307	Case-control	Smoking	Increased risk of FD among smokers (OR 1.3) adjusted for education, year and antenatal care
Gray R. et al. 2009[147]	≥24 weeks	Scotland 1994-2003	529 317	Retrospective cohort	Smoking SES	Increased risk of FD the most deprived category (OR 1.5) when controlled for smoking (OR 1.3), 38% of inequality explained by smoking
Aliyu M.H. et al. 2010[146]	≥20 weeks	United States 1978-1997	633 849	Retrospective cohort	Smoking	Increased risk of FD among smoking adolescent (<15 years) (HR 3.3), than women 20-24 years (HR 1.5)
Cupul-Uicab L.A: et al. 2011[149]	≥20 weeks	Norway 1999-2008	76 357	Retrospective cohort	Smoking	In utero exposure to maternal smoking did not increase the daughters risk of FD
Aliyu M.H. et al. 2011[145]	≥20 weeks	United States 1989-2005	1 312 505	Retrospective cohort	Smoking	Increasing risk of FD with increasing quantity of cigarettes smoked (<20 cigarettes/day OR 1.2) vs. (≥20 cigarettes/day OR1.3)
Faden V.B et al. 1997[152]	>28 weeks	United States 1988	13 262	Case-control	Alcohol	Increased risk of FD in women consuming alcohol during pregnancy (OR 1.01). Each additional drink per week increased the risk by 1%
Kesmodel U. et al. 2002[1153]	≥28 weeks	Denmark 1989-1996	24 768	Prospective cohort	Alcohol Caffeine	Increased risk of FD in women >5 drinks/week (RR 3.0) compared to <1 drink/week. >3 cups of coffee per day) (RR 1.7)
Aliyu M.H: et al. 2008[157]	≥20 weeks	United States 1989-1997	691 046	Retrospective cohort	Alcohol	Increased risk of early FD (<28 weeks) among drinkers (HR 1.8) when adjusted for marital status, education, antenatal care, fetal sex and birth year
Strandberg-Larsen K. et al. 2008[154]	≥22 weeks	Denmark 1996-2002	98 201	Retrospective cohort	Alcohol	Increased risk of FD when ≥3 binge drinking episodes during pregnancy (HR 1.6) adjusted for previous abortion, coffee, time to pregnancy, occupation
Andersen A.M. et al. 2012[156]	≥22 weeks	Denmark 1996-2003	91 843	Prospective cohort	Alcohol	No increased risk of FD (≥16 weeks), adjustment made for age, parity, previous abortion, smoking, coffee, change in alcohol consumption
O'Leary C. et al. 2012[155]	≥400 g or ≥20 weeks	Australia 1983-2007	85 083	Retrospective cohort	Alcohol	Increased risk of FD if any alcohol diagnosis recorded (non-Aboriginal OR 1.4 and Aboriginal OR 1.3) adjusted for age, year, marital status, parity, illicit drugs, mental health
Wisborg K. et al. 2003[158]	≥28 weeks	Denmark 1989-1996	18 478	Prospective cohort	Coffee	Women drinking >8 cups of coffee per day have increased risk of FD (OR 3.0)

*Bech B.H. et al. 2005[159]	20-27 weeks and >28 weeks	Denmark 1996-2002	88 482	Prospective cohort	Coffee	Increased risk of FD (20-27 weeks) associated with 4-7 cups of coffee per day (HR 1.5) and >8 (HR 2.3). Not significant risk of FD >28 weeks
Haglund B. et al. 1993[164]	≥28 weeks	Sweden 1985-1986	185 156	Prospective cohort	SES Education	Highest risk of FD among unskilled blue-collar workers (OR 1.8) and women with <9 years of education (OR 1.6), after adjusting for age, parity and smoking
Copper R.L. et al. 1994[160]	≥20 weeks	United States 1982-1986	34 350	Prospective cohort	Race	Black women had increased risk of FD compared to White women (OR 1.6)
Stephansson O. et al. 2001[168]	≥28 weeks	Sweden 1987-1996	1 404	Case-control	SES	Higher prevalence of unskilled blue-collar workers among cases (OR 1.9), after adjusting for age, country of birth, BMI, height, smoking
Guilddea Z.E.S. et al. 2001[163]	≥20 weeks	United Kingdom 1993-1998	212 219	Retrospective cohort	Social deprivation	Fetal mortality rate significantly associated with social deprivation
Vangen S. et al. 2002[169]	≥22 weeks	Norway 1986-1998	703 925	Cross-sectional	Ethnicity	Higher risk of FD among women of Somali origin (OR 2.5) compared to Norwegian women
Craig E.D. et al. 2004[161]	≥28 weeks	New-Zealand 1980-2001	1 194 895	Retrospective cohort	Ethnicity	During 1996-2001 Pacific women (OR 1.3) and Indian women (OR 1.7) had highest risk of FD
Salihu H.M. et al. 2004[181]	≥24 weeks	United States 1995-1998	14 348 318	Retrospective cohort	Race	Black women had increased risk of FD compared to White women (OR 2.9)
Getahun D. et al. 2005[162]	≥20 weeks	United States 1995-2001	21 005 786	Retrospective cohort	Race	Increased risk of FD parents Black (RR 1.7), mother Black/father White (RR 1.4), mother White/father Black (RR 1.2)
Luo Z. et al. 2006[166]	≥22 weeks	Canada 1991-2000	825 349	Retrospective cohort	SES Education	Increased risk of FD low maternal education (OR 1.5) and neighborhood income associated (OR 1.3)
Healy A.J. et al. 2006[165]	>24 weeks	United States 1999-2002	35 529	Prospective cohort	Race	Increased risk of FD in Black women (OR 3.1) compared to White women
Saastad E. et al. 2007[167]	≥24 weeks	Norway 1998-2003	356	Retrospective audit	Ethnicity	Increased risk of FD among non-Western women (OR 2.2) and increased risk of sub-optimal care (OR 2.4)
Getahun D. et al. 2007[175]	≥20 weeks	United States 1989-1997	626 883	Cross-sectional	Race	Increased risk of FD among Black women (5.6/1000) compared to White women (3.4/1000)
Goy J. et al. 2008[148]	Birth weight ≥500 g	Canada 1999-2001	510	Case-control	SES Smoking Previous loss	Increased risk of FD in lowest household income category (OR 2.8), adjusted for age, province, smoking, inactivity, previous loss, fertility treatment. Increased risk among smokers (OR 2.1),with previous loss (OR 2.0)

*Willinger M. et al. 2009[24]	≥20 weeks	United States 2001-2002	5 138 122	Retrospective cohort	Race	Black women increased risk of FD throughout pregnancy, highest risk week 20-23 (RR 2.8), week 41 weeks (RR 1.7)
Villadsen S.F. et al. 2009[183]	≥28 weeks	Denmark¨ 1981-2003	1 333 452	Retrospective cohort	Ethnicity	Increased risk of FD among Turkish (RR 1.3), Pakistani (RR 1.6) and Somali (RR 2.2) women, not higher among Lebanese and Former Yugoslavian women
Villadsen S.F et al. 2010[184]	Differed according to country	Turkish women in 9 countries 1990-2005	239 387	Retrospective cohort	Ethnicity	Increased risk of FD among the Turkish group than the native populations (OR 1.1 – 1.7)
Ravelli A.C.J. et al. 2011[179]	≥24 weeks	Netherlands 2000-2006	554 234	Retrospective cohort	Ethnicity	Increased risk of FD in African (OR 1.7), South Asian (OR 1.8), Turkish/Moroccan (OR 1.) and other non-Western women (OR 1.3) adjusted for age, smoking, urbanisation, SES, low income, booking visit, disease
Ekéus C. et al. 2011[174]	≥28 weeks	Sweden 1992-2005	1 313 978	Retrospective cohort	Ethnicity	Increased risk of FD among immigrants from Africa (OR 2.3) and the Middle East (OR 1.4) adjusted for year, parity, income, place of residence
Stacey T. et al. 2011[182]	≥28 weeks	New Zealand 2006-2009	465	Case-control	Ethnicity	No increased risk of FD among Pacific women after adjustment for age, BMI, parity, smoking, SES
Reeske A. et al. 2011[180]	Birth weight ≥500 g	Germany 2004-2007	2 670 048	Retrospective cohort	Ethnicity	Increased risk of FD among women from Middle East/N. Africa (RR 1.3), Asia (RR 1.2), Mediterranean(RR 1.1)
Rom A.L. et al. 2012[170]	≥28 weeks	Norway, Sweden Finland, Denmark 1981-2000	4 583 485	Retrospective cohort	Education	Clear educational gradient in stillbirth in all four countries
*Auger N. et al. 2012[25]	Birth weight ≥500 g	Canada 1981-2006	2 152 080	Retrospective cohort	Education	Increased risk of FD throughout gestation among women with low education
Wood A.M. et al. 2012[172]	≥28 weeks	Scotland 1985-2008	1 386 967	Retrospective cohort	SES	Increased risk of FD among women with low SES compared to high SES (OR 1.3), adjusted for age, height, parity, marital status, hospital throughput
Lorch S.A. et al. 2012[177]	>400 g or ≥23 weeks	United States 1993-2005	7 104 674	Retrospective cohort	Race/ Ethnicity	Increased risk of FD among Black and Hispanic women compared to White women, risk mediated by different risk factors in different racial/ethnic groups
Drysdale H. et al. 2012[173]	≥37 weeks	Australia 2001-2011	44 326	Retrospective cohort	Ethnicity	Increased risk of FD among South Asian born women OR 2.5
Khalil A. et al. 2013[185]	≥24 weeks	United Kingdom	76 158	Retrospective cohort	Ethnicity	Increased risk of FD among Afro-Caribbean women (OR 2.4) but not among South Asian or East Asian women, after adjusting for age, height, weight, mode of conception, smoking, disease, prior adverse outcome

*Auger N. et al. 2013[186]	≥24 weeks	Canada 1981-2009	2 407 954	Retrospective cohort	Ethnicity	Increased risk of FD among Inuit and First Nations populations, with higher risk at term than before term
Hogue C.J. et al. 2013[176]	≥20 weeks	United States 2006-2008	1 968	Case-control	Race	Increased risk of significant life events (SLE) among Blacks and SLE associated with FD
Luque-Fernandez M.A. et al. 2013[178]	≥500 g or ≥22 weeks	Spain 2007-2010	1 920 235	Retrospective cohort	Ethnicity	Increased risk of FD among African-born women in Spain (OR 1.8)
Savard N. et al. 2013[171]	≥500 g	Canada 1981-2009	2 397 971	Retrospective cohort	Education	Increased risk of FD among mothers with low education (RR 2.0) adjusted for age, parity, marital status, ethnicity
Kramer M.S. et al. 1990[191]		Canada 1980-1986	8 719	Retrospective cohort	BW/IUGR	Increasing IUGR was associated with increasing risk of FD from 3 per 1000 births in non-IUGR to 71 per 1000 births in severe IUGR
Divon M.Y et al. 1998[189]	≥40 weeks	Sweden 1987-1992	181 524	Retrospective cohort	BW/IUGR Post-term	IUGR associated with increased risk of FD: week 41 (OR 10.0) >42 weeks (OR 7.1). Increased risk of FD: 41 weeks (OR 1.5), 42 weeks (OR 1.8), 43 weeks (OR 2.9)
Ahlenius I. et al. 1999[8]	≥28 weeks	Sweden 1984 and 1991	218 471	Case-control	BW/IUGR	Increased risk of FD in growth restricted fetuses, most severely IUGR (OR >20) and for fetuses large for gestational age also increased risk of fetal death (OR 3)
Clausson B. et al. 1999[187]	≥37 weeks	Sweden 1991-1995	510 029	Retrospective cohort	BW/IUGR	IUGR at term (37-41 weeks) increases risk of FD (OR 8.0) and even higher risk post-term (>42 weeks) (OR 10.6)
Clausson B. et al. 2001[188]	≥28 weeks	Sweden 1992-1995	326 377	Retrospective cohort	BW/IUGR	IUGR fetuses according to population birth weight standard (OR 1.2) and customized birth weight standard (OR 6.1) had increased risk of FD
Frøen J.F. et al. 2004[190]	≥22 weeks	Norway 1986-1995	76	Case-control	BW/IUGR	52% of unexplained FD were IUGR (OR 7.2)
Zhang X. et al. 2007[192]	≥28 weeks	Sweden 1992-2001	782 303	Retrospective cohort	BW/IUGR	IUGR fetuses according to population birth weight standard (OR 1.4) and customized birth weight standard (OR 7.8) had increased risk of FD
*Pilliod R.A. et al. 2012[193]	≥24 weeks	United States 2005	3 399 816	Retrospective cohort	BW/IUGR	Increased risk of FD in fetuses in the 3rd, 5th and 10th percentile, and risk increases with pregnancy
Stacey T. et al. 2012[194]	≥28 weeks	New Zealand 2006-2009	465	Case-control	BW/IUGR	Factor associated with FD: SGA (OR 9.7)
*Trudell A.S. et al. 2013[195]	≥20 weeks	United States 1999-2009	57 195	Retrospective cohort	BW/IUGR	Increased risk of FD among SGA and risk increased through gestation
Cotzias C.S. et al. 1999[198]	≥35 weeks	United Kingdom 1989-1991	171 527	Retrospective cohort	Post-term	Increased risk of fetal death as pregnancy progressed 41 weeks (1.7 per 1000 ongoing pregnancies), 42 weeks (1.8 per 1000) and 43 weeks (2.2 per 1000)

Smith G.C.S. 2001[200]	≥37 weeks	United Kingdom 1985-1996	700 878	Retrospective cohort	Post-term	Increased risk of fetal death as pregnancy progresses, 41 weeks (1.2 per 1000 ongoing pregnancies), 42 weeks (1.9 per 1000) and 43 weeks (6.3 per 1000)
Caughey A.B. et al. 2004[197]	≥37 weeks	United States 1992-2002	45 673	Retrospective cohort	Post-term	Increased risk of fetal death as pregnancy progressed 41 weeks (0,9 per 1000 ongoing pregnancies) and >42 weeks (3,5 per 1000)
Heimstad R. et al. 2006[199]	≥37 weeks	Norway 1990-2001	27 514	Prospective cohort	Post-term	Increased risk of fetal death as pregnancy progressed 41 weeks (0,8 per 1000 ongoing pregnancies) and 42 weeks (1,6 per 1000)
Rosenstein M.G. et al. 2012[201]	≥37 weeks	United States 1997-2006	3 820 826	Retrospective cohort	Post-term	Increased risk of FD as pregnancy progresses, past 38 week higher mortality with expectant mortality than delivery
Mandujano A. et al. 2013[202]	≥34 weeks	United States 2003-2005	8 797 909	Retrospective cohort	Post-term	Increased risk of FD as pregnancy progresses, FD exceed neonatal death at 37-38 weeks in low risk and at 36 weeks in high risk pregnancies
Samueloff A. et al.1993[203]	≥20 weeks	United States 1976-1989	48 479	Case-control	Recurrent risk	Women with previous FD had increased risk of FD in the second pregnancy (OR 10.2)
Surkan P.J. et al. 2004[210]	≥28 weeks	Sweden 1983-1997	410 021	Retrospective cohort	Recurrent risk	Previous delivery of a SGA increases risk of FD (OR 2.1), if previous very pre-term delivery of SGA infant (OR 5.0)
Salihu H.M. et al. 2006[208]	≥20 weeks	United States 1978-1997	402 015	Retrospective cohort	Recurrent risk	Higher risk of FD in second pregnancy when first infant was SGA compared to non-SGA (OR 1.6)
Sharma P.P. et al. 2007[204]	≥20 weeks	United States 1978-1997	261 384	Case-control	Recurrent risk	Women with previous fetal death had increased risk of fetal death in the second pregnancy (HR 5.8)
Smith G.C.S. et al. 2007[209]	≥24 weeks	United Kingdom 1992-2001	133 163	Retrospective cohort	Recurrent risk	Women with previous pre-term birth (HR 2.0), SGA (HR 2.1), preeclampsia (HR 1.7)
*Melve K.K. et al. 2010[206]	≥20 weeks	Norway 1967-2004	567 148	Retrospective cohort	Recurrent risk	Gestation-age specific recurrence risk of FD in second pregnancy highest at week 20-27 (OR 25.7) and lowest at term (OR 2.3)
Bhattacharya S. et al. 2010[205]	≥24 weeks	Scotland 1981-2005	309 304	Retrospective cohort	Recurrent risk	Increased risk of FD in second pregnancy in women with FD in first pregnancy (OR 1.9)
Gordon A. et al. 2012[208]	≥20 weeks or ≥400 g	Australia 2002-2006	230 499	Retrospective cohort	Recurrent risk	Increased risk of FD in second pregnancy when prior SGA birth or preterm birth but not prior FD

