Fetal death
Population-based studies of pregnancies in Norway

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Lørenskog, October 2014
Ashi Sarfraz Ahmad
PAPERS INCLUDED IN THIS THESIS

Paper I.

Paper II.

Paper III.

Paper IV.
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

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

In Norway more than 200 infants >22 weeks of gestation are stillborn each year. 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. 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. 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. Most of this decline happened between 1950 and 1980, but recently it has slowed. In high-income countries fetal mortality rates have stagnated, and sometimes risen, 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, while in others the availability of prenatal diagnostics and induced termination of pregnancies may be the explanation.

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. Norwegian studies reported between 19% and 43% of stillbirths as unexplained. 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. 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. Recent studies have reported that the causes of fetal death also vary by gestational age. 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,\textsuperscript{23} racial disparity,\textsuperscript{24} and educational level\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.

\textbf{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, \textit{irrespective of the duration of pregnancy}; the death is indicated by the
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.\textsuperscript{28}

The WHO further distinguishes between \textit{early fetal deaths/stillbirths} (death of a fetus with a birth weight $\geq 500$ g, if birth weight not available gestational age $\geq 22$ weeks or crown-heel length $\geq 25$ cm) and \textit{late fetal deaths/stillbirths} (death of a fetus with a birth weight $\geq 1000$ g, if birth weight not available gestational age $\geq 28$ weeks or crown-heel length $\geq 35$ 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.\textsuperscript{29}

\textbf{Figure 1.} Defining stillbirths and associated pregnancy outcomes. Reprinted from The Lancet 2011;377 (9775):1448-63.\textsuperscript{29} Copyright (2011), with permission from Elsevier.
Stillbirth is the informal term that covers both early and late fetal deaths. 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. 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.

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. 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. 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. The quality of the data in national vital registries also varies due to local legal definitions, and varying social, economic and cultural factors.

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. 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

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

** Most States


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, and in 2009 between 1.5 per 1000 births in Czech Republic and 4.3 per 1000 in France. 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. Although the stillbirth rate has declined the above described inequalities in the incidence indicates that further improvement is achievable.
Figure 2. Country variation in third trimester (>28 weeks) stillbirth rates in 2008.
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). 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. 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.](image-url)
2.1 Maternal age

The demographic distribution of pregnant women has increasingly shifted to the right in most high-income countries. 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.

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 and large population-based cohort studies (Table 3). 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.

The cause of this increased risk remains unclear. Older women have a higher prevalence of medical conditions (hypertension, diabetes) and of complications during pregnancy (preterm births, small for gestational age (SGA) births). However, even after adjustment for these confounding factors the increased risk remains statistically significant, indicating that increased maternal age is independently associated with increased risk of fetal death. The incidence of fetal anomalies increases with maternal age, however, detection and termination of anomalous fetuses have resulted in decreased impact of this cause in recent times.

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.

Gestational age is an effect modifier of the relative risk (RR) of fetal death in older women, 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, and no increased risk. 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. However, when analyses are adjusted for sociodemographic factors and preterm birth, 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. 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, and biological immaturity.

2.2 Parity

Increased risk of fetal death in nulliparas (women with no previous births) is reported in several studies; case-control, hospital-based and population-based retrospective cohort studies (OR 1.2-1.9). Some of the risk may be explained by increased prevalence of hypertensive disorders (namely pre-eclampsia) and IUGR. Multiparity (>3 pervious births) has also been reported to increase the risk of fetal death (OR 1.7-2.9) and may partly be explained by selective fertility (replacement of a infant loss by new pregnancy).

2.3 Maternal weight

The proportion of overweight (25 kg/m^2 > body mass index (BMI)<30 kg/m^2) and obese (BMI >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 >20 years were obese in 2009-2010 (compared to 15% in 1960). 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 >25 kg/m.

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. 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\textsuperscript{90-92} and retrospective cohort studies\textsuperscript{68;70;82;93-97} and two case-control study\textsuperscript{89;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\%).\textsuperscript{99}

Weight gain during pregnancy was not associated with fetal death,\textsuperscript{92;98} whereas weight gain between pregnancies was reported to increase the risk.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{83;90;98} Studies assessing risk of fetal death in women with low BMI did not find any significant result.\textsuperscript{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.\textsuperscript{91;92}

Furthermore one study reported that the risk of fetal death in overweight and obese women was modified by gestational age.\textsuperscript{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).\textsuperscript{92} However, a more recent study could not confirm the interaction between BMI and gestational age.\textsuperscript{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,\textsuperscript{91} b) hyperlipidemia resulting in lower levels of prostacycline and higher levels of thromboxane production increasing the risk of placental thrombosis,\textsuperscript{94} c) higher risk of congenital anomalies in the offspring and medical disorders as diabetes and hypertensive disorders in the mother,\textsuperscript{97} d) impaired ability to detect decreased fetal movements.\textsuperscript{97}

\section*{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),\textsuperscript{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.\textsuperscript{53;55;66;88;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).\textsuperscript{103} Increased risk of fetal death is also reported among women with preeclampsia and pregnancy induced hypertension,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. Among women with preeclampsia higher risk of fetal death was reported in early preeclampsia compared to late preeclampsia. 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, most likely due to reduced uteroplacental blood flow.

Pregnancy in women with diabetes is associated with an increased risk of fetal death, and the incidence of this disorder is increasing. Studies included in the review reported a 3 to 4-fold increased risk of fetal death in women with diabetes type 1, and a 2 to 3-fold increased risk among women with diabetes type 2 or pregestational diabetes, but higher risk in women requiring adjunctive insulin treatment.

One of the largest studies on diabetes type 1 was a multi-center study conducted in Denmark in 1993-1999 (n=1218), 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. Factors contributing to the increased risk of fetal death in diabetic pregnancies are congenital anomalies (especially cardiac anomalies), pre-term births and fetal macrosomia. Diabetic women also have a three- to six-fold increased risk of hypertensive disorders.

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, whereas three studies did not report any increased risk of fetal death, but reported higher risk of preeclampsia, caesarean section, macrosomia, preterm deliveres. 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 stillbirth rates in pre-diabetic women (who were later diagnosed with diabetes) compared to non-diabetic controls (OR 4.7).\textsuperscript{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,\textsuperscript{122} b) utero-placental impairment caused by microangiopathy, in particular among women with long duration type 1 or type 2 diabetes,\textsuperscript{133} c) fetal hyperglycemia leading to hyperinsulinemia, which further increases anaerobic metabolism and eventually hypoxia and acidosis.\textsuperscript{136}

### Table 2. Prevalence of maternal medical conditions associated with fetal death.\textsuperscript{10;32;101;103-105;112;113;121-124;127-133;137-141}

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

### 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.\textsuperscript{16;53;60;66-70;79;83;142-148} There is a linear relationship between increasing risk of fetal death and increasing quantity of tobacco used.\textsuperscript{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.\textsuperscript{143} Women, who smoked during their first pregnancy, but not their second pregnancy, have the same risk in the second pregnancy as non-smokers.\textsuperscript{142} Maternal tobacco
exposure in utero is not associated with increased risk of stillbirth in the daughters of mothers that smoked during pregnancy.  

The retrospective cohort study by Gray and colleagues reported that 38% of the inequality in stillbirth occurrence in Scotland could be attributed to smoking. 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). 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.  

2.6 Alcohol and coffee consumption

There are few studies of the association between alcohol consumption and the risk of fetal death. 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, whereas the other study reported that each additional drink per week increased the risk by 1%. 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. 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. Kesmodel and colleagues conducted a prospective cohort study (n=24,768 women), and reported an increased risk of stillbirth in women who consumed ≥5 drinks per week, compared to women consuming ≤1 drink per week (RR 3.0, 95% CI 1.4-6.4).
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.\textsuperscript{153}

Coffee consumption during pregnancy has been associated with increased risk of fetal death, however, only when moderate to high amounts are consumed; \( \geq 3 \) cups of coffee per day (RR 1.7, 95% CI 1.0-2.8),\textsuperscript{153} \( \geq 5 \) cups of coffee per day (OR 1.4, 95% CI 1.0-1.8),\textsuperscript{79} \( \geq 8 \) cups of coffee per day (OR 3.0, 95% CI 1.5-1.9).\textsuperscript{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 \( \geq 4 \) cups of coffee per day, whereas the risk was not significantly increased at gestational age \( \geq 28 \) weeks.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{164,166,168} especially for antepartum fetal deaths.\textsuperscript{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.\textsuperscript{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.\textsuperscript{148,168} Educational inequality in stillbirth is reported by several studies, and appears to persist over time.\textsuperscript{170,171} In addition, social disparity is more strongly associated with specific causes of stillbirth (unexplained,\textsuperscript{25,172} SGA,\textsuperscript{25,172} diabetes\textsuperscript{25}), and stillbirth at preterm gestation.\textsuperscript{25}

Substantial racial and ethnical disparity in stillbirth risk has recently been reported by several studies in high-income countries.\textsuperscript{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),\textsuperscript{24,160,162,165,176,177,181} and a higher incidence of IUGR and pre-term births.\textsuperscript{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.\textsuperscript{24} A Canadian study reported highest risk at late gestation (>37 weeks) among Aboriginal Canadian compared to non-Aboriginal Canadian.\textsuperscript{186} Ethnical inequality in stillbirth has been reported by studies comparing outcome among native-born and immigrant populations throughout Europe.\textsuperscript{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,\textsuperscript{177,183} higher prevalence of maternal diseases,\textsuperscript{185,186} teenage pregnancies, and late start of prenatal care,\textsuperscript{179} consanguinity and congenital anomalies.\textsuperscript{186} Other studies did not confirm these associations.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{80,188,190,192}

Of thirteen reviewed studies, nine retrospective cohort studies\textsuperscript{70,84,187-189,191-193,195} and four case-control studies,\textsuperscript{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).\textsuperscript{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 as 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{196}
2.9 Gestational age

Several studies have reported increased risk of fetal death as pregnancy continues past term.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{201;202}

The association between stillbirth and certain risk factors such as maternal age $>$35 years, BMI $>$25, SGA, educational attainment and race is modified by gestational age.\textsuperscript{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 $>$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).\textsuperscript{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),\textsuperscript{203;204} and two population-based cohort studies.\textsuperscript{205;206} Samueloff and colleagues reported higher incidence of diabetes, hypertensive disorders and low birth weight infants among women with recurrent fetal death.\textsuperscript{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.\textsuperscript{207-210}
Table 3. Studies of risk factors for fetal death.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Outcome fetal death</th>
<th>Country and study period</th>
<th>Sample size</th>
<th>Study design</th>
<th>Independent variable</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raymond E.G. et al. 1994</td>
<td>&gt;28 weeks</td>
<td>Sweden 1986-1989</td>
<td>638 242</td>
<td>Retrospective cohort</td>
<td>Maternal age Parity Smoking</td>
<td>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 &gt;32 weeks</td>
</tr>
<tr>
<td>Nybo-Andersen A. et al. 2000</td>
<td>&gt;28 weeks</td>
<td>Denmark 1978-1992</td>
<td>634 272</td>
<td>Prospective cohort</td>
<td>Maternal age</td>
<td>Increased risk of FD for women aged &lt;19 or ≥35 years</td>
</tr>
<tr>
<td>Jolly M. et al. 2000</td>
<td>≥24 weeks</td>
<td>United Kingdom 1988-1997</td>
<td>341 708</td>
<td>Retrospective cohort</td>
<td>Maternal age</td>
<td>No increased risk of FD in women &lt;18 years, after adjusting for ethnicity, parity, BMI, hypertension, diabetes, smoking</td>
</tr>
<tr>
<td>Jolly M. et al. 2000</td>
<td>≥24 weeks</td>
<td>United Kingdom 1988-1997</td>
<td>385 120</td>
<td>Retrospective cohort</td>
<td>Maternal age</td>
<td>Increased risk of FD in women aged 35-40 years (OR 1.4), &gt;40 years (OR 1.8), adjusted for GD, PE, smoking</td>
</tr>
<tr>
<td>Salihu H.M. et al. 2003</td>
<td>≥20 weeks</td>
<td>United States 1997-1999</td>
<td>12 066 854</td>
<td>Retrospective cohort</td>
<td>Maternal age CH, PIH, Any diabetes (GD + PD)</td>
<td>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</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Week(s)</td>
<td>Cohort Type</td>
<td>Maternal Age</td>
<td>Risk Factors</td>
<td>Results</td>
</tr>
<tr>
<td>-----------------------</td>
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<tr>
<td>Jacobsson B. et al. 2004&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Sweden 1987-2001</td>
<td>&gt;28</td>
<td>Retrospective cohort</td>
<td>Maternal age</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Bateman B.T. et al. 2006&lt;sup&gt;54&lt;/sup&gt;</td>
<td>United States 1995-2000</td>
<td>&gt;22</td>
<td>Retrospective cohort</td>
<td>Maternal age</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>*Reddy U.M. et al. 2006&lt;sup&gt;23&lt;/sup&gt;</td>
<td>United States 2001-2002</td>
<td>&gt;20</td>
<td>Retrospective cohort</td>
<td>Maternal age</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>O'Leary C.M. et al. 2007&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Australia 1984-2003</td>
<td>&gt;20</td>
<td>Retrospective cohort</td>
<td>Parity</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Hoffman M.C. et al. 2007&lt;sup&gt;52&lt;/sup&gt;</td>
<td>United States 1989-2004</td>
<td>&gt;20</td>
<td>Retrospective cohort</td>
<td>Maternal age</td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>Haldre K. et al. 2007&lt;sup&gt;75&lt;/sup&gt;</td>
<td>Estonia 1992-2002</td>
<td>&gt;500</td>
<td>Retrospective cohort</td>
<td>Maternal age</td>
<td>Women aged ≤17 or 18-19 years did not have increased risk of FD relative to women aged 20-24 years</td>
<td></td>
</tr>
<tr>
<td>Salihu H.M. et al. 2008&lt;sup&gt;63&lt;/sup&gt;</td>
<td>United States 1978-1997</td>
<td>&gt;20</td>
<td>Retrospective cohort</td>
<td>Maternal age</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>De Vienne C.M. et al. 2009&lt;sup&gt;73&lt;/sup&gt;</td>
<td>France 1994-2001</td>
<td>&gt;22</td>
<td>Retrospective cohort</td>
<td>Maternal age</td>
<td>Increased risk of FD among teenagers (RR 1.4-1.2) compared to women aged 20 years</td>
<td></td>
</tr>
<tr>
<td>Reddy U.M. et al. 2010&lt;sup&gt;68&lt;/sup&gt;</td>
<td>United States 2002-2008</td>
<td>&gt;23</td>
<td>Retrospective cohort</td>
<td>Maternal age, race, parity, BMI(18.5-24.9), PD, CH, smoking, alcohol</td>
<td>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&gt;30 (HR 1.3), PD (HR 2.7), CH (HR 2.0), smoking (HR 1.6), Alcohol during pregnancy (HR 1.7)</td>
<td></td>
</tr>
<tr>
<td>Study Authors</td>
<td>Gestational Age</td>
<td>Country</td>
<td>Sample Size</td>
<td>Study Design</td>
<td>Maternal Age</td>
<td>Risk Factors</td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td>Saade G.R. et al. 2011&lt;sup&gt;69&lt;/sup&gt;</td>
<td>&gt;20 weeks</td>
<td>United States</td>
<td>2430</td>
<td>Case-control</td>
<td>Maternal age, race, PD, smoking, BMI (18.5-24.9), recurrence</td>
<td></td>
</tr>
<tr>
<td>Helgadottir L.B. et al. 2011&lt;sup&gt;53&lt;/sup&gt;</td>
<td>&gt;23 weeks or &gt;500g</td>
<td>Norway</td>
<td>88,987</td>
<td>Case-control</td>
<td>Maternal age, PD, CH, smoking</td>
<td></td>
</tr>
<tr>
<td>Balayla J. et al. 2011&lt;sup&gt;67&lt;/sup&gt;</td>
<td>&gt;24 weeks</td>
<td>United States</td>
<td>37,504,230</td>
<td>Retrospective cohort</td>
<td>Maternal age</td>
<td>Women &lt;15 years had increased risk of FD (OR 1.3), 35-40 year (OR 1.3), 40-45 years (OR 1.6), and &gt;45 years (OR 2.2) compared to women aged 25-30 years.</td>
</tr>
<tr>
<td>Kenny L.C. et al. 2013&lt;sup&gt;62&lt;/sup&gt;</td>
<td>&gt;24 weeks</td>
<td>United Kingdom</td>
<td>274,563</td>
<td>Retrospective cohort</td>
<td>Maternal age</td>
<td>Increased risk of FD among women aged 30-34 years (adjusted RR 1.2), 35-39 years (1.4), &gt;40 years (1.8) compared to women aged 20-29 years.</td>
</tr>
<tr>
<td>*Gordon A. et al. 2013&lt;sup&gt;66&lt;/sup&gt;</td>
<td>&gt;22 weeks</td>
<td>Australia</td>
<td>327,690</td>
<td>Retrospective cohort</td>
<td>Maternal age, parity</td>
<td>Increased risk of FD among women 35-39 years (adjusted HR 1.4), and &gt;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)</td>
</tr>
<tr>
<td>*Lisonkova S. et al. 2013&lt;sup&gt;65&lt;/sup&gt;</td>
<td>&gt;22 weeks</td>
<td>United States</td>
<td>6,846,695</td>
<td>Retrospective cohort</td>
<td>Maternal age</td>
<td>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)</td>
</tr>
<tr>
<td>*Page J.M. et al. 2013&lt;sup&gt;64&lt;/sup&gt;</td>
<td>&gt;37 weeks</td>
<td>United States</td>
<td>2,961,382</td>
<td>Retrospective cohort</td>
<td>Maternal age</td>
<td>Increased risk of FD with increasing gestation at term especially among older mothers</td>
</tr>
<tr>
<td>Warshak C.R. et al. 2013&lt;sup&gt;74&lt;/sup&gt;</td>
<td>&gt;20 weeks</td>
<td>United States</td>
<td>529,445</td>
<td>Retrospective cohort</td>
<td>Maternal age</td>
<td>Women aged &lt;18 years increased risk of FD (adjusted RR 1.2) compared to women 18-35 years.</td>
</tr>
<tr>
<td>Gardosi J. et al. 2013&lt;sup&gt;70&lt;/sup&gt;</td>
<td>&gt;24 weeks</td>
<td>United Kingdom</td>
<td>92,218</td>
<td>Retrospective cohort</td>
<td>Maternal age, parity, ethnicity, BMI (18.5-24.9), smoking, PD, IUGR</td>
<td></td>
</tr>
<tr>
<td>Little R.E. et al. 1993&lt;sup&gt;79&lt;/sup&gt;</td>
<td>≥28 weeks or ≥1000g</td>
<td>United States</td>
<td>4,667</td>
<td>Case-control</td>
<td>Maternal age, parity, BMI (reference &lt;18.2), Smoking, Alcohol, Coffee/tea</td>
<td></td>
</tr>
</tbody>
</table>

