Fetal death:
high maternal age at childbirth and the placenta

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To my most beloved father,

who I lost while writing this thesis.

You have been in my thoughts every day since you had to let life go.

I wish you could have been here with me today.

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Lørenskog, January 2014

Camilla Haavaldsen

Abbreviations

ART	Assisted reproductive technology
BMI	Body mass index
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CTG	Cardiotocography
FGF	Fibroblast growth factor
hCG	Human chorionic gonadotropin
hCT	Human chorionic thyreotropin
hPL	Human placental lactogen
ICD-10	International Classification of Diseases, 10th Revision
NICU	Neonatal intensive care unit
OR	Odds ratio
PI	Pulsatility index
PLGF	Placental growth factor
PROM	Premature rupture of membranes
PPROM	Preterm premature rupture of membranes
RR	Relative risk
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

Papers included in the thesis

I Haavaldsen C, Sarfraz AA, Samuelsen SO, Eskild A. The impact of maternal age on fetal death: does length of gestation matter? *Am J Obstet Gynecol* 2010;203:554.e1-554.e8.

II Haavaldsen C, Samuelsen SO, Eskild A. Fetal death and placental weight/birthweight ratio: a population study. *Acta Obstet Gynecol Scand* 2013;92:583-590

III Haavaldsen C, Samuelsen SO, Eskild A. The association of maternal age with placental weight: a population-based study of 536 954 pregnancies. *BJOG* 2011;118:1470-1476.

1 Introduction

1.1 Fetal death

1.1.1 Definition

The definition of fetal death varies considerably between countries.[1,2] Some countries define fetal death as the birth of a dead fetus at 18 weeks of gestation or above, while others set the limit at 28 weeks or above.[1] When length of gestation is unknown, birthweight is often used to distinguish fetal death from a miscarriage, and the birthweights used to define fetal death vary from 350 to 500 grams or above.[3,4] The International Classification of Diseases, 10th Revision (ICD-10),[5] compiled by the World Health Organization (WHO), describes fetal death as "death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscles."[6] Furthermore, the WHO defines fetal death by a birthweight of 500 grams or above, or a gestational length of 22 weeks or above. If both birthweight and length of gestation are unknown, a crown-heel length of the fetus of 25 centimetres or above is used.[5] Many countries, including Norway, have adopted the WHO's definition of fetal death.[7]

The varying definitions of fetal death make comparison of fetal death rates between countries difficult. Therefore, for international comparability, the WHO recommends reporting of the birth of a dead fetus born at 28 weeks of gestation or above, or with a birthweight of 1000 grams or above.[6]

1.1.2 Fetal death rates

It is difficult to obtain reliable global estimates of fetal death rates, not only because of the varying definitions, but also because of the lack of systematic reporting in many countries.[8] Thus, fetal death rates are probably underestimated, particularly in developing countries. In a WHO report from the year 2000, 3.3 million fetal deaths were estimated to occur every

year.[6] However, the latest study, which was supported by the WHO, gave a global estimate of 2.6 million fetal deaths for the year 2009.[9] Although the global fetal death rate is declining, the differences in rates between countries are still substantial, with 2 deaths per 1000 births at 28 weeks of gestation or above in Finland and Singapore, and 47 deaths per 1000 births in Pakistan (Figure 1).[9] Large countries like China, India, Bangladesh and Mexico have made progress in reducing the number of fetal deaths, whereas the decline has been small in other countries in south Asia and in sub-Saharan Africa, where 76.2% of all fetal deaths occur.[9] In these countries, access to antenatal care and skilled birth attendance is limited, and the caesarean section rate is low, particularly in rural areas.[1]

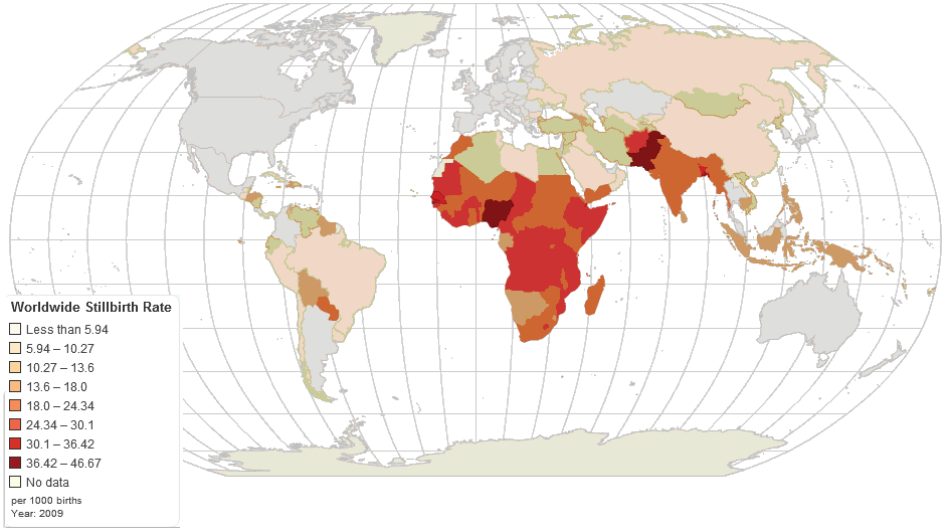


Figure 1. Global fetal death rates (referred to as stillbirth rate in the figure) per 1000 births at 28 weeks of gestation or above, or with birthweight of 1000 grams or above, in 2009. Adapted from: www.chartsbin.com.

According to the Medical Birth Registry of Norway, the fetal death rate in Norway in 2009 was 2.2 per 1000 births at 28 weeks of gestation or above.[10] Thus, Norway has one of the lowest fetal death rates in the world. Since 1967, the fetal death rate at 22 weeks of gestation or above has declined by almost 70% (Figure 2).[11] This reduction may be explained by improved diagnostic tools to determine fetal well-being, such as ultrasonographic examinations and the introduction of cardiotocography (CTG).

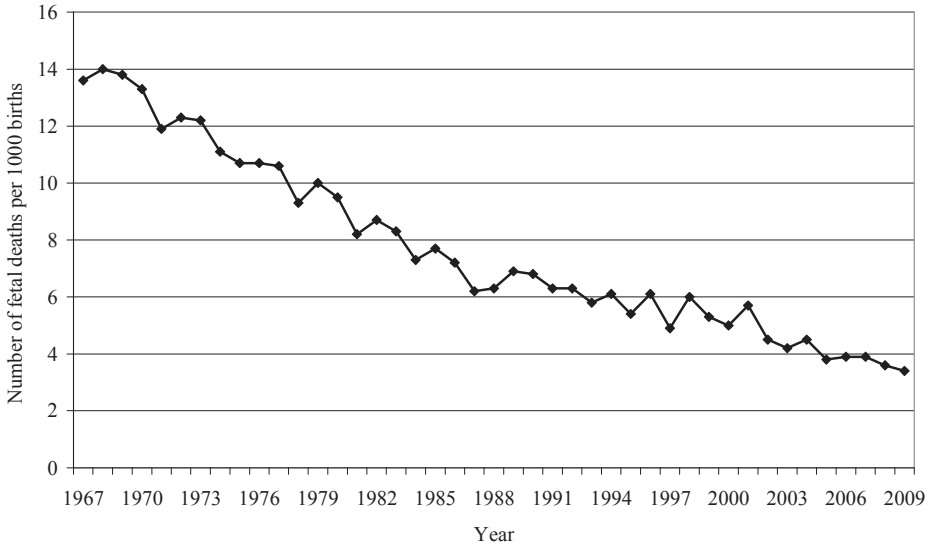


Figure 2. Changes in fetal death rates at 22 weeks of gestation or above in Norway during the period 1967-2009.
Source: Medical Birth Registry of Norway, www.mfr.no.

1.1.3 Classification systems

The classification of fetal death is a crucial step towards the goal of reducing its occurrence, but classification is also important in research to address knowledge gaps and to enable regional and international comparisons.[12] The use of suboptimal classification systems leads to a high proportion of unclassifiable, and thereby unexplained fetal deaths, which are often interpreted as unavoidable.[12] There is a wide variety of classification systems for fetal death in the literature, which reflect differences in criteria and in available information over time and between countries.[13] Fetal death may be classified by length of gestation at birth, where death before 28 weeks of gestation is defined as early fetal death and death at 28 weeks of gestation or above is defined as late fetal death.[14] Fetal death can also be classified according to the onset of labour, where antepartum fetal deaths occur before the onset of labour, and intrapartum fetal deaths occur after the onset of labour, but before the completion of delivery.[14] Finally, fetal deaths may be classified according to cause of death. Numerous attempts have been made to classify the causes of fetal death, but no classification system has been universally accepted.[15] One reason for the lack of a

cause-specific classification system may be that the causes of fetal death remain largely unknown.