Abbreviations: FD, fetal death; OR, odds ratio; RR, relative risk; HR, hazard ratio; CH, chronic hypertension; PIH, pregnancy induced hypertension; PE, pre-eclampsia; GH, gestational hypertension; SuPE, superimposed pre-eclampsia; GD, gestational diabetes; PD, pregestaional diabetes (type 1 + type 2); Dia1, diabetes type 1; Dia2, diabetes type 2; IUGR, intrauterine growth restriction; BW, birth weight; *, gestational-age-specific risk estimated

3. CAUSES AND CONSEQUENCES OF STILLBIRTH

Causes

Several classification systems of perinatal death have been developed since the Aberdeen classification was developed by Baird and colleagues in 1954.[211] They developed the system after thorough examinations of 1008 perinatal deaths occurring during 1938-1952. The Aberdeen classification system identifies maternal and obstetrical clinical conditions that initiated the event leading to fetal demise. In 1986 the extended Wigglesworth system was published, which implemented the pathophysiological processes leading to fetal death.[212] These two systems are the most widely used, but they have a high number of unexplained deaths.[213] Moreover, placental causes of death are not included. More than 30 classification systems have been developed; however, the ReCoDe system and the Tulip system are reported to perform better than other systems.[36]

Several studies have been conducted aiming to establish the cause of fetal death, but the proportion of unexplained deaths in these studies varied greatly, both due to the classification system applied and the intensity of investigations performed after stillbirth.[12-14;16;17]

Fetal conditions

In high-income countries approximately 5-10% of fetal deaths are caused by fetal conditions, namely congenital anomalies (chromosomal anomalies and congenital malformations).[17;19;214] Data from the Wisconsin Stillbirth Service Program reported that the most common disorders associated with fetal death are malformation syndromes and single malformations.[215] In Canada, Liu and colleagues reported a declining fetal mortality rate due to congenital anomalies at term, presumably a result of the implementation of ultrasound screening (and other prenatal diagnostic tools) in antenatal care and selective termination of affected pregnancies.[216]

Infections

Maternal bacterial or viral infections during pregnancy have been reported to account for approximately 12% of fetal deaths in high-income countries.[14] The microorganisms most frequently isolated in fetal death are group B streptococcus, Escherichia coli and Enterococcus fecalis.[217] However the mere presence of

microorganisms does not prove causality, as chorioamnionitis or isolation of bacteria from the placenta is a common finding not only in cases of fetal death, but also in healthy controls.

Some perinatal viral and protozoan infections have been associated with fetal death including human parvovirus B19 (PVB), cytomegalovirus, enterovirus, rubella, varicella zoster and *Toxoplasmosa gondii (T. gondii)*.[217] The majority of studies on viral infection and fetal death concern PVB, but show inconsistent results.[218-224] Three Swedish hospital-based studies carried out in 1992-1999 reported that between 7% and 15% of fetal deaths were PVB DNA-positive in fetal or placental tissue, compared to non PVB DNA-positive placentas among live born controls.[220;223;224] However in these studies only a few cases had concomitant positive fetal and placenta specimens, and the use of placentas from live births as controls have been questioned. Hence the association of maternal PVB infection with fetal death needs to be further explored.

The proposed mechanisms that may lead to fetal death in women with any type of infection are: a) high maternal fever, b) infection of the placenta causing impaired placental function, c) chronic fetal infection, which may lead to congenital anomalies, organ damage and pneumonia, d) infections promoting pre-term labor, increasing the risk of fetal death (in the very premature fetus).[217]

Umbilical cord abnormalities and cord accidents

Umbilical cord abnormalities and cord accidents such as cord prolapse, nuchal cord and true knots may cause fetal death.[13;14]

Placental pathology

Placental pathology is involved in more than 25% of fetal deaths.[14] A comprehensive Dutch prospective cohort study of 750 intrauterine fetal deaths (>20 weeks of gestation) during 2000-2006, reported placental pathology as the main cause of fetal death.[225] They reported that the pathology involved differed according to gestational age: fetal death <32 weeks involved placental bed pathology (i.e. spiral artery pathology or inadequate spiral artery remodelling causing placental abruption and infarction), whereas for fetal deaths >32 weeks of gestation, placental developmental

pathology (i.e. morphologic abnormalities due to abnormal development, causing placental hypoplasia and villus immaturity) dominated.
Fetal maternal haemorrhage may cause fetal death if there is sufficient blood loss, leading to cardiovascular collapse.

Prematurity/immaturity

Preterm premature rupture of membranes, preterm labor and cervical incompetence may cause intrapartum death in the immature fetus.[13]

Consequences

Women who have given birth to a stillborn infant in the past more often report symptoms of anxiety than do women with live-born infants.[226] A case-control study from the United Kingdom reported an increased risk of depression, post-traumatic stress disorder and anxiety in the subsequent pregnancy of women with previous fetal death (>18 weeks gestation) compared to women with one previous live birth.[227] The authors conducted a 7-year follow-up study to assess the long-term psychosocial sequelae among these women. They reported no difference between cases and controls with respect to depression and post-traumatic stress disorder. However, the subgroup of women who reported symptoms of post-traumatic stress disorder 7 years earlier reported significantly higher levels of symptoms in the follow-up study.[228]

A population-based cohort study conducted by Calderon-Margalitt and colleagues reported higher premature mortality in women with one prior fetal death (>28 weeks) compared to women with only live births (HR 1.40, 95% CI 1.11-1.77), even after adjusting for age, SES, parity, medical conditions at cohort enrolment and placental syndrome.[229] Women with prior fetal death were at increased risk of death from coronary heart disease, circulatory or renal disorders. However, this association may have been confounded by pre-pregnancy BMI. A recent Danish study by Ranthe and colleagues with >15,000,000 person-years of follow up reported increased incidence of myocardial infarction, cerebral infarction and renovascular hypertension in women with prior stillbirth.[230] It has been proposed that previous fetal death can be utilized as a sex-specific predictor of future cardiovascular disease.[231]

4. CONCERNS AND GAPS RELATED TO STUDIES OF STILLBIRTH

The literature review revealed several risk factors associated with fetal death. The association between maternal age and fetal death has been most frequently explored, and all studies reported an increased risk of fetal death among women aged ≥40 years,[23;50-70] and all but three reported an increased risk among women ≥35 years,[53;69;70] whereas six[54;58;67;72-74] studies reported increased risk associated with young maternal age and three[55;75;76] reported no risk. The studies applied different definitions of stillbirth and different reference groups. The effect of maternal age on the risk of stillbirth remains an object of concern, and further research is needed to elucidate the causal mechanisms involved.

Primiparity was associated with fetal death,[23;50;59;60;66;68;70;79-81;83-85] whereas six studies reported increased risk of fetal death in multiparous women.[50;59;70;78;80;81]

Obesity was associated with increased risk of fetal death in all the reviewed papers but one, whereas five studies also reported an increased risk among overweight women.[68-70;79;82;83;90-100] Four of these five studies utilized >15 years old data,[79;83;94;98] hence, lack of an association between fetal death and maternal overweight in the majority of studies in this review, may be due to increased surveillance and interventions among these women.

Increased risk of stillbirth in women with pregestaional diabetes was reported by 22 studies,[53;55;66;68-70;98;111;119-133] seven studies reported on diabetes type 1,[119;121-125;127] and two studies reported on diabetes type 2.[124;129] Gestational diabetes was associated with increased risk of fetal death in two studies,[98;134] whereas three did not report an increased risk.[66;126;135] Chronic hypertension was reported to increase the risk of fetal death in 15 studies.[53;55;66;68;101;104;105;107-113;117] One Australian study did not report increased risk of fetal death among women with chronic hypertension, [103] however, the authors reported a significantly higher elective Caesarean rate in these women compared to normotensive women and women with pregnancy hypertension. Preeclampsia was associated with increased risk in four studies,[66;102;114;115] and no risk in three studies.[104;110;117]

Sixteen studies reported an increased risk of fetal death among smokers and the result was very consistent.[16;53;60;66;68-70;79;84;142-148] Studies on alcohol consumption during pregnancy and risk of fetal death were few and very heterogeneous; one study reported increased risk among abstainers, whereas the majority of studies

reported increased risk associated with alcohol consumption.[68;79;152-157] However, two studies reported that the risk was only significantly increased at early gestation (<16 weeks and <28 weeks, respectively).[156;157] Moderate to high amounts of coffee consumption was associated with increased risk of fetal death in 4 studies.[79;153;158;232]
Low SES measured by educational attainment, household income or employment, was associated with an increased risk of stillbirth.[25;147;148;163;164;166;168;170-172] Likewise, a consistent strong association between fetal death and ethnic minority status or being Black was reported by large number of studies (24 papers).[24;68-70;160-162;165;167;169;173-186] Understanding why disadvantaged women have a poorer pregnancy outcome and how to create prenatal care that is better targeted to this group is required.
IUGR assessed by the proxy SGA was associated with increased risk of fetal death in 13 studies.[8;70;80;84;187-195] A better understanding and ability to identify true pathological growth is warranted. In addition an optimal timing for the delivery of cases with pathological growth needs to be estimated.
Post term pregnancy is associated with increased risk of stillbirth.[85;189;197-202] In high-risk pregnancies, in which diabetes, pre-eclampsia or severe SGA are a factor, labor is routinely induced near term. However, there is continuing controversy about the appropriate management of low-risk singleton pregnancies past term.
Women with a previous stillbirth have an increased risk of recurrence,[203-210] and previous stillbirth was claimed to be the strongest pre-pregnancy risk factor in one study.[69]

Stillbirth is the endpoint of numerous pathways, and different risk factors are associated with different causes. In Figure 4, a conceptual model of risk factors associated with fetal death from the literature review is depicted. Risk factors may be both directly and indirectly associated with stillbirth, for example high maternal age, which is directly associated with stillbirth but also indirectly associated through the increased risk of medical conditions or high BMI. The figure further depicts the link between sociodemographic, behavioral and pregnancy-related risk factors and more proximate factors in the causal pathway to fetal death (congenital anomalies, placental disorders, infections and preterm labor). However, the Figure is not exhaustive.

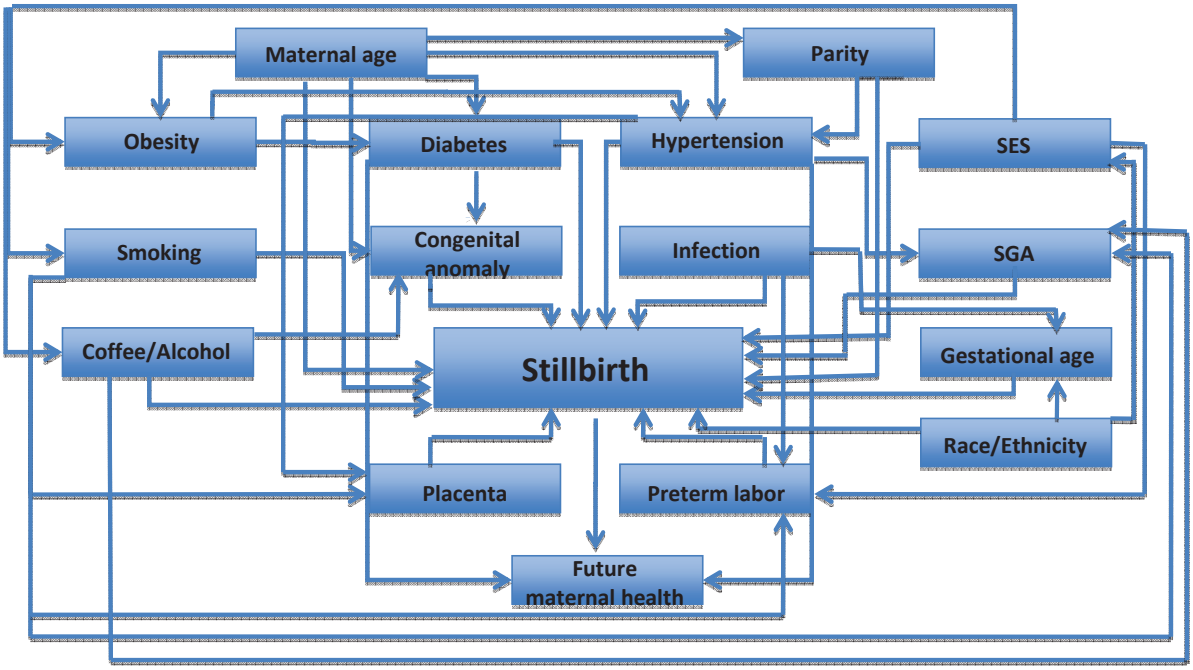

Figure 4. A conceptual model illustrating causes and risk factors associated with fetal death.

During the last century fetal mortality rates in most high-income countries have declined.[233] However, there is still significant inter- and intra-country inequality in stillbirth.[44;45;234] To address these differences and achieve further reductions it is imperative that the specific causes of, and risk factors for fetal death are identified, and predictive models established. Even though several risk factors have been identified, understanding and prevention is hampered by limitations and gaps in the knowledge on fetal death.[70] The only antenatal screening method in recent time, that has been shown to reduce risk of stillbirth is the use of fetal umbilical Doppler blood flow measurements in high-risk pregnancies.[235;236]

Epidemiological research on fetal death is conducted using observational studies, which harbor the inherent risk of finding an association due to chance or bias. However, the probability of finding a “true” association increases when observations

are repeated in different populations with consistent results, and at the same time are plausible and exhibit a biological gradient. Furthermore, it has been indicated that real-life observational studies of mortality trends may provide strong reality-based evidence, in particular when studying fetal mortality in obstetrics as non-interventional studies are not feasible due to ethical considerations.[237]

Cohort studies of outcomes that are as rare as fetal death require large datasets. Hence most research to-date has taken the form of retrospective studies utilizing vital statistics from registries data that often lack detailed information on confounders. Several large population-based cohort studies conducted in the United States obtained data on fetal death from the Centers for Disease Control and Prevention's National Center for Health Statistics, which receives standard reports of fetal death from the independent reporting areas (states and territories). However, reporting requirements and criteria vary between the reporting areas, and fetal death reports are flawed by underreporting, missing data and low accuracy.[238;239]

We were able to study fetal death in Norway by utilizing data from the MBRN. This registry, like the other Nordic medical birth registries, is a valuable resource for population-based data that has been prospectively collected in a standardized manner with nearly 100% coverage of all births in Norway.[6] The use of MBRN data eliminates selection bias due to non-response. Longitudinal monitoring over time enables the study of trends to elucidate changes in disease/mortality patterns in the population, and at the same time facilitates the evaluation of healthcare services delivered. However, as will be elaborated upon later, the use of secondary data (data generated for a different purpose) has certain drawbacks, such as inaccuracy in the measurement of exposure and outcome, and limited data on confounders.[240]

5. AIMS OF THE THESIS

The main aim of this thesis was to study trends of fetal death and associated factors in Norway.

It has been reported that infection is an important cause of stillbirth, specifically in early fetal deaths (<28 weeks of gestation).[22;217] Hence, studies of late fetal death (>28 weeks) may underestimate the impact of infection. Moreover, knowledge on viral causes of fetal death is limited due to complex detection techniques, so studies in high-income countries differ in the reported rate of infection as a cause of fetal death, due to different study designs and the degree to which investigations were performed, with higher numbers reported in prospective studies with extensive investigation protocols (culture, serology, histology, molecular biology techniques).[17;241]

PVB has been reported to be an important cause of fetal death throughout gestation, however, studies on PVB and fetal death are not consistent. Hence we aimed to study the association between PVB and fetal death in a large population-based study in Norway in Paper I.