Note: PD = preeclampsia, CH = chronic hypotension, CH = chronic hypertension, PE = preeclampsia, IUGR = intrauterine growth restriction, OR = odds ratio, RR = relative risk.
<table>
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<tr>
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<tr>
<td>Cnattingius S. et al. 1998</td>
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<td>Retrospective cohort</td>
<td>Parity, BW/IUGR</td>
<td>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</td>
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<tr>
<td>Cnattingius S. et al. 1998</td>
<td>Sweden</td>
<td>1992-1993</td>
<td>Retrospective cohort</td>
<td>Parity, BMI (&lt;20)</td>
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<tr>
<td>Aliyu M.H. et al. 2005</td>
<td>United States</td>
<td>1989-2000</td>
<td>Retrospective cohort</td>
<td>Parity</td>
<td>Fetal mortality increased with increasing parity among women with 5-9 (OR 1.1), 10-14 (OR 2.0) and &gt;15 (OR 2.3) prior live births</td>
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<tr>
<td>Jacquemyn Y. et al. 2006</td>
<td>Belgium</td>
<td>2003</td>
<td>Case-control</td>
<td>Parity</td>
<td>Women with 5-9 prior births had an increased risk of FD compared to women with 2-4 prior births</td>
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<tr>
<td>Hilder L. et al. 2007</td>
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<tr>
<td>McCowan L.M.E. et al. 2007</td>
<td>New Zealand</td>
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<td>Case-control</td>
<td>Parity, BW/IUGR</td>
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<td>Sebire N.J. et al. 2001</td>
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<td>Retrospective cohort</td>
<td>BMI (20-25)</td>
<td>Increased risk of FD in women with BMI 25-30 (OR 1.1) and BMI &gt;30 (OR 1.4), after adjusting for diabetes, pre-eclampsia and smoking</td>
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<td>BMI (&lt;19.9)</td>
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<td>Weeks</td>
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<td>Nohr E.A. et al. 2005</td>
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<td>Salihu H.M. et al. 2007</td>
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<td>Bhattacharya S. et al. 2007</td>
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<td>Tennant P.W.G. et al. 2011</td>
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<td>Whiteman V.E. et al. 2011</td>
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<tr>
<td>Scott-Pillai R. et al. 2013</td>
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<tr>
<td>Ananth C.V. et al. 1995</td>
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<td>*Smulian J.C. et al. 2002</td>
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<td>Allen V.M. et al. 2004</td>
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<td>Roberts C.L. et al.</td>
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<td>Gilbert W.M. et al.</td>
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<td>*Hutcheon J.A. et al.</td>
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<td>Tuuli M.G. et al.</td>
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<td>Cruz M.O. et al.</td>
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<td>GH, mild PE, mild CH</td>
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<td>Klungsøy K. et al.</td>
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<td>Lauenborg J. et al. 2003</td>
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<td>Jensen D.M. et al. 2004</td>
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<td>*Silva I.S. et al. 2005</td>
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<td>Aliyu M.H. et al. 2010</td>
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<td>Haglund B. et al. 1993</td>
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<tr>
<td>Study</td>
<td>Race/Ethnicity</td>
<td>Country</td>
<td>Method</td>
<td>Follow-up Period</td>
<td>Findings</td>
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<tr>
<td>Willinger M. et al. 2009&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Race</td>
<td>United States 2001-2002</td>
<td>Retrospective cohort</td>
<td>&gt;20 weeks</td>
<td>Increased risk of FD throughout pregnancy, highest risk week 20-23 (RR 2.8), week 41 weeks (RR 1.7)</td>
</tr>
<tr>
<td>Villadsen S.F. et al. 2009&lt;sup&gt;183&lt;/sup&gt;</td>
<td>Ethnicity</td>
<td>Denmark 1981-2003</td>
<td>Retrospective cohort</td>
<td>&gt;28 weeks</td>
<td>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</td>
</tr>
<tr>
<td>Villadsen S.F et al. 2010&lt;sup&gt;184&lt;/sup&gt;</td>
<td>Ethnicity</td>
<td>Turkish women in 9 countries 1990-2005</td>
<td>Retrospective cohort</td>
<td>Diff ered according to country</td>
<td>Increased risk of FD among the Turkish group than the native populations (OR 1.1 – 1.7)</td>
</tr>
<tr>
<td>Ravelli A.C.J. et al. 2011&lt;sup&gt;179&lt;/sup&gt;</td>
<td>Ethnicity</td>
<td>Netherlands 2000-2006</td>
<td>Retrospective cohort</td>
<td>&gt;24 weeks</td>
<td>Increased risk of FD in African (OR 1.7), South Asian (OR 1.8), Turkish/Moroccan (OR 1.1) and other non-Western women (OR 1.3) adjusted for age, smoking, urbanisation, SES, low income, booking visit, disease</td>
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<tr>
<td>Ekéus C. et al. 2011&lt;sup&gt;174&lt;/sup&gt;</td>
<td>Ethnicity</td>
<td>Sweden 1992-2005</td>
<td>Retrospective cohort</td>
<td>&gt;28 weeks</td>
<td>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</td>
</tr>
<tr>
<td>Stacey T. et al. 2011&lt;sup&gt;182&lt;/sup&gt;</td>
<td>Ethnicity</td>
<td>New Zealand 2006-2009</td>
<td>Case-control</td>
<td>&gt;28 weeks</td>
<td>No increased risk of FD among Pacific women after adjustment for age, BMI, parity, smoking, SES</td>
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<tr>
<td>Reeske A. et al. 2011&lt;sup&gt;180&lt;/sup&gt;</td>
<td>Ethnicity</td>
<td>Germany 2004-2007</td>
<td>Retrospective cohort</td>
<td>Birth weight &gt;500 g</td>
<td>Increased risk of FD among women from Middle East/N. Africa (RR 1.3), Asia (RR 1.2), Mediterranean (RR 1.1)</td>
</tr>
<tr>
<td>Rom A.L. et al. 2012&lt;sup&gt;170&lt;/sup&gt;</td>
<td>Education</td>
<td>Norway, Sweden, Finland, Denmark 1981-2000</td>
<td>Retrospective cohort</td>
<td>&gt;28 weeks</td>
<td>Clear educational gradient in stillbirth in all four countries</td>
</tr>
<tr>
<td>*Auger N. et al. 2012&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Education</td>
<td>Canada 1981-2006</td>
<td>Retrospective cohort</td>
<td>Birth weight &gt;500 g</td>
<td>Increased risk of FD throughout gestation among women with low education</td>
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<tr>
<td>Wood A.M. et al. 2012&lt;sup&gt;172&lt;/sup&gt;</td>
<td>SES</td>
<td>Scotland 1985-2008</td>
<td>Retrospective cohort</td>
<td>&gt;28 weeks</td>
<td>Increased risk of FD among Black and Hispanic women compared to high SES (OR 1.3), adjusted for age, height, parity, marital status, hospital throughput</td>
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<td>Lorch S.A. et al. 2012&lt;sup&gt;177&lt;/sup&gt;</td>
<td>Race/Ethnicity</td>
<td>United States 1993-2005</td>
<td>Retrospective cohort</td>
<td>&gt;400 g or &gt;23 weeks</td>
<td>Increased risk of FD among South Asian born women OR 2.5</td>
</tr>
<tr>
<td>Drysdale H. et al. 2012&lt;sup&gt;173&lt;/sup&gt;</td>
<td>Ethnicity</td>
<td>Australia 2001-2011</td>
<td>Retrospective cohort</td>
<td>&gt;37 weeks</td>
<td>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</td>
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<tr>
<td>Khalil A. et al. 2013&lt;sup&gt;185&lt;/sup&gt;</td>
<td>Ethnicity</td>
<td>United Kingdom</td>
<td>Retrospective cohort</td>
<td>&gt;24 weeks</td>
<td>Increased risk of FD among South Asian born women OR 2.5</td>
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<tr>
<td>Author et al. Year</td>
<td>Term</td>
<td>Country</td>
<td>Period</td>
<td>Study Type</td>
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<tr>
<td>*Auger N. et al. 2013</td>
<td>&gt;24 weeks</td>
<td>Canada</td>
<td>1981-2009</td>
<td>Retrospective cohort</td>
<td>Ethnicity</td>
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<td>Hogue C.J. et al. 2013</td>
<td>&gt;20 weeks</td>
<td>United States</td>
<td>2006-2008</td>
<td>Case-control</td>
<td>Race</td>
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<td>Luque-Fernandez M.A. et al. 2013</td>
<td>&gt;500 g or &gt;22 weeks</td>
<td>Spain</td>
<td>2007-2010</td>
<td>Retrospective cohort</td>
<td>Ethnicity</td>
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<td>Savard N. et al. 2013</td>
<td>&gt;500 g</td>
<td>Canada</td>
<td>1981-2009</td>
<td>Retrospective cohort</td>
<td>Education</td>
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<tr>
<td>Kramer M.S. et al. 1990</td>
<td>Canada 1980-1986</td>
<td>Retrospective cohort</td>
<td>BW/IUGR</td>
<td>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</td>
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<tr>
<td>Divon M.Y et al. 1998</td>
<td>&gt;40 weeks</td>
<td>Sweden</td>
<td>1987-1992</td>
<td>Retrospective cohort</td>
<td>Post-term</td>
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<tr>
<td>Ahlenius I. et al. 1999</td>
<td>&gt;28 weeks</td>
<td>Sweden</td>
<td>1984 and 1991</td>
<td>Case-control</td>
<td>BW/IUGR</td>
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<td>Clausson B. et al. 1999</td>
<td>&gt;37 weeks</td>
<td>Sweden</td>
<td>1991-1995</td>
<td>Retrospective cohort</td>
<td>BW/IUGR</td>
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<td>Clausson B. et al. 2001</td>
<td>&gt;28 weeks</td>
<td>Sweden</td>
<td>1992-1995</td>
<td>Retrospective cohort</td>
<td>BW/IUGR</td>
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<td>Frøen J.F. et al. 2004</td>
<td>Norway</td>
<td>1986-1995</td>
<td>Case-control</td>
<td>BW/IUGR</td>
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<tr>
<td>Zhang X. et al. 2007</td>
<td>&gt;28 weeks</td>
<td>Sweden</td>
<td>1992-2001</td>
<td>Retrospective cohort</td>
<td>BW/IUGR</td>
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<td>*Trudell A.S. et al. 2013</td>
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<td>United States</td>
<td>1999-2009</td>
<td>Retrospective cohort</td>
<td>BW/IUGR</td>
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<td>Cotzias C.S. et al. 1999</td>
<td>&gt;35 weeks</td>
<td>United Kingdom</td>
<td>1989-1991</td>
<td>Retrospective cohort</td>
<td>Post-term</td>
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<tr>
<td>Smith G.C.S. 2001&lt;sup&gt;200&lt;/sup&gt;</td>
<td>&gt;37</td>
<td>United Kingdom</td>
<td>Retrospective</td>
<td>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)</td>
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<tr>
<td>Caughey A.B. et al. 2004&lt;sup&gt;197&lt;/sup&gt;</td>
<td>&gt;37</td>
<td>United States</td>
<td>Retrospective</td>
<td>Increased risk of fetal death as pregnancy progressed 41 weeks (0.9 per 1000 ongoing pregnancies) and &gt;42 weeks (3.5 per 1000)</td>
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<tr>
<td>Heimstad R. et al. 2006&lt;sup&gt;199&lt;/sup&gt;</td>
<td>&gt;37</td>
<td>Norway</td>
<td>Prospective</td>
<td>Increased risk of fetal death as pregnancy progressed 41 weeks (0.8 per 1000 ongoing pregnancies) and 42 weeks (1.6 per 1000)</td>
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<tr>
<td>Rosenstein M.G. et al. 2012&lt;sup&gt;201&lt;/sup&gt;</td>
<td>&gt;37</td>
<td>United States</td>
<td>Retrospective</td>
<td>Increased risk of FD as pregnancy progresses, past 38 week higher mortality with expectant mortality than delivery</td>
<td></td>
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<tr>
<td>Mandujano A. et al. 2013&lt;sup&gt;202&lt;/sup&gt;</td>
<td>&gt;34</td>
<td>United States</td>
<td>Retrospective</td>
<td>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</td>
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<tr>
<td>Samueloff A. et al. 1993&lt;sup&gt;203&lt;/sup&gt;</td>
<td>&gt;20</td>
<td>United States</td>
<td>Case-control</td>
<td>Women with previous FD had increased risk of FD in the second pregnancy (OR 10.2)</td>
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<tr>
<td>Surkan P.J. et al. 2004&lt;sup&gt;210&lt;/sup&gt;</td>
<td>&gt;28</td>
<td>Sweden</td>
<td>Retrospective</td>
<td>Previous delivery of a SGA increases risk of FD (OR 2.1), if previous very pre-term delivery of SGA infant (OR 5.0)</td>
<td></td>
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<tr>
<td>Salihu H.M. et al. 2006&lt;sup&gt;208&lt;/sup&gt;</td>
<td>&gt;20</td>
<td>United States</td>
<td>Retrospective</td>
<td>Higher risk of FD in second pregnancy when first infant was SGA compared to non-SGA (OR 1.6)</td>
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<tr>
<td>Sharma P.P. et al. 2007&lt;sup&gt;204&lt;/sup&gt;</td>
<td>&gt;20</td>
<td>United States</td>
<td>Case-control</td>
<td>Women with previous fetal death had increased risk of fetal death in the second pregnancy (HR 5.8)</td>
<td></td>
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<tr>
<td>Smith G.C.S. et al. 2007&lt;sup&gt;209&lt;/sup&gt;</td>
<td>&gt;24</td>
<td>United Kingdom</td>
<td>Retrospective</td>
<td>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)</td>
<td></td>
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<tr>
<td>*Melve K.K. et al. 2010&lt;sup&gt;206&lt;/sup&gt;</td>
<td>&gt;20</td>
<td>Norway</td>
<td>Retrospective</td>
<td>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)</td>
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<tr>
<td>Bhattacharya S. et al. 2010&lt;sup&gt;205&lt;/sup&gt;</td>
<td>&gt;24</td>
<td>Scotland</td>
<td>Retrospective</td>
<td>Increased risk of FD in second pregnancy in women with FD in first pregnancy (OR 1.9)</td>
<td></td>
</tr>
<tr>
<td>Gordon A. et al. 2012&lt;sup&gt;208&lt;/sup&gt;</td>
<td>&gt;20 or &gt;400 g</td>
<td>Australia</td>
<td>Retrospective</td>
<td>Increased risk of FD in second pregnancy when prior SGA birth or preterm birth but not prior FD</td>
<td></td>
</tr>
</tbody>
</table>

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. 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. These two systems are the most widely used, but they have a high number of unexplained deaths. 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.