1.1.4 Aetiology

It is difficult to differentiate between the causes of, and the risk factors for fetal death. The cause, or aetiology, of fetal death is the direct reason why death occurs, while the risk factors increase the chance of fetal demise. However, different maternal medical disorders, such as diabetes, chronic hypertension and preeclampsia, have been suggested as direct causes of fetal death by some authors,[16] but are considered risk factors by others.[17] Whether some factors, such as maternal medical disorders, will lead to fetal death may depend on the availability of antenatal and obstetric care. For instance, in many developing countries, preeclampsia is a leading cause of fetal death.[16] In Norway, preeclampsia is no longer associated with an increased risk of fetal death, probably because of timely intervention in preeclamptic pregnancies.[18] Several studies have been performed with the aim to understand the causes of fetal death,[19] but often the cause could not be explained by placental, fetal, or maternal factors. Of all fetal deaths in Norway, a large proportion has no identified cause.[20] In the following, some of the factors that have been suggested to be direct causes of fetal death are presented.

1.1.4.1 Placental causes of fetal death (25-35%)[21]

Uteroplacental insufficiency. Low uteroplacental blood flow can cause acute hypoxia, or if long-standing, chronic hypoxaemia with intrauterine growth restriction and eventually cessation of circulation and thereby fetal death.[22] A further description of uteroplacental insufficiency as a possible cause of fetal death is presented below (1.3.3).

Umbilical cord complications. Umbilical cord complications occur occasionally and may be life-threatening to the fetus. For instance, umbilical cord prolapse can compromise the blood flow through the umbilical vessels and thereby cause fetal death. Cord occlusion and cord abnormalities, such as vasa praevia, are other umbilical cord complications that may result in fetal death.[23]

Placental abruption. The separation of the placenta from the decidua may lead to

intrauterine growth restriction or preterm delivery in mild cases of abruption. However, in massive abruptions, the risk of fetal death due to haemorrhage and hypoxia is high.[24] Although the prevalence of placental abruption is low (about 1% of all pregnancies), it contributes to a substantial proportion of all fetal deaths.[25]

Placenta praevia. Placenta praevia refers to the presence of placental tissue proximate to, or extending over, the internal cervical os.[26] Severe bleedings from a placenta praevia may cause fetal death due to haemorrhage and hypoxia. However placenta praevia has been an uncommon cause of fetal death in the Western world since the introduction of ultrasonographic examinations in pregnancy.[27] This may be attributed to early detection, increased monitoring during pregnancy and performance of caesarean section in cases with placenta praevia.

Feto-maternal haemorrhage. Feto-maternal haemorrhage, which may occur spontaneously or due to traumatic injuries to the placental interface, is defined as the loss of fetal blood cells into the maternal circulation.[28] It may lead to cardiovascular decompensation, stroke, disseminated intravascular coagulation and death due to hypoxia.[29] An acute loss of one-fifth of the fetoplacental blood volume, which represents 50 ml or above at term, is generally considered lethal.[28]

1.1.4.2 Fetal causes of fetal death (25-40%)[21]

Chromosomal abnormalities. Chromosomal abnormalities of fetal karyotype, such as trisomies, monosomy X and chromosome rearrangements, generally cause miscarriage in the first trimester, but are also associated with 5-10% of fetal deaths.[30]

Congenital anomalies. Congenital anomalies unrelated to chromosomal abnormalities are a major cause of miscarriage. Some anomalies are incompatible with *in utero* survival. In Europe, 2% of pregnancies with congenital anomalies result in fetal death.[31] The global rates of fetal death caused by congenital anomalies vary, and depend on maternal nutrition, environmental exposures, availability of prenatal diagnostic tools and access to induced abortion at the woman's request.[32]

Infections. Infections may cause fetal death through different pathways.[33,34] Severe

maternal infections can result in fetal death without the infectious agent ever being transmitted to the placenta or the fetus. In these cases, fetal death may occur as a consequence of maternal respiratory distress, high maternal fever, or other systemic reactions to the infection.[34] Placental infections can result in placental damage, and thus reduced blood flow from the placenta to the fetus, without transmitting the infectious agent to the fetus. Malaria (*Plasmodium falciparum*) is an example of an infectious disease that causes placental damage.[34] Direct infection of the fetus through the placenta or infected membranes (chorioamnionitis) can also cause fetal death through the destruction of fetal vital organs.[34] The infectious agent may be spread haematogenously, as is the case for the rubella virus, or may ascend from the vagina into the uterus, as in group B streptococcal chorioamnionitis.[34] Fetal death due to infection is more frequent in developing countries and is more likely to occur in the second than the third trimester.[27,33,34]

1.1.4.3 Maternal causes of fetal death (5-10%)[21]

Uterine rupture. Although uterine rupture is rare, it can have catastrophic consequences for mother and fetus.[35] Fetal death occurs in these cases as a result of haemorrhage and hypoxia.

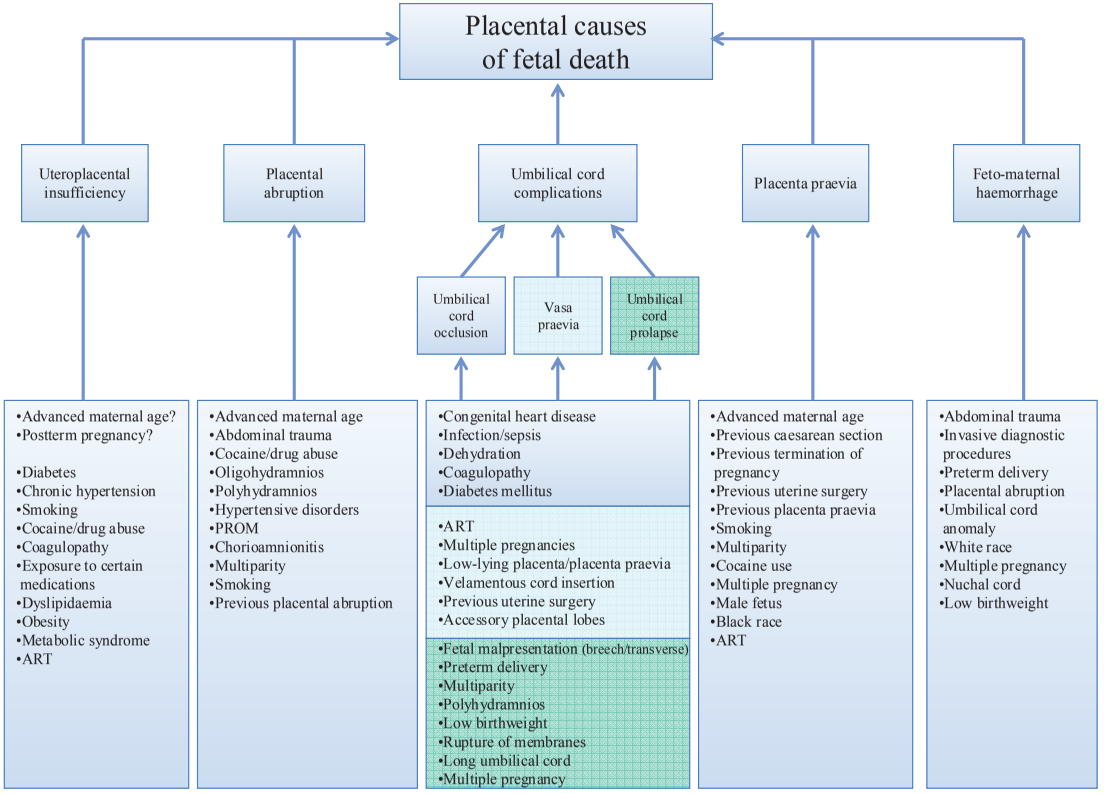
Delivery complications. Delivery complications such as shoulder dystocia, malpresentation of the fetus, or prolonged labour may cause intrapartum asphyxia, defined as an acute severe deficient supply of oxygen to the fetus. An umbilical artery pH-value below 7.00 and base deficit of 12 mmol/l or above,[36] influences the brain and vital tissues of the fetus. It can cause neonatal encephalopathy, neurological impairment, multiorgan failure, or fetal death.[37] Some of the fetal deaths caused by delivery complications with asphyxia could also be categorised as having fetal causes.

Rhesus isoimmunisation. Rhesus isoimmunisation causes fetal haemolysis and has become a very rare cause of fetal death in developed countries.[38] There are no reliable estimates of fetal deaths related to Rhesus isoimmunisation in developing countries, as many of them lack the necessary diagnostic capabilities.