In Norway, there have been large changes in the management of pregnant women, especially since the 1980s, with the introduction of ultrasound, cardiotocography, increasing numbers of caesarean sections and inductions of labor performed. We wanted to study trends in fetal death at different gestational ages in Paper II. Moreover, in this thesis we wanted to estimate the impact of certain risk factors reported to be associated with fetal death, such as high maternal age in Paper III, and hypertensive disorders in Paper IV. There is a lack of knowledge on gestational-age-specific risk of fetal death in high-risk pregnancies, and therefore this was further explored in this thesis.

More specifically we aimed to:

1. Study the association between past and present maternal human PVB infection and fetal death, birth weight and length of gestation.
2. To study trends in fetal mortality at different gestational ages in Norway in 1967-2006.

3. To study changes in the association of fetal death with maternal age at different gestational ages.
4. To study changes in the association of fetal death with maternal hypertensive disorders (pre-eclampsia, gestational hypertension and chronic hypertension).

6. MATERIALS AND METHODS

6.1 Toxoplasmosis Study (Paper I)

In the first study we used data from the Toxoplasmosis Study. This nationwide prospective study was conducted by the Norwegian Institute of Public Health from June 1992 to May 1994, and included approximately 60% of all pregnant women in Norway during this period (n=35 940 pregnant women).[242] It was primarily designed to study risk factors, prevalence, incidence and vertical transmission rate of *T. gondii* among pregnant women.

Women were invited to participate in the study at their first antenatal visit to the primary healthcare center (mean gestational age 10.2 weeks) where the first of three serum samples was requested. Retesting was requested for the women without antibodies against *T. gondii* at 22 and 38 weeks of gestation (76.3% women provided all three serum samples). If any sample indicated possible primary infection an additional sample was requested for confirmation. An additional serum sample was also requested in the case of fetal death or miscarriage.

6.1.1 Study design and population

A linkage between the Toxoplasmosis Study Registry and the MBRN was performed by personal identification numbers so as to identify women with live-born (n=957 controls) and stillborn ($\geq$16 weeks of gestation) (n=281 cases) infants (Figure 5). Based on this a case-control study was conducted.

6.1.2 Blood sampling and analysis

The blood samples were collected during June 1992 to May 1994 and stored at –20℃ at the Norwegian Institute of Public Health. The sera were analyzed for PVB antibodies during 1996. The first serum sample from each woman was tested separately for immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies against PVB (IDEIA, DAKO A/S, Copenhagen, Denmark). If the first serum sample was negative the last available serum sample from the woman was analyzed to detect seroconversion. Serum that tested positive within the grey zone was retested.

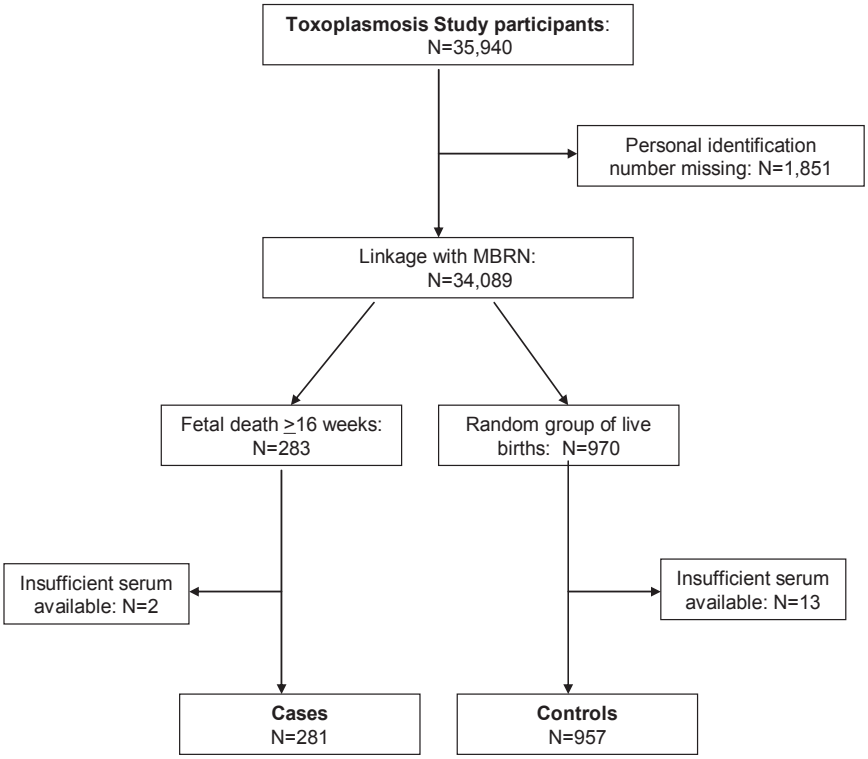

Figure 5. Study population for Paper I.

6.1.3 Variables

Main outcome variable

Fetal death was defined as death ≥16 weeks of gestation as notified to the MBRN. No distinction was made between antepartum and intrapartum deaths.

Secondary outcome variables

Birth weight information on birth weight (g) was obtained from the MBRN. Previous studies have reported higher than expected proportion of small for gestational age infants among serologically confirmed maternal PVB infection.[218]

Gestational age (weeks) was obtained from the MBRN. Perinatal infections generally have been associated with preterm delivery.[217]

Explanatory variables

Maternal PVB antibody status was categorized in the following manner:

1. Antibodies against PVB not detected: *no past or present infection.*
2. Presence of IgG antibodies against PVB in the first serum sample (but no IgM antibodies): *previous infection.*
3. Presence of IgM antibodies against PVB in the first serum sample: *acute infection.*
4. Seroconversion (occurrence of IgG or IgM antibodies in seronegative women): *acute infection.*

Maternal age at delivery was categorized as (<30 or ≥30 years). Previous studies have reported increased risk of fetal death at both extremes of maternal age,[58] and seroprevalence of IgG increases with age.[243]

Parity was defined as the number of previous births (after ≥16 weeks of gestation) and was categorized as 0,1 and ≥2. High parity is associated with increased risk of fetal death, and increased risk of acquiring PVB infection.[244]

6.1.4 Statistical analysis

The association (ORs with 95% CIs) between maternal PVB antibody status (exposure) and fetal death (outcome) was estimated by contingency tables. Hypothesis testing was performed by chi-squared test (χ^2), and by Fishers exact test when the expected frequencies were less than 5. Multivariate logistic regression models were applied to assess the relationship between exposure and outcome allowing for adjustment for the confounding effect of maternal age and parity. Among women followed with regard to seroconversion additional adjustment for follow-up time was made.

Differences in mean birthweight and length of gestation among cases and among controls according to maternal PVB antibody status were tested by the Student t-test. Among cases with presence or absence of IgM antibodies or occurrence of IgG or IgM antibodies, the Mann-Whitney test (non-parametric) was applied due to small numbers and non-normally distributed outcomes as this test is more robust to

outliers. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 15.0; SPSS Inc., Chicago, Illinois, USA).

6.1.5 Ethical aspects

The study was approved by the Norwegian Data Inspectorate, the National Board of Health, the Regional Ethical Committee for Medical Research and the Advisory Committee for the MBRN.

6.2 The Medical Birth Registry of Norway (Papers II-IV)

In the Papers II-IV we used data from the MBRN, which was established in 1967 with the following purpose:
"to perform epidemiological surveillance of birth defects and other perinatal health problems in order to detect increases in rates."[6]

It is mandatory to report all births (live births and fetal deaths) ≥16 weeks of gestation (since 1999, 12 weeks of gestation) to the registry. A standardized notification form is filled in after the delivery by the attending midwife or physician within 7 days of delivery. The form contains information on maternal health (before and during pregnancy) and outcome of the pregnancy (maternal and neonatal). The form went unchanged from 1967-1998, but as from 1999 a new form was implemented. The main changes in the new form were the inclusion of information regarding maternal smoking habits, use of nutritional supplements, and the former text regarding maternal health was replaced by pre-coded fields for maternal disorders. Before 1988 terminated pregnancies were only infrequently notified to MBRN, and from 1988 to 1998 terminations due to serious congenital anomalies were notified as stillbirths. In 1999 a separate register for pregnancy terminations after 12 weeks of gestation was established within the MBRN. Complete case ascertainment (births and deaths) is maintained in the registry due to routinely executed record linkage with the Cause of Death Registry and the National Population Registry.

6.2.1 Study design and population

In the Papers II-IV we conducted population-based retrospective cohort studies. For details about the population and exclusion criteria see Figure 6. The inclusion and exclusion criteria were the same in Papers II-III whereas in Paper IV we included only pregnancies ≥20 weeks and excluded multiple pregnancies.

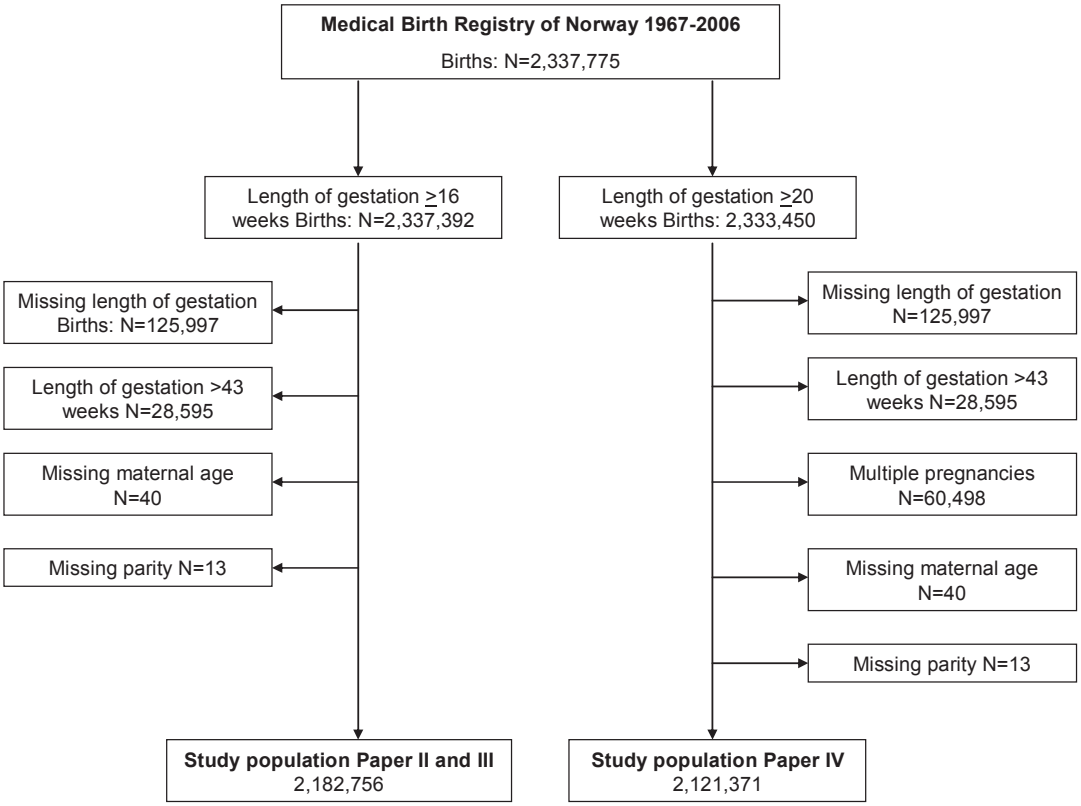

Figure 6. Study population for Papers II-IV.

6.2.2 Variables

Main outcome variables

Paper II

Fetal death was defined as death at ≥16 weeks of gestation as notified to the birth registry. We studied fetal death at different equal lengths of gestation: 16^{+0}-22^{+6}, 23^{+0}-29^{+6}, 30^{+0}-36^{+6} and 37^{+0}-43^{+6} weeks (the superscripts denote days in addition to completed weeks).

Perinatal mortality was defined as the sum of fetal death at ≥22 weeks of gestation and infant death within 7 days of birth.

Early neonatal mortality was defined as the number of infant deaths within 7 days of birth.

Stillbirth (Paper II) was defined as fetal death ≥22 weeks of gestation.

Paper III

Fetal death was defined as death at ≥16 weeks of gestation as notified to the birth registry. We studied fetal death at different equal lengths of gestation: 16^{+0}-22^{+6}, 23^{+0}-29^{+6}, 30^{+0}-36^{+6} and 37^{+0}-43^{+6} weeks. We also studied fetal death at: 38^{+0}-39^{+6}, 40^{+0}-41^{+6}, and 42^{+0}-43^{+6} weeks of gestation.

Paper IV

Fetal death was defined as death at ≥20 weeks of gestation. We studied risk of fetal death at the following equal lengths of gestation: 20^{+0}-23^{+6}, 24^{+0}-27^{+6}, 28^{+0}-31^{+6}, 32^{+0}-35^{+6}, 36^{+0}-39^{+6} and 40^{+0}-43^{+6} weeks.

Perinatal mortality was defined as the sum of fetal death at ≥22 weeks of gestation and infant death within 7 days of birth.

Explanatory variables

Paper II

Period of delivery (year) or year of birth as reported to the MBRN was the main explanatory variable, and was categorized as: 1967-1971, 1972-1976, 1977-1981,

1982-1986, 1987-1991, 1992-1996, 1997-2001 and 2002-2006. In the analysis the years 1967-1971 was used as reference to study trends in fetal death.

Maternal age at delivery was categorized as <20, 20-24, 25-29, 30-34, 35-39, 40-44, and ≥45 years. Previous studies have reported increased risk of fetal death at both extremes of maternal age,[23;58] and maternal age at delivery has increased in recent years.[1]

Parity was defined as the number of previous births (after ≥16 weeks of gestation) and was categorized as 0,1,2,3 and ≥4. Primiparity and also grand multiparity may increase the risk of fetal death.[60;78]

Plurality was coded as either a single infant or two infants or more. Multiple pregnancies confer an increased risk of fetal death,[36] and the number of multiple pregnancies has also increased in the last 40 years.[1]

Paternal age was categorized as <30, 30-39, ≥40 years and missing (1%). High paternal age is associated with increased risk of fetal death.[245] Paternal age is correlated with maternal age, and as maternal age has increased, paternal age may also have changed.

Pre-eclampsia was defined as an increase in blood pressure to at least 140/90 mmHg combined with proteinuria after completed 20 weeks of gestation (1967-1998: ICD-8 codes 637.4 / 637.5 / 637.6 / 637.9 and 1999-2006: ICD-10 codes O13 and O14). Preeclampsia is associated with fetal death[102] and increased prevalence in Norway since 1967 has been reported.[246]

Paper III

Maternal age at delivery was the main explanatory variable and was categorized as <20, 20-24 (reference), 25-29, 30-34, 35-39, 40-44, and ≥45 years. The last two categories (40-44 and ≥45 years) were merged due to insufficient numbers in certain analyses.

Period of delivery (year) was categorized as: 1967-1971, 1972-1976, 1977-1981, 1982-1986, 1987-1991, 1992-1996, 1997-2001 and 2002-2006.

Parity was defined as the number of previous births (after ≥16 weeks of gestation) and was categorized as 0,1,2,3 and ≥4. Primiparity and also grand multiparity may increase the risk of fetal death and is associated with maternal age.[60;78]

Plurality was coded as either a single infant or two infants or more. Multiple pregnancies confer an increased risk of fetal death[36] and are associated with high maternal age.[247]

Paternal age was categorized as <30, 30-39, ≥40 years and missing (1%). High paternal age is associated with increased risk of fetal death.[245], and is correlated with maternal age.