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.

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). Data from the Wisconsin Stillbirth Service Program reported that the most common disorders associated with fetal death are malformation syndromes and single malformations. 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.

Infections
Maternal bacterial or viral infections during pregnancy have been reported to account for approximately 12% of fetal deaths in high-income countries. The microorganisms most frequently isolated in fetal death are group B streptococcus, Escherichia coli and Enterococcus fecalis. 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*). The majority of studies on viral infection and fetal death concern PVB, but show inconsistent results. 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. 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).

**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.

**Placental pathology**

Placental pathology is involved in more than 25% of fetal deaths. 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. 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
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 $\geq 40$ years, $23;50-70$ and all but three reported an increased risk among women $\geq 35$ years, $53;69;70$ whereas six studies reported increased risk associated with young maternal age and three 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. However, two studies reported that the risk was only significantly increased at early gestation (<16 weeks and <28 weeks, respectively). Moderate to high amounts of coffee consumption was associated with increased risk of fetal death in 4 studies.

Low SES measured by educational attainment, household income or employment, was associated with an increased risk of stillbirth. Likewise, a consistent strong association between fetal death and ethnic minority status or being Black was reported by large number of studies (24 papers). 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. 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. 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, and previous stillbirth was claimed to be the strongest pre-pregnancy risk factor in one study.

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. However, there is still significant inter- and intra-country inequality in stillbirth. 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. 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.

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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).\textsuperscript{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.
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). 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 (≥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°C 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.\textsuperscript{217}

**Explanatory variables**

Maternal PVB antibody status was categorized in the following manner:

1. Antibodies against PVB not detected: \textit{no past or present infection}.
2. Presence of IgG antibodies against PVB in the first serum sample (but no IgM antibodies): \textit{previous infection}.
3. Presence of IgM antibodies against PVB in the first serum sample: \textit{acute infection}.
4. Seroconversion (occurrence of IgG or IgM antibodies in seronegative women): \textit{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,\textsuperscript{58} and seroprevalence of IgG increases with age.\textsuperscript{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.\textsuperscript{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 ($\chi^2$), 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.”

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

Perinatal mortality was defined as the sum of fetal death at $\geq 22$ 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 $\geq 22$ weeks of gestation.

Paper III

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

Paper IV

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

Perinatal mortality was defined as the sum of fetal death at $\geq 22$ 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,

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, 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, 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.⁶⁰,⁷⁸ 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 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.


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\textsuperscript{36} and are associated with high maternal age.\textsuperscript{247}

Paternal age was categorized as <30, 30-39, \geq 40 years and missing (1%). High paternal age is associated with increased risk of fetal death.\textsuperscript{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,\textsuperscript{102} and also associated with maternal age.\textsuperscript{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 \geq 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 \geq 140 mmHg or diastolic blood pressure at \geq 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 \leq 19, 20-24, 25-29, 30-34, 35-39 and \geq 40 years. Maternal age is associated with fetal death and older women have higher prevalence of hypertensive disorders.\textsuperscript{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\textsuperscript{78} and primiparity is associated with pre-eclampsia.\textsuperscript{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 through 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.\textsuperscript{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:

\[
\text{Stillbirth rate in week } i = \frac{\text{number of stillbirths}(i)}{\text{total births}(i)}
\]

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.\textsuperscript{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.\textsuperscript{251}

The second problem with the conventional definition regards the paradox of intersecting gestational-age-specific perinatal mortality curves.\textsuperscript{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\textsuperscript{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):

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

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,\textsuperscript{249} hence, justifying early selective delivery for medical indications.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 (irrespective 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 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 1967-1971 to 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 \( \geq 16 \) 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 \( \geq 40 \) 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 \( \geq 40 \) 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 (\( \geq 40 \) 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.\textsuperscript{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.\textsuperscript{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 months, whereas IgG is detectable only after 2 weeks.\textsuperscript{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,\textsuperscript{38} and the high quality of information in the MBRN is maintained by routine linkage to other population registries, and comprehensive quality assurance.\textsuperscript{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.\textsuperscript{261} The fetal mortality rate at ≥16 weeks of gestation in the MBRN was 9-10 per 1000 births during the same period.\textsuperscript{1} In our study 25% of fetal deaths occurred before 21 weeks of gestation (25% of 283

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fetal deaths), 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, as have several other validated variables in the registry.

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 antenatal care during 1986. 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. 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. 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. 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%). 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, 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, 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.  

![Figure 9. Causal diagram with Confounding](image)

In Paper I the association between maternal PVB infection and fetal death could be confounded by maternal age\textsuperscript{58,243} and parity,\textsuperscript{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.\textsuperscript{275} Data on potential confounders such as maternal stress\textsuperscript{276,277} and SES\textsuperscript{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.\textsuperscript{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. 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 and varies by calendar period (year), 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). Since BMI is differentially associated with advanced gestation, 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, 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 and hypertensive disorders are associated with an increased risk of fetal death, and as the prevalence of these disorders has increased, 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 assess 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, several large prospective cohort studies of pregnant women with serologically-confirmed PVB infection have shown an increased risk of fetal death of 5-11%, whereas others did not report an increased risk. 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).

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 ≥1 prior stillbirth compared to only 1% among women with live birth. Thus some of the increased risk of fetal death in PVB seropositive 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. 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%.

Higher risk of fetal demise has been reported when maternal PVB infection occurs at <20 gestational weeks, with most fetal deaths occurring between 13-20
weeks of gestation. 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. 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. 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. Tolfvenstam and colleagues examined 47 cases of fetal death (≥22 weeks of gestation). 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. 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. 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. Recently Riipinen and colleagues retrospectively studied 169 cases of late fetal death (≥22 weeks), and only detected PVB DNA in four cases (2.4%).

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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. 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.

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, 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. 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%. 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. 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. 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; 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. 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. 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 >28 weeks of gestation in the United States, but a steady fetal mortality rate at 20-27 weeks of gestation. 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. 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. In Norway, the proportion of childbearing women treated with excisional cervical surgery increased more than 20-

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fold between the periods 1967-1979 and 2000-2003, and cumulative incidence of treatment is higher among older women.\textsuperscript{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\%.\textsuperscript{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.\textsuperscript{36,305} The mechanisms involved remain uncertain, as the increased risk may be attenuated, but not completely explained, by medical conditions,\textsuperscript{50,60} uteroplacental insufficiency,\textsuperscript{306} high BMI or low SES.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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).\textsuperscript{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 <500g.\textsuperscript{259} However, under-registration of these fetuses is also of concern,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{23,64-66} Uteroplacental insufficiency has been proposed as a possible link between maternal age and fetal death at late gestational age,\textsuperscript{57} whereas others have rejected this.\textsuperscript{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). In 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). 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. 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. 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. 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. 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. 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. 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. Similar trends have been reported by several studies from high-income countries. 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. 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.

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, 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.

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. This is further supported by the increased risk of SGA
infants in hypertensive pregnancies. 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. 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
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. 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 preeclamptic 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. 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, 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. 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, and social inequalities in fetal mortality 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.
10. Reference List


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Ref Type: Online Source


Ref Type: Online Source


Ref Type: Online Source


Ref Type: Online Source


Ref Type: Online Source


(75) Haldre K, Rahu K, Karro H, Rahu M. Is a poor pregnancy outcome related to young maternal age? A study of teenagers in Estonia during the period


Ref Type: Online Source


Ref Type: Report

(274) [Definisjonsrapporter for variabler i Medisinsk fødselsregister Del 1.] In Norwegian. Available at: [http://www.fhi.no/dokumenter/0a3d4061ec.pdf]. 2009.
Ref Type: Report


(278) Ananth CV, Chauhan SP. Epidemiology of twinning in developed countries. Semin Perinatol 2012; 36(3):156-161.


Ref Type: Online Source


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

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>1.41 (1.03-1.92)</td>
</tr>
<tr>
<td>20-24</td>
<td>1</td>
</tr>
<tr>
<td>25-29</td>
<td>0.99 (0.83-1.18)</td>
</tr>
<tr>
<td>30-34</td>
<td>1.15 (0.96-1.39)</td>
</tr>
<tr>
<td>35-39</td>
<td>1.29 (1.04-1.59)</td>
</tr>
<tr>
<td>40-44</td>
<td>1.44 (1.06-1.95)</td>
</tr>
<tr>
<td>&gt;45</td>
<td>1.71 (0.63-4.66)</td>
</tr>
</tbody>
</table>

### Gestational week 23-29

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>1.27 (0.81-2.00)</td>
</tr>
<tr>
<td>20-24</td>
<td>1</td>
</tr>
<tr>
<td>25-29</td>
<td>1.03 (0.80-1.33)</td>
</tr>
<tr>
<td>30-34</td>
<td>1.07 (0.80-1.41)</td>
</tr>
<tr>
<td>35-39</td>
<td>1.11 (0.80-1.55)</td>
</tr>
<tr>
<td>40-44</td>
<td>1.20 (0.71-2.04)</td>
</tr>
<tr>
<td>&gt;45</td>
<td></td>
</tr>
</tbody>
</table>

### Gestational week 30-36

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>0.95 (0.51-1.75)</td>
</tr>
<tr>
<td>20-24</td>
<td>1</td>
</tr>
<tr>
<td>25-29</td>
<td>1.06 (0.79-1.43)</td>
</tr>
<tr>
<td>30-34</td>
<td>1.41 (1.03-1.93)</td>
</tr>
<tr>
<td>35-39</td>
<td>1.62 (1.12-2.34)</td>
</tr>
<tr>
<td>40-44</td>
<td>2.42 (1.43-4.12)</td>
</tr>
<tr>
<td>&gt;45</td>
<td>2.50 (0.34-18.38)</td>
</tr>
</tbody>
</table>

### Gestational week 37-43

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>1.74 (1.12-2.72)</td>
</tr>
<tr>
<td>20-24</td>
<td>1</td>
</tr>
<tr>
<td>25-29</td>
<td>1.41 (1.09-1.83)</td>
</tr>
<tr>
<td>30-34</td>
<td>1.53 (1.16-2.03)</td>
</tr>
<tr>
<td>35-39</td>
<td>2.19 (1.60-3.00)</td>
</tr>
<tr>
<td>40-44</td>
<td>2.24 (1.38-3.65)</td>
</tr>
<tr>
<td>&gt;45</td>
<td></td>
</tr>
</tbody>
</table>

* 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**

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

**Gestational week 23-29**

<table>
<thead>
<tr>
<th>Year</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1967-1971</td>
<td>1</td>
</tr>
<tr>
<td>1972-1976</td>
<td>1.10 (1.00-1.22)</td>
</tr>
<tr>
<td>1977-1981</td>
<td>1.06 (0.95-1.18)</td>
</tr>
<tr>
<td>1982-1986</td>
<td>0.91 (0.82-1.02)</td>
</tr>
<tr>
<td>1987-1991</td>
<td>0.79 (0.70-0.88)</td>
</tr>
<tr>
<td>1992-1996</td>
<td>0.72 (0.64-0.81)</td>
</tr>
<tr>
<td>1997-2001</td>
<td>0.57 (0.50-0.64)</td>
</tr>
<tr>
<td>2002-2006</td>
<td>0.44 (0.39-0.50)</td>
</tr>
</tbody>
</table>

**Gestational week 30-36**

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

**Gestational week 37-43**

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

* 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).

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>1.10 (0.97-1.26)</td>
</tr>
<tr>
<td>20-24</td>
<td>1</td>
</tr>
<tr>
<td>25-29</td>
<td>1.05 (0.97-1.15)</td>
</tr>
<tr>
<td>30-34</td>
<td>1.22 (1.10-1.34)</td>
</tr>
<tr>
<td>35-39</td>
<td>1.52 (1.36-1.70)</td>
</tr>
<tr>
<td>40-44</td>
<td>2.06 (1.74-2.43)</td>
</tr>
<tr>
<td>&gt;45</td>
<td>1.22 (0.58-2.58)</td>
</tr>
</tbody>
</table>

Gestational week 23-29

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>1.08 (0.96-1.22)</td>
</tr>
<tr>
<td>20-24</td>
<td>1</td>
</tr>
<tr>
<td>25-29</td>
<td>1.03 (0.95-1.13)</td>
</tr>
<tr>
<td>30-34</td>
<td>1.17 (1.05-1.30)</td>
</tr>
<tr>
<td>35-39</td>
<td>1.32 (1.15-1.52)</td>
</tr>
<tr>
<td>40-44</td>
<td>1.43 (1.14-1.80)</td>
</tr>
<tr>
<td>&gt;45</td>
<td>2.14 (1.14-4.04)</td>
</tr>
</tbody>
</table>

Gestational week 30-36

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>0.85 (0.76-0.96)</td>
</tr>
<tr>
<td>20-24</td>
<td>1</td>
</tr>
<tr>
<td>25-29</td>
<td>1.10 (1.01-1.19)</td>
</tr>
<tr>
<td>30-34</td>
<td>1.34 (1.21-1.48)</td>
</tr>
<tr>
<td>35-39</td>
<td>1.70 (1.49-1.93)</td>
</tr>
<tr>
<td>40-44</td>
<td>2.23 (1.85-2.70)</td>
</tr>
<tr>
<td>&gt;45</td>
<td>2.68 (1.56-4.60)</td>
</tr>
</tbody>
</table>

Gestational week 37-43

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>0.78 (0.70-0.88)</td>
</tr>
<tr>
<td>20-24</td>
<td>1</td>
</tr>
<tr>
<td>25-29</td>
<td>1.24 (1.15-1.33)</td>
</tr>
<tr>
<td>30-34</td>
<td>1.49 (1.35-1.63)</td>
</tr>
<tr>
<td>35-39</td>
<td>1.98 (1.76-2.23)</td>
</tr>
<tr>
<td>40-44</td>
<td>2.76 (2.32-3.29)</td>
</tr>
<tr>
<td>&gt;45</td>
<td>3.42 (2.06-5.67)</td>
</tr>
</tbody>
</table>

* 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**

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

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

**Gestational week 23-29**

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

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

**Gestational week 30-36**

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

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

**Gestational week 37-43**

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

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

120
Maternal human parvovirus B19 infection and the risk of fetal death and low birthweight: a case–control study within 35 940 pregnant women

AA Sarfraz, SO Samuelsen, A-L Bruu, PA Jenum, A Eskild

Department of Gynecology and Obstetrics and Medical Faculty Division, Akershus University Hospital, Lørenskog, Norway
Department of Mathematics, University of Oslo, Oslo, Norway
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Objectives To assess the association between maternal parvovirus B19 infection and fetal death, birthweight and length of gestation.

Design Case–control study.

Setting Population based.

Population Cases were all 281 women with fetal death within a cohort of 35 940 pregnant women in Norway. The control group consisted of a random sample of 957 women with a live born child.

Method Information on pregnancy outcome was obtained from the Medical Birth Registry of Norway. First trimester serum samples were tested for antibodies against parvovirus B19 (IgM and IgG). In seronegative women, further serum was analysed to detect seroconversion during pregnancy.

Main outcome measures Fetal death, length of gestation and birthweight.

Results Two of 281 (0.7%) of the women who experienced fetal death and nine of 957 (0.9%) of the controls had presence of IgM antibodies, crude odds ratio 0.8; 95% CI (0.2–3.5). In initially, seronegative women, 3.1% (2/65) with fetal death and 2.6% (8/307) with a live birth seroconverted, crude odds ratio 1.2; 95% CI (0.2–5.7). Presence of maternal parvovirus-specific IgG or IgM antibodies in the first trimester, or seroconversion during pregnancy were not associated with lower birthweight or reduced length of gestation in live born children, but was associated with low birthweight in stillborn offspring.

Conclusion Maternal parvovirus B19 infection was not associated with fetal death in our study. Very few cases of fetal death may be attributed to maternal parvovirus B19 infection.

Keywords Fetal death, infection, parvovirus B19, pregnancy, risk factors.