Preterm delivery. Spontaneous uterine contractions occurring before the offspring is mature enough to survive *ex utero* may cause intrapartum fetal death or death shortly after

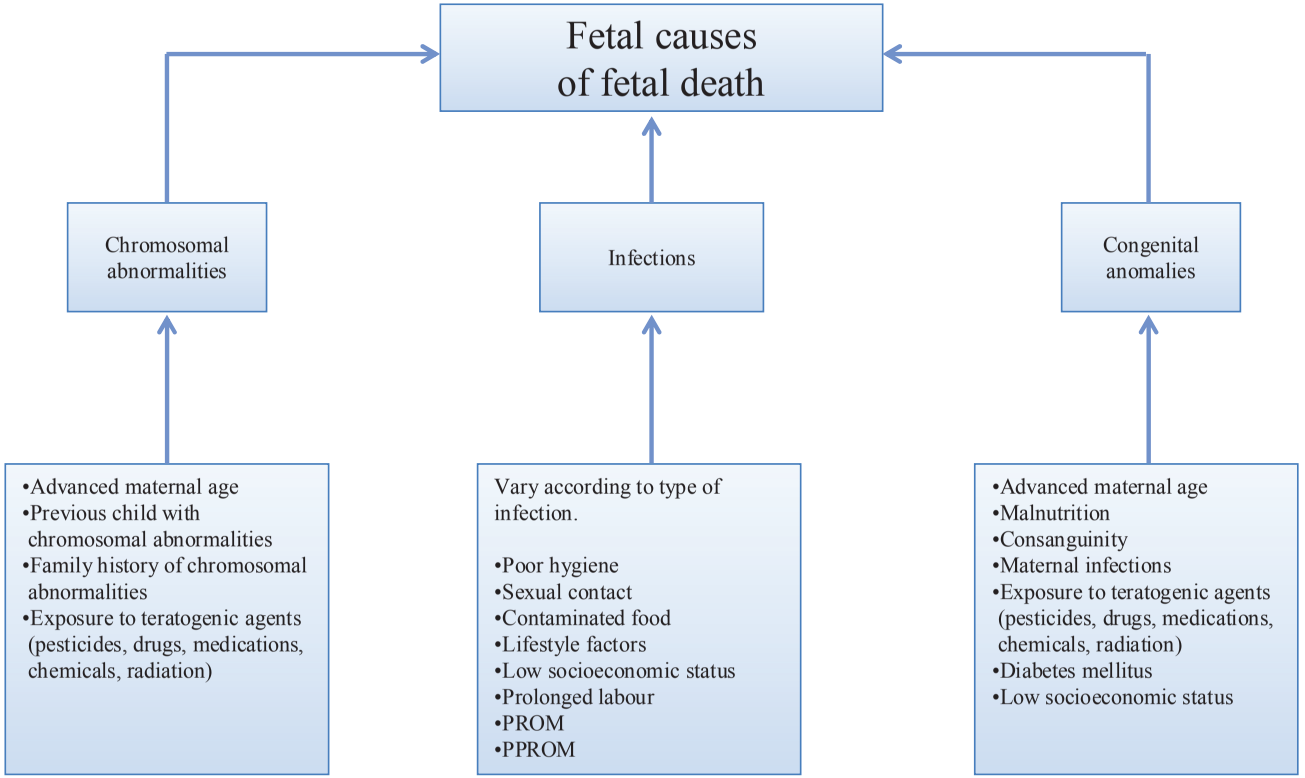
delivery.[39] However, guidelines for antenatal and postnatal care have changed with the increasing availability of diagnostic and therapeutic facilities for immature infants, and thus the prognosis of survival has changed accordingly.[40]

The causes of fetal death vary between developing and developed countries. In the developing world a larger proportion of fetal deaths occur intrapartum,[41] and one of the main causes of fetal death is delivery complications with intrapartum asphyxia. Other frequently reported causes of fetal death in developing countries are congenital anomalies, infections and fetal deaths related to maternal hypertension.[42] Common causes of fetal death in the Western world are intrauterine growth restriction as a consequence of placental dysfunction, placental abruption and congenital anomalies. However, in developed countries, most fetal deaths are still unexplained.[42] Potential causes of fetal death and their associated risk factors are presented below (Figures 3-5).



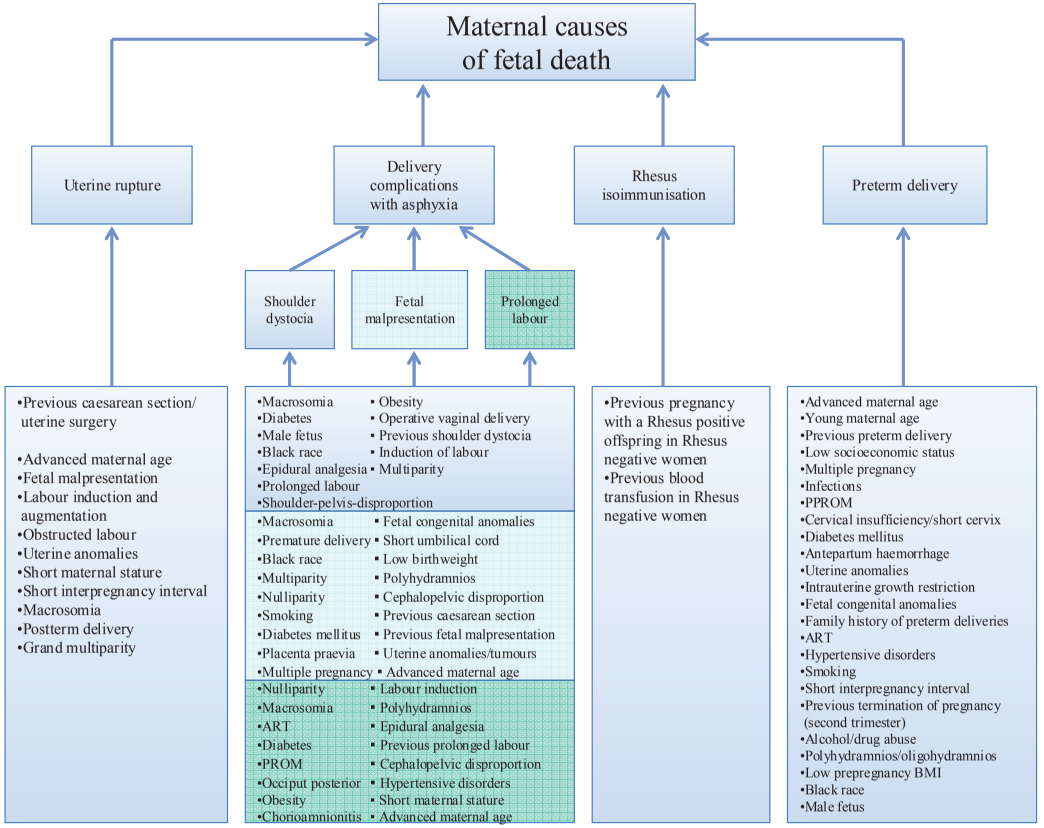
ART: Assisted reproductive technology
PROM: Premature rupture of membranes

Figure 3. Placental causes of fetal death and their associated risk factors.



PPROM: Preterm premature rupture of membranes

Figure 4. Fetal causes of fetal death and their associated risk factors.



BMI: Body mass index

Figure 5. Maternal causes of fetal death and their associated risk factors.

1.1.5 Risk factors

Identification of factors that increase the risk of fetal death may increase our understanding of the mechanisms and the causes of fetal death. In a review by Fretts et al, which included 113 studies performed in developed countries, several risk factors for fetal death were identified (Table 1).[19]

Table 1. The estimated associations of maternal risk factors with the risk of fetal death. Adapted from: Fretts RC. Etiology and prevention of stillbirth. *Am J Obstet Gynecol* 2005;193:1923-1925.

Condition	Prevalence (%)	Stillbirths per 1000 births	Odds ratio
All pregnancies		6.4	1.0
Low risk pregnancies	80	4.0-5.5	0.86
Nulliparity	40	7-8	1.2-3.0
Hypertensive disorder			
Chronic hypertension	6-10	6-25	1.5-2.7
Pregnancy induced hypertension			
Mild	5.8-7.7	9-51	1.2-4.0
Severe	1.3-3.3	12-29	1.8-4.4
Diabetes			
Treated with diet	2.5-5	6-10	1.2-2.2
Treated with insulin	2.4	6-35	1.7-7.0
Systemic lupus erythematosus	<1	40-150	6-20
Renal disease	<1	15-200	2.2-30
Thyroid disorders	0.2-2	12-20	2.2-3.0
Thrombophilia	1-5	18-40	2.8-5.0
Cholestasis of pregnancy	<0.1	12-30	1.9-4.4
Smoking > 10 cigarettes	10-20	10-15	1.7-3.0
Obesity (prepregnancy)			
BMI 25-29.9 kg/m^2	21	12-15	1.9-2.7
BMI >30 kg/m^2	20	13-18	2.1-2.8
Low educational attainment	30	10-13	1.6-2.0
Previous growth restricted infant	6.7	12-30	2-4.6
Previous caesarean section	24-28	6-13	1.0-2.0
Previous stillbirth	0.5-1.0	9-20	1.4-3.2
Multiple gestation	2-3.5		
Twins	2.7	12	1.0-2.8
Triplets	0.14	34	2.8-3.7
Advanced maternal age (ref <35)			
35-39	15-18	11-14	1.8-2.2
40+	2	11-21	1.8-3.3
Black compared to white	15	12-14	2.0-2.2

In addition to the risk factors presented in the table above, other factors have also been suggested to be associated with fetal death:

Preeclampsia. Hypertensive disorders in pregnancy often include chronic hypertension, pregnancy induced hypertension and preeclampsia.[43] However, preeclampsia was not listed as a hypertensive disorder in Table 1. Preeclampsia increases the risk of placental

abruption, preterm delivery, intrauterine growth restriction, and may also be directly associated with fetal death.[16] The relative risk (RR) for fetal death in pregnancies with preeclampsia has decreased in Norway in recent time: RR 1.17 (95% confidence interval (CI) 1.04-1.33) compared to normotensive pregnancies.[43]

Multiparity. Parity has a U-shaped association with fetal death, as the risk of fetal death is increased in both nulliparous and multiparous women. However, the reporting of fetal death risk in multiparous women is not consistent.[44,45] In women with more than four previous births, the risk of fetal death has been suggested to increase consistently with ascending parity: odds ratio (OR) 1.05 (95% CI 1.02-1.05) in women with 5-9 previous live births compared to women with 1-4 previous live births. The corresponding OR in women with 10-14 previous live births is 1.97 (95% CI 1.81-2.15).[46]

Marital status. Women who are neither married nor cohabiting have been suggested to have a higher risk of fetal death: OR 1.9 (95% CI 1.4-2.6) compared to married or cohabiting women.[47]

Advanced paternal age. Advanced paternal age has, independent of maternal age, been suggested to increase the risk of fetal death, and the risk seems to increase when paternal age exceeds 45 years.[48] The risk of fetal death is particularly high when an older father is paired with a woman aged 30 years or older.[49] However, the increased risk of fetal death in older compared to younger fathers is small.