Pre-eclampsia was defined as an increase in blood pressure to at least 140/90 mmHg combined with proteinuria after completed 20 weeks of gestation (1967-1998: ICD-8 codes 637.4 / 637.5 / 637.6 / 637.9 and 1999-2006: ICD-10 codes O13 and O14). Preeclampsia is associated with fetal death,[102] and also associated with maternal age.[56]

Paper IV

Pre-eclampsia, gestational hypertension and chronic hypertension were the main explanatory variables:

Pre-eclampsia was defined as an increase in blood pressure to at least 140/90 mmHg combined with proteinuria after completed 20 weeks of gestation (1967-1998: ICD-8 codes 637.4 / 637.5 / 637.6 / 637.9 and 1999-2006: ICD-10 codes O13 and O14). Eclampsia was defined as preeclampsia with seizures. Eclampsia and HELLP (Hemolysis, Elevated Liver Enzymes, and Low Platelets) were grouped together with pre-eclampsia. Women with chronic hypertension who developed preeclampsia during pregnancy were assigned to the preeclampsia group.

Gestational hypertension was defined as an increase in blood pressure to ≥140/90 mmHg after 20 weeks of gestation without concomitant proteinuria (1967-98: ICD-8 codes 637.0/637.2 and 1999-2006 ICD-10 code O16).

Chronic hypertension was defined as pre-pregnancy systolic blood pressure at ≥140 mmHg or diastolic blood pressure at ≥90 mmHg, or an increase in blood pressure to these values before 20 weeks of gestation (1967-1998: ICD-8 codes 400-404 and 1999-2006: ICD-10 codes I10/I11/I12/I13/I15/O10/O11).

Maternal age at delivery was the main explanatory variable and was categorized as ≤19, 20-24, 25-29, 30-34, 35-39 and ≥40 years. Maternal age is associated with fetal death and older women have higher prevalence of hypertensive disorders.[56]

Parity was defined as the number of previous births (after ≥16 weeks of gestation) and was categorized as 0,1,2,3 and ≥4. Primiparity and also grand multiparity may increase the risk of fetal death[78] and primiparity is associated with pre-eclampsia.[248]

6.2.3 Data preparation

The source of data for the studies was raw data file from the MBRN. The file was examined and data converted trough several syntaxes. Fetal death was collapsed into one category, and then grouped according to gestational age at death. For the regression analyses continuous variables were categorized to be able to adjust for explanatory variables.

6.2.4 Theoretical basis of the statistical analysis in Papers II-IV

The concept of stillbirth risk has to be further elaborated. The overall stillbirth risk is straightforward calculated as the proportion of stillbirths among all births. However, gestational-age-specific risk of stillbirth is more complicated, but nevertheless important in the understanding and prevention of this outcome. There is an ongoing dispute on which epidemiologic method to apply when estimating gestational-age-specific risk of stillbirth.[249-253] The conventional definition is the number of stillbirths at a given gestational week divided by all births (live birth + stillbirths) at that gestational week:

$$\textit{Stillbirth rate in week } i = \frac{\textit{number of stillbirths}(i)}{\textit{total births}(i)}$$

By applying the conventional definition, the fetal death risk is highest early in gestation, declines with advancing pregnancy duration, and then rises slightly at post term gestational age.[249] This is claimed to be inconsistent with the observed changes in obstetric practice, where increasing rates of medically indicated iatrogenic preterm deliveries has coincided with declining stillbirth rates.[251]

The second problem with the conventional definition regards the paradox of intersecting gestational-age-specific perinatal mortality curves.[251] This phenomenon pertains to the observed difference in the gestational-age-specific perinatal mortality

rates for different risk factors such as smoking or race. For such factors the stillbirth rate curves are expected to intersect as gestation advances; with high risk women (smokers) having relatively lower risk of stillbirth in early gestation and relatively higher risk at late gestation compared to low risk women (non-smokers). The alternative definition proposed to circumvent these issues is by applying the "fetus-at-risk" model.

The "fetus-at-risk" model first proposed by Yudkin and colleagues[21] has the following definition (numbers of stillbirths at a given week divided by number of total births at a given week of gestation or greater):

$$\textit{Stillbirth rate in week } i = \frac{\textit{number of stillbirths}(i)}{\sum \textit{total births}(j \geq i)}$$

As not only fetuses delivered at a specific gestational week are at risk of fetal death but all ongoing pregnancies are included in the denominator. By applying the "fetus at risk" definition the fetal mortality rate is very small in early gestational age and increases exponential with gestation,[249] hence, justifying early selective delivery for medical indications.[251] Platt and colleagues further proposed that gestational age should be considered as the timescale in time to event analysis with "fetus's-at-risk" as denominator. [254] The risk of stillbirth is then compared between different groups by Cox-regression analysis.

Both models of estimating gestational-age-specific rate of fetal death are widely applied in the literature, and may answer different clinical questions.[250] In Paper II and III we applied the "fetus-at-risk" model, whereas in Paper IV the conventional model was applied.

6.2.5 Statistical analysis

Papers II-III

In Papers II-III Cox regression (or proportional hazards) models were applied to compare the rate of fetal death among the exposed and unexposed, and adjustment for confounding was made by including these variables as explanatory variables. These models were applied to estimate the hazard rate ratio (referred to as RR in the

Papers II and III) of fetal death according to period of delivery (Paper II) and maternal age (Paper III), as we had censored data with varying follow-up times. Event times (or “survival times as fetuses”) were gestational age until the study outcome (fetal death). Live births were treated as censored observations. Separate analyses were performed for the different gestational age intervals since the purpose of the studies was to investigate gestational specific differences. A fetus not born at the end of an interval was treated as a censored observation in that interval (irrespectively of the eventual outcome of pregnancy).

Due to the fairly short gestational age intervals the results are not very sensitive to the proportional hazards assumption. To illustrate this I used a standard technique for validating the proportional hazards assumption, namely the log-minus-log plots. Assuming that the hazard ratio between the exposed and unexposed groups is constant, the log-minus-log plot of survival against gestational age should give parallel lines. The proportional hazards assumption was fairly good when stratified by short gestational length groups as illustrated by parallel lines in Figure 7, compared to complete pregnancy in Figure 8 where the curves crossed.

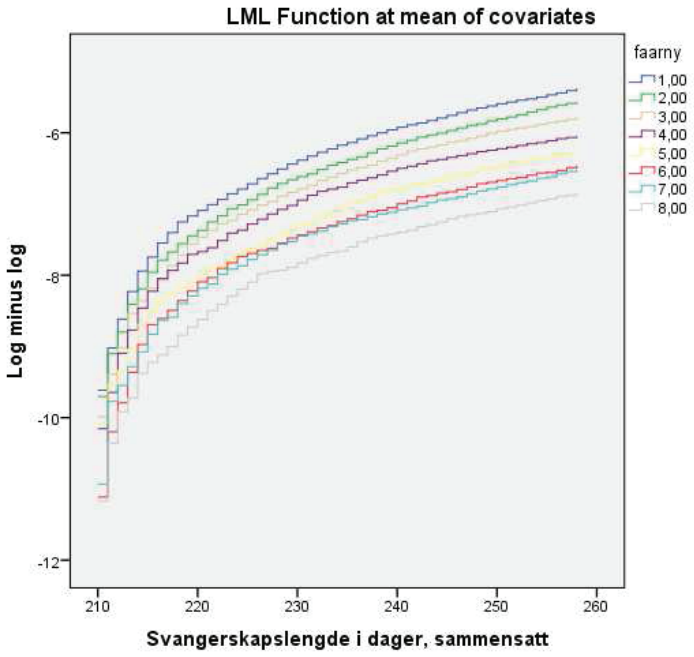

Figure 7. Logminuslog plot for gestational weeks 30-36.*

*(*faarny: birth year group; svangerskapslengde i dager: gestational length in days)*

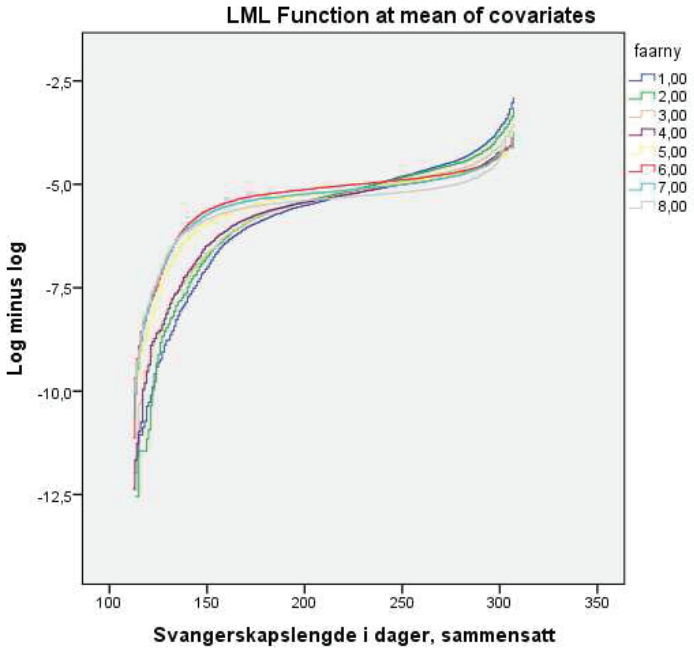

Figure 8. Logminuslog plot for gestational weeks 16-43.*
*(*faarny: birth year group; svangerskapslengde i dager: gestational length in days)*

Perinatal mortality, early neonatal mortality and stillbirth rates were estimated per 1000 births. The occurrence of fetal death at different gestational ages was estimated per 1000 ongoing pregnancies, and for the last gestational age group (37-43 weeks of gestation) a correction was made to more accurately estimate the incidence rate, by multiplying the denominator with a correction factor (0.5), as only fetus's in utero are under risk of fetal death.

Paper IV

In Paper IV the models applied were different than those in Papers II-III, as presence of the time-dependent covariates pre-eclampsia and gestational hypertension were only registered at delivery. Therefore it was not possible to address the hazard rates of fetal death at different periods of pregnancy. It was, however, possible to estimate the probability of a fetal death given a birth at a specific time by applying the conventional model to estimate the gestational-age-specific stillbirth risk. Thus the

proportion of fetal death per 1000 births for the different hypertensive disorders in different time intervals of pregnancy were estimated. Furthermore, at each time interval regression models were applied to calculate (adjusted) RRs of fetal death given a birth.

Instead of using a logistic regression model we estimated the associations between the different hypertensive disorders and fetal death by RRs by applying generalized linear models with a log-link to the binary outcome fetal death (yes/no). This model was applied in order to have an easy parameter interpretation. With this model one estimates risk ratios or the ratio of probabilities of fetal death among different groups adjusted for the confounder. When the outcome is rare the RR-estimates are approximately equal to the ORs, but for non-rare events such as the risk of fetal death early in the pregnancy, the interpretation of OR is not straightforward. Uncertainty of estimates was reported by 95% CIs.

All statistical analyses were performed by using the SPSS, version 16.0 (SPSS Inc., Chicago, Illinois, USA).

6.2.6 Ethical aspects

The MBRN was approved by the Norwegian Data Inspectorate. The Publishing Committee of the MBRN approved our study.

7. MAIN RESULTS (summary of Papers I-IV)

7.1 Paper I

Maternal human parvovirus B19 infection and the risk of fetal death and low birth weight: a case-control study within 35 940 pregnant women.

Aim: The aim of this study was to assess the association between maternal PVB infection and fetal death, birth weight and length of gestation.
Method: We conducted a population-based case-control study in Norway. Cases (n=281) were all women who experienced fetal death within a cohort of 35 940 pregnant women that participated in the Toxoplasmosis Study during 1992-1994, and the control group consisted of a random sample of 957 women with a live-born child. Information on pregnancy outcome was obtained from the MBRN. First trimester serum samples were tested for antibodies against PVB (IgM and IgG). In seronegative women, additional sera were analyzed to detect seroconversion during pregnancy. The association between parvovirus B19 infection and fetal death was estimated by contingency tables and logistic regression. The mean birth weight and length of gestation among cases and controls according to maternal antibody status was calculated and differences tested with the Student t-test and the Mann-Whitney test.
Results: Two of the 281 (0.7%) women who experienced fetal death, and nine of the 957 (0.9%) controls had IgM antibodies (crude OR 0.8, 95% CI 0.2-3.5). In women who were seronegative in the first trimester, 3.1% (2/65) with fetal death and 2.6% (8/307) with a live birth seroconverted (crude OR 1.2, 95% CI 0.2-5.7). Neither presence of maternal PVB-specific IgG or IgM antibodies in the first trimester, nor was seroconversion during pregnancy associated with lower birth weight or reduced length of gestation in live-born children, but it was associated with low birth weight in stillborn infants, however, this difference was not statistically significant (P=0.1).
Conclusion: In this case-control study PBV infection was not significantly associated with risk of fetal death, and only four of the 281 women with fetal death were infected. However, the lack of association may also be due to sample size limitations.

7.2 Paper II

Changes in fetal death risk during 40 years - different trends for different gestational ages: a population-based study in Norway.

Aim: The aim of this study was to study trends in perinatal mortality, early neonatal mortality and gestational-age-specific risk of fetal death during 1967-2006.
Method: We conducted a register-based observational study of all pregnancies (≥16 weeks of gestation) during 40 years in Norway (n=2 182 756). Data was obtained from the MBRN. Changes in the absolute risks and hazard ratios (HR) of fetal death in ongoing pregnancies were estimated. Cox regression models were applied to estimate the HRs of fetal death according to period of delivery (1967-1971, as reference) in the following gestational weeks: 16-22, 23-29, 30-36 and 37-43. Adjustment for confounding was made by including these variables as explanatory variables in multivariable Cox regression models.
Results: In all pregnancies lasting longer than 22 weeks, the fetal mortality rate decreased during 1967-2006. The greatest absolute decline was in term pregnancies (37-43 weeks) in which fetal mortality rates declined from 10.8 per 1000 ongoing in 1967-1971to 3.3 in 2002-2006 (crude HR 0.35, 95% CI 0.31-0.38). In pregnancies at 30-36 weeks the fetal mortality rate declined from 4.5 to 1.1 per 1000 (crude HR 0.23, 95% CI 0.21-0.26). At 23-29 weeks, the rate declined from 2.8 to 1.3 per 1000 (crude HR 0.46, 95% CI 0.40-0.52). An opposite trend was observed at early gestation (16-22 weeks) with an increase from 1.7 to 3.4 fetal deaths per 1000 ongoing pregnancies (crude HR 2.05, 95% CI 1.84-2.27). Adjustments for maternal age, parity, multiple pregnancies, paternal age and pre-eclampsia did not significantly alter the estimated associations.
Conclusion: Since 1967 the risk of fetal death has been reduced by almost 70% in pregnancies lasting longer than 22 weeks. However, at 16-22 weeks of gestation an increase in risk was observed. This increase may be artificial, perhaps caused by improved reporting routines of early fetal deaths. However, we speculate that some of this increase may be caused by an increased proportion of childbearing women being treated with cervical cone excision prior to pregnancy.

7.3 Paper III

The impact of maternal age on fetal death: does length of gestation matter?

Aim: Several studies have reported an increased risk of fetal death among older women. The aim of this paper was to study the association between fetal death and maternal age by length of gestation in Norway.

Method: We conducted a population-based observational study including all ongoing pregnancies ≥16 weeks of gestation in Norway in 1967-2006 (n=2 182 756). Data was obtained from the MBRN. Changes in the absolute risks and HRs of fetal death in ongoing pregnancies were estimated. Cox regression models were applied to estimate the HR of fetal death according to maternal age at delivery categorized as less than 20, 20-24 (reference), 25-29, 30-34, 35-39, 40-44, and 45 years and older in the following gestational weeks: 16-22, 23-29, 30-36 and 37-43. Adjustment for confounding was made by including these variables as explanatory variables in multivariable Cox regression models.

Results: The risk of fetal death was 1.4 times higher in women 40-44 years old than in women aged 20-24 in mid-pregnancy (crude HR 1.43, 95% CI 1.18-1.74), but 2.8 times higher at term (crude HR 2.8, 95% CI 2.43-3.23). In term pregnancies the relative importance of maternal age increased with each additional week of pregnancy. In gestational weeks 42-43, the crude risk was 5.1 times higher in mothers ≥40 years (crude HR 5.09, 95% CI 3.55-7.31). In the more recent period (1987-2006), the elevated risk of fetal death in elderly mothers at term was attenuated.