Introduction Studies have revealed a relationship between fetal death and human parvovirus B19. The virus may cause a wide spectrum of clinical symptoms ranging from erythema infectiosum (the fifth disease), arthropathy to triggering of autoimmune disorders and transient aplastic crises in patients with increased red cell turnover. Special attention has been focused on its fetal impact since 1984, when a link between human parvovirus B19 and adverse pregnancy outcome was first proposed; namely non-immune hydrops fetalis and fetal death.

Human parvovirus B19 is a common virus with increasing seroprevalence with age. Antibody studies among pregnant women indicate that 30–57% are susceptible, and that the incidence of seroconversion among these women is 1–2%, but may increase up to 16.7% during an epidemic. The estimated fetal transmission rate is approximately 30%. A few prospective studies on the association between fetal death and parvovirus B19 have been carried out. A study from England, including 190 pregnant women with symptomatic infection, reported a fetal death risk of 9% with a clustering in the second trimester. Other studies
have found a risk of fetal death of 7–13%, and 3% of hydrops fetalis.7,13–17 In other studies, however, there was no relationship between maternal parvovirus B19 infection and adverse pregnancy outcome.11,18 Approximately, 50% of parvovirus B19 infections in pregnant women are asymptomatic.14 Most of the previous studies of parvovirus B19 infection and fetal death did not include a group of non-infected women for comparison.13–16 However, in one study including all fetal deaths (n = 47) among 14 147 pregnancies, seven (15%) of the dead fetuses were parvovirus B19 DNA positive while none of the 50 live born children tested were positive.19 As previous studies were based on small and selected samples, and have shown conflicting results, the attributable risk of maternal parvovirus B19 infection for fetal death in the general population remains largely unknown.

The aim of our study was to assess the association of fetal death with past and present maternal human parvovirus B19 infection. We also studied the association of maternal parvovirus B19 infection with fetal birthweight and length of gestation.

**Materials and methods**

**Study population**

The source population comprised 35 940 pregnant women in Norway. They participated in a prospective study on *Toxoplasma gondii* infection in pregnancy performed by the Norwegian Institute of Public Health from June 1992 to May 1994.20 The serum samples from this study were stored in a biobank. The study population included almost 100% of the pregnant women in 11 of 19 counties in Norway and approximately 60% of all pregnant women in Norway during the study inclusion period.21

All women who had experienced fetal death and a control group with live born children were identified by linkage between the Toxoplasmosis Study Registry and the Medical Birth Registry of Norway by personal identification numbers.22,23 This registry contains information on all births after 16 weeks of gestation in Norway and is obtained by compulsory notification on standardised forms.

The personal identification numbers of 1851 of the 35 940 women (5%) in the toxoplasmosis study could not be obtained and these women were excluded. Two hundred and eighty-three (0.8%) women with fetal death after 16 weeks of gestation were identified.22,23 A control group of 970 women were randomly selected among all women in the cohort who delivered a live born child (n = 35 657). For 15 of the 1253 women there was insufficient serum available for antibody testing (2 cases and 13 controls). Thus, 1238 women, 281 cases and 957 controls, were available for antibody testing (2 cases and 13 controls).

### Serum sampling

The women were included in the study at their first antenatal visit to the primary healthcare centre (mean 10.2 weeks of gestation). Serum samples were requested at the first antenatal visit; and for the women without antibodies against *T. gondii*, additional serum was requested at the 22nd and the 38th week of pregnancy. The serum collection was performed at regular visits. If a fetal death was notified to the study administrator an additional serum sample from the woman was requested.20 Serum sampling after delivery was otherwise not performed according to the toxoplasmosis study protocol.

### Detection of antibodies against parvovirus B19

The serum samples were stored at −20 °C and analysed for human parvovirus B19 antibodies during the autumn of 1996 at the Department of Virology, Norwegian Institute of Public Health. All sera were sampled, stored and tested under identical conditions by one technician without knowledge of pregnancy outcome.

The first serum sample from each woman was tested separately for immunoglobulin G (IgG) and M (IgM) antibodies against parvovirus B19 (IDEIA Parvovirus B-19 IgM and IgG; DAKO A/S, Copenhagen, Denmark). If the first serum sample from the pregnancy period was negative for IgG and IgM antibodies, the last available sample from the woman was also analysed for IgG and IgM antibodies to detect possible seroconversion. Serum that tested positive within the grey zone was retested.

Antibody status against parvovirus B19 was categorised as follows:

1. **No previous infection**: antibodies against B19 not detected.

2. **Previous B19 infection**: presence of IgG antibodies against parvovirus B19 in the first serum sample, but no IgM antibodies.

3. **Presence of IgM antibodies**: presence of IgM with or without concomitant IgG antibodies against parvovirus B19 in the first serum sample.

4. **Seroconversion**: occurrence of IgG or IgM antibodies against parvovirus B19 in initially seronegative women.

### Fetal outcome variables

Information on fetal death, birthweight and length of gestation was obtained from the Medical Birth Registry. Fetal death was defined as death after 16 weeks of gestation. The
distribution of fetal deaths in this study sample according to length of gestation is presented elsewhere.\(^{24}\)

**Statistical analysis**

Differences in maternal parvovirus B19 antibody status between cases and controls were analysed by Fisher’s exact test and chi-square test. The associations between maternal parvovirus B19 infection and fetal death were estimated as crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI), adjustment was made for parity and maternal age, and for the women followed with regard to seroconversion, adjustment was also made for time between first and last serum sample. Differences in mean birth-weight and length of gestation according to maternal parvovirus B19 antibody status in live born and stillborn offspring were tested with Student’s \(t\)-test and Mann–Whitney test. All statistical analyses were performed by using the Statistical Package for the Social Sciences (SPSS, version 15.0; SPSS Inc., Chicago, IL, USA).

**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 Medical Birth Registry of Norway.

**Results**

**Maternal parvovirus B19 infection and fetal death**

In total, 64% (796/1238) of all women had presence of IgG antibodies against parvovirus B19 in the first serum sample and were therefore not susceptible to primary infection. Among the women who experienced fetal death, 68% (190/281) had parvovirus B19-specific IgG, and 63% (606/957) of the women without fetal death were positive (\(P = 0.2, \text{chi square test}\) OR 1.2 [0.9–1.6, 95% CI]) (Table 1).

Eleven women had presence of IgM antibodies against parvovirus B19 in first trimester, representing 0.9% of all women (11/1238) and 2.5% (11/442) of the susceptible women. Eight of these 11 women had presence of IgG in addition to IgM antibodies. A total of 0.7% (2/281) of the women who experienced fetal death and 0.9% (9/957) of the controls (\(P = 1.0, \text{Fisher’s exact test}\)) had presence of IgM antibodies, giving a crude OR of 0.8 (0.2–3.5, 95% CI). Adjustment for parity and maternal age did not change the estimated risk significantly (Table 1).

Ten women had serological evidence of seroconversion during pregnancy, representing 0.9% (10/1238) of all women. Of the 442 women who were parvovirus B19 seronegative in the first serum sample, 372 women had two or more stored serum samples and could be followed with regard to seroconversion. Among these, 3.1% (2/65) with fetal death and 2.6% (8/307) with a live born offspring seroconverted (\(P = 0.7, \text{Fisher’s exact test}\)), crude OR 1.2 (0.2–5.7, 95% CI). Among the 10 women who seroconverted during pregnancy, only two had presence of IgM antibodies against parvovirus B19 without concomitant IgG antibodies. After adjustment for parity, maternal age and time between first and last serum sample (follow-up time) the OR of fetal death was 0.8 (0.2–4.5, 95% CI). The mean follow-up time for cases was 19.0 and 25.5 weeks for controls.

<table>
<thead>
<tr>
<th>Table 1. The risk (odds ratio (OR) with 95% confidence interval [CI]) of fetal death associated with presence or occurrence of antibodies against parvovirus B19, immunoglobulin G (IgG) or immunoglobulin M (IgM), in a case–control study within a cohort of 35 940 pregnant women in Norway</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fetal death</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td><strong>Presence of IgG antibodies</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td><strong>Presence of IgM antibodies</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td><strong>Occurrence of antibodies</strong>*</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

*Adjusted for maternal age and parity.
**Additional adjustment for follow-up time (time between first and last serum collected).
***Only women susceptible to parvovirus B19 infection who had two or more serum samples collected are included (65 women with fetal death and 307 women without fetal death).
Table 2. Mean [SE] length of gestation and birthweight in 281 stillborn and 957 live born offspring according to maternal parvovirus B19 antibody status

<table>
<thead>
<tr>
<th>Maternal antibody status</th>
<th>n</th>
<th>Length of gestation (weeks)</th>
<th>Birthweight (grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live born</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of IgG antibodies</td>
<td>Yes</td>
<td>606</td>
<td>39.9 [0.1]</td>
</tr>
<tr>
<td>No</td>
<td>351</td>
<td>39.7 [0.1]</td>
<td>3533 [23]</td>
</tr>
<tr>
<td>Presence of IgM antibodies/occurrence of antibodies</td>
<td>Yes</td>
<td>17</td>
<td>40.1 [0.6]</td>
</tr>
<tr>
<td>No</td>
<td>940</td>
<td>39.8 [0.1]</td>
<td>3550 [19]</td>
</tr>
<tr>
<td><strong>Stillborn</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of IgG antibodies</td>
<td>Yes</td>
<td>190</td>
<td>28.3 [0.6]</td>
</tr>
<tr>
<td>No</td>
<td>91</td>
<td>27.9 [0.9]</td>
<td>1280 [137]</td>
</tr>
<tr>
<td>Presence of IgM antibodies/occurrence of antibodies</td>
<td>Yes</td>
<td>4</td>
<td>23.0 [1.8]</td>
</tr>
<tr>
<td>No</td>
<td>277</td>
<td>28.3 [0.5]</td>
<td>1309 [76]</td>
</tr>
</tbody>
</table>

Presence of antibodies in first trimester was studied in 1238 pregnant women. Occurrence of antibodies was studied in n = 372 women without antibodies in the first trimester who were followed during pregnancy.

Hence, among the 281 women who experienced fetal death, only four had serological signs of acute parvovirus B19 infection in pregnancy, either presence of IgM antibodies in the first serum sample or seroconversion.

**Maternal parvovirus B19 infection, length of gestation and offspring birthweight**

Past and present maternal parvovirus B19 infection was not significantly associated with birthweight or length of gestation in live born offspring (Table 2).

In women with stillborn offspring, the mean length of gestation was 23.0 weeks for women with acute parvovirus B19 infection and 28.3 weeks in women without acute parvovirus B19 infection (P = 0.3, Mann–Whitney test). The mean birthweight in the stillborn offspring was 338 g for women with acute infection, and 1309 g in women without acute parvovirus B19 infection (P = 0.1, Mann–Whitney test) (Table 2).

**Discussion**

In this case–control study within a cohort of 35 940 pregnant women, we found no association between maternal parvovirus B19 infection and the risk of fetal death. Of 281 fetal deaths only four were born to mothers with serological signs of acute parvovirus B19 infection in pregnancy. Maternal antibody status had no association with birthweight and length of gestation in live born children.

Since the first case reports, parvovirus B19 infection has been linked to adverse outcome of pregnancy. To our knowledge, no prior study has explored the association between maternal parvovirus B19 antibody status, length of gestation and birthweight.

Prior estimates of the risk of fetal death associated with parvovirus B19 have varied. Such variation may be because of differences in study design, selection of study sample and diagnostic methods. In some prior studies only women with symptomatic parvovirus B19 infection in pregnancy have been included. Yaegashi et al. followed 48 pregnant women either exposed to infected persons or having symptoms of infection. Among these women eight offspring with hydrops fetalis and seven cases (15%) of fetal deaths were reported. In the Netherlands, 2567 pregnant women within an unselected population were followed prospectively, with occurrence of antiparvovirus B19 IgG. They reported 18 cases of seroconversion, and no fetal deaths. In that study, under detection of acute infection may have occurred, as women with acute infection in first trimester might present with both IgG and IgM antibodies. A Swedish case-control study within 14 147 pregnancies, reported that 15% (7/47) of the cases of intrauterine fetal death after 22nd pregnancy week, and none of the controls (0/53), were parvovirus B19 DNA positive. This study did not describe the selection of the control group nor reported uncertainty of the risk estimates. Possible differences between cases and controls in type of tissue or number of tissue samples tested for parvovirus DNA were not described in detail.

Our study included all cases of fetal death (281) after 16th pregnancy week within 35 940 pregnancies. As we included almost all pregnant women in 11 counties in Norway during the inclusion period and have drawn controls at random, we believe no selection bias has occurred.

We used commercially available kits for detection of maternal antibodies against parvovirus B19 (IDEIA Parvovirus B-19 IgM and IgG). These kits have been shown to have the highest specificity (94.8%) compared with five other tests. However, as the specificity is not 100%, there is a risk of false positive results. We retested borderline positive (grey zone) sera to increase the specificity. Since parvovirus B19-specific IgM antibodies may persist for 2–3 months after infection, some of the women with presence of IgM antibodies in the first trimester may have been infected prior to onset of pregnancy. Also, presence of IgM antibodies without concomitant presence of IgG antibodies may be an unspecific serological reaction. However, of the 11 women with presence of IgM in the first serum sample had concomitant presence of IgG antibodies against...
parvovirus B19. We do not believe over diagnosis is an important source of error in our study. During 1993–1994 there was an outbreak of parvovirus B19 infection in Norway and we found 4.8% (21/442) of the susceptible women to have signs of acute infection during pregnancy. Other studies have reported seroconversion rates as high as 16.7% during epidemics.

Lack of follow up during pregnancy could potentially have caused biased estimates. Sixty-eight of the parvovirus B19 susceptible women (68/442) did not have follow-up serum and could therefore not be studied with regard to seroconversion. Twenty-five of these women experienced fetal death, of whom nine lacked follow-up serum as they had IgG antibodies against T. gondii in the first trimester. For T. gondii IgG positive women, no additional serum was requested according to the study protocol. Hence, 16 women with fetal death were true losses to follow up. Even if all cases lost to follow up had acquired parvovirus B19 in pregnancy, maternal infection could only be linked to 29 cases out of a total of 281 cases of fetal death in this cohort of 35 940 women. It is, however, very unlikely that lack of follow up was associated with increased risk of parvovirus B19 infection, and that such increased infection risk was differential according to offspring vital status.

Follow-up serum from after delivery was not routinely collected for all women in this study, but was requested in women with fetal death. Hence, parvovirus B19 seroconversion before delivery may have been under detected. In total, 10 of 1238 women (8 controls and 2 cases) seroconverted during a mean follow-up time of 24.5 weeks (25.5 weeks for controls and 19.0 weeks for cases). It is unlikely that serum sampling for all women after delivery would significantly increase the estimated impact of parvovirus B19 infection on fetal death. Since the incidence of parvovirus B19 was low in our study, additional 2–3 weeks of follow-up time would probably not have added many seroconverters. The potential lost seroconverters in pregnancy are most likely to be among the controls, as more cases than controls had serum available from after delivery. Among the 65 women with fetal death who were followed with regard to seroconversion, 35 women had serum drawn at or after delivery.

In our study, stillborn offspring of women with signs of acute parvovirus B19 infection in pregnancy had lower mean birthweight than women without acute infection. This observation may be spurious or may suggest growth restriction as a cause of fetal death in these cases. Other studies have reported a higher than expected proportion of small for gestational age offspring among pregnant women with serologically confirmed parvovirus B19 infection. Further research is required to confirm these observations.

In conclusion, we found no association between maternal parvovirus B19 in pregnancy and the risk of fetal death. Nor was exposure to parvovirus B19 during pregnancy associated with shorter length of gestation. Among the 281 women out of a cohort of 35 940 pregnancies, who experienced fetal death, only four had signs of acute parvovirus B19 infection in pregnancy. These observations may be of importance for clinicians dealing with prophylactic strategies and follow-up care of pregnant women with fetal death. In our study, parvovirus B19 was a seldom cause of fetal death and just as many women with a live born child as women experiencing stillbirth had an incident infection during pregnancy. Our findings do not suggest that parvovirus B19 is an important cause of fetal death.

Disclosure of interests

There are no conflicts of interest.

Contribution to authorship

Aahshi A. Sarfraz has analysed the data and written the manuscript. Sven O. Samuelsen has contributed to data analysis, the interpretation of the results and writing of the manuscript. Anne-Lise Bruu has been responsible for the serum analysis and interpretation of the results. Pål A. Jenum was the principal investigator of the toxoplasmosis study, Anne Eskild is the principal investigator of the fetal death study and the supervisor for Aahshi A. Sarfraz. All authors have contributed to the manuscript and approved the final version.