Caffeine consumption. Excessive coffee consumption (≥8 cups of coffee/day) during pregnancy has been suggested to increase the risk of fetal death: OR 3.0 (95% CI 1.5-5.9) compared to women who did not drink coffee during pregnancy.[50]

Low socioeconomic status. Unskilled workers performing manual labour (blue-collar workers) have been suggested to have an increased risk of fetal death: OR 2.2 (95% CI 1.3-3.7) compared to workers in high-level professional, managerial, or administrative positions (white-collar workers).[51]

ART. Pregnancies conceived by ART have an increased risk of fetal death: OR 2.55 (95% CI 1.78-3.64) compared to spontaneously conceived pregnancies.[52]

Length of gestation. The causes of fetal death may differ by length of gestation.[15,27] For instance, infectious causes of fetal death are probably more important in the second trimester,[27,33] while uteroplacental insufficiency plays a greater role in fetal deaths at term.[53] Fetal death rates have also been shown to vary according to length of gestation, described as moderate at 20-22 weeks of gestation and lowest at 27-33 weeks, whereas the highest rates have been seen in term, and particularly in postterm pregnancies.[54,55] In a Swedish study with data from 1987-1992, a significantly increased OR for fetal death was reported among offspring delivered at 41 weeks of gestation or above: OR 1.48 (95% CI 1.13-1.95), 1.77 (95% CI 1.22-2.56) and 2.90 (95% CI 1.27-6.61) at 41, 42 and 43 weeks of gestation, respectively, compared to gestational week 40.[56] The increased risk of fetal death in postterm pregnancies has mainly been attributed to uteroplacental insufficiency and umbilical cord compression due to oligohydramnios.[56] Increased knowledge about gestational age-specific risk factors for fetal death is needed in order to understand the mechanisms of, and to prevent fetal death.

Advanced maternal age. Older mothers have a higher prevalence of hypertension and diabetes, as well as several other factors related to fetal death, such as multiple pregnancy (referred to as multiple gestation in Table I), premature delivery, chromosomal abnormalities and different placental complications.[57-59] However, despite the higher prevalence of these factors among older mothers, large studies have suggested that advanced maternal age is an independent risk factor for fetal death. In the review by Fretts et al, the OR for fetal death in women aged 40 years or older was estimated to be 1.8-3.3, compared to women younger than 35 years (Table 1).[19] In another systematic review, including 31 cohort or case-control studies, older mothers, mainly defined as mothers aged 35 years or older, had a RR for fetal death of 1.20-4.53.[60] The mechanisms behind this increased risk are largely unknown.

In this thesis, we aimed to study the risk factors for, and the mechanisms behind the increased risk of fetal death in women with high age at childbirth.

1.2 Fetal death: high maternal age at childbirth

1.2.1 Maternal age at childbirth: changing trends and consequences for pregnancy outcome

It has become increasingly common to postpone childbirth until late in reproductive life. Thus, in the Western world, maternal age at delivery is increasing.[61-63] In particular, the age of first-time mothers has increased. In some European countries, such as Italy and Greece, mean maternal age at first delivery has exceeded 30 years.[64] The corresponding ages in 1980 were 25.1 and 23.3 years, respectively (Figure 6).[64]

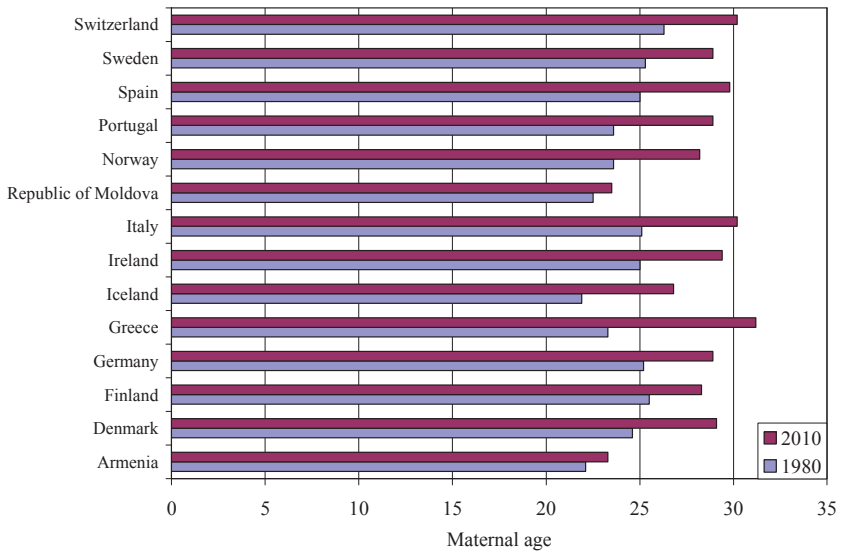


Figure 6. Maternal age at first delivery by country in 1980 and 2010.
Adapted from the Statistical Database of United Nations Economic Commission of Europe: www.unece.org.

Hence, second and higher-order deliveries are also being postponed. In 2011 in Europe, Liechtenstein and Ireland had the highest mean maternal age at delivery, irrespective of parity, at 31.5 years (Figure 7).[65]

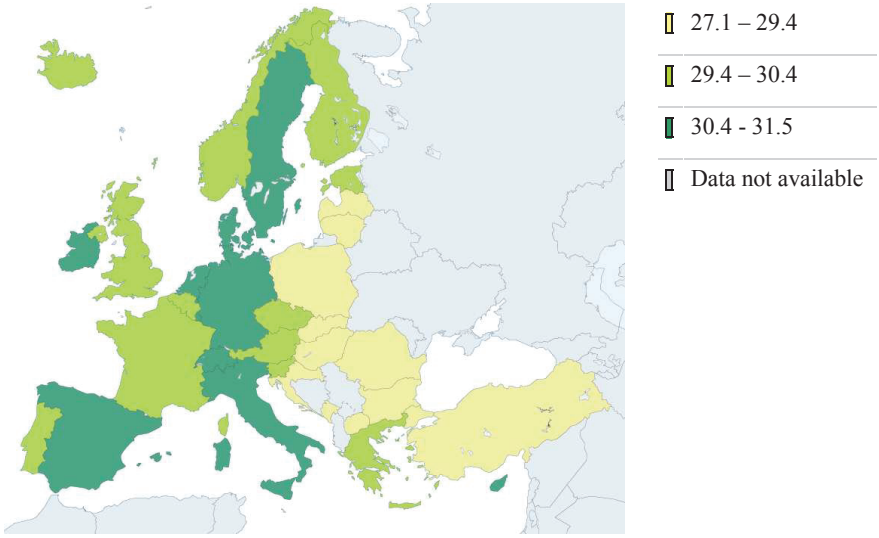


Figure 7. Mean maternal age at delivery in Europe in 2011.
Exceptions Italy, Montenegro, Malta, Croatia, the United Kingdom, France and Turkey (data from 2010), and Belgium (data from 2009).
Adapted from Eurostat: http://epp.eurostat.ec.europa.eu.

In Norway, mean maternal age at first delivery was 27.7 years, whereas mean maternal age among all women, irrespective of parity, was 29.8 years in 2011 (Figure 8).[10] A total of 19.7% of the women were 35 years old or older at delivery.[10] This is a considerable increase from 20 years earlier, when only 9.8% of women were 35 years old or older at delivery.[10] The corresponding figures for women aged 40 years or older were 3.4% in 2011 and 1.3% in 1991 (Figure 9). The distribution of maternal age at delivery changed during the period 1967-2006 (Figure 10). The main change has been in the proportion of childbearing women aged 25 years or younger.