Conclusions: Women ≥40 years had the highest risk of fetal death throughout pregnancy, particularly in term and post-term pregnancies. Improved obstetric care may explain the attenuation of risk of fetal death (≥40 weeks of gestation) associated with age in recent time.

7.4 Paper IV

Hypertensive disorders in pregnancy and fetal death at different gestational lengths: a population-based study of 2,121,371 pregnancies.

Aim: The aim of this paper was to compare the proportion of stillborn infants in pregnancies with pre-eclampsia, gestational hypertension or chronic hypertension with normotensive pregnancies.

Method: We conducted a register based observational study including all singleton births ≥20 completed weeks of gestation in Norway in 1967-2006 (n= 2 121 371). Data was obtained from the MBRN. The proportion of fetal death per 1000 births was estimated in normotensive pregnancies, and in pregnancies with pre-eclampsia, gestational hypertension and chronic hypertension at different lengths of gestation. The associations between the different hypertensive disorders and fetal death were estimated as RRs, by applying log-link models for binary data. Also changes in the proportions of stillborn infants by maternal hypertensive disorder from 1967-1986 to 1987-2006 were estimated.

Results The prevalence of hypertensive disorders in pregnancy was 4.7%. In total 17,933 fetal deaths occurred and 9.2% of these were in hypertensive pregnancies. In normotensive pregnancies 0.8% (16 290/2 022 400) experienced fetal death. That was true for 1.9% (1 170/62 261) of the pregnancies with pre-eclampsia, 1.2% (390/32 068) with gestational hypertension and 1.8% (83/4 642) with chronic hypertension. There was a 44% overall reduction in the fetal mortality rate from 1967-1986 to 1987-2006. The largest decline was in women with pre-eclampsia (80% reduction). In women with gestational hypertension and chronic hypertension the overall reduction in fetal mortality rates was 49% and 57% respectively, comparable to the 41% decline in normotensive pregnancies.

Conclusion In our nationwide study during 1967-2006 the risk of fetal death among women with hypertensive disorders in pregnancy was greatly reduced, especially among pre-eclamptic women at term.

8. DISCUSSION

The main findings in this thesis are:

1. Maternal PVB infection was not found to be significantly associated with fetal death. PVB infection does not seem to have any sizeable contribution to the overall risk of fetal death, since only four of 281 cases of fetal death were infected.
2. The risk of fetal death in Norway has been reduced by nearly 70% in pregnancies lasting longer than 22 weeks during 1967-2006, however, at 16-22 weeks of gestation, an increase in risk was observed.
3. Women 40 years old or older had the highest risk of fetal death throughout pregnancy, particularly in term and post-term pregnancies. However, the risk associated with high maternal age was attenuated in recent times.
4. In our nationwide study during 1967-2006, the risk of fetal death among women with hypertensive disorders in pregnancy was shown to be greatly reduced, especially among pre-eclamptic women at term. The risk of fetal death among women with gestational or chronic hypertension decreased, but in a different manner

In the following sections the methods used in the thesis are briefly discussed (the individual Papers contain more in-depth considerations). Thereafter the individual results of the Papers included in the thesis are discussed.

8.1 Methodological considerations

Epidemiological studies are conducted with the purpose to achieve reliable and valid estimates of the association between exposures and disease. Imprecision of estimates are caused by random error and improvement is generally achieved by increasing the sample size. CIs are computed to assess the precision of point estimates, thus the narrower the CI the more precise is the estimate.

The validity of epidemiological studies has two aspects: internal and external validity. Internal validity relates to the inference of the estimates to the study population.

Internal validity is impaired in epidemiological studies by selection bias, information bias and confounding. High internal validity is a requirement for external validity, which relates to inference beyond the study population.[255]

Sample size considerations

Paper I Fetal death and PVB infection in pregnancy are rare events; hence a case-control design was chosen in Paper I. The reported lack of association between PVB infection and fetal death in our study may be due to sample size limitations (type 2 error), as indeed numbers were limited in the sub-analysis (only 4 cases among 281 were PVB-positive by serology). In our study, 17 women among 957 controls had either IgM in the first serum sample or seroconverted. It was estimated that approximately 9000 women (cases + controls) would be needed in the study to detect a OR of 1.5 with 80% power using a two-sided 5% test.[256;257]

Papers II-IV In Papers II-IV we utilized population-based data from the MBRN (>2 million births and >17 000 fetal deaths). By utilizing this resource, we were able to study the rare outcome of fetal death with limited random error and narrow confidence intervals.

Selection bias

Selection bias is caused by systematic error in the selection process of the study sample, leading to a different association of exposures and outcomes in participants relative to non-participants.[255]

Paper I In Paper I, we conducted a case-control study within the nationwide prospective Toxoplasmosis Study. In this study the risk of selection bias was limited, as cases were all fetal deaths occurring in the cohort of 35 940 pregnant women who had participated in the Toxoplasmosis Study.[242] The exact participation rate is not known, but is assumed to be very high judging by the number of live births in the 11 participating counties.[242] Controls were randomly selected among all women in the Toxoplasmosis Study cohort delivering a live-born child at the end of follow-up, thus assuring that the exposure distribution of controls reflected the exposure distribution in the source population for cases.

Selection bias may also be considered due to incomplete/losses to follow-up of initially seronegative women (n=442) in the Toxoplasmosis Study cohort. These women did not have IgG antibodies against PVB in the first serum sample and therefore were at risk of seroconversion, but 68 of these women did not have follow-up serum available, and therefore PVB seroconversion could not be determined. This could cause biased estimates if the association between PVB infection and fetal death differed among women lost to follow-up compared to women with more than one serum sample collected. However, there were 25 cases of fetal death among these women, and for nine of these women the lack of follow-up was according to Toxoplasmosis Study protocol, as they had IgG antibodies against *T. gondii* in the first trimester. We do not believe that this would bias our estimates, as we only encountered 10 seroconversions among 372 susceptible women, and it is unlikely that lack of follow-up or presence of antibodies against *T.gondii* is associated with an increased risk of PVB infection.

The study has limited generalizability beyond the Norwegian study population, as the seroprevalence of IgG (35%-81%) and seroconversion rate among pregnant women has been reported to vary across countries, and genetic susceptibility may be different as well.[243]

Papers II-IV In Papers II-IV we conducted population-based retrospective cohort studies using the MBRN, which comprises information on all live births and fetal deaths from 16 weeks of gestation in Norway, hence selection bias was limited. Fetal deaths are prone to underreporting in vital registries,[258] however, temporal increases in early fetal deaths (birth weight <500 g corresponding to approximately 20-22 weeks of gestation) due to better registration have been reported.[259] Potential increased registration of early fetal deaths in the MBRN in recent time could have biased our results, causing some of the observed association between period (year) and early fetal death in Paper II. In Paper III, however, the results are not likely to be biased as registration of early fetal death is not associated with maternal age.

Information bias

Information bias occurs when the obtained information about exposure or outcome is erroneous (misclassification). Misclassification can be non-differential, that is,

unrelated to other variables, while differential misclassification differs according to other study variables.[255]

Paper I In Paper I the risk of information bias for the exposure (maternal antibody status) was low, as maternal antibody status was determined by serological testing in the laboratory. The kits used for detection of antibodies have a high specificity, and retesting of borderline positive sera was performed to further increase the specificity. Moreover, as serum samples were prospectively collected (prior to birth outcome), any potential misclassification of PVB infection according to fetal vital status would be non-differential, leading to attenuation of the association. Non-differential misclassification of a dichotomous explanatory variable causes bias in the estimates toward the null value.[255]

Another potential source of non-differential misclassification for the exposure may be due to the timing of the serum sampling. After infection there is a serological window of approximately 7 days where IgM and IgG are not detectable. IgM then rises and is detectable from day 7-10 and then decreases during 2-3 moths, whereas IgG is detectable only after 2 weeks.[260] If the women acquired PVB infection prior to pregnancy, but had persistent IgM at the time of serum sampling, they may have been erroneously categorized as having an acute infection, whereas women infected shortly prior to serum sampling may erroneously be categorized as un-infected.

Information on outcome (fetal death or live birth) was obtained from the MBRN. Notification of these outcomes to the MBRN is reported to be good,[38] and the high quality of information in the MBRN is maintained by routine linkage to other population registries, and comprehensive quality assurance.[6] However, as previously mentioned, before 1999 some elective pregnancy terminations (due to serious congenital anomalies) may have been misclassified as fetal death, which may underestimate the association between fetal death and PVB infection in our study. According to a national study, the estimated induced abortion rate after 16 weeks of gestation in Norway in 1996-1997 was 2-3 per 1000 births, and induced abortions were seldom performed after 21 weeks of gestation.[261] The fetal mortality rate at $\geq$16 weeks of gestation in the MBRN was 9-10 per 1000 births during the same period.[1] In our study 25% of fetal deaths occurred before 21 weeks of gestation (25% of 283

fetal deaths),[262] hence between 14-23 fetal deaths (<21 weeks of gestation) (that is 2-3 induced abortions per 9-10 fetal deaths) could potentially have been misclassified.

Fetal death occurring at the lower limit of registration (16 weeks of gestation) may have been underestimated if the women were not hospitalized or if the length of gestation was uncertain. The impact of this bias is probably low and independent of the exposure (PVB).

Papers II-IV In all three papers fetal death was the main outcome measure. This variable has not been validated in the MBRN, but the diagnosis of unexplained antepartum fetal death (≥28 weeks) has been validated in the registry, and has been reported to have high validity,[263] as have several other validated variables in the registry.[264-269]

As formerly stated, some elective pregnancy terminations (due to serious congenital anomalies) during 1986-1998 could have been differentially misclassified as fetal death. This would cause a falsely increased rate of fetal death between 16-20 weeks of gestation, since induced abortions were seldom performed after 21 weeks of gestation after the implementation of ultrasound examinations in antennal care during 1986.[261] This may have biased the association between early fetal death and period (1986-1998) in Paper II. Indeed the highest risk of early fetal death (gestational weeks 16-22) was observed during 1992-1996, though the risk remained significantly increased during the most recent period (2002-2006) as well.

High maternal age is associated with a higher number of pregnancy terminations due to the increased risk of malformations or anomalies detected at prenatal ultrasound examinations.[71] Hence, the observed association of early fetal death and high maternal age in Paper III may be overestimated. This was further explored by repeating analysis including births during 1999-2006 only. The analysis demonstrated an attenuated HR of fetal death among women aged 40-44 years (relative to women aged 20-24 years) at gestational weeks 16-22 (Appendix I, Table A).

Misclassification of gestational age could have biased our results in Paper II-IV. Gestational age estimations were based on the women's reporting of the first day of her LMP during 1967-1998, whereas from 1999 ultrasound dating was available in the MBRN.[6] LMP could cause inaccurate determination of length of gestation in women with irregular menstrual cycles, or uncertain first day of LMP. Studies comparing the accuracy of ultrasound and LMP to estimate gestational age have reported higher incidence of post term (≥42 weeks) births when LMP is applied, whereas there were only minor discrepancies in the prediction of preterm (<37 weeks) and term births.[270;271]
This could have caused biased estimates in Paper II, however, any overestimation of post-term pregnancies caused by applying LMP to predict term (before 1999) would underestimate, rather than overestimate, the reduction in fetal death post term in the later time period (1987-2006).
As misclassification of gestational age estimations is probably not differential according to maternal age or hypertensive disorders in pregnancy, the results in Paper III-VI are most likely not biased.

In Paper IV, maternal hypertensive disorders in pregnancy were studied, however, only pre-eclampsia has been validated previously (reporting positive predictive value of 64%-88%).[272] Blood pressure measurements and urine examinations are an essential part of the Norwegian public antenatal care program, and clinical findings are registered in the standard antenatal form that the women bring to the hospital at the time of delivery. As compulsory notification of birth to the MBRN is made on standardized forms shortly after delivery, differential misclassification due to recall bias or according to vital status of the infant is probably low. However, non-differential misclassification is more likely and would attenuate the association between exposure and outcome in the study.

Although the diagnostic criteria for hypertensive disorders in pregnancy have remained nearly unchanged,[272] the registration of hypertensive disorders may have become more complete (less frequently misclassified) after 1998, when the MBRN introduced a new form with pre-coded check boxes regarding maternal hypertensive disorders. This would most likely not differentially affect any one type of hypertensive disorder,[273;274] or differ according to fetal vital status.

Confounding

Confounding, or mixing of effects, occurs when the effect of an exposure on the outcome is distorted by a confounding variable. The confounding variable is associated both with the exposure and outcome (but is not an effect of outcome or exposure) (Figure 9). Figure 9 depicts a causal diagram of confounding, with the confounder being a common cause of both the exposure and the outcome variable. Known confounders can be dealt with at the analysis stage of the study, e.g. by including it as an explanatory variable in multivariable regression models, or by stratification, given that this variable has been measured.[255]

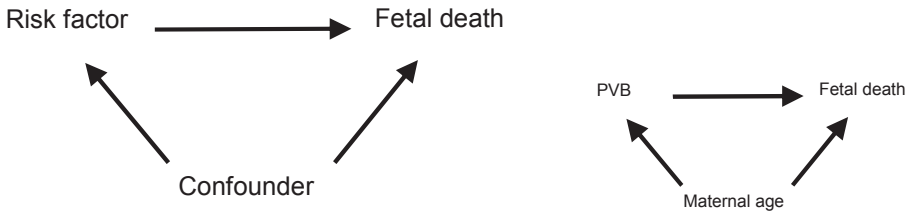

Figure 9. Causal diagram with Confounding

In Paper I the association between maternal PVB infection and fetal death could be confounded by maternal age[58;243] and parity,[60;244] hence, effect estimates were adjusted for these risk factors.

Residual confounding refers to the distortion that remains after adjustment for confounders, and is due to additional confounding factors that were either not considered or not available.[275] Data on potential confounders such as maternal stress[276;277] and SES[170;244] were not available, and thus their contribution could not be assessed. However, previous studies have indicated that parity/number of children in the household has a stronger association with seroconversion (exposure) in susceptible women compared to other risk factors.[244]

In Paper II we adjusted for maternal age, parity, multiple pregnancies, paternal age and pre-eclampsia, as these risk factors are associated both with the explanatory variable (period) and outcome (fetal death). Other risk factors were not adjusted for either because we lacked information on the variable or because no confounding effect was suspected.

In Papers II-III we adjusted the risk estimates for the confounding effect of multiple pregnancies (plurality) whereas in Paper IV multiple pregnancies were excluded from the sample. In retrospect, the latter approach is preferable as multiple pregnancies differ in many aspects from singletons pregnancies; multiple pregnancies are more susceptible to low birth weight, short gestational age, higher perinatal mortality, and have an increased risk of complications during delivery.[278] In the study sample of Papers II-III, only 2.7% were multiple pregnancies, and subsequently exclusion of multiple pregnancies from did not significantly alter the risk estimates (Appendix I, Table B and C).

We lacked information on maternal BMI, smoking, SES and ethnicity, and thus where not able to control for the effect of these factors.
Maternal BMI is associated with risk of fetal death[36;83] and varies by calendar period (year),[279] thus BMI may have biased our results. However, as high BMI is associated with fetal death and the prevalence of high BMI in our population has increased, our estimates of temporal declines in the rate of fetal death may be underestimates. In Paper III, BMI is a potential mediator associated with both the outcome (fetal death) and the explanatory variable (maternal age).[280] Since BMI is differentially associated with advanced gestation,[92] the observed increased risk of fetal death as gestation advances among older women may partly be explained by BMI. In Paper IV, as hypertensive disorders in pregnancy are associated with BMI,[281] the observed risk of fetal death may represent overestimates.

In Papers II and III we did not adjust for maternal diabetes or hypertensive disorders in pregnancy (apart from pre-eclampsia). Diabetes[55;69] and hypertensive disorders[13;248] are associated with an increased risk of fetal death, and as the prevalence of these disorders has increased,[1] our estimates may be deflated. In Paper III we did not adjust for these risk factors, as they were perceived as mediators

of the association between maternal age and fetal death, and as such should not be adjusted for (Figure 10).