Details of ethics approval

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 Medical Birth Registry of Norway.

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Acknowledgements

The authors would like to acknowledge the Medical Birth Registry of Norway in providing data on pregnancy outcome.

References

The incidence of acute primary maternal Parvovirus B19 infection during pregnancy is about 2–4%. It is often due to contact with young infected children, and is mostly asymptomatic in the mother. Maternal infection is usually demonstrated by the finding of positive IgM, or by IgG seroconversion. In mothers with primary infection, about 25–30% develop clinical manifestations and become infected themselves by vertical transmission. Perinatal complications of fetal infection occur in about 10% of fetuses of infected mothers, and these include fetal anaemia and myocarditis. This can lead to fetal hydrops (in 2–6%) and occasionally fetal death, although this is rare if infection occurs after 20 weeks (Enders M, et al. 2004).

Apart from detecting hydropic changes in the fetuses of infected mothers, ultrasound can also screen for the development of fetal anaemia by measurement of the peak systolic velocity (PSV) of the middle cerebral artery (MCA) and using a threshold of >1.5 multiples of the median (MoM). If the MCA PSV values are <1.5 MoM, serial ultrasound scans are recommended for 10–12 weeks after the exposure, because fetal infection and anaemia can occur late. If MCA PSV is >1.5 MoM, or if there is fetal hydrops, fetal transfusion is indicated.
Screening of pregnant women for parvovirus B19 is not recommended, as only about one in 5000 screened women would be at risk for fetal hydrops caused by this virus; the risk of fetal death is even lower. In this article [Sarfraz A, et al. BJOG 2009;116:1492–8], a nested case–control study, it is confirmed that very few cases of fetal death may be attributable to parvovirus B19 infection. This is supported by data from the USA suggesting that fewer than 1% of stillbirths result from this infection (Goldenberg RL, Thompson C. The infectious origins of stillbirth. Am J Obstet Gynecol 2003;189:861–73).


The current study found no difference in the incidence of a positive IgM (leading to the diagnosis of primary maternal infection) in the serum of 281 susceptible women who had fetal deaths versus 957 susceptible women who did not. Given that parvovirus is known to cause fetal anaemia and hydrops, which in turn are associated with fetal death, how can this be explained? The most likely reason is that this is due to a type 2 error (i.e. the sample sizes are too small to show a difference). Nevertheless, the findings are important: it appears that parvovirus B19 is rarely a cause of late fetal death, and women with a live born child have incident parvovirus infections during pregnancy as often as those with fetal loss. Based on this and other available data, one logical conclusion could be that testing for Parvovirus is important when the fetal death occurs before 24 weeks, when it is associated with exposure to parvovirus or close contact with children, or when there are fetal findings associated with this infection such as hydrops or anaemia. The value of testing for Parvovirus in the absence of such features is questionable, and merits further research.

Conflict of interest
Neither author has a conflict to declare.

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

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Objective To study changes in gestational-age-specific fetal death risks during a 40-year period.

Design Register-based observational study.

Setting The Medical Birth Registry of Norway.

Population All pregnancies after 16 weeks of gestation in Norway from 1967 to 2006 (n = 2,182,756).

Method Changes in fetal death risk since 1967–1971 (reference) were estimated as absolute risks (rates) and relative risks (RR) in ongoing pregnancies at the following gestational weeks; 16–22, 23–29, 30–36 and 37–43.

Main outcome measures Fetal death.

Results In all pregnancies lasting longer than 22 weeks, the fetal death rate decreased during 1967–2006. The greatest decline was in term pregnancies (37–43 weeks) from 10.8 to 3.3 fetal deaths per 1000 at risk (crude RR 0.35; 95% CI 0.31–0.38) comparing 1967–1971 with 2002–2006. In pregnancies at 30–36 weeks the fetal death rate declined from 4.5 to 1.1 per 1000 (crude RR 0.23; 95% CI 0.21–0.26). At 23–29 weeks, the rate declined from 2.8 to 1.3 per 1000 (crude RR 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 RR 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 there was an increase in risk. The causes of this increase should be further explored because it may be attributed to an increase in early delivery caused by the increased proportion of women being treated with cervical cone excision before pregnancy.

Keywords Fetal death, gestational age, pregnancy, risk factors, stillbirth.

Introduction

Fetal death is a devastating outcome of pregnancy, and each year more than 3 million fetal deaths after 28 weeks of gestation occur worldwide. The incidence varies between populations, from 4 to 40 fetal deaths per 1000 births, but is subject to underestimation. Up to 50% of fetal deaths are of unknown cause. There is a lack of good-quality data for comparisons of fetal death rates between populations and over time. Such knowledge is important in understanding the causes of fetal death, for clinical practice and for health care evaluation.

Perinatal mortality was one of the earliest quantitative measurements of quality in obstetric care. This measure is ambiguous for the purpose because it comprises both stillbirths after 22 weeks of gestation and early neonatal deaths, defined as offspring deaths occurring within 7 days after birth. These events may have different aetiologies and risk factors. It has therefore been suggested that stillbirths and early neonatal deaths should be reported separately. These two entities had more common aetiology 50 years ago than today, namely asphyxia, whereas preterm birth and congenital anomalies are now the leading causes of early neonatal death in the western world.
In the western world the stillbirth rate has declined since the 1950s. The decline was most pronounced early in this period, indeed increasing stillbirth rates have been reported since 2001.

Gestational-age-specific fetal mortality has been suggested as an indicator of antenatal and obstetric care, but this measure is not widely adopted. It is likely that the causes of fetal death differ by length of gestation. Infections are assumed to be linked to mid-pregnancy fetal deaths, whereas fetal deaths at or near term may be caused by pre-eclampsia, placental abruption, fetal growth restriction or complications during delivery. The improvements of obstetric care may have been more beneficial at term than in early pregnancy. Hence, knowledge of changes in gestational-age-specific mortality over time may reveal underlying causes of fetal death and also be an evaluation of obstetric care.

Our aim was to study changes in gestational-age-specific risk of fetal death among all pregnancies after 16 weeks of gestation in Norway from 1967 to 2006. We also compared changes in stillbirth rate with perinatal mortality and with early neonatal mortality from 1967 to 2006.

**Methods**

**Study design and population**

The study was a population-based registry study. Data were obtained from the Medical Birth Registry of Norway. All births in Norway are compulsorily notified to the registry; notification is made on standardised forms and the data elements have remained almost unchanged since 1967. The study population comprised all births after 16 weeks of gestation in Norway during the period 1967–2006, a total of 2,337,392 births. Some pregnancies (of gestation in Norway during the period 1967–2006, a

The study population comprised all births after 16 weeks of gestation in Norway during the period 1967–2006, a total of 2,337,392 births. Some pregnancies (n = 28,595) were recorded as lasting longer than 43 weeks but a proportion of these were miscoded. We could not determine with certainty which were miscoded so all pregnancies recorded as lasting longer than 43 weeks were excluded. Information on length of gestation at birth was missing for 125,997 offspring and an additional 44 births lacked information on potentially confounding variables, as a result 2,182,756 births could be included.

**Study factors**

Perinatal mortality is defined as the number of offspring deaths in pregnancies lasting ≥22 weeks (154 days) and within the first 7 days after birth per 1000 births. Early neonatal mortality is the number of infant deaths occurring within 7 days after birth per 1000 liveborn infants, and the stillbirth rate is number of fetal deaths per 1000 births in pregnancies lasting ≥22 weeks. We defined fetal death as the birth of a dead fetus after 16 weeks of gestation and studied fetal death for the following equal gestational length intervals; 16–22, 23–29, 30–36 37–43 weeks of gestation. Information on length of gestation at delivery was based on the woman’s reporting of her first day of the last menstrual period in standardised antenatal care forms, or term date was estimated from ultrasound examination of the fetus, if available.


As potential confounding factors we included maternal age at delivery, parity, multiple pregnancy, paternal age and pre-eclampsia. Maternal age at delivery was coded: <20, 20–24, 25–29, 30–34, 35–39, 40–44 and ≥45 years old. Parity was defined as number of previous deliveries after the 16th week of gestation coded as 0, 1, 2, 3 and ≥4. Multiple pregnancy was coded no or yes. Pre-eclampsia was defined as maternal blood pressure ≥140/90 mmHg after 20 weeks of gestation combined with proteinuria on dipstick of ≥+1. Paternal age was coded as <30, 30–39, ≥40 years old and missing.

**Statistical methods**

Perinatal mortality, early neonatal mortality and stillbirth rate were calculated according to the World Health Organization definitions, as defined above. We calculated rates of fetal death per 1000 ongoing pregnancies according to period of delivery (year). The denominator included all women with a fetus still in utero at the gestational length being studied, and the numerator included women experiencing fetal death during the same period of gestation. For instance, for calculations of fetal death rate at 23–29 weeks, only pregnant women who delivered at 23 weeks of gestation or after were included.

Cox regression models were applied to estimate the relative risk of fetal death according to period of delivery, with 1967–1971 as the reference period. The relative risk was estimated separately for each gestational length interval. The time variable in the Cox regression models was gestational age (in days) and the outcome variable was fetal death. Infants born alive and live fetuses still in utero at the end of a gestational length interval were treated as censored observations. Adjustments were made for potential confounding factors. All statistical analyses were performed by using spss version 16.0 (SPSS Inc., Chicago, IL, USA).

**Results**

All births in Norway from 1967 to 2006 (n = 2,182,756), were included in our study, and 93.2% of the births occurred at or beyond the 37th week of pregnancy. A total
of 22,754 fetal deaths occurred in the study period, representing 1.04% of all births after 16 weeks of gestation. Characteristics of the study population are presented in Table 1.

The perinatal mortality decreased by 72%, from 21.9 per 1000 births in the years 1967–1971 to 6.1 per 1000 births in the years 2002–2006. The decline was most pronounced early in the period (Figure 1). The early neonatal mortality decreased by 82% from 8.8 to 1.6 per 1000 live births, and the stillbirth rate in pregnancies lasting 22 weeks or longer decreased by 69% from 13.3 to 4.1 per 1000 births.

The change in fetal death rate was most pronounced in pregnancies at 37–43 weeks, with a decline from 10.8 fetal deaths per 1000 ongoing pregnancies in 1967–1971, to 3.3 fetal deaths per 1000 in 2002–2006 (Figure 2). The fetal death rate at 30–36 weeks of gestation declined from 4.5 to 1.1 per 1000 ongoing pregnancies, whereas the corresponding numbers at 23–29 weeks of gestation were from 2.8 to 1.3 per 1000 ongoing pregnancies. At 16–22 weeks of gestation, we estimated an increase in fetal death rate from 1.7 to 3.4 per 1000 ongoing pregnancies from 1967–1971 to 2002–2006.

The crude relative risk of fetal death at 37–43 weeks of gestation was 0.35 (95% CI 0.31–0.38) comparing births during 2002–2006 with the reference period, 1967–1971 (Table 2). The crude relative risk of fetal death was 0.23 (95% CI 0.21–0.26) at 30–36 weeks and 0.46 (95% CI 0.40–0.52) at 23–29 weeks. At 16–22 weeks the crude relative risk of fetal death was estimated to be 2.05 (95% CI 1.84–2.27) during 2002–2006 compared with 1967–1971. Adjustment for the potentially confounding factors did not significantly alter the associations of year of delivery with fetal death risk.

Discussion

During our study period, 1967–2006, the fetal death rate declined in pregnancies lasting longer than 22 weeks, and the decline was most prominent in pregnancies at term. For pregnancies at 16–22 weeks of gestation, an opposite trend was observed, with a two-fold increase in fetal death.
In recent years, the fetal death rate in early pregnancy has reached the rate at term. In the western world, perinatal mortality has declined since the mid-19th century from 26 to 43 per 1000 births to a level of 5–10 per 1000 births in the first decade of the 21st century. Also the fetal death rate has been reported to decline. In Europe, the fetal death rate after 28 weeks of gestation has declined from 25–45 to 3–5 per 1000 births from 1940 to 2000.

Previous studies have used various definitions of fetal death. The occurrence of fetal death with regard to length of gestation and labour has varied so comparison of rates...
between studies are difficult. Also the definition of pregnancies at risk has varied, and few studies have excluded pregnancies from the denominator at the time of delivery of a liveborn infant when estimating fetal death rate. Hence, fetal death rates in term and post-term pregnancies may have been underestimated.

Studies on changes in fetal death rate at or near term report declining rates in recent periods. A study from a tertiary centre in New York reported a decrease from 3.5 to 1.2 fetal deaths per 1000 ongoing pregnancies at term during 1996–2005. In another study from the USA of pregnancies at 40–43 of gestation, the decline was from 1.22 to 0.95 per 1000 pregnancies at risk during 1991–1997.

Fetal death rates in mid-pregnancy have shown less marked trends. A Canadian study reported a minor reduction in fetal death rate during 1988–1999 from 3.6 to 3.1 per 1000 pregnancies lasting <34 weeks. Others have reported stable rates. In pregnancies lasting <22 weeks, increasing fetal death rates have been reported. In a Canadian study of pregnancies at 20–21 weeks of gestation, the rate increased from 0.51 to 0.86 per 1000 pregnancies at risk during 1991–1998. Also, a study from the USA reported a small increase in fetal death rates at 20–22 weeks of gestation from 1.06 in 1991 to 1.25 in 1997 per 1000 ongoing pregnancies.

Few studies have reported gestational-age-specific fetal death rates within the same study population over time, and these studies suffer from selected study samples and short observation periods.

Our study was based on all births in Norway from 1967 to 2006 so biased estimates caused by a skewed study sample is unlikely. Maternal age at childbearing is an important risk factor of fetal death, and the maternal age has increased during our study period. Adjustment for maternal age attenuated the estimated increase in early gestation fetal deaths, whereas the decrease in fetal deaths at term was strengthened, but not significantly. We lacked information on body mass index, smoking habits and social status, all known risk factors of fetal death. The prevalence of high body mass index, daily smokers and low social status has changed during our study period. The impact of these factors on fetal death at different gestations is not known but it may partly explain the temporal changes in fetal death rates.

Up to 1998, the estimation of gestational length at birth by the Medical Birth Registry was based on a woman’s report of the first day of her last menstrual period. After 1998 gestational length estimates were based on fetal ultrasound examinations. Last menstrual period may be an unreliable measurement in women with irregular cycles or uncertain first day of the last menstrual period. Studies comparing ultrasound and last menstrual period for gestational age estimation reveal minor discrepancies in predicting term and preterm births, whereas the proportion of post-term births increased when last menstrual period was employed. It is, however, unlikely that change in estimation of gestational length has significantly biased our results because gestational age was grouped into 7-week intervals, and term pregnancies were defined as 37 weeks of gestation or above. Any overestimation of term pregnancies by using last menstrual period for prediction of term, will rather underestimate than overestimate the reduction in fetal death rate at term in the later time periods of this study.

Fetal deaths at 16–22 weeks of gestation may have been subjected to under-reporting because the routines of reporting to the Medical Birth Registry have been less established for deliveries at early gestation than at late gestation. Hence, improved reporting routines may have caused an artificial increase in rates. Also, from the mid-1980s when fetal diagnostics were improved and until 1999, some induced abortions may have been misclassified as fetal deaths. After 1999, however, terminated pregnancies were reported separately to the Medical Birth Registry and could therefore be excluded from our study. Our estimated rates of early fetal deaths after 1999 are therefore calculated from pregnancies intended to last to term.

Our study shows an increase in fetal death rate at 16–22 weeks of gestation. A large proportion of these early fetal deaths are likely to be caused by preterm labour and fetal immaturity. The increase in early gestation fetal deaths therefore suggests an increase in preterm labour. One explanation for an increase in preterm labour may be an increase in women being treated with cervical cone excision because of cervical intraepithelial neoplasia. Treatment with cervical cone excision increases the risk of preterm labour, particularly in early pregnancy. In Norway, the proportion of childbearing women undergoing such treatment increased from 0.7 per 1000 in the years 1967–1979 to 18.1 per 1000 during 2000–2003. Our results therefore suggest that the high rate of early fetal deaths may be explained by an increased prevalence of childbearing women who have undergone treatment with cervical cone excision.

In pregnancies lasting longer than 22 weeks, the fetal death rates have been declining and the greatest decline was observed at term. This decline is likely to be explained by improved antenatal and obstetric care. Antenatal routine examinations, including screening for pre-eclampsia and diabetes, are offered to all pregnant women free of charge in a public healthcare setting. It is interesting to note that the largest decrease in fetal deaths occurred before the mid-1980s when fetal ultrasound examinations came into general use in Norway. Fetal cardiocotography, however, was gradually introduced in Norway in the 1970s, and the caesarean section rate increased from 1.8 to 16.4% during our observation period.
It may be postulated that the decrease in fetal deaths in the last part of pregnancy is caused by a decrease in congenital anomalies, and that such a decrease is attributable to prenatal screening for anomalies and selective pregnancy terminations. Additional analysis of our data (not shown) excluding offspring with serious congenital malformations, did not alter the relative risk estimates of year of delivery for any of the gestational ages studied.