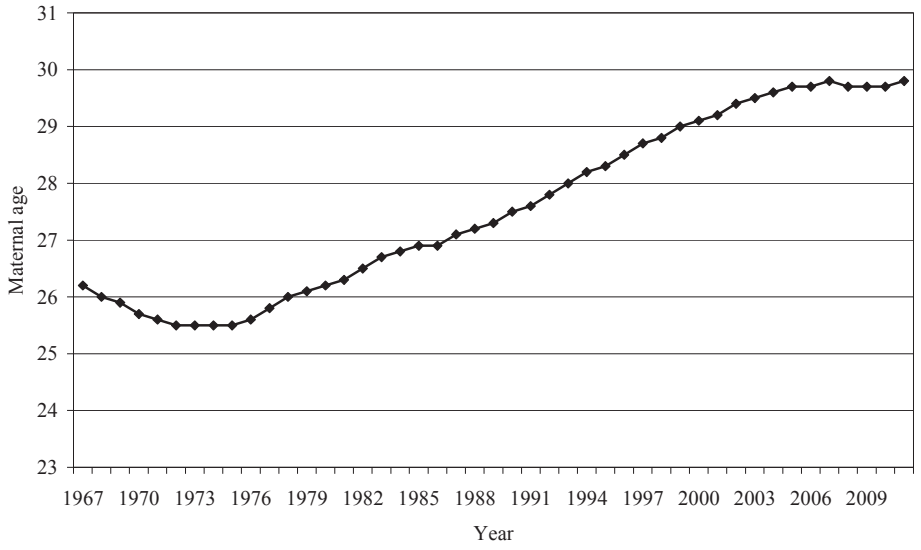


Figure 8. Mean maternal age at delivery in Norway during the period 1967-2011.
Source: Medical Birth Registry of Norway, www.mfr.no.

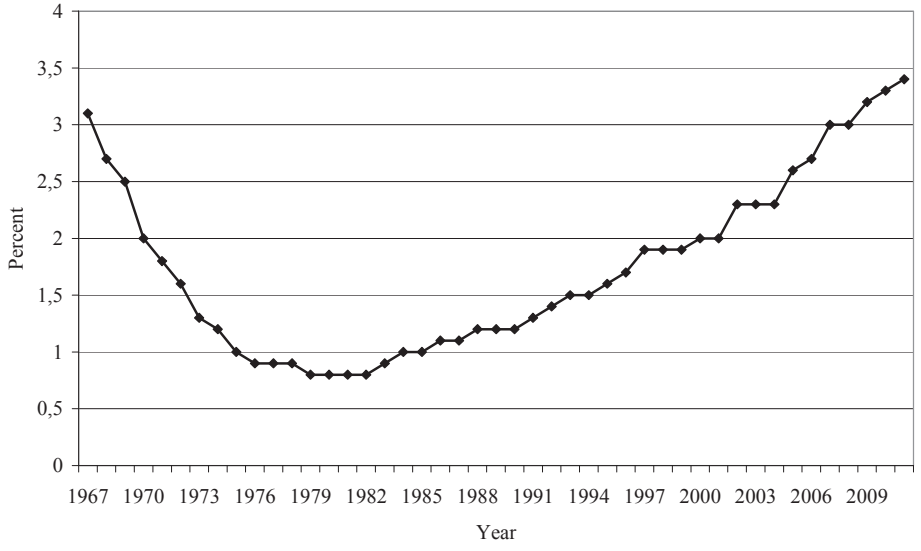


Figure 9. Percentage of women aged 40 years or older at delivery during the period 1967-2011.
Source: Medical Birth Registry of Norway, www.mfr.no.

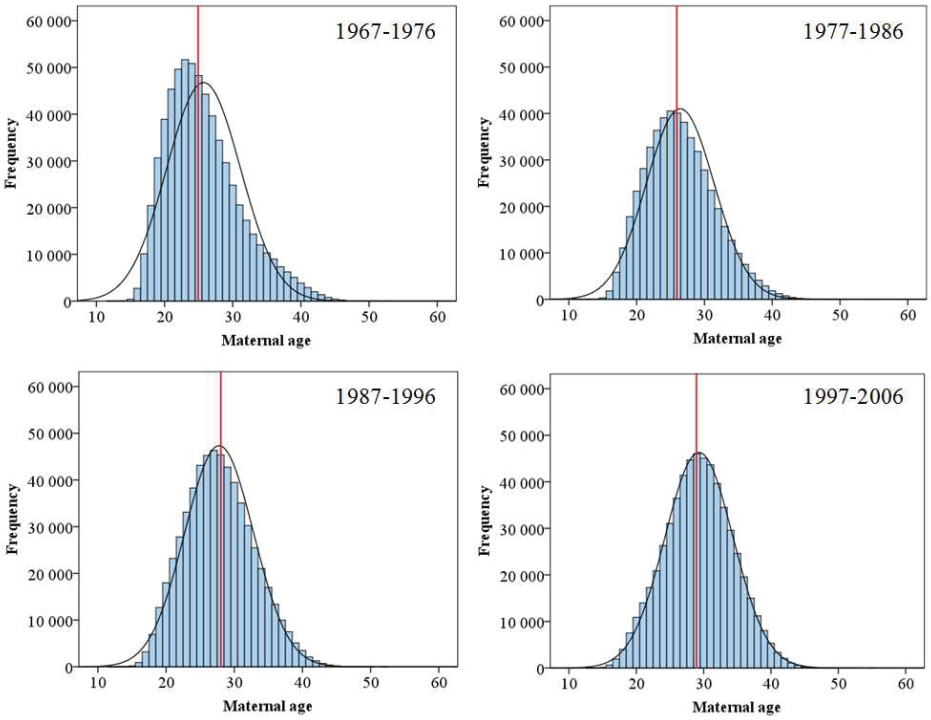


Figure 10. Distribution of maternal age according to period of delivery. The median is marked in red.

Source: Medical Birth Registry of Norway, www.mfr.no.

1.2.1.1 Possible reasons for postponement of childbirth

The reasons for delaying childbirth may vary.[66] Some women pursue education and career, some wish to explore other aspects of life before becoming a mother, and for others economic matters are of importance. In Norway, only women with paid work are eligible for paid maternity leave and receive the maximum welfare benefits linked to childbirth.[67] Women without paid work receive only limited economic support at childbirth.

Norwegian women are also postponing marriage. According to Statistics Norway, the mean age at first marriage was 31.1 years among women in 2011.[68] The corresponding figure for the period 1966-1970 was 22.8 years.[69] However, it is not certain that the increased age at first marriage is directly related to higher maternal age at delivery, as an increasing number of children are born out of wedlock.

The divorce rates in Norway are also increasing: 3.3 per 1000 marriages were dissolved each year during the period 1966-1970,[70] and 11.5 per 1000 of all marriages ended in divorce in 2011.[71] After a divorce, many women may get pregnant with a new partner, and thus at an older age.

Contraception has provided women with the opportunity to make reproductive choices, and the methods of preventing pregnancy have improved. A wide range of effective contraceptives with few side-effects are available, and the use of contraceptives in Norway is high. This is reflected in high sales figures, particularly for hormonal contraceptives and intrauterine devices.[72] Recently, access to contraceptives has also improved. Hormonal contraceptives are free of charge for females aged 16-19 years in Norway, and an expansion of this system to women aged 20-24 years is being discussed.[73] Reliable methods and improved access to contraceptives, but also induced abortions at the woman's request have made unwanted pregnancies and births preventable and family planning easier. However, the induced abortion rates have been relatively stable among young women since the legalisation of abortion in Norway in 1979, and therefore its influence on the postponement of childbirth is probably limited.[74]

1.2.1.2 The consequences of postponing childbirth

There may be positive effects of becoming a mother at an older age: better economical solvency, a secure job situation, and possibly a more stable relationship between the mother and the father. There may also be psychological benefits of being an older mother. In addition, increasing maternal age has been associated with improved health and development of children up to five years of age.[75]

However, there are negative consequences of high maternal age at reproduction which cannot be ignored. The age at which the mother is defined as old, and thus at a greater risk of pregnancy complications, is difficult to assess. There is no universal definition of advanced maternal age, since the effects of increasing age on pregnancy seem to occur gradually rather than occurring as a threshold effect.

First and foremost, it may be more difficult to become pregnant at an older age. At a certain age reproduction is no longer biologically possible for women. Studies have shown

that in populations where the use of contraceptives is prohibited, seven out of eight women ceases to reproduce and are presumably also unable to reproduce by the age of 45.[76] For a long time the assumption has been that a woman's reproductive life begins at menarche and ends at menopause. However, studies in sexually active women who do not use contraceptives have reported that a woman's last birth occurs on average 10 years before menopause.[77]

Infertility has been shown to be a major problem among older women, and nearly 50% of all infertility treatment is administered to women aged 35 years or older. In Norway, more than 2000 children are born as a result of ART every year, and many of them are born to women in this age group. However, in many women, the ART treatment is not successful. During the period 2009-2010, a total of 2980 women aged 35 years or older received ART treatment. Only 530 of these women gave birth to an infant.[78] The higher prevalence of infertility among older women is probably caused by the decreased number and reduced quality of oocytes.[79] Uterine factors, such as decreased receptivity of the endometrium with age, have also been suggested.[80] If conception is successful in older women, the risk of miscarriage is increased, maybe as a consequence of abnormalities that occur in the oocytes with age.[81]

During pregnancy, the risk of developing diseases such as preeclampsia, pregnancy induced hypertension, and gestational diabetes is higher among older women.[82] There is also a higher risk of placental disorders such as placental abruption and placenta praevia.[83] Older women have a higher risk of uterine rupture,[84] preterm birth[85] and of giving birth to an infant that is small for gestational age.[86] It has also been suggested that older women have a higher risk for breech delivery[87] and for prolonged labour.[88] The increased risk of fetal[60] and also perinatal death[89] in older mothers is well-known. In some studies, anal sphincter tears have been associated with maternal age,[90] and caesarean section rates among older women are high.[82,91] Congenital anomalies[92] and chromosomal abnormalities, such as Down syndrome and trisomy 13 and 18, occur more frequently among older mothers.[93,94] The prevalence of Down syndrome increases from approximately 0.6 per 1000 births among women aged 20 years, to 10 per 1000 births in women 40 years of age.[95]

After delivery, older women are at increased risk of postpartum haemorrhage,[96] and they also have an increased risk of long-term pelvic floor disorders like urinary incontinence

and pelvic organ prolapse.[97] In addition, advanced maternal age at first delivery increases the risk of developing breast cancer later in life.[98]

Many of the complications associated with high maternal age are caused by age-related diseases such as leiomyomas, type-II diabetes mellitus, chronic hypertension and multiparity.[59] Older women also have a higher cumulative risk of being treated by cervical conisation for cervical intraepithelial neoplasia (CIN) which increases the risk of preterm birth.[99] The reasons behind the higher risk of pregnancy complications among older women without age-related diseases are largely unknown.