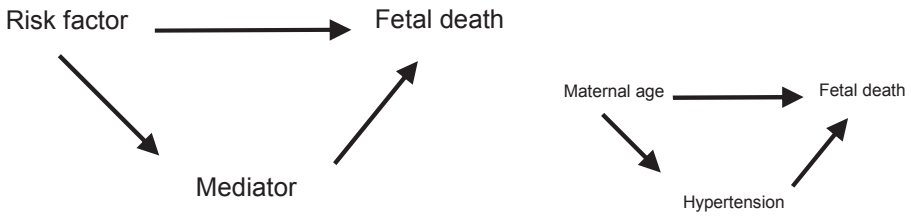

Figure 10. Causal diagram with Mediator

In Papers II-III we did not test for interaction between exposures and confounders as we had no reason to believe that it would influence fetal death at different gestational lengths. This assumption was subsequently explored by conducting analysis of gestational-age-specific risk of fetal death according to maternal age stratified by parity (Appendix I, Table D). This exercise revealed that the detrimental effect of high maternal age on risk of fetal death is more pronounced among nulliparous than multiparous women. However, within each strata high maternal age was associated with an increased risk of fetal death.

8.2 Interpretation of the results

8.2.1 Maternal human parvovirus B19 infection and risk of fetal death

The main aim of Paper I was to asses the association between maternal PVB infection (serological confirmed) and risk of fetal death (≥16 weeks of gestation) in the Norwegian population. In our study maternal PVB infection was not associated with fetal death, as the proportion of pregnant women exposed to PVB infection did not differ among cases and controls (presence of IgM: crude OR 0.76, 95% CI 0.16-3.52; seroconversion: crude OR 1.18, 95% CI 0.25-5.70). In addition, maternal PVB

antibody status was not significantly associated with gestational age or birth weight. There are several possible explanations for the lack of association in our study:
1) In our population PVB was not significantly associated with fetal death.
2) Our study is underpowered to find an association.
3) Lack of complete follow-up/under ascertainment.
4) Low diagnostically accuracy.

Since the first case reports in the early 1980s,[282] several large prospective cohort studies of pregnant women with serologically-confirmed PVB infection have shown an increased risk of fetal death of 5-11%,[218;219;283;284] whereas others did not report an increased risk.[285;286] The increased fetal mortality rate reported by some of these studies could be due to inclusion of pregnant women with symptoms of PVB infection, as being symptomatic may be associated with more severe infection. This is supported by the recent prospective cohort study by Bonvicini and colleagues, who reported higher PVB IgM and DNA values in symptomatic women compared to women with PVB infection discovered during routine screening (asymptomatic).[287] Hence, some of the association reported in these studies may be due to the selection of symptomatic women (non-representative sample). In one of the first large prospective studies of PVB serology positive women (n=190), 11% of the women who experienced a fetal loss had $\geq$1 prior stillbirth compared to only 1% among women with live birth.[218] Thus some of the increased risk of fetal death in PVB seropostive women could be due to factors other than PVB infection. We included all cases of fetal death from a large population-based cohort, hence, the risk of selection bias was limited and we also had a representative control group for comparison.

PVB IgG antibodies were present in the first serum sample of 64% of the women, rendering 36% susceptible to infection. This is comparable to previous reports.[276;285;288-290] Among 442 susceptible women 21 had serological signs of infection (4.8%). Previous studies have reported seroconversion rates among susceptible pregnant women during endemic periods between 0.6%-1.5% and during epidemic period up to 13.5%.[244;276;289]

Higher risk of fetal demise has been reported when maternal PVB infection occurs at $\leq$20 gestational weeks,[218;219;287] with most fetal deaths occurring between 13-20

weeks of gestation.[218;219;291] The increased vulnerability at early gestational ages is explained by the increased expression of P-antigen receptor in the trophoblast during the first and second trimesters, whereas it is missing in the third trimester. This receptor is utilized by PVB for transplacental transfer, followed by destruction of erythroid precursors that may cause severe fetal anemia. The anemic fetus may develop hydrops fetalis, which is associated with increased risk of fetal death, although most cases resolve spontaneously.[243] Recently, Weiffenbach and colleagues proposed that increased vulnerability prior to 20 weeks of gestation, may be due to limited transfer of maternal IgG across the placenta to the fetus, coupled with a poor fetal antibody response, by which the fetuses ability to control the infection is impaired.[292]
As we only included cases of fetal death ≥16 weeks of gestation, early fetal deaths associated with PVB were excluded, but also some cases >16 weeks may have been missed if the women were not hospitalized. Thus low ascertainment may have caused attenuation of the association.

Three Swedish studies reported PVB infection to be a common cause of non-hydropic fetal death in the third trimester.[220;223;224] Tolfvenstam and colleagues examined 47 cases of fetal death (≥22 weeks of gestation).[224] Seven of the cases (15%) and none of the healthy controls were PVB DNA-positive. However, PVB DNA was detected in different specimens among cases (placental or fetal tissue) and controls (placental tissue). The suitability of placentas from live births as control material has been questioned.[219] The majority of fetuses (n=5) were non-hydropic and no specific organ manifestation was detected, and maternal serology was negative. It remains unclear if these findings are spurious, or if the differing clinical picture presents manifestations of PVB-related late fetal death. The authors speculated that the pathophysiological mechanism involved in the third trimester may be different than in the second trimester, and may involve persistent low-grade infection and placental dysfunction.[293] If PVB is a common cause of late fetal deaths occurring in PVB seronegative women, we may have underestimated the number of fetal deaths associated with PVB. However, others have questioned the Swedish studies.[294;295] Recently Riipinen and colleagues retrospectively studied 169 cases of late fetal death (>22 weeks), and only detected PVB DNA in four cases (2.4%).[295]

Detection methods for maternal PVB infection may be direct (PCR) or by serology. In our study serological testing was utilized to confirm maternal infection, as this diagnostic method has high specificity and sensitivity. Molecular techniques for the detection of the viral genome by PCR have an even higher sensitivity, but contamination can also increase the number of false-positives. Thus it is possible that we missed some cases of fetal death caused by PVB, as we did not use the most reliable diagnostic methods: serology in combination with PCR.[287;296]

PVB is not a common cause of fetal death in the Norwegian population, but for the time being, PVB investigation should remain a part of the work-up after fetal death, as some fetal death may be caused by PVB, and for a grieving couple, knowing the cause of fetal death can have immense value.

8.2.2 Trends in fetal death in Norway

The main aim of this paper was to study temporal trends and gestational-age-specific changes in fetal death. We reported a significant reduction in the fetal mortality rate (≥22 weeks) during 1967-2006. The largest absolute decline was in pregnancies at term (≥37 weeks), however, for pregnancies at 16-22 weeks an opposite trend was observed.

The majority of high-income countries (Sweden, Denmark, Norway, Iceland, France, Spain, Italy, the United Kingdom, the Netherlands, Wales, the United States) have reported declining trends in fetal death, from 25-45 fetal deaths (≥28 weeks) per 1000 births in 1940, to 3-5 per 1000 births in the year 2000,[233] and between 1.5-4.3 per 1000 births in 2009.[44] In the United States the fetal mortality rate (≥20 weeks) was reported to have declined from 18.4 per 1000 births in 1950 to 6.2 per 1000 in 2005.[297] This trend is likely explained by improvements in general public health and in maternity care. In Norway, all pregnant women are offered routine antenatal examinations free of charge and the attendance rate is high (>99%).[298] A Norwegian cross-sectional study by Backe reported that the mean number of antenatal visits increased slightly from the 1980s to 1996, and a follow-up study reported a similar number of antenatal visits in 2000 (mean=12).[298] In addition, advances in obstetric services, such as routine ultrasound, extensive use of cardiotocography, induction of

labor and the increased caesarean section rate, has contributed to the success of modern obstetrics.

The European project for monitoring and evaluating perinatal outcomes on the European level (EURO-PERISTAT Project) estimated fetal mortality rates from European countries/regions in 2004 and 2009, and reported large inter-country differences in fetal mortality rates (≥22 weeks), from 2.6 to 9.1 per 1000 in 2004 and from 4 to 8 per 1000 in 2009.[43;44] Differences were most likely due to differing registration policies, inclusion of pregnancy terminations in some countries and differing prevalence of risk factors and perinatal care. Hence the underlying causes of the observed trends are best studied at the national level.[299]

In our study the fetal mortality rate varied according to length of gestation, and the largest absolute decline occurred in term pregnancies (≥37 weeks). This trend has been confirmed by others,[300;301] and may be attributed increased fetal surveillance and intervention at term. Indeed, some of the racial inequality in stillbirth at term in the United States was linked to Black women being less likely to undergo induction compared to non-Hispanic Whites.[24;239] Willinger and colleagues demonstrated that women with medical conditions, such as diabetes or hypertensive disorders in pregnancy, have an increased risk of fetal death at term (week 37-41), and exclusion of women with these conditions from their analysis reduced the hazard of fetal death by 5-10%.[24] Thus some of the decline in late stillbirths in our population may be due to close monitoring and timely delivery of women with medical conditions.
Postponement of childbearing may also contribute to increased risk at term and post term, as reported in Paper III and other studies.[23;65;66] The hazard of fetal death at term declined further when we adjusted for maternal age and preeclampsia, as both risk factors have increased in our population. We lacked information on BMI, smoking, ethnicity and SES, which may have a differential impact on term births. A recent study from Norway demonstrated that the effect of social inequality on offspring mortality was lowest at term and post term (week 37-43), and increased during preterm gestation and 1 week after birth.[302] The authors attributed the observed risk reduction to equal access to public health care.
During our extensive observation time (1967-2006) the method for the estimation of term date has changed: during 1967-1998 it was based on LMP, but from 1999 it was

based on ultrasound examinations. The proportion of post term pregnancies may have been overestimated before the introduction of ultrasound;[271] however, any overestimation of post term pregnancies due to the use of LMP to predict term may have underestimated the temporal reduction in term fetal mortality.

Contrary to the reduction in fetal death at term, we report an almost doubled fetal mortality rate at 16-22 weeks of gestation in 2002-2006 compared to 1967-1971. This observation could be due to increased registration or the observed trend is real and merits further investigation.

Increased case ascertainment over time may be a possible explanation for our findings; however, increased risk of fetal death at early gestation has been confirmed by other studies.[11;23;24] Joseph and colleagues conducted a retrospective cohort study of births in British Columbia during 2000-2010, and reported an increasing number of stillbirths with a birth weight <500 g, which was largely attributed to pregnancy terminations due to congenital anomalies.[11] However, even after exclusion of pregnancy terminations, the rate of fetal death at early gestation exceeded the rate in mid-gestation (week 28-36). Compared to spontaneous fetal death with birth weight >1000g, which declined significantly during 2000-2010, fetal deaths with birth weight <500 g declined non-significantly. Similarly, Martin and colleagues reported a declining trend in late fetal mortality at $\geq$28 weeks of gestation in the United States, but a steady fetal mortality rate at 20-27 weeks of gestation.[301] However, after 1999 our data did not include pregnancy terminations.

Our findings could reflect a true increase, and some of this increase may be due to the advancing age of childbearing women. This is supported by the observed attenuation of the risk of fetal death in gestational week 16-22 when adjustment for maternal age was performed (in 2002-2006, crude RR 2.05 vs. adjusted RR 1.87). Reddy and colleagues also reported an increased risk of fetal death at early gestation among older women.[23]

This reported trend could also be caused by a higher number of women undergoing treatment with excisional cervical surgery due to cervical intraepithelial neoplasia, as this treatment increases the risk of perinatal mortality and extreme preterm delivery with intrapartum death as a consequence.[303] In Norway, the proportion of childbearing women treated with excisional cervical surgery increased more than 20-

fold between the periods 1967-1979 and 2000-2003, and cumulative incidence of treatment is higher among older women.[304] Another possible cause of the increased fetal mortality rate could be infections, as infections are assumed to be related to fetal death at early gestation.
Willinger and colleagues reported that women with certain pregnancy risk factors (incompetent cervix, premature rupture of membranes, uterine bleeding, hypertensive disorders in pregnancy) have an increased risk of fetal death at early gestation (week 20-27), and demonstrated that exclusion of women with these conditions from their analysis reduced the hazard of fetal death by 15-22%.[24]

The perinatal mortality rate is a quality parameter of obstetric and neonatal care, hence it is important to study temporal trends to evaluate interventions and healthcare services delivered. Variations in gestational-age-specific fetal death may reveal further differences in registration practice and quality of care.

8.2.3 The impact of maternal age and fetal death

The aim of Paper III was to assess the association of maternal age with fetal death by gestational age and by time period by applying the fetuses-at-risk model. We reported an increased risk of fetal death with advancing maternal age throughout pregnancy; the risk was particularly increased in early gestation, and as pregnancy progressed to term and past term the increased risk in older women intensified.

An association between high maternal age and increased risk of fetal death has been reported in several studies.[36;305] The mechanisms involved remain uncertain, as the increased risk may be attenuated, but not completely explained, by medical conditions,[50;60] uteroplacental insufficiency,[306] high BMI or low SES.[62] In two recent, large population-based studies from the United States and the United Kingdom, when only non-anomalous deliveries were included in the study the association between maternal age and stillbirth risk disappeared.[69;70] However, our estimates did not change when we repeated our analysis excluding deliveries with congenital anomalies.

In a recent multi-center case-control study from Italy, of 254 fetal deaths (cases) and 497 live births (controls), maternal age >35 years was not associated with increased risk of fetal death. BMI >25 was the only risk factor significantly associated with fetal death at term (OR 7.70, 95% CI 2.9-20.5).[307] Hence, in some populations the increased risk of fetal death in older mothers may be explained by an increased prevalence of overweight and obesity. Carolan and colleagues conducted a systematic review of advanced maternal age and adverse perinatal outcome.[305] The review included nine studies (>40 million women), but only one study adjusted for maternal BMI, and after adjustment the increased risk of perinatal mortality in women 35-39 years old was no longer significant (adjusted OR 1.1, 95% CI 0.6-1.9). However, the risk in women ≥40 years was still increased (adjusted OR 2.2, 95% CI 1.1-4.5).[308] As we lacked information of maternal BMI in the registry, we were not able to adjust for this confounding factor.

The reported increased risk among older mothers at gestational week 16-22 could be due to: a) increased registration of early fetal losses by time (years), b) a true increase that may be caused by higher cumulative incidence of treatment with excisional cervical surgery. Both alternatives are likely to contribute, as studies from other high-income countries have reported increased registration of fetal deaths weighing <500 g.[259] However, under-registration of these fetuses is also of concern,[258] hence our high estimate in the last time period may be an underestimate rather than an overestimate.
As already mentioned, the proportion of childbearing women treated with excisional cervical surgery increased more than 20-fold in Norway during 1967-2003, and cumulative incidence of treatment is higher among older women.[304] This treatment increases the risk of perinatal mortality (RR 2.08, 95% CI 1.04-4.13) and extreme preterm delivery (<28 weeks, RR 13.00, 95% CI 1.70-99.12) with intrapartum death as a consequence.[303;309]

Our reported association between advanced maternal age and risk of fetal death at term and post term is in accordance with several recent studies.[23;64-66] Uteroplacental insufficiency has been proposed as a possible link between maternal age and fetal death at late gestational age,[57] whereas others have rejected this.[306]

Interestingly, the impact of maternal age on the risk of fetal death at term and post term was attenuated in the most recent time period 1987-2006 compared to 1967-1986. This is most likely due to a "cohort effect". During the last decades, vast advances in antenatal and obstetric care have occurred, which may have benefited older women and enabled safe delivery. Our observations are supported by the declining rates of post term births in Norway (the proportion of women giving birth in week 42 declined from 9.4% in 1967 to 3.8% in 2012) and the increase in the caesarean section rate (1.8% in 1967 to 16.3% in 2006).[1] Herstad and colleagues analyzed population-based Norwegian data for 1999-2006 and reported a significantly higher incidence of elective caesarean section in low-risk women ≥40 years old relative to women aged 20-24 years (RR 11.7, 95% CI 8.9-15.4).[310]
The other possible explanation is "the healthy mother effect", i.e. older childbearing women in recent times may be healthier and better-educated than mothers of the same age 40 year ago. Data from the EURO-PERISTAT project support this theory.[311] Wide variations in the proportion of childbearing women ≥35 years old across 12 European countries were reported, from 7.4% in Estonia to 21.9% in Ireland. The association between high maternal age and risk of fetal death decreased as the prevalence of childbearing women aged ≥35 years increased in the populations studied. The authors proposed two possible explanations for this: a) higher SES among older childbearing women, b) adaptation of clinical practice in countries with a high prevalence of older pregnant women.