Conclusion

Among all pregnancies in Norway during a 40-year period the fetal death rate in pregnancies >22 weeks of gestation has declined by nearly 70% and the greatest absolute decline was observed in term pregnancies. The fetal death rate at 16–22 weeks of gestation has doubled during the period, and is presently at the same level as in pregnancies at term. Our findings suggest an increasing fetal death rate in early pregnancy. Such possible trend needs to be confirmed in other studies, and investigation into possible causes is warranted.

Disclosure of interest

There are no conflicts of interest.

Contribution to authorship

AAS analysed the data and wrote the manuscript. SOS contributed to the data analysis, the interpretation of the results and writing of the manuscript. AE is the principal investigator, contributed the idea and to the writing of the manuscript. All authors have approved this final version of the manuscript.

Details of ethics approval

The Medical Birth Registry of Norway is approved by the Norwegian Data Inspectorate. The Publishing Committee of the Medical Birth Registry approved our study.

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Acknowledgement

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References

28 Olsen O, Clausen JA. [Determination of the expected day of delivery—ultrasound has not been shown to be more accurate than the calendar method]. *Ugeskr Laeger* 1998;160:2088–90.
The impact of maternal age on fetal death: does length of gestation matter?

Camilla Haavaldsen, MD; Aahshi A. Sarfraz, MD; Sven O. Samuelsen, PhD; Anne Eskild, PhD

OBJECTIVE: The objective of the investigation was to study the association of fetal death with maternal age by length of gestation.

STUDY DESIGN: This was a population study including all ongoing pregnancies after 16 weeks of gestation in Norway during the period 1967-2006 (n = 2,182,756).

RESULTS: The risk of fetal death was 1.4 times higher in women 40-44 years old than in women aged 20-24 years in midpregnancy but 2.8 times higher at term. In term pregnancies the relative importance of maternal age increased by additional pregnancy weeks. In gestational weeks 42-43, the crude risk was 5.1 times higher in mothers 40 years old or older. In the recent period, the elevated risk of fetal death in elderly mothers at term has been attenuated.

CONCLUSION: Women 40 years old or older had the highest risk of fetal death throughout pregnancy, particularly in term and postterm pregnancies. Improved obstetric care may explain the attenuation of risk associated with age in recent time.

Key words: fetal death, gestational length, maternal age


In the Western world, it has become increasingly common to postpone child-bearing. The mean age of primiparous women has increased during the last decades. According to the Medical Birth Registry of Norway, more than 19% of child-bearing women were 35 years old or older in 2008. For comparison, only 8% were 35 years old or older 20 years ago. The mean age of all women giving birth was 29.8 years in 2006, more than 4 years older than women delivering 30 years earlier.

The negative impact of high maternal age on fetal death risk is well known. Recent knowledge suggests that the risk of fetal death varies considerably according to length of gestation. The fetal death rate seems to be high at 20-22 weeks of gestation and lowest at 27-33 weeks, before it increases rapidly from 37 through 43 gestational weeks. The knowledge of the impact of maternal age on fetal death at different gestational ages is limited. Such knowledge, however, may be important in understanding causes of fetal death. It has been suggested that infectious causes play a greater role in midpregnancy than in fetal death at term, whereas pregnancy-related maternal disease and placenta insufficiency seem to be increasingly important as the pregnancy proceeds.

In a study comprising births from 36 states in the United States during 2001-2002, women of advanced maternal age had a higher risk of stillbirth across all gestational ages, with a peak risk postterm. This study is essential; however, the lack of follow-up after the 41st gestational week and the high level of obstetrical interventions may have caused an underestimation of the fetal death risk in term and postterm pregnancies.

Obstetrical ultrasonographic examination was gradually introduced in the public obstetric health in Norway by the mid-1980s, and since then almost all pregnancies have been examined at pregnancy weeks 17-19. This may have improved the term prediction in pregnancy and also the diagnosis of fetal failure to thrive when used later in pregnancy. Because elderly mothers are at increased risk of fetal death, they may in particular have gained from improved obstetrical diagnostic tools, if such tools are advantageous.

In all ongoing pregnancies after 16 weeks of gestation in Norway during the years 1967-2006, we estimated the risk of fetal death according to maternal age at different lengths of gestation. We also studied whether the fetal death risk at term in elderly mothers has changed after ultrasonographic examinations were introduced in obstetrical care.

Materials and Methods

Data were obtained from the Medical Birth Registry of Norway. This registry contains information on all births after 16 weeks of gestation. Compulsory notification of birth is made on standardized forms by the midwife or attending physician at the delivery, and the data elements in the notification form have been almost...
Pregnancies lasting 38 weeks or longer and 37 or more weeks of gestation.

We studied fetal death risk at the follow-up of 16-22, 23-29, 30-36, and 37 or more weeks of gestation. Of all pregnancies, 93.2% of the births were at the 37th gestational week or later. Women aged 40 years or older had the highest risk of fetal death at all gestational ages, but their increased risk was unchanged since the start of the registration in 1967 (http://www.mfr.no).17

The study population comprised deliveries after 16 weeks of gestation in Norway during the period 1967-2006, a total of 2,337,392 births. A total of 28,595 fetal deaths were recorded after 16 weeks of gestation in Norway during the period 1967-2006. We used the Statistical Package for the Social Sciences for statistical analyses. In the adjusted analysis, the confounders were included as categorical variables with categorization as given in earlier text. Separate analyses were carried out for the different gestational length intervals. For term and postterm pregnancies, we also estimated the association of fetal death with maternal age in 2 different time periods: 1967-1986 and 1987-2006. We used the Statistical Package for the Social Sciences for statistical analyses (version 16.0; SPSS, Chicago, IL).

The study was approved by the Norwegian Data Inspectorate and the Publishing Committee for the Medical Birth Registry of Norway.

RESULTS
A total of 22,754 fetal deaths occurred in 2,182,756 births during the study period, representing 1.04% of all births after 16 weeks of gestation. Of all pregnancies, 10.3% were in women 35 years old or older and 93.2% of the births were at the 37th gestational week or later.

The absolute risk of fetal death varied according to length of gestation (Figure 1). Women aged 40 years or older had the highest risk of fetal death at all gestational ages, but their increased risk was most pronounced in early gestation and at term. After gestational week 36, the risk of fetal death increased rapidly in all age groups. However, the increase in risk seemed to be highest in women 40 years old or older.

### Table 1
Characteristics of the study population, 2,182,756 pregnancies during 1967–2006 in Norway

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total births</th>
<th>Percent</th>
<th>Fetal deaths, n</th>
<th>Fetal deaths per 1000 births, n</th>
</tr>
</thead>
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<td>Parity</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>901,171</td>
<td>41.3</td>
<td>9508</td>
<td>10.6</td>
</tr>
<tr>
<td>1</td>
<td>758,413</td>
<td>34.7</td>
<td>6456</td>
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<td>2</td>
<td>356,952</td>
<td>16.4</td>
<td>3965</td>
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<tr>
<td>≥3</td>
<td>166,220</td>
<td>7.6</td>
<td>2825</td>
<td>17.0</td>
</tr>
<tr>
<td>Plurality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2,125,470</td>
<td>97.4</td>
<td>20,633</td>
<td>9.7</td>
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<tr>
<td>≥2</td>
<td>57,286</td>
<td>2.6</td>
<td>2121</td>
<td>37.0</td>
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<tr>
<td>Paternal age, y</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;30</td>
<td>1,058,341</td>
<td>48.5</td>
<td>8661</td>
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</tr>
<tr>
<td>30–39</td>
<td>932,983</td>
<td>42.7</td>
<td>8261</td>
<td>8.9</td>
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<tr>
<td>≥40</td>
<td>169,195</td>
<td>7.8</td>
<td>2252</td>
<td>13.3</td>
</tr>
<tr>
<td>Missing</td>
<td>22,237</td>
<td>1.0</td>
<td>3580</td>
<td>161.0</td>
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<td>Preeclampsia</td>
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<td>Yes</td>
<td>67,200</td>
<td>3.1</td>
<td>1242</td>
<td>18.5</td>
</tr>
<tr>
<td>No</td>
<td>2,115,556</td>
<td>96.9</td>
<td>21,512</td>
<td>10.2</td>
</tr>
<tr>
<td>Total</td>
<td>2,182,756</td>
<td></td>
<td>22,754</td>
<td>10.4</td>
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</table>

The relative importance of high maternal age on fetal death risk was confirmed to be elevated at term and in early gestation by Cox regression analyses (Table 2). The crude relative risk of fetal death in gestational weeks 16-22 was 3.45 (95% confidence interval [CI], 3.00–3.96) in women 40-44 years old as compared with women aged 20-24 years (reference), and it was 1.95 (95% CI, 1.66–2.28) after adjustment for period of delivery, parity, plurality, and paternal age.

In gestational weeks 23-29, the crude relative risk of fetal death in mothers 40-44 years old was 1.43 (95% CI, 1.18–1.74) as compared with women 20-24 years old (reference), and it was 1.95 (95% CI, 1.66–2.28) after adjustment for period of delivery, parity, plurality, and paternal age.

In gestational weeks 38-39, the crude relative risk in mothers aged 40 years or older was 2.74 (95% CI, 2.19–3.43) as compared with the reference group. In gestational weeks 42-43, the corresponding risk was 5.09 (95% CI, 3.55–7.31) (Table 3). These increased relative risks for elderly mothers remained essentially unchanged after adjustment for the other study factors and were significantly higher in gestational weeks 42-43 as compared with weeks 38-39. Women 45 years old or older were not studied separately because of the lack of statistical power in postterm pregnancies.

In term and postterm pregnancies, we also studied the association of fetal death risk with maternal age in the years before and after 1986 (Table 4 and Figure 2). In the years 1967-1986, the crude relative risk of fetal death in the gestational weeks 42-43 was 7.31 (95% CI, 4.96–10.76) for women 40 years or older, as compared with women 20-24 years old. In comparison, the corresponding risk was 1.94 (95% CI, 0.70–5.41) during 1987-2006.

**Comment**

In this population-based study, including more than 2 million births from 1967 through 2006, women 40 years old or older had an overall higher risk of fetal death compared with younger mothers throughout pregnancy. The fetal death risk increased after 36 weeks of pregnancy and the increase was highest in the oldest women. Interestingly, there was a higher impact of maternal age on fetal death risk at term during the period 1967-1986 as compared with 1987-2006. The association between high maternal age and risk of fetal death is well known. In a review of 37 studies examining the association of high maternal age with stillbirth risk, most studies demonstrated a significant increased risk of stillbirth in women of advanced age.

In accordance with other studies, our results suggest the risk of fetal death to
vary according to gestational length.\textsuperscript{6,7} To our knowledge, only 1 previous study has explored the association between fetal death and maternal age at different gestational ages.\textsuperscript{14} This study included more than 5 million births of singletons without malformations in the United States from 2001 through 2002. Births from 20 through 41 weeks of gestation were included. Their limitations include the reliability of fetal death and birth certificate data and the exclusion of births with congenital anomalies.\textsuperscript{20} Also, their cesarean section rate was high, around 25%.\textsuperscript{15,16} Despite the difference in study sample, the absolute and relative impact of maternal age on fetal death were similar to our estimates for term pregnancies in recent years. However, our data obtained during a 40 years period show a large decrease in fetal risk at term, and

### Table 2

<table>
<thead>
<tr>
<th>Gestational length</th>
<th>Maternal age, y</th>
<th>Fetal deaths, n</th>
<th>Number at risk</th>
<th>Crude RR</th>
<th>95% CI</th>
<th>Adjusted RR\textsuperscript{a}</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational wks 16–22 (d 112–160)</td>
<td>&lt;20</td>
<td>345</td>
<td>125,009</td>
<td>1.31</td>
<td>1.17–1.48</td>
<td>1.09</td>
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<tr>
<td></td>
<td>20–24</td>
<td>1211</td>
<td>576,584</td>
<td>1.00</td>
<td></td>
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<tr>
<td></td>
<td>25–29</td>
<td>1826</td>
<td>753,530</td>
<td>1.15</td>
<td>1.07–1.24</td>
<td>1.03</td>
<td>0.95–1.11</td>
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<td></td>
<td>30–34</td>
<td>1691</td>
<td>503,648</td>
<td>1.60</td>
<td>1.49–1.72</td>
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<td>35–39</td>
<td>897</td>
<td>188,760</td>
<td>2.27</td>
<td>2.08–2.47</td>
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<td></td>
<td>40–44</td>
<td>242</td>
<td>33,597</td>
<td>3.45</td>
<td>3.00–3.96</td>
<td>1.95</td>
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<tr>
<td></td>
<td>≥45</td>
<td>7</td>
<td>1628</td>
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<td>0.98–4.32</td>
<td>1.13</td>
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<td>Total</td>
<td>6219</td>
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<tr>
<td>Gestational wks 23–29 (d 161–209)</td>
<td>&lt;20</td>
<td>443</td>
<td>124,581</td>
<td>1.54</td>
<td>1.38–1.72</td>
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<td>0.98–1.22</td>
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<td></td>
<td>20–24</td>
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<td>574,978</td>
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<td>25–29</td>
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<td>751,093</td>
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<td>30–34</td>
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<td>474</td>
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<td>40–44</td>
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<td>33,254</td>
<td>1.43</td>
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<td>1.25</td>
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<tr>
<td></td>
<td>≥45</td>
<td>15</td>
<td>1615</td>
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<td>1.44–5.00</td>
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<tr>
<td>Total</td>
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<tr>
<td>Gestational wks 30–36 (d 210–258)</td>
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<td>123,108</td>
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<td>1.14–1.42</td>
<td>0.87</td>
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<td>746,149</td>
<td>0.85</td>
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<td>1.11</td>
<td>1.02–1.19</td>
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<td>1.19–1.45</td>
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<td>35–39</td>
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<td>185,788</td>
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<td>1.66</td>
<td>1.47–1.87</td>
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<td></td>
<td>40–44</td>
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<td>1.90–2.59</td>
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<td>1.82–2.63</td>
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<td></td>
<td>≥45</td>
<td>15</td>
<td>1590</td>
<td>3.80</td>
<td>2.29–6.32</td>
<td>2.80</td>
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<tr>
<td>Gestational wks ≥37 (d 259–307)</td>
<td>&lt;20</td>
<td>414</td>
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<td>40–44</td>
<td>216</td>
<td>30,245</td>
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<td>2.43–3.23</td>
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<td>2.24–3.15</td>
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<td>≥45</td>
<td>17</td>
<td>1418</td>
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\textsuperscript{a} Adjusted for period of delivery, parity, plurality, paternal age, and preeclampsia. In gestational weeks 16–22, preeclampsia is not adjusted for.

this decrease has been most prominent in mothers older than 40 years.

Almost all deliveries in Norway during our study period have been at public hospitals, and reporting of births after 16 weeks of gestation to the Medical Birth Registry is compulsory by law; hence, we do not believe significant underreporting of fetal deaths has occurred. However, for fetal deaths in 16-22 weeks of gestation, the routines of reporting to the Medical Birth Registry are less established than at higher gestational lengths. Despite possible underreporting of early fetal deaths, we have no reason to believe that there has been a differential underreporting according to maternal age.

Before the introduction of ultrasonographic examinations in the 1980s, information on length of gestation at delivery was based on women’s reporting of the first day of her last menstrual period. This may be an unreliable measurement and could cause an inaccurate determination of the gestational length in women with irregular cycles or uncertain of the first day of the last menstrual period. The absolute fetal death risk in the gestational weeks 38–39, 40–41, and 42–43, according to maternal age during 1967–2006

<table>
<thead>
<tr>
<th>Gestational length</th>
<th>Maternal age, y</th>
<th>Fetal deaths, n</th>
<th>Number at risk</th>
<th>Crude RR</th>
<th>95% CI</th>
<th>Adjusted RR*</th>
<th>95% CI</th>
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<tr>
<td>Gestational wks</td>
<td>38–39 (d 266–279)</td>
<td>20–24</td>
<td>598</td>
<td>517,220</td>
<td>1.00</td>
<td>0.79–0.99</td>
<td>0.97–1.23</td>
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<td>25–29</td>
<td>686</td>
<td>677,188</td>
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<td>30–34</td>
<td>474</td>
<td>446,432</td>
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<td>35–39</td>
<td>249</td>
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<td>1.20–1.61</td>
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<td></td>
<td>≥40</td>
<td>87</td>
<td>29,635</td>
<td>2.74</td>
<td>2.19–3.43</td>
<td>2.53</td>
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<td>30–34</td>
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<td>35–39</td>
<td>259</td>
<td>100,137</td>
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<td>1.52–2.03</td>
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CI: confidence interval; RR, relative risk.
* Adjusted for period of delivery, parity, plurality, maternal age, and preeclampsia.