1.2.2 Maternal age and gestational age-specific fetal death

Low uteroplacental perfusion due to poor uterine vasculature, and related difficulties in adapting to the increased haemodynamic demands of pregnancy, has been suggested as a possible explanation for the increased risk of fetal death in older women.[89] As pregnancy progresses, the fetus has an increasing demand for oxygen and nutrition.[100] If low uteroplacental perfusion, and thus reduced placental function, is an important cause of fetal death in older women, it is conceivable that the risk of fetal death increases by increasing length of gestation, thereby leaving older women at a particularly high risk of fetal death in term and postterm pregnancies. However, this has not been thoroughly studied and needs to be explored.

1.3 Fetal death: the placenta

1.3.1 Placental function

The placenta is essential in supplying the fetus with oxygen and nutrition.[101] It removes toxic waste and carbon dioxide from fetal blood before returning it to the maternal circulation. The placenta also has an endocrine function, producing hormones such as progesterone, oestrogen, human chorionic gonadotropin (hCG), human placental lactogen (hPL), and human chorionic thyreotropin (hCT). In addition, the placenta functions as an immunological barrier between the mother and the fetus. Hence, a well-functioning placenta is required for optimal fetal growth and development.

1.3.2 Placental development

To gain a better understanding of placental function, knowledge of placental development is a necessity. Within four days after fertilisation, the embryo has differentiated into two cell types: embryoblast, which develops into the fetus, and trophoblast, which develops into the placenta and external membranes.[101,102] The trophoblast represents the outer layer of the blastocyst, and differentiates into the underlying cytotrophoblast and the overlying syncytiotrophoblast.

The implantation of the blastocyst into the endometrium normally begins seven days after fertilisation.[101,102] At the implantation site, the maternal endometrium changes and forms the *decidua basalis* (the maternal placenta). After the implantation of the blastocyst, intercommunicating spaces (lacunes) appear within the syncytiotrophoblast layer, and these are filled with maternal blood. Implantation is an important step in placental development and is probably also essential for subsequent placental function.

The cytotrophoblast and the syncytiotrophoblast form, together with amnion and extraembryonic mesenchyma, the chorionic plate.[101,102] Chorionic villi emerge from the chorionic plate and are filled with embryonic blood. The lacunes expand and form intervillous spaces. In the beginning, the *chorion villosum* surrounds the whole embryo. Then, the chorionic villi farthest away from the maternal blood supply degenerate and form the *chorion laeve*, whereas the chorionic villi closest to the maternal blood supply expand to form the *chorion frondosum* (the fetal placenta). Spiral arteries transport maternal blood from the *decidua basalis* into the intervillous space, where oxygen and nutrition are transferred into the villous tree and thereby to the fetal circulation through diffusion, pinocytosis, or by active transport.

The vein in the umbilical cord (*V. umbilicalis*) transports oxygenated blood from the placenta to the fetus, and two arteries (*Aa. umbilicales*) lead the deoxygenated and nutrient-poor blood back from the fetus to the placenta (Figure 11).[101,102]

Development and growth of the placental villous structure are regulated by growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), placental growth factor (PLGF) and angiopoietins.[103] Successful implantation and

placentation require coordinated, finely regulated vascular development.[104] hCG has a role in modulating the endometrial production of cytokines and growth factors, and has therefore been suggested to be the conductor of placental development.[104]

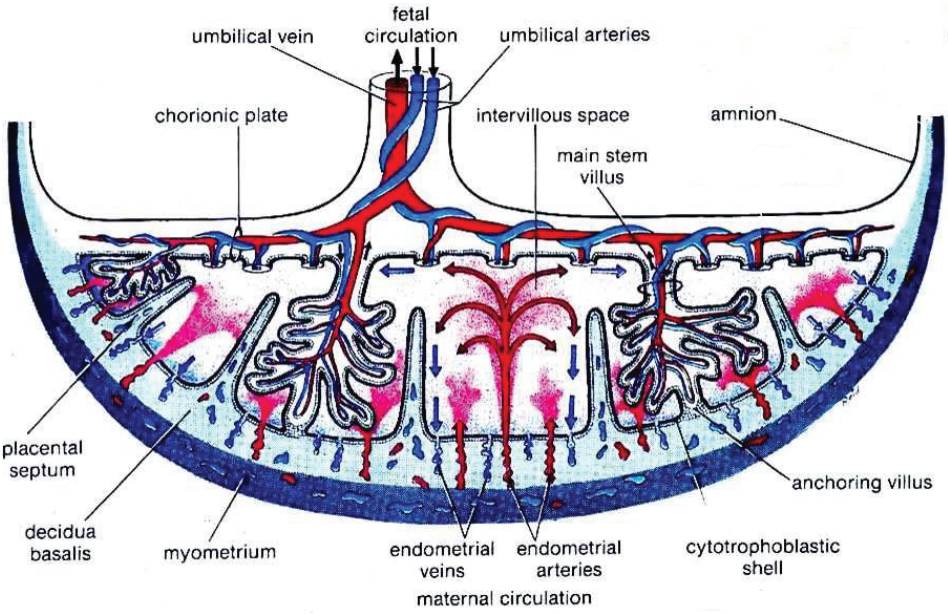


Figure 11. The placental blood circulation.
Adapted and processed from: www.studyblue.com/notes/note/n/gallicano/deck/1056160.

1.3.3 Uteroplacental insufficiency and fetal death

Uteroplacental insufficiency is a failure in the exchange of gases and nutrients between the mother and the fetus, and is divided into acute and chronic insufficiency.[101] Acute uteroplacental insufficiency is revealed in minutes or hours. It is caused by a sudden reduction in blood flow, for instance due to a severe placental infarction.[30] If the acute situation is not resolved, fetal death by hypoxia may occur.

Chronic uteroplacental insufficiency may be caused by maternal conditions, such as diabetes, chronic hypertension, thrombophilia, severe anaemia, multiparity, short interpregnancy interval, smoking, or drug abuse.[101] Chronic uteroplacental insufficiency

may lead to oligohydramnios, intrauterine growth restriction, and eventually fetal death.[101]

Uteroplacental insufficiency in general increases the risk of caesarean section and preterm delivery. Reduced fetal oxygenation is also a risk factor for the development of cerebral palsy and learning disabilities.[105]

1.3.4 Indicators of placental function

Placental function may be assessed in antenatal care by ultrasonographic examination, and Doppler assessment of the placental circulation plays an important role in screening for impaired placentation.[106] An increased uterine artery pulsatility index (PI), or the presence of early diastolic notching are parameters being used for the identification of pregnancies with placental insufficiency particularly in the second trimester of pregnancy.[107,108] Ultrasonographic examination can also be used to detect placental and umbilical cord abnormalities, such as abnormal placental shapes, abnormal placental textures, marginal or velamentous umbilical cord insertions, or two-vessel cords.[108] In addition, ultrasonographic diagnosis of intrauterine growth restriction may be a strong indicator of placental insufficiency.[108]

In epidemiological studies, birthweight has been suggested as a proximate measure of the intrauterine environment, and placental weight is closely correlated with birthweight.[109] Placental weight and other gross placental measures, such as placental disc shape, distance from cord insertion to closest placental margin, large or small diameter of the placenta, placental disc thickness and umbilical cord length, have been reported to be indicators of placental function.[109-111] Placental weight is a summary of gross placental measures and one of the most important predictors of birthweight, and thus placental function.[109,110]

It has been suggested that small placental size, rather than the alteration of nutrient metabolism or placental transfer capacity, is the major limitation of fetal growth.[112] Upon histological examination, a small placenta may show increased intervillous volume, decreased villous parenchymal volume, smaller terminal villi and sparser villous numbers.[110] The low amount of functional tissue generally results in a small area for exchange of oxygen and nutrition between mother and fetus. Thus, small placentas are assumed to be dysfunctional.[110,111]

Placental weight in relation to birthweight (placental weight/birthweight ratio) decreases throughout pregnancy.[113] It is conceivable that the metabolism of glucose and oxygen in the placenta is higher in mid-pregnancy than at term, and that nutrient and glucose transport from the placenta to the fetus increases according to length of gestation to allow for fetal growth.[114] The placental weight/birthweight ratio has also been suggested as a marker of placental function and has been used as a proximate measure of placental nutrient transport efficiency.[115,116] If the placenta is small relative to birthweight, it may be classified as dysfunctional. However, it has also been suggested that small placentas relative to birthweight are more efficient, because of the grams of fetus produced per gram of placenta.[116] The function of a placenta that is large relative to offspring size is not known. In previous studies, high placental weight/birthweight ratios have been associated with an increased risk of adverse pregnancy outcomes,[117] admission of the infant to the neonatal intensive care unit (NICU),[117,118] Apgar score below 7 at five minutes after birth,[118,119] and long-term adverse health outcomes.[120,121]

Placental function is difficult to measure at a population level, but is likely to be associated with placental weight and placental weight/birthweight ratio. Knowledge of the association of placental weight and placental weight/birthweight ratio with fetal death is scarce and may be important in understanding the role of placental function in fetal death.