In the last period (1987-2006) we observed an increased risk of fetal death among women aged <20 years old (HR 1.77, 95% CI 1.20-2.60) in gestational weeks 38-39. This observation may be explained by increased immigration in Norway during the last decades. Ethnic background has been related to teenage pregnancies and an increased risk of fetal death.[183;312] This observation was further confirmed when additional analyses were conducted, limiting the study period 1999-2006, and demonstrated a significant increased risk of fetal death at gestational weeks 16-22 and 37-43 among women aged <20 years relative to women aged 20-24 years (Appendix I, Table A).
Results from prior studies diverge regarding the risk of fetal death among young women. A recent study reported an increased risk of fetal death among women 16 years of age (adjusted RR 1.37, 95% CI 1.09-1.7) and women 18 years of age

(adjusted RR 1.17, 95% CI 1.04-1.30) relative to 20-year-old women.[73] The authors hypothesized that childbearing young women in recent times may have a more disadvantageous risk profile (low SES, high BMI, increased prevalence of smoking) than older women.

8.2.4 Hypertensive disorders in pregnancy and risk of fetal death

The main aim of Paper IV was to study and compare the association between different hypertensive disorders in pregnancy and fetal death.

The prevalence of hypertensive disorders in our study was: preeclampsia 2.9%, gestational hypertension 1.5% and chronic hypertension 0.5%. The prevalence of gestational hypertension and chronic hypertension were lower than those reported in other studies, as the prevalence of gestational hypertension is reported to be 2-3% and approximately 0.5-2% for chronic hypertension.[109;248] Hence, these diseases may have been under reported in the registry, and may attenuate the association. As the "normotensive" population is large misclassification of hypertensive disorders would not have affected the prevalence in this group.

Our study demonstrated an increased risk of fetal death in women with pre-eclampsia (RR 2.3), gestational hypertension (RR 1.5), and chronic hypertension (RR 2.1) relative to normotensive women during the study period 1967-2006. Previous studies in Norway only reported on preeclampsia.[102;114] During the 40 years studied, the stillbirth rate among women with any hypertensive disorder in pregnancy declined, but the largest decline was observed in women with preeclampsia. This decline is likely due to the changes in the organization and execution of antenatal care. In 1983, a committee appointed by the government of Norway developed the "Maternal healthcard" and systematic guidelines regarding antenatal care. Early detection and timely delivery of infants at increased risk of fetal death likely contributed to the reported decline.[102] Klungsøyr and colleagues reported an increased proportion of preeclamptic singleton pregnancies delivered by caesarean section (RR 3.0) and induced labor (RR 1.3) during 1967-2008 in Norway.[114] Similar trends have been reported by several studies from high-income countries.[70;110;115;117;307] Cruz and colleagues conducted a retrospective cohort study

including 12 723 pregnant women with hypertensive disorders, and reported significantly more fetal deaths in the control group (defined by the absence of past and present medical conditions). The authors hypothesized that this may be due to higher rates of induction of labor prior to the event of fetal death.[117] Facchinetti and colleagues reported pre-eclampsia to be a protective factor in modern maternity care (OR 0.4, 95% CI 0.2-0.8), attributing this to increased alertness to the clinical presentation of this disorder, and to extensive access to antenatal care.[307]

A decline in the risk of stillbirth among women with gestational hypertension and chronic hypertension was also observed, but to a lesser extent than for preeclampsia. This may be due to improved registration after implementation of the new notification form with pre-coded check boxes in 1999, or to less clinical alertness and intervention on the part of healthcare professionals in these women compared to preeclamptic pregnancies. This could also be due to the demographic change in Norway during the study period, with increased incidence of pregnancies among women of advanced age and non-Western women. Women with chronic hypertension are more likely to be either older, Black or to have diabetes,[110;117] and a high rate of stillbirth is reported among women with both chronic hypertension and diabetes mellitus due to a proposed additive effect of these conditions.[111]

We studied the gestational-age-specific risk of fetal death among women with hypertensive disorders, and reported an increased risk as pregnancy advanced relative to normotensive pregnancies, with the highest RR at term and post-term. This may imply that the mechanism involved in the increased risk of fetal death is placental dysfunction.[115] This is further supported by the increased risk of SGA infants in hypertensive pregnancies.[248] Helgadottir and colleagues studied 377 cases of fetal death occurring in two hospitals in Norway during 1990-2003, and observed that the risk of fetal death in hypertensive pregnancies was mediated by SGA infants, as the risk of fetal death among pregnant women with hypertensive disorders but without a SGA infant was only moderately increased .[53]
In the later period 1987-2006, a paradoxical relationship between preeclampsia and gestational-age-specific fetal death was observed, with a higher risk among preeclamptic pregnancies compared to normotensive pregnancies at term, but a

lower risk or protective effect of preeclampsia in early gestation. This observation could be true or spurious.

Infants delivered preterm due to preeclampsia may have a more favorable outcome than the control group of infants delivered preterm for other pathological causes, such as infection.[313]

Yet another possibility is the potentially increased survival advantage among fetuses in preeclamptic pregnancies, due to an increased level of maternal cortisol, which may lead to expedited lung maturation.[248]

When studying fetal death at early gestation by applying the conventional method to estimate risk, we conditioned on birth and in this case, preterm birth. However, according to knowledge obtained from direct acyclic graphs (DAG), gestational age is a collider, a common effect, and conditioning on a collider (collider stratification) may cause spurious effects to occur, or even reversal of the association (Figure 11).[314] Preeclampsia is associated with fetal death, and preterm birth is a common effect, therefore conditioning on births (and not all ongoing pregnancies) introduces bias, and may cause reversal of the association from increased risk to a protective effect (*personal communication with Dr. Allen J. Wilcox*). This can be avoided by applying the fetus-at-risk model, but this was not possible within the present data, as gestational age at preeclampsia occurrence is not registered in the MBRN.

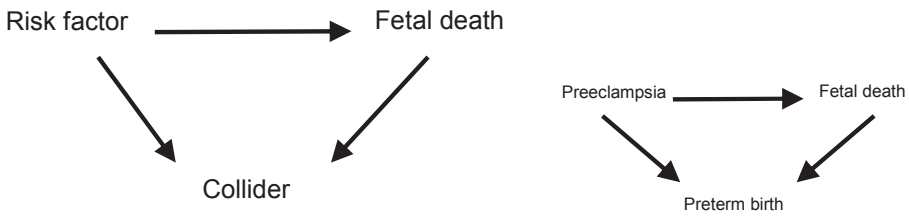

Figure 11. Causal diagram with Collider.

However, our choice to apply the conventional model for the estimation of stillbirth risk in Paper IV may be justified, as stillbirths and live births could be considered competing events. In that case the conventional measure of fetal death risk can be interpreted as the ratio between the hazards toward live births and towards stillbirths

(*personal communication with my supervisor Sven Ove Samuelsen*). Thus the "protective effect" of the exposure (pre-eclampsia), especially around gestational weeks 28-35 may be due to a larger impact towards live birth than stillbirth.

The benefit of maternal anti-hypertensive therapy on the risk of fetal death is limited.[315] Thus, the most efficient means to reduce fetal deaths in pregnant women with hypertensive disorders is close clinical follow-up and induction of delivery in threatened pregnancies. Our study indicates that pregnant women with hypertensive disorders would benefit from closer follow-up near term.

9. CLINICAL IMPLICATIONS AND FUTURE CHALLENGES

In conclusion, we showed that:
PVB infection was not significantly associated with fetal death in our population-based study.
The risk of fetal death has significantly declined over the last 40 years in pregnancies ≥22 weeks of gestation, with the absolute largest reduction observed at term (>37 weeks). However, the risk increased at 16-22 weeks.
Advanced maternal age is associated with increased risk of fetal death in early gestation (weeks 16-22) and late gestation (week 37-43); however, in recent years the risk associated with age has attenuated.
Women with disorders in pregnancy have an increased risk of fetal death, however, the risk has been greatly reduced during 1967-2006, especially among preeclamtic women at term.
We speculate that this decline is most likely due to widespread access to free, high-quality antenatal care and advances in obstetric care.[310] The largest decline in fetal death in our studies was observed at >37 weeks of gestation, when the gestational-age-specific risk in most studies is reported to increase, which further supports that the decline is due to obstetric intervention.

The clinical implications of our study are:

PVB should remain part of the investigations after fetal death. Even though PVB was not significantly associated with fetal death in our study, our study may have been underpowered. However, we do not think PVB is a common cause of fetal death in our population; hence, investigations should only be performed when indicated by the clinical picture.
Women >35 years have an increased risk of fetal death past term, at which point they should be monitored closely. This has already been implemented in the clinic at our institution.
Women with any hypertensive disorders in pregnancy have an increased risk of fetal death past term and should be followed with equal vigilance.

The comprehensive Lancet Stillbirth Series, published in 2011,[316] presented priority areas for stillbirth prevention in high-income countries, and suggested that to achieve further improvement in the future, focus should be placed on specific risk factors and specific vulnerable groups. Indeed the largest reductions in fetal death happened when intervention strategies were developed and applied for specific causes, such as rhesus isoimmunization or implementation of population-based prenatal screening for congenital anomalies.[10] Hence, to achieve further reductions in fetal death, judicious estimates of risk should be made. Research should aim to estimate the gestational-age-specific risks of fetal death in women with certain risk factors and to estimate the effect of interaction between risk factors.
Maternal overweight and obesity is reported to be the highest ranking modifiable risk factor, contributing to nearly 8000 stillbirths per year. Hence there is a need for preventive strategies that target this modifiable risk factor.
Sub-optimal care (both self-care and care delivered by health professionals) has been associated with up to 60% of stillbirths, and may explain some of the variation in fetal mortality that exists in high-income countries. Racial and ethnic disparities,[179;317] and social inequalities in fetal mortality[170;318] needs to be addressed.
Recent studies have concluded that pregnancy risk factors known at pregnancy start have limited predictive value; hence, future research should explore new risk factors. The importance of environmental factors, health care related factors, occupational hazards, psychological stress, diet, physical activity need to be further explored.

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APPENDIX I.

Table A. Adjusted hazard ratio with 95% CI of fetal death in gestational weeks 16-43 according to maternal age in the period 1999 to 2006 (corresponding to Table 2 in Paper III, but limited to the year 1999 to 2006).

Year of delivery 1999-2006

Gestational week 16-22

Maternal age	Adjusted HR* (95% CI)
<20	1.41 (1.03-1.92)
20-24	1
25-29	0.99 (0.83-1.18)
30-34	1.15 (0.96-1.39)
35-39	1.29 (1.04-1.59)
40-44	1.44 (1.06-1.95)
≥45	1.71 (0.63-4.66)

Gestational week 23-29

Maternal age	Adjusted HR* (95% CI)
<20	1.27 (0.81-2.00)
20-24	1
25-29	1.03 (0.80-1.33)
30-34	1.07 (0.80-1.41)
35-39	1.11 (0.80-1.55)
40-44	1.20 (0.71-2.04)
≥45	

Gestational week 30-36

Maternal age	Adjusted HR* (95% CI)
<20	0.95 (0.51-1.75)
20-24	1
25-29	1.06 (0.79-1.43)
30-34	1.41 (1.03-1.93)
35-39	1.62 (1.12-2.34)
40-44	2.42 (1.43-4.12)
≥45	2.50 (0.34-18.38)

Gestational week 37-43

Maternal age	Adjusted HR* (95% CI)
<20	1.74 (1.12-2.72)
20-24	1
25-29	1.41 (1.09-1.83)
30-34	1.53 (1.16-2.03)
35-39	2.19 (1.60-3.00)
40-44	2.24 (1.38-3.65)
≥45	

* Adjusted for period of delivery, paternal age, parity and pre-eclampsia. At 16-22 weeks pre-eclampsia is not adjusted for.

Table B. Adjusted hazard ratio with 95% CI of fetal death in gestational weeks 16-43 according to year of delivery among singletons (corresponding to Table 2 in Paper II, but limited to singletons).

Gestational week 16-22

Year	Adjusted HR* (95% CI)
1967-1971	1
1972-1976	1.14 (1.00-1.30)
1977-1981	1.26 (1.10-1.43)
1982-1986	1.43 (1.26-1.63)
1987-1991	2.03 (1.81-2.28)
1992-1996	2.68 (2.41-3.00)
1997-2001	2.35 (2.10-2.63)
2002-2006	1.92 (1.71-2.16)

Gestational week 23-29

Year	Adjusted HR* (95% CI)
1967-1971	1
1972-1976	1.10 (1.00-1.22)
1977-1981	1.06 (0.95-1.18)
1982-1986	0.91 (0.82-1.02)
1987-1991	0.79 (0.70-0.88)
1992-1996	0.72 (0.64-0.81)
1997-2001	0..57 (0.50-0.64)
2002-2006	0.44 (0.39-0.50)

Gestational week 30-36

Year	Adjusted HR* (95% CI)
1967-1971	1
1972-1976	0.82 (0.75-0.89)
1977-1981	0.67 (0.62-0.74)
1982-1986	0.48 (0.43-0.53)
1987-1991	0.38 (0.34-0.43)
1992-1996	0.30 (0.26-0.33)
1997-2001	0.26 (0.22-0.30)
2002-2006	0.19 (0.16-0.21)

Gestational week 37-43

Year	Adjusted HR* (95% CI)
1967-1971	1
1972-1976	0.79 (0.74-0.86)
1977-1981	0.58 (0.53-0.64)
1982-1986	0.44 (0.40-0.49)
1987-1991	0.36 (0.32-0.39)
1992-1996	0.35 (0.31-0.39)
1997-2001	0.37 (0.34-0.41)
2002-2006	0.30 (0.26-0.33)

* Adjusted for maternal age, paternal age, parity and pre-eclampsia. At 16-22 weeks pre-eclampsia is not adjusted for.

Table C. Adjusted hazard ratio with 95% CI of fetal death in gestational weeks 16-43 according to maternal age among singletons (corresponding to Table 2 in Paper III, but limited to singletons).

Gestational week 16-22

Maternal age	Adjusted HR* (95% CI)
<20	1.10 (0.97-1.26)
20-24	1
25-29	1.05 (0.97-1.15)
30-34	1.22 (1.10-1.34)
35-39	1.52 (1.36-1.70)
40-44	2.06 (1.74-2.43)
≥45	1.22 (0.58-2.58)

Gestational week 23-29

Maternal age	Adjusted HR* (95% CI)
<20	1.08 (0.96-1.22)
20-24	1
25-29	1.03 (0.95-1.13)
30-34	1.17 (1.05-1.30)
35-39	1.32 (1.15-1.52)
40-44	1.43 (1.14-1.80)
≥45	2.14 (1.14-4.04)

Gestational week 30-36

Maternal age	Adjusted HR* (95% CI)
<20	0.85 (0.76-0.96)
20-24	1
25-29	1.10 (1.01-1.19)
30-34	1.34 (1.21-1.48)
35-39	1.70 (1.49-1.93)
40-44	2.23 (1.85-2.70)
≥45	2.68 (1.56-4.60)

Gestational week 37-43

Maternal age	Adjusted HR* (95% CI)
<20	0.78 (0.70-0.88)
20-24	1
25-29	1.24 (1.15-1.33)
30-34	1.49 (1.35-1.63)
35-39	1.98 (1.76-2.23)
40-44	2.76 (2.32-3.29)
≥45	3.42 (2.06-5.67)

* Adjusted for period of delivery, paternal age, parity and pre-eclampsia. At 16-22 weeks pre-eclampsia is not adjusted for.