Another explanation of the increased risk in early gestation could be related to a higher cumulative incidence of being treated with cervical cone excisions in older rather than younger women. The relative risk of preterm delivery, associated with cone excision, increases with decreasing duration in pregnancy. In preterm deliveries, fetal deaths are likely to happen during labor and are caused by immaturity.

After 36 weeks of gestation, an increasing difference in risk of fetal death between younger and older mothers was observed. A failure of the uterine vasculature to adapt adequately to the increased hemodynamic demands of pregnancy, most pronounced in the oldest women, has been discussed. However, fetal growth restriction has not been shown to have a stronger association with increased fetal death risk in the third trimester in older as compared with younger mothers.

Obstetric practice in Norway has gone through major changes since the mid-1980s. This change may be attributed to the introduction of ultrasonographic examinations and extensive use of cardiotocography. The intervention rate has increased and the share of postterm pregnancies has decreased. The cesarean section rate has increased from 1.8% in 1967 to 16.3% in 2006. A total of 9.3% of the women delivered in gestational week 42 in 1967, as compared with 6.9% in 2006. The proportion of mothers delivering in gestational weeks 43 or after was 4.4% in 1967 and 0.3% in 2006.

Term predicted by ultrasonographic examination may, for many obstetricians, be more trustworthy than term predicted by last menstrual period. Hence, induction of labor may have been more common in pregnancies estimated to be postterm by ultrasonographic examination, than by the last menstrual period. Also, the treatment used for the induction of labor may have improved during our study period. It is likely that older women have been overrepresented to induction of labor in recent time because the tools used in pregnancy to diagnose fe-

### Table 4

<table>
<thead>
<tr>
<th>Gestational length</th>
<th>Maternal age, y</th>
<th>Fetal deaths, n</th>
<th>Number at risk</th>
<th>Crude RR (95% CI)</th>
<th>Fetal deaths, n</th>
<th>Number at risk</th>
<th>Crude RR (95% CI)</th>
</tr>
</thead>
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<td>Gestational wks 38–39 (d 266–279)</td>
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<td>0.81–1.21</td>
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<td>30–34</td>
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<td>1.02–1.40</td>
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<td>1.12–1.67</td>
<td>61</td>
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<td>30–34</td>
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<td>1.41–2.29</td>
<td>55</td>
<td>31,117</td>
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<td>4.96–10.76</td>
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CI, confidence interval; RR, relative risk.

Fetal deaths according to gestational length and maternal age during 1967-2006 and 1987-2006


ACKNOWLEDGMENT
We would like to acknowledge the Medical Birth Registry of Norway for providing data on pregnancy outcome.

REFERENCES
21. Olsen O, Clausen JA. Determination of the expected day of delivery—ultrasound has not been shown to be more accurate than the calendar method]. Ugeskr Laeger 1998;160:2088-90.
Objective To compare the proportion of offspring that was stillborn in pregnancies with pre-eclampsia, gestational hypertension or chronic hypertension with those in normotensive pregnancies.

Design Register-based observational study.

Setting The Medical Birth Registry of Norway.

Population All singleton births after 20 completed weeks of gestation in Norway from 1967 to 2006 (n = 2,121,371).

Methods The proportion of stillborn offspring was estimated in normotensive pregnancies, and in pregnancies with pre-eclampsia, gestational and chronic hypertension at different gestational lengths. In addition, changes in the proportions of stillborn offspring by maternal hypertensive disorder from 1967–1986 to 1987–2006 were estimated.

Main outcome measures Fetal death.

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. This was true for 1.9% (1170/62,261) 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 fetal death 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 reductions in fetal death rates were 49% and 57%, respectively, comparable with the 41% decline in normotensive pregnancies.

Conclusions In our nationwide study during 1967–2006, the risk of fetal death among women with hypertensive disorders in pregnancy has been greatly reduced, especially among pre-eclamptic women at term. The risk of fetal death among women with gestational or chronic hypertension has also decreased, but in a different manner.

Keywords Fetal death, gestational age, hypertensive disorders in pregnancy, risk factors.

Introduction Hypertensive disorders are present in 5–10% of all pregnancies and, in these pregnancies, the risk of fetal death is increased.1–6 Hypertensive disorders in pregnancy include pre-eclampsia, gestational hypertension and chronic hypertension (hypertension prior to pregnancy). These conditions may have different risk factors and clinical manifestations, and therefore the influence on pregnancy outcomes may also differ.7–9

The contributions of hypertensive disorders to the risk of fetal death have not been studied thoroughly. It is known, however, that the risk of fetal death varies by the length of gestation and that the risk increases after 37 weeks of pregnancy.10–12 As the prevalence of maternal hypertensive disorders also increases with increasing gestational age,13 the increased risk of fetal death around term may be attributed in part to hypertension.

The overall risk of fetal death has decreased substantially during recent decades, particularly in term pregnancies.
Moreover, in pregnancies with pre-eclampsia, the fetal death rate after 23 weeks of gestation has also decreased.\(^{14}\)

In women with gestational hypertension or chronic hypertension, the risk of fetal death has been studied in lesser detail. However, the different hypertensive disorders of pregnancy may differentially alter the risk and timing of fetal death.\(^5\) An improved knowledge of the risk of fetal death by gestational age and hypertensive disorder is necessary for the prevention of such deaths.

Among all births in Norway during 1967–2006, we compared the overall proportions of offspring that were stillborn, and the proportions of stillborn offspring by gestational week in pregnancies with pre-eclampsia, gestational hypertension or chronic hypertension with those in normotensive pregnancies. We also studied changes in the prevalence of fetal death and perinatal mortality by maternal hypertensive disorder from 1967–1986 to 1987–2006.

Methods

Study population

Data were obtained from the Medical Birth Registry of Norway.\(^{17}\) This registry was established in 1967 and includes information on offspring and maternal characteristics of all births in Norway after 16 weeks of gestation. The information is obtained from standardised forms. From 1967 to 1998, these forms had open text fields regarding maternal health that were completed by the attending midwife or doctor shortly after delivery. In 1999, the Medical Birth Registry of Norway introduced new forms with pre-coded fields for maternal disorders. Notification to the Medical Birth Registry is mandatory by law.

Between 1967 and 2006, there were 2 337 775 births in Norway; we included singleton births only in our study sample. Hence, multiple pregnancies (\(n = 60 \text{,}498; 2.6\%\)), pregnancies with missing length of gestation (\(n = 125 \text{,}997; 5.4\%\)), pregnancies recorded to last longer than 43 weeks (\(n = 28 \text{,}595; 1.2\%\)) or <20 weeks (\(n = 4325; 0.2\%\)) and pregnancies with missing information on maternal age or parity (\(n = 53\)) were excluded. A total of 2 121 371 births was therefore included in our analysis.

Study factors

The outcome measure, fetal death, was defined as the birth of a dead offspring after 20 weeks of gestation. We studied the overall proportion of stillborn offspring and the proportions by gestational age at birth. Gestational age at birth was calculated from the date of the last menstrual period for births before 1999 and, thereafter, on estimations of term date at routine fetal ultrasonographic examinations at pregnancy week 17–19. Perinatal mortality was defined as the number of offspring deaths in pregnancies lasting \(\geq 22\) weeks (154 days) and within the first 7 days after birth per 1000 births.

Pre-eclampsia, gestational hypertension, chronic hypertension, eclampsia and HELLP (haemolysis, elevated liver enzymes and low platelets) are reported as separate categories to the Medical Birth Registry.\(^{18}\) Before 1999, the hypertensive diagnoses in the Medical Birth Registry were defined according to the International Classification of Diseases, Eighth Revision (ICD-8) and, thereafter, according to ICD-10. Maternal hypertension in pregnancy was grouped into three mutually exclusive categories of hypertensive disorders in our analysis: pre-eclampsia, gestational hypertension and chronic hypertension.\(^5\)

Pre-eclampsia was defined as an increase in blood pressure to at least 140/90 mmHg combined with proteinuria after completion of 20 weeks of gestation (ICD-8 codes 637.4/637.5/637.6/637.9 and ICD-10 codes O13 and O14). Eclampsia was defined as pre-eclampsia with seizures. Eclampsia and HELLP were grouped together with pre-eclampsia. In addition, women with chronic hypertension who developed pre-eclampsia during pregnancy were grouped as pre-eclampsia.

Gestational hypertension was defined as an increase in blood pressure to \(\geq 140/90\) mmHg after the completion of 20 weeks of gestation, or an increase in systolic blood pressure of \(30\) mmHg or of diastolic blood pressure of \(15\) mmHg or more without concomitant proteinuria (ICD-8 codes 637.0/637.2 and ICD-10 code O16). Chronic hypertension was defined as a pre-pregnancy systolic blood pressure of \(\geq 140\) mmHg or diastolic blood pressure of \(\geq 90\) mmHg, or an increase in blood pressure to these values before 20 weeks of gestation (ICD-8 codes 400–404 and ICD-10 codes I10/I11/I12/I13/I15/O10/O11). Women who were not in any of these categories were labelled as normotensive in our study.

We made adjustments for maternal age at delivery and parity, as these are known independent risk factors for fetal death, and as the distribution of parity and maternal age has changed over the time periods.\(^{19,20}\) Maternal age was categorised as ≤19, 20–24, 25–29, 30–34, 35–39 and ≥40 years at delivery. Parity was defined as the number of previous deliveries after 16 weeks of gestation, and categorised as 0, 1, 2, 3 and ≥4 deliveries.

Statistical methods

We calculated the overall proportion of deliveries with fetal death and the proportions with fetal death in each pregnancy week in pregnancies with pre-eclampsia, gestational hypertension, chronic hypertension and in normotensive pregnancies. We further studied the changes in fetal death rate among women with the different hypertensive disorders relative to the fetal death rate among normotensive women. The associations of the different hypertensive
disorders with fetal death were estimated as crude and adjusted relative risks (RRs). For these analyses, we used the GENLIN (generalised linear model) command in SPSS 16.0 with binomial response and log-link. The uncertainty of the estimates is reported by 95% confidence intervals (95% CIs). Normotensive pregnancies were used as the reference. Adjustments were made for maternal age at delivery and parity. These analyses were also performed separately for deliveries in the two time periods: 1967–1986 and 1987–2006.

We used SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA) for statistical analyses.

**Results**

Among all singleton pregnancies (2,121,371), there were a total of 17,933 fetal deaths (0.8%), and 9.2% (n = 1643) of these were in pregnancies with hypertensive disorders. Among the 2,022,400 women who were normotensive at delivery (95.3% of all pregnancies), 0.8% (n = 16,290) experienced fetal death (Table 1). In total, 62,261 women had pre-eclampsia (2.9% of all pregnancies), and 1.9% of these women experienced fetal death, giving an RR of 2.3 (95% CI, 2.2–2.5) with normotensive pregnancies as the reference. Among the 32,068 women with gestational hypertension (1.5% of all pregnancies), 1.2% experienced fetal death (RR, 1.5; 95% CI, 1.3–1.6). Likewise, among the 4642 women with chronic hypertension (0.2% of all pregnancies), there were 1.8% fetal deaths (RR, 2.1; 95% CI, 1.7–2.6) (Table 1).

The proportion of offspring that was stillborn varied according to the length of gestation (Figure 1). In gestational week 28, 20.3% of all offspring were stillborn, whereas this was true for 0.2% of the offspring in gestational week 40 and 0.5% in gestational week 43. At term, the proportion of births with stillborn offspring was higher in hypertensive relative to normotensive pregnancies. In gestational week 41, 0.5% of births in hypertensive pregnancies were stillborn, whereas this was true for 0.2% in normotensive pregnancies (RR, 2.5; 95% CI, 2.0–3.2). After adjustment for maternal age and parity, the RR remained essentially the same: adjusted RR of 2.3 (95% CI, 1.8–3.0).

There was an overall decline in the fetal death rate in all hypertension groups during our study period; however the decline occurred earlier and was larger among pre-eclamptic pregnancies (Figure 2). In normotensive pregnancies,

| Table 1. Relative risks (RRs) with 95% confidence intervals (95% CIs) of fetal deaths in pregnancies with pre-eclampsia, gestational or chronic hypertension relative to normotensive pregnancies in Norway during 1967–2006 |
|-----------------------------------|-------------------|-----------------|-----------------|-----------------|
|                                  | Fetal deaths/births | Fetal deaths/1000 births | Crude RR (95% CI) | Adjusted RR* (95% CI) |
| All                              | 17933/2121371       | 8.5              | Reference        | Reference        |
| Normotensive                     | 16290/2022400       | 8.1              | Reference        | Reference        |
| Pre-eclampsia                    | 1170/62261          | 18.8             | 2.33 (2.20–2.47) | 2.29 (2.16–2.43) |
| Gestational hypertension         | 390/32068           | 12.2             | 1.51 (1.37–1.67) | 1.46 (1.32–1.61) |
| Chronic hypertension             | 83/4642             | 17.9             | 2.22 (1.79–2.75) | 2.12 (1.71–2.63) |

*Adjustments were made for maternal age and parity.

**Figure 1.** Number of fetal deaths per 1000 births at each gestational week in pregnancies with pre-eclampsia, gestational or chronic hypertension and in normotensive pregnancies in Norway during 1967–2006.
the proportion of stillborn offspring declined from 10.1 to 6.0 per 1000 births from 1967–1986 to 1987–2006 (41% reduction), whereas, in pregnancies with pre-eclampsia, the decline was from 36.2 to 7.2 per 1000 births (80% reduction) (Table 2). In 1967–1986, the adjusted RR of fetal death in pregnancies with pre-eclampsia was 3.4 (95% CI, 3.2–3.6) relative to normotensive pregnancies, whereas, in 1987–2006, the RR was reduced to 1.2 (95% CI, 1.0–1.3).

When studying gestational weeks 40–43 separately, the adjusted RR of fetal death associated with pre-eclampsia was 3.0 (95% CI, 2.5–3.7) in 1967–1986, but 1.2 (95% CI, 0.8–1.8) in 1987–2006, using normotensive pregnancies as the reference (Table 3).

In pregnancies with gestational hypertension, the overall decline in fetal death rate was from 15.8 per 1000 births in 1967–1986 to 8.0 per 1000 births in 1987–2006 (49% reduction). The adjusted RRs of fetal death in women with gestational hypertension were 1.5 (95% CI, 1.3–1.6) in 1967–86 and 1.3 (95% CI, 1.1–1.6) in 1987–2006 relative to normotensive pregnancies (Table 2). In deliveries at 40–43 weeks of pregnancy, the adjusted RRs of fetal death associated with gestational hypertension were 2.2 (95% CI, 1.7–2.8) in 1967–1986 and 2.1 (95% CI, 1.4–3.1) in 1987–2006.

In pregnancies with chronic hypertension, the fetal death rate declined from 31.8 to 13.6 per 1000 births (57% reduction) from 1967–1986 to 1987–2006. In these pregnancies, the adjusted RRs of fetal death were 2.8 (95% CI, 2.0–3.9) in 1967–1986 and 2.1 (95% CI, 1.6–2.8) in 1987–2006. However, as shown in Figure 2, there was a considerable decline in the fetal death rate among pregnancies with chronic hypertension after 1996. In deliveries at 40–43 weeks of pregnancy, the adjusted RRs of fetal death associated with chronic hypertension were 1.6 (95% CI, 0.5–5.0) in 1967–1986 and 2.3 (95% CI, 1.0–5.1) in 1987–2006.

Figure 2. Number of fetal deaths per 1000 births in pregnancies with pre-eclampsia, gestational or chronic hypertension and in normotensive pregnancies in Norway during 1967–2006.