1.3.5 Maternal age and placental function

It is likely that placental dysfunction is an important cause of fetal death.[22] Advanced maternal age is associated with an increased risk of fetal death,[60] and with lower uteroplacental perfusion, which may be associated with reduced placental function and thereby a reduced supply of oxygen and nutrition to the fetus.[89] Based on these findings, it is conceivable that older women have a reduced placental function compared to younger women. Thus, placental weight and placental weight/birthweight ratio, as indicators of placental function, may vary with maternal age.

Knowledge of the association of placental weight and placental weight/birthweight ratio with maternal age could be an important piece in the puzzle when it comes to understanding the increased risk of fetal death in older women.

2 Background and objectives of the thesis

Maternal age at delivery is rising, and the total number of women at increased risk of fetal death is increasing accordingly.[61-63] In order to prevent fetal death, more knowledge about the associated risk factors is needed. In addition, studies of women at advanced age at childbirth may provide insight into the causes of fetal death in general.

It is well known that the risk of fetal death increases with maternal age.[60] It has also been shown that the risk of fetal death varies considerably according to length of gestation, and is particularly high in term and postterm pregnancies.[54,55] The relationship between adverse pregnancy outcome and maternal age is not sufficiently understood, and may vary by length of gestation. In particular, if the fetal demand for oxygen and nutrition increases with increasing length of gestation, and if a relative placental dysfunction is more common in older mothers, it is conceivable that the risk of fetal death in older mothers is particularly high in term and postterm pregnancies. We therefore studied whether the association of fetal death and maternal age differed by length of gestation. We also studied whether the gestational age-specific risk of fetal death by maternal age has changed during the period 1967-2006.

Placental function is essential for fetal growth and well-being, and placental dysfunction is most likely an important cause of fetal death.[22] Low placental weight is strongly associated with intrauterine growth restriction.[122] Intrauterine growth restriction is often presented in the third trimester, and is closely associated with fetal death.[45,123] To explore the role of the placenta in fetal death, we studied whether placental weight and placental weight relative to birthweight were associated with fetal death. We also studied whether the associations of placental weight and placental weight/birthweight ratio with fetal death differed between preterm and term pregnancies.

Impaired placental function is probably an important cause of fetal death,[22] and such impairment may be more common in older mothers. Placental weight and placental weight/birthweight ratio have been suggested as indicators of placental function.[109-111,115] It is therefore possible that placental weight and placental weight/birthweight ratio differ by maternal age. We hypothesised that the association of gestational age-specific fetal death

with maternal age could be mediated by impaired placental function, and studied whether maternal age was associated with placental weight and placental weight/birthweight ratio. A model of our hypothesis is presented in Figure 12.

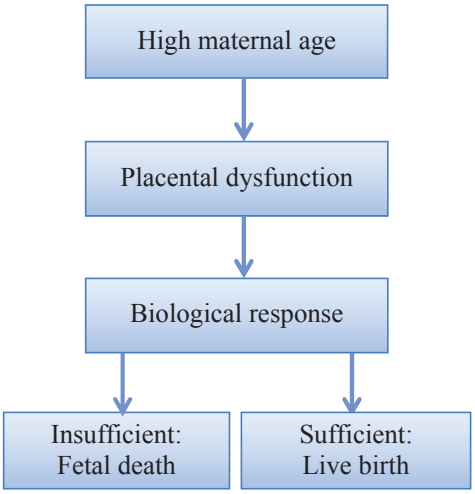


Figure 12. A model of our hypothesis.

3 Study objectives

- To study
    i) whether the risk of fetal death according to maternal age varies at different lengths of gestation (Paper I).
    ii) changes in the gestational age-specific risk of fetal death according to maternal age during the period 1967-2006 (Paper I).
- To study the association of placental weight, birthweight and placental weight/birthweight ratio with gestational-age specific fetal death (Paper II).
- To study the association of maternal age with placental weight, birthweight and placental weight/birthweight ratio (Paper III).

4 Materials and methods

4.1 The Medical Birth Registry of Norway

Data for Papers I-III were obtained from the Medical Birth Registry of Norway.[124] The Medical Birth Registry was established in 1967, in the wake of the thalidomide disaster in the early 1960s, for the surveillance of birth defects. The registry contains information on all births in Norway after 16 completed weeks of gestation since 1967, and after 12 completed weeks of gestation since December 1998. The notification to the Medical Birth Registry is compulsory and is made by the midwife or attending physician shortly after delivery. All records of live-born offspring are matched with those of the Central Person Registry to ensure medical notification of every live-born offspring in the country. The notification forms did not change from the establishment of the Medical Birth Registry until December 1998. However, in December 1998, a new form with pre-coded answer alternatives was introduced. In this form, additional information such as the date of term based on ultrasonographic examination, placental weight and smoking habits are registered. The notification forms are attached in the appendix.

4.1.1 Paper I – Aim, design, study population, variables and statistical analyses

4.1.1.1 Aim

We studied whether the risk of fetal death according to maternal age varies at different lengths of gestation. We also studied changes in the gestational age-specific risk of fetal death according to maternal age during the period 1967-2006.

4.1.1.2 Design

We defined this study as a population-based retrospective cohort study.

4.1.1.3 Study population

Our study population included all women giving birth after 16 completed weeks of gestation

in Norway during the period 1967-2006 (n = 2 337 392). We excluded 28 595 pregnancies with a length of gestation above 43 weeks, since a proportion of these were miscoded, and this proportion could not be determined with certainty. Information on length of gestation was missing for 125 997 births, and of these remaining, an additional 44 births lacked information on potentially confounding factors. Hence, a total of 2 182 756 births were included in Paper I (Figure 13).

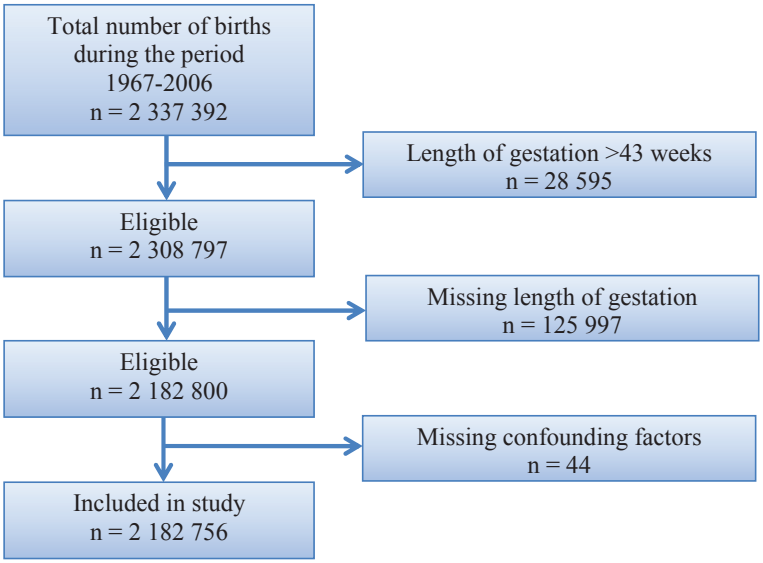


Figure 13. Study sample in Paper I.

4.1.1.4 Main outcome variables

Vital status at birth. Vital status at birth was categorised as fetal death: yes or no.

4.1.1.5 Main explanatory variable

Maternal age. Maternal age was defined as age in years at delivery. It was categorised as <20, 20-24, 25-29, 30-34, 35-39, 40-44, or ≥45 years.

4.1.1.6 Other study factors

Year of delivery. The risk of fetal death and also maternal age at the time of delivery has changed over time, and therefore we adjusted for year of delivery.[11] Year of delivery was categorised as 1967-1971, 1972-1976, 1977-1981, 1982-1986, 1987-1991, 1992-1996, 1997-2001, or 2002-2006.

Parity. Parity is positively associated with maternal age[55] and has also shown a U-shaped association with fetal death.[19,44,45] Parity was defined as previous births after 16 completed weeks of gestation, and was categorised as 0, 1, 2, 3, or ≥4 births.