Table D. Hazard ratio with 95% CI of fetal death in gestational weeks 16-43 according to maternal age, stratified by parity (corresponding to Table 2 in Paper III, but stratified by parity to check for interaction). The P-value was obtained by incorporating an interaction term between maternal age and parity into the regression model. Nulliparous women 35 years and older had increased risk of fetal death compared to multiparous women.

Gestational week 16-22

	Parity*		
Maternal age	0	1	2
<20	1.38 (1.20-1.57)	1.52 (1.06-2.16)	1.63 (0.40-6.60)
20-24	1	1	1
25-29	1.22 (1.09-1.35)	1.00 (0.88-1.13)	0.96 (0.77-1.21)
30-34	1.52 (1.34-1.74)	1.31 (1.15-1.45)	1.23 (0.99-1.52)
35-39	2.38 (1.98-2.85)	2.01 (1.71-2.37)	1.50 (1.12-1.90)
40-44	4.08 (2.90-5.75)	3.36 (2.49-4.53)	2.26 (1.63-3.14)
≥45	2.70 (0.38-19.18)	2.56 (0.36-18.18)	1.25 (0.17-8.93)

* P-value for interaction term in regression analysis p=0.008

Gestational week 23-29

	Parity**		
Maternal age	0	1	2
<20	1.50 (1.33-1.70)	1.79 (1.29-2.49)	4.32 (1.76-10.64)
20-24	1	1	1
25-29	0.85 (0.76-0.95)	0.77 (0.67-0.87)	0.84 (0.67-1.06)
30-34	0.98 (0.85-1.13)	0.76 (0.66-0.89)	0.67 (0.53-0.85)
35-39	1.34 (1.07-1.66)	0.79 (0.62-0.99)	0.83 (0.63-1.08)
40-44	1.64 (1.00-2.68)	1.19 (0.73-1.93)	0.85 (0.53-1.39)
≥45	2.28 (0.32-16.19)	2.56 (0.36-18.22)	1.31 (0.18-9.40)

** P-value for interaction term in regression analysis p=0.032

Gestational week 30-36

	Parity***		
Maternal age	0	1	2
<20	1.26 (1.12-1.439	1.04 (0.69-1.57)	0.92 (0.13-6.59)
20-24	1	1	1
25-29	0.83 (0.75-0.92)	0.81 (0.72-0.92)	0.83 (0.65-1.05)
30-34	0.98 (0.86-1.12)	0.82 (0.71-0.94)	0.77 (0.61-0.98)
35-39	1.41 (1.15-1.72)	1.30 (1.08-1.56)	0.91 (0.70-1.18)
40-44	1.90 (1.22-2.96)	1.64 (1.09-2.45)	1.87 (1.29-2.69)
≥45	13.20 (5.91-29.5)	4.91 (1.22-19.68)	1.36 (0.19-9.75)

*** P-value for interaction term in regression analysis p=0.160

Gestational week 37-43

	Parity****		
Maternal age	0	1	2
<20	1.06 (0.95-1.19)	1.08 (0.71-1.64)	0
20-24	1	1	1
25-29	0.92 (0.84-1.01)	1.04 (0.92-1.18)	0.92 (0.74-1.15)
30-34	1.15 (1.02-1.29)	1.03 (0.90-1.19)	0.92 (0.74-1.15)
35-39	2.14 (1.81-2.52)	1.70 (1.14-2.05)	1.08 (0.84-1.38)
40-44	2.57 (1.74-3.79)	2.05 (2.15-4.33)	1.76 (1.12-2.57)
≥45			1.54 (0.21-11.02)

**** P-value for interaction term in regression analysis p=0.031

I

II

III

IV

Registreringsskjema fra 1967-1998

STATENS HELSETILSYN
Postboks 8128 Dep.
0032 OSLO

Medisinsk registrering av fødsel

Sendes 9. dag etter fødselen til fylkeslegen (stadsfysikus) i det fylket der moren er bosatt.

Merk: Det skal fylles ut blankett for hvert barn (foster). Dør barnet etter fødselen, skal det også fylles ut legeerklæring om dødsfall, og/eller dødsfallet meldes til skifteretten (lensmannen).

Barnet

Barnet var 1 ☐ Levende født 2 ☐ Dødfødt foster | Født dag, mnd., år | Klokkeslett | Personnr. | Skriv ikke her

1 ☐ Enkel 2 ☐ Tvilling 3 ☐ Trilling 4 ☐ Firling | Kjønn 1 ☐ Gutt 2 ☐ Pike

Etternavn, alle fornavn (bare for levendefødte)

Fødested. Navn og adresse på sykehuset/fødehjemmet | Kommune

Faren

Etternavn, alle fornavn | Født dag, mnd., år | Bostedskommune

Moren

Etternavn, alle fornavn. Pikenavn | Født dag, mnd., år

Bosted. Adresse | Kommune

Ekteskapelig status 1 ☐ Ugift 6 ☐ Samboende 2 ☐ Gift 3 ☐ Enke 4 ☐ Separert 5 ☐ Skilt | Ekteskapsår (gifte)

Antall tidligere fødte (før denne fødselen) | Levende fødte | Av disse i live | Dødfødte

Er moren i slekt med faren? 1 ☐ Nei 2 ☐ Ja. Hvilket slektskapsforhold:

Morens helse før svangerskapet

1 ☐ Normal 2 ☐ Sykdom (spesifiser):

Siste menstruasjons første blødningsdag

Morens helse under svangerskapet

1 ☐ Normal 2 ☐ Komplikasjoner (spesifiser):

Ble fødselen provosert

1 ☐ Nei 2 ☐ Ja

Inngrep under fødselen

1 ☐ Nei 2 ☐ Ja (spesifiser):

Inngrepet utført av 1 ☐ Lege 2 ☐ Jordmor

Komplikasjoner i forbindelse med fødselen

1 ☐ Nei 2 ☐ Ja (spesifiser):

Fostervann, placenta og navlesnor

1 ☐ Normalt 2 ☐ Patologisk (spesifiser):

Barnets tilstand

Bare for levende fødte. Tegn på asfyksi? 1 ☐ Nei 2 ☐ Ja | Apgarscore etter 1 min. | etter 5 min.

For levende fødte og dødfødte. Tegn på medfødt anomali, på skade eller sykdom? 1 ☐ Nei 2 ☐ Ja. Hvilke:

Lengde (i cm) | Hode-omkr. (i cm) | Vekt (i g) | For døde innen 24 timer Livet varte i | Timer | Min

For dødfødte. Døden inntrådte 1 ☐ Før fødselen 2 ☐ Under fødselen
Dødsårsak:

Seksjon? 1 ☐ Nei 2 ☐ Ja

Alvorlige arvelige lidelser i slekten

1 ☐ Nei 2 ☐ Ja Sykdommens art og hos hvilke slektninger:

Sted (sykehusets stempel) | Dato | Jordmor | Lege

50 000. 5.96. SEM GRAFISK

MFR

Melding om avsluttet svangerskap etter 12. uke – Fødsel, dødfødsel, spontanabort

Se utfyllingsinstruks for blanketten på baksiden

Sosial- og helsedirektoratet

A – Sivile opplysninger

Institusjonsnr: | Institusjonsnavn

Fødsel utenfor institusjon: ☐ Hjemme, planlagt ☐ Hjemme, ikke planlagt ☐ Under transport ☐ Annet sted

Mors fulle navn og adresse

Pikenavn (etternavn):

Mors sivilstatus ☐ Gift ☐ Ugift/enslig ☐ Annet ☐ Samboer ☐ Skilt/separert/enke

Slektskap mellom barnets foreldre? ☐ Nei ☐ Ja Hvis ja, hvorledes:

Mors bokommune

Fars fødselsdato | Fars fulle navn

Mors fødselsnr:

B – Om svangerskap og mors helse

Siste menstr. 1. blødn.dag ☐ Sikker ☐ Usikker

Mors tidligere svangerskap/fødte Levende-fødte | Dødfødte (24. uke og over) | Spontanabort/Død-fødte (12.–23. uke) | Spontanaborter (under 12. uke)

Ultralyd utført? ☐ Nei ☐ Ja UL termin:

Annen prenatal diagnostikk? ☐ Nei ☐ Ja, angi type:

Patologiske funn ved prenatal diagnostikk? ☐ Nei ☐ Ja, hvis bekreftet – spesifiser

Spesielle forhold før svangerskapet: ☐ Intet spesielt
☐ Astma ☐ Allergi ☐ Tidligere sectio ☐ Res. urinveisinfeksjon ☐ Kronisk nyresykdom ☐ Kronisk hypertensjon ☐ Reumatoid artritt ☐ Hjertesykom ☐ Epilepsi ☐ Diabetes type 1 ☐ Diabetes type 2 ☐ Annet, spesifiser i «B»

Regelmessig kosttilskudd: ☐ Nei — Før sv.sk. — I sv.sk.
Multivitaminer ☐ ☐
Folat/Folsyre ☐ ☐

Spesifikasjon av forhold før eller under svangerskapet: B

Spesielle forhold under svangerskapet: ☐ Intet spesielt
☐ Blødning < 13 uke ☐ Blødning 13–28 uke ☐ Blødning > 28 uke ☐ Glukosuri ☐ Svangerskapsdiabetes ☐ Hypertensjon alene ☐ Preeklampsi lett ☐ Preeklampsi alvorlig ☐ Preeklampsi før 34. uke ☐ HELLP syndrom ☐ Eklampsi ☐ Hb < 9.0 g/dl ☐ Hb > 13.5 g/dl ☐ Trombose, beh. ☐ Infeksjon, spes. i «B» ☐ Annet, spesifiser i «B»

Legemidler i svangerskapet: ☐ Nei ☐ Ja – spesifiser i «B»

Røyking og yrke Forutsetter mors samtykke – se rettledning på baksiden

☐ Skriftlig orientering gitt til mor ☐ Samtykker ikke for røykeoppl.

Røykte mor ved sv.sk. begynnelse? ☐ Nei ☐ Av og til ☐ Daglig Ant. sig. dagl.:

- ved sv.sk. avslutning? ☐ Nei ☐ Av og til ☐ Daglig Ant. sig. dagl.:

Mors yrke ☐ Samtykker ikke for yrkesoppl. ☐ Ikke yrkesaktiv ☐ Yrkesaktiv heltid ☐ Yrkesaktiv deltid

Mors yrke

Bransje:

C – Om fødselen

Leie/presentasjon: ☐ Normal bakhode ☐ Sete ☐ Tverrleie ☐ Avvikende hodefødsel ☐ Annet, spesifiser i «C»

Fødselstart: ☐ Spontan ☐ Indusert ☐ Sectio

Ev. induksjons-metode: ☐ Prostaglandin ☐ Oxytocin ☐ Amniotomi ☐ Annet, spesifiser i «C»

Indikasjon for inngrep og/eller induksjon ☐ Komplikasjoner som beskrevet nedenfor ☐ Fostermisdannelser ☐ Overtid ☐ Annet, spesifiser i «C»

Inngrep/tiltak ☐ Ingen
☐ Utskj. tang, hodeleie ☐ Annen tang, hodeleie ☐ Vakuumekstraktor ☐ Episitomi

Fremhj. ved setefødsel: ☐ Vanlig fremhjelp ☐ Uttrekning ☐ Tang på etterk. hode

Sectio: Var sectio planlagt før fødsel? ☐ Nei ☐ Ja
☐ Utført som elektiv sectio ☐ Utført som akutt sectio

Spesifikasjon av forhold ved fødselen/andre komplikasjoner C

Komplikasjoner ☐ Ingen
☐ Vannavg. 12–24 timer ☐ Vannavg. > 24 timer ☐ Mekaniske misforhold ☐ Vanskelig skulderforløsning ☐ Placenta previa ☐ Abruptio placentae ☐ Perinealruptur (grad 1-2) ☐ Sphincterruptur (gr. 3-4) ☐ Blødn.> 1500 ml, transf. ☐ Blødning 500–1500 ml ☐ Eklampsi under fødsel ☐ Navlesnorfremfall ☐ Truende intrauterin asfyksi ☐ Risvekkelse, stimulert ☐ Langsom fremgang ☐ Uterus atoni ☐ Annet:

Anestesi/analgesi: ☐ Ingen
☐ Lystgass ☐ Petidin ☐ Epidural ☐ Spinal ☐ Pudendal ☐ Infiltrasjon ☐ Paracervical blokk ☐ Narkose ☐ Annet:

Placenta: ☐ Normal ☐ Hinnerester ☐ Ufullstendig ☐ Infarkter ☐ Koagler ☐ Utskrapning ☐ Manuell uthenting Placenta-vekt

Navlesnor ☐ Normal ☐ Velamentøst feste ☐ Marginalt feste ☐ Karanomalier ☐ Omslyng rundt hals ☐ Annet omslyng ☐ Ekte knute Navlesnor-lengde:

Fostervann ☐ Normal ☐ Polyhydramnion ☐ Oligohydramnion ☐ Misfarget ☐ Stinkende, infisert ☐ Blodtilblandet

Komplikasjoner hos mor etter fødsel ☐ Intet spesielt ☐ Feber > 38.5° ☐ Trombose ☐ Eklampsi post partum ☐ Mor overflyttet ☐ Mor intensivbeh. ☐ Sepsis ☐ Annet, spesifiser

D – Om barnet

Fødselsdato | **Klokken**

Pluralitet ☐ Enkeltfødsel ☐ Flerfødsel For flerfødsel: Nr. Av totalt

Kjønn ☐ Gutt ☐ Pike Ved tvil spesifiser i «D» For dødfødte: ☐ Usikkert kjønn

Barnets vekt: | Hode-omkrets:

Total lengde: | Eventuelt sete–issemål:

Apgar score: 1 min | 5 min

Barnet var: ☐ Levendefødt

For dødfødte: ☐ Dødfødt/sp.abort Oppgi dødsårsak i «D»

☐ Død før fødsel ☐ Død under fødselen ☐ Ukjent dødstidspunkt

For dødfødte, oppgi også ☐ Død før innkomst ☐ Død etter innkomst

Levendefødt, død innen 24 timer Livet varte: Timer | Min.

Død senere (dato): | **Klokken**

Overfl. barneavd. ☐ Nei ☐ Ja Dato:

Overfl. til

Indikasjon for overflytting: ☐ Respirasjonsproblem ☐ Prematur ☐ Medfødte misd. ☐ Perinatale infeksjoner ☐ Annet, spesifiser

Neonatale diagn.: (Fylles ut av lege/pediater) ☐ Intet spesielt
☐ Hypoglyk. (< 2 mmol/l) ☐ Medf. anemi (Hb < 13.5 g/dl) ☐ Hofteleddsdyspl. beh. m/pute ☐ Transit. tachypnoe ☐ Resp. distress syndr. ☐ Aspirasjonssyndrom ☐ Intrakraniell blødning ☐ Cerebral irritasjon ☐ Cerebral depresjon ☐ Abstinens ☐ Neonatale kramper ☐ Konjunktivitt beh. ☐ Navle./hudinf. beh. ☐ Perinat. inf. bakterielle ☐ Perinat. inf. andre ☐ Fract. claviculae ☐ Annen fraktur ☐ Facialisparese ☐ Plexusskade

Behandlingskoder: ☐ Systemisk antibiotika ☐ Respiratorbeh. ☐ CPAP beh.

Icterus behandlet: ☐ Lysbehandlet ☐ Utskifting

Årsak:

Tegn til medfødte misdannelser: ☐ Nei ☐ Ja

D Spesifikasjon av skader, neonatale diagnoser og medfødte misdannelser – utfylles av lege

☐ AB0 uforlik. ☐ RH immunisering ☐ Fysiologisk ☐ Annen årsak

☐ **Kryss av hvis skjema er oppfølgingsskjema**

Jordmor v/fødsel:

Jordmor v/utskrivning:

Lege barsel/barneavd:

Lege:

Utskrivningsdato Mor: | Barn:

Protokollnr.: /

IS-1002 23011. 07.06. Andvord Grafisk.