Table 2. Relative risks (RRs) with 95% confidence intervals (95% CIs) of fetal deaths in pregnancies with pre-eclampsia, gestational or chronic hypertension relative to normotensive pregnancies in Norway during 1967–1986 and 1987–2006

<table>
<thead>
<tr>
<th></th>
<th>Fetal deaths/births</th>
<th>Fetal deaths/1000 births</th>
<th>Crude RR (95% CI)</th>
<th>Adjusted RR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1967–1986 (All)</td>
<td>11414/1051654</td>
<td>10.9</td>
<td></td>
<td>Reference</td>
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<tr>
<td>Normotensive</td>
<td>10205/1008503</td>
<td>10.1</td>
<td>3.58 (3.35–3.83)</td>
<td>3.39 (3.17–3.63)</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>903/24930</td>
<td>36.2</td>
<td>1.57 (1.39–1.76)</td>
<td>1.46 (1.29–1.64)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>271/17119</td>
<td>15.8</td>
<td>3.14 (2.26–4.35)</td>
<td>2.80 (2.02–3.88)</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>35/1102</td>
<td>31.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987–2006 (All)</td>
<td>6519/1069717</td>
<td>6.1</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>Normotensive</td>
<td>6085/1013897</td>
<td>6.0</td>
<td>1.19 (1.05–1.35)</td>
<td>1.17 (1.04–1.33)</td>
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<tr>
<td>Pre-eclampsia</td>
<td>267/37331</td>
<td>7.2</td>
<td>1.33 (1.11–1.59)</td>
<td>1.29 (1.08–1.55)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>119/14949</td>
<td>8.0</td>
<td>2.26 (1.70–3.00)</td>
<td>2.12 (1.61–2.83)</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>48/3540</td>
<td>13.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjustments were made for maternal age and parity.
The perinatal mortality also declined during the study period from 15.5 per 1000 births in 1967–1986 to 7.0 per 1000 births in 1987–2006 (Table 4). Among normotensive pregnancies, the rate declined by 54%, and the corresponding declines among pregnancies with pre-eclampsia, gestational hypertension and chronic hypertension were 79%, 51% and 62%, respectively.

**Discussion**

In this study of more than 2 million singleton pregnancies in Norway during 1967–2006, women with hypertension showed an increased risk of fetal death. There was a 44% overall reduction in fetal death rate from 1967–1986 to 1987–2006. The largest decline was in women with pre-eclampsia (80% reduction). The fetal death rate among women with gestational and chronic hypertension also declined (49% and 57%, respectively). Hence, compared with the large decrease in fetal death among pre-eclamptic women, the RR of fetal death among women with gestational and chronic hypertension (relative to normotensive women) has declined in a different manner.

The strength of our study is that it included all singleton births in Norway after 20 weeks of gestation over 40 years. Almost all deliveries in Norway take place in public hospitals and the reporting of births is compulsory by law. Hence, we believe that there is no selection bias in our study. The diagnostic criteria for hypertensive disorders in pregnancy have remained unchanged during our study period. After the implementation of the new form with pre-coded tick boxes regarding maternal hypertensive disorders by the Medical Birth Registry of Norway, the incidence of all three categories of hypertension increased. This may be an indication of increased ascertainment, or there may have been a true increase as childbearing women in Norway have become older and may have become heavier. Increased reporting would most likely lead to increased registration of cases with milder disease, resulting in the attenuation of the risk estimates.

### Table 3. Relative risks (RRs) with 95% confidence intervals (95% CIs) of fetal deaths in pregnancies with pre-eclampsia, gestational and chronic hypertension relative to normotensive pregnancies by weeks of gestation during 1967–1986 (A) and 1987–2006 (B)

(A) 1967–1986

<table>
<thead>
<tr>
<th>Gestational weeks (n = 11 414)</th>
<th>Total fetal deaths</th>
<th>Total births (n = 1 051 654)</th>
<th>Pre-eclampsia (n = 903/24 930)</th>
<th>Gestational hypertension (n = 271/17 119)</th>
<th>Chronic hypertension (n = 35/1102)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Fetal deaths/births</td>
<td>Adjusted RR* (95% CI)</td>
<td>Fetal deaths/births</td>
<td>Adjusted RR* (95% CI)</td>
<td>Fetal deaths/births</td>
</tr>
<tr>
<td>20–23</td>
<td>1716</td>
<td>2191</td>
<td>12/16</td>
<td>0.98 (0.74–1.30)</td>
<td>6/9</td>
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<tr>
<td>24–27</td>
<td>1548</td>
<td>3666</td>
<td>56/98</td>
<td>1.35 (1.13–1.60)</td>
<td>14/24</td>
</tr>
<tr>
<td>28–31</td>
<td>1455</td>
<td>6820</td>
<td>175/480</td>
<td>1.71 (1.51–1.95)</td>
<td>41/87</td>
</tr>
<tr>
<td>32–35</td>
<td>2094</td>
<td>25 988</td>
<td>299/1823</td>
<td>2.21 (1.97–2.47)</td>
<td>59/401</td>
</tr>
<tr>
<td>40–43</td>
<td>2038</td>
<td>666 616</td>
<td>113/1870</td>
<td>3.02 (2.50–3.65)</td>
<td>72/10191</td>
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</table>

(B) 1987–2006

<table>
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<tr>
<th>Gestational weeks (n = 6519)</th>
<th>Total fetal deaths</th>
<th>Total births (n = 1 069 717)</th>
<th>Pre-eclampsia (n = 267/37 331)</th>
<th>Gestational hypertension (n = 119/14 949)</th>
<th>Chronic hypertension (n = 48/3540)</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>Adjusted RR* (95% CI)</td>
<td>Fetal deaths/births</td>
<td>Adjusted RR* (95% CI)</td>
<td>Fetal deaths/births</td>
</tr>
<tr>
<td>20–23</td>
<td>1878</td>
<td>2543</td>
<td>26/48</td>
<td>0.73 (0.56–0.95)</td>
<td>9/14</td>
</tr>
<tr>
<td>24–27</td>
<td>946</td>
<td>3445</td>
<td>61/419</td>
<td>0.50 (0.39–0.64)</td>
<td>16/42</td>
</tr>
<tr>
<td>28–31</td>
<td>701</td>
<td>6875</td>
<td>56/1508</td>
<td>0.31 (0.24–0.41)</td>
<td>15/121</td>
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<tr>
<td>32–35</td>
<td>825</td>
<td>27 487</td>
<td>46/4052</td>
<td>0.35 (0.26–0.48)</td>
<td>27/558</td>
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<tr>
<td>36–39</td>
<td>1289</td>
<td>406 001</td>
<td>55/18035</td>
<td>0.95 (0.73–1.25)</td>
<td>28/6325</td>
</tr>
<tr>
<td>40–43</td>
<td>880</td>
<td>623 366</td>
<td>23/13269</td>
<td>1.19 (0.79–1.80)</td>
<td>24/7889</td>
</tr>
</tbody>
</table>

*Adjustments were made for maternal age and parity.

The perinatal mortality also declined during the study period from 15.5 per 1000 births in 1967–1986 to 7.0 per 1000 births in 1987–2006 (Table 4). Among normotensive pregnancies, the rate declined by 54%, and the corresponding declines among pregnancies with pre-eclampsia, gestational hypertension and chronic hypertension were 79%, 51% and 62%, respectively.
The prevalence of the different hypertensive disorders in our study is largely in agreement with other reports.\textsuperscript{21–26} Pre-eclampsia has been reported to complicate between 1.4% and 7% of all pregnancies,\textsuperscript{13,21,22,24,27} and gestational hypertension between 1% and 4.3% of all pregnancies.\textsuperscript{21,22,24,25} The prevalence of chronic hypertension varies between 0.2% and 5%, and the highest prevalence is among the oldest women.\textsuperscript{22–25,28} Discrepancies between rates are probably a result of different diagnostic criteria, different sources of information (birth records or hospital records) and differences in the source populations with regard to risk factors.\textsuperscript{29,30}

The diagnosis of hypertensive disorders in our study was based on blood pressure measurements and urine examinations in antenatal care from 8 to 12 weeks of pregnancy onwards.\textsuperscript{31} Close to 100% of pregnant women in Norway take part in the public antenatal care programme which is free of charge, and the standard number of examinations in the programme is ten.\textsuperscript{31} Maternal disease and clinical findings at each antenatal examination are recorded prospectively and reported to the Medical Birth Registry shortly after delivery. Differential misclassification of hypertensive disorders in pregnancy according to offspring vital status at birth is therefore unlikely. Furthermore, misclassifications are more likely to underestimate than overestimate associations.

We lacked information on body mass index, which is a known risk factor for both hypertension and fetal death.\textsuperscript{32} As women with high body mass index more often have hypertension, our estimated association of hypertension with fetal death may represent overestimates.\textsuperscript{33} However, a differential association of high body mass index with type of hypertension and fetal death is unlikely.

Previous studies on a possible differential association of type of hypertension with fetal death report diverging estimates, and most studies are small.\textsuperscript{26,34} Population studies on the association of hypertension with fetal death from the USA have been published, but discrimination between types of hypertension in pregnancy could not be made.\textsuperscript{1,16,35} One of these studies reported changes from 1990–1991 to 2003–04, and found an increase in pregnancy-induced hypertension (from 3 to 3.8%) and a decrease in stillbirth rate (from 6.1 to 4.8 per 1000 births) after 24 weeks of gestation.\textsuperscript{1} However, the odds ratio of fetal death associated with hypertension increased between the two study periods from 1.37 to 1.52.

A Canadian study of 1948 singleton pregnancies complicated with hypertension during 1986–1995 reported off-spring death rates during the period 20 weeks of gestation until 30 days after birth. The death rate was 16/1000 in pregnancies with gestational hypertension, 32/1000 in chronic hypertension and 59/1000 in pre-eclampsia.\textsuperscript{26} An Italian study of 965 pregnancies with hypertension during 1986–1995 reported perinatal mortality (≥24 weeks of gestation until 7 days after birth) to be 12/1000 in pregnancies with gestational hypertension, 6/1000 in chronic hypertension and 26/1000 in pre-eclampsia.\textsuperscript{34} A Chinese population-based observational study among 16 000 pregnancies reported higher perinatal mortality in pregnancies with pre-eclampsia (17.8/1000) relative to pregnancies with gestational hypertension (10.2/1000).\textsuperscript{36} A review including 46 studies suggested that chronic hypertension tripled the risk of perinatal mortality relative to normotensive pregnancies.\textsuperscript{28}

Moreover, the risk of fetal death seems to vary by type of hypertensive disease.\textsuperscript{24} One retrospective study from the USA, including more than 8000 pregnant women with hypertension, reported odds ratios of 2.9 for fetal death associated with chronic hypertension and 1.9 for fetal death associated with pregnancy-induced hypertension relative to normotensive women.\textsuperscript{16} A Swedish study of more than 1 million pregnancies during 1983–1992 reported fetal death
rates after 28 weeks of gestation of 4.2/1000 in women with gestational hypertension, 5.3/1000 in women with pre-eclampsia and 11.2/1000 in women with chronic hypertension. In recent time, chronic hypertension, in particular, seems to be associated with a higher risk of fetal death.

The RR of fetal death associated with hypertension is highest in term and post-term pregnancies. A study of more than 300 000 pregnancies reported an increase in the odds ratio of fetal death in women with chronic hypertension from 2.2 before 28 weeks of gestation to 3.3 at 28 weeks of gestation and beyond. The corresponding increase in women with pregnancy-induced hypertension was from 0.7 to 1.4, with normotensive women as the reference. In a study in the USA among 11 000 000 deliveries, the RRs of fetal death associated with pregnancy-induced hypertension were 1.2 at week 36 and 2.5 at week 41. In women with chronic hypertension, the RRs were 2.1 at week 36 and 4.4 at week 41, with low-risk pregnancies as reference. In a recent study of 171 000 women with chronic hypertension, the risk of fetal death increased from gestational week 38 (1.1 per 1000 ongoing pregnancies) to week 41 (3.5 per 1000).

In our study, the risk of fetal death was increased in pregnancies with hypertension relative to normotensive women. The proportion of offspring that was stillborn was highest in early pregnancy, as intrauterine fetal death is an important reason for preterm induction and very preterm offspring may not survive birth because of immaturity. The patterns of fetal death risk associated with hypertension, however, were similar independent of the type of hypertension, with the highest RR of fetal death at and after term. These findings suggest that, for all types of maternal hypertensive disease, offspring are at increased risk of fetal death, and such pregnancies should be given similar clinical follow-up to ensure timely interventions.

In the time period 1987–2006, pregnancies with pre-eclampsia showed no increased risk of fetal death. In the Norwegian antenatal care programme, screening for pre-eclampsia is performed. In addition, women with pre-eclampsia may have more symptoms and may seek health care beyond the scheduled number of antenatal examinations. Thus, the reduction in fetal death in women with pre-eclampsia may therefore be attributed to the early detection of offspring at increased risk of death and to timely intervention in these pregnancies. The rate of premature deliveries (<37 weeks of gestation) increased significantly among women with pre-eclampsia during the study period (14.0% in 1967–1986 to 22.6% in 1987–2006, P < 0.001). This was also the case for women with gestational hypertension, whereas, for women with chronic hypertension, there was no change in the proportion that delivered prematurely (10.8 to 11.0%, P = 0.089). Despite the increased number of prematurely delivered infants among pre-eclamptic women, the perinatal mortality declined in the same manner as the fetal death rate; this has also been confirmed by earlier reports.

In this registry study, we have no information on the use of anti-hypertensive treatment before or during pregnancy. The benefit of maternal anti-hypertensive therapy on the risk of fetal death is limited. Thus, the most efficient means to reduce fetal deaths in pregnancies with hypertension is to provide close clinical follow-up and induction of delivery in threatened pregnancies.

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

Disclosure of interests
There are no conflicts of interest.

Contribution to authorship
ASA analysed the data and wrote the manuscript. SOS contributed to data analysis, interpretation of the results and writing of the manuscript. Both authors approved the final version of the manuscript.

Details of ethics approval
The Medical Birth Registry of Norway is approved by the Norwegian Data Inspectorate. The Publishing Committee of the Medical Birth Registry approved our study.

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Acknowledgements
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References
Ahmad, Samuelsen


33 Ulset E, Undheim R, Malterud K. [Has the obesity epidemic reached Norway?]. Tidsskr Nor Laegeforen 2007;127:34–7.


 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.


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Etternavn, alle fornavn (bare for levendeledd):

Fødested. Navn og adresse på sykehuset/fødehemmet:

Kommune:

Faren

Etternavn, alle fornavn:

Født dag, mnd., år:

Bosteds kommune:

Moren

Etternavn, alle fornavn, Pikerleiv:

Bosted. Adresse:

Kommune:

Ekteskapelig status:

1 | Ugift | 6 | Samboende | 2 | Gift | 3 | Enke | 4 | Separert | 5 | Skilt |

Antall tidligere fødte (før denne fødselen):

Levende fødte:

Av disse i live:

Dødlede:

Er moren i slett med laren?

1 | Nei | 2 | Ja |

Hvilket slektskapsforhold:

Mores helset før svangerskapet:

1 | Normal | 2 | Sykdom (spesifiser) |

Siste menstruasjons / første bloedningsdag:

Mores helset under svangerskapet:

1 | Normal | 2 | Komplikasjoner (spesifiser) |

Ble fødselen provisert:

1 | Nei | 2 | Ja |

Inngrep under fødselen:

1 | Nei | 2 | Ja (spesifiser) |

Inngrepet utført av

1 | Legge | 2 | Jordmor |

Komplika-
sjoner i forbindelse med fødselen:

1 | Nei | 2 | Ja (spesifiser) |

Forekomst, placenta og navlensar:

1 | Normal | 2 | Fysiologisk (spesifiser) |

Både for levende født. Tegn på sykdom?

1 | Nei | 2 | Ja |

Apargarscore etter 1 min. etter 5 min.

For levende født og dødlede. Tegn på medfødt anomali, på skade etter sykdom?

1 | Nei | 2 | Ja |

Hvilke:

Lengde (i cm): Hode-omkr. (i cm): Vekt (i g): For døds innen 24 timer: Timer: Livel varte i:

For dødelede. Døden innfødste:

Dødsforårs:

1 | For fødselen | 2 | Under fødselen |

Sekspjør?

1 | Nei | 2 | Ja |

Avvigelige anvevde ledeler i slektst

1 | Nei | 2 | Ja |

Sykdommens art og hos hvilke elektringer:

Sted (sykehusets stempel): Dato: Jordmor: Lege:

IK - 1002
**Protokollnr.:**

**D – Om barnet**

**C – Om fødselen**

**B – Om svangerskap og mors helse**

**A – Sivile opplysninger**

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**Fødselsdato:**

- Dødsdato: 

**Dødsårsak:**

-setState: 

**Overfedtler:**

- Jordmor/far: 

**Fødselssted:**

- Barn: 

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**Utskrivningsnr.:**

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