Plurality. Plurality (multiple pregnancy) increases the risk of fetal death,[19] and is more frequent in older than in younger women.[125,126] It was defined as the number of fetuses *in utero*, and was categorised as 1 or ≥2 offspring.

Paternal age. Advanced paternal age is associated with an increased risk of fetal death,[48,49] and is also correlated with maternal age. It was defined as paternal age in years at delivery, and was categorised as <30, 30-39, ≥40 years, or missing.

Preeclampsia. Preeclampsia is associated with a higher risk of fetal death.[16] Although preeclampsia is generally described as a disease that occurs during a first pregnancy,[16] it also seems to occur more often in older mothers.[82,127,128] Preeclampsia was defined as blood pressure ≥140/90 mmHg and proteinuria with dipstick ≥1 after 20 weeks of gestation, and was categorised as preeclampsia: yes or no.

An overview of the variables used in Papers I-III is presented in Table 2.

Table 2. Variables used in Papers I-III.

	Paper I	Paper II	Paper III
Main outcome variables	Vital status at birth	Vital status at birth	Placental weight Birthweight Placental weight/ birthweigt ratio
Main explanatory variables	Maternal age	Placental weight Birthweight Placental weight/ birthweigt ratio	Maternal age
Other study factors	Year of delivery Parity Plurality Paternal age Preeclampsia	Maternal age Preeclampsia Diabetes Smoking Parity ART	Birthweight* Parity Smoking Preeclampsia Diabetes

* In analyses with placental weight as the main outcome variable.

4.1.1.7 Statistical analyses

We calculated the absolute risk of fetal death for each gestational week after 16 completed weeks of gestation (number of fetal deaths per 100 ongoing pregnancies) according to maternal age, and used all women with a fetus still *in utero* at the length of gestation studied as the denominator. The numerator was women with fetal death at that same length of gestation. Additionally, Cox regression models were applied to estimate crude and adjusted RRs of fetal death according to maternal age. The analyses were performed separately for the following lengths of gestation: 16-22, 23-29, 30-36, and 37 weeks of gestation or above. Pregnancies lasting 38 weeks or longer were also subdivided into groups of two-week intervals: 38-39, 40-41 and 42-43 weeks of gestation. Time (days) to

fetal death was the main outcome variable in the Cox regression models. Births of live infants, or live fetuses still *in utero* at the end of the gestational length interval studied were treated as censored observations. Women aged 20-24 years were used as the reference group, as women in this age group were assumed to have the lowest risk of fetal death. We adjusted for potential confounding factors (Table 2). For term and postterm pregnancies, the association of fetal death with maternal age was estimated for two time periods: 1967-1986 and 1987-2006.

4.1.2 Paper II – Aim, design, study population, variables and statistical analyses

4.1.2.1 Aim

We studied the association of placental weight, birthweight and placental weight/birthweight ratio with gestational-age specific fetal death.

4.1.2.2 Design

This study was a population-based cross-sectional study.

4.1.2.3 Study population

Of all singleton deliveries during the period 1999-2008 (n = 567 176), we excluded 28 812 births with missing information on length of gestation, placental weight or birthweight. We excluded 2943 births with a recorded gestational length of less than 23 weeks or 43 weeks or above. Of the remaining births eligible for study, we excluded 529 births with outlying values of placental weight and birthweight. Thus, a total of 534 892 births were included in this study (Figure 14).

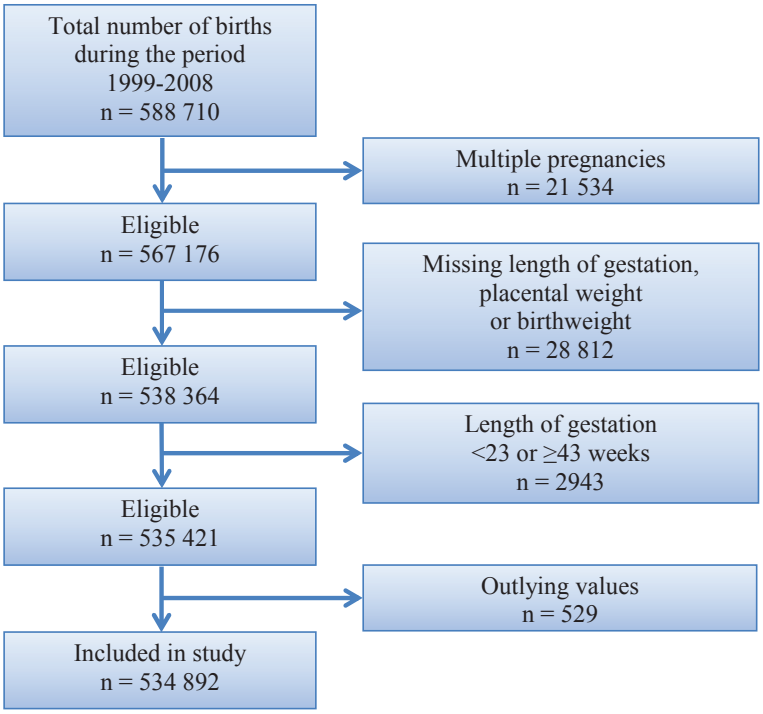


Figure 14. Study sample in Paper II.

4.1.2.4 Main outcome variable

Vital status at birth. Vital status at birth was categorised as fetal death: yes or no.

4.1.2.5 Main explanatory variables

Placental weight. Placental weight was reported in grams, and the placentas were measured fresh, with membranes and umbilical cord attached within one hour of delivery. Placental weights were divided into gestational age-specific quartiles (four equal groups if normally distributed). The lowest quartile represented the 25% smallest placentas and the highest quartile the 25% largest placentas.

Birthweight. Birthweight was reported in grams and divided into quartiles as described above.

Placental weight/birthweight ratio. Placental weight/birthweight ratios were created by dividing placental weight by birthweight in grams. A high placental weight/birthweight ratio represented a large placenta relative to birthweight. The placental weight/birthweight ratios were also divided into gestational age-specific quartiles.

4.1.2.6 Other study factors

Maternal age. Maternal age is associated with increased placental weight (Paper III) and also with an increased risk of fetal death.[19,60] Maternal age was therefore included as a confounder in this study, and was categorised as <20, 20-24, 25-29, 30-34, 35-39, 40-44, or ≥45 years.

Preeclampsia. Preeclampsia is associated with both small and large placentas.[122,129] An enlargement of the placenta has been reported to be present particularly in preeclamptic pregnancies with offspring large for gestational age.[129] Preeclampsia was defined as described for Paper I.

Diabetes. Diabetes is associated with increased placental weight, birthweight and placental weight/birthweight ratio.[130] Diabetes is also associated with a higher risk of fetal death.[131-133] Diabetes included type-I or type-II diabetes mellitus, gestational diabetes, or use of anti-diabetic medication during pregnancy.

Smoking. Smoking is associated with increased placental weight/birthweight ratio[134] and a higher risk of fetal death.[135] Information on smoking was registered at the first antenatal care visit and women who reported occasional or daily smoking were defined as smokers.

Parity. Parity is associated with increased birthweight and placental weight[109,136] and also with increased risk of fetal death as described above. Parity was categorised as 0 or ≥1 previous births after 16 completed weeks of gestation.

ART. ART pregnancies are associated with increased placental weight and placental weight/birthweight ratio.[137] However, offspring birthweight in pregnancies conceived by ART is lower compared to spontaneously conceived pregnancies.[137] ART pregnancies are associated with increased risk of fetal death.[52] ART was categorised as ART: yes or no.

4.1.2.7 Statistical analyses

We calculated the means of placental weight, birthweight and placental weight/birthweight ratio for each two-week interval of gestational length according to vital status at delivery. In term deliveries (≥37 weeks of gestation), we also calculated the mean placental weight/birthweight ratio in 500-gram categories of birthweight to study the consistency of our findings. Placental weight, birthweight and placental weight/birthweight ratio were divided into gestational age-specific quartiles, and the proportions of live births and fetal deaths in the lowest and the highest quartile were calculated for each two-week interval of gestational length. In a logistic regression model, the OR for fetal death according to placental weight/birth weight ratio in quartiles was estimated, and adjustments were made for factors associated with placental weight/birthweight ratio and fetal death. The second and the third quartiles were combined and used as the reference group.

4.1.3 Paper III – Aim, design, study population, variables and statistical analyses

4.1.3.1 Aim

We studied the association of maternal age with placental weight, birthweight and placental weight/birthweight ratio.

4.1.3.2 Design

This study was a population-based cross-sectional study.

4.1.3.3 Study population

Of all births in Norway during the period 1999-2008 (n = 588 710), we excluded 25 501 births with missing information on placental weight. Maternal age was not registered for 60 women, and information on length of gestation and birthweight was not available for 3848 and 782 births, respectively. Of the remaining births eligible for study, we excluded 21 565 multiple pregnancies, births with missing information on offspring sex, births with a recorded length of gestation less than 22 weeks, and births with outlying values on length of gestation, placental weight or birthweight. In total, 536 954 births were included in this

study (Figure 15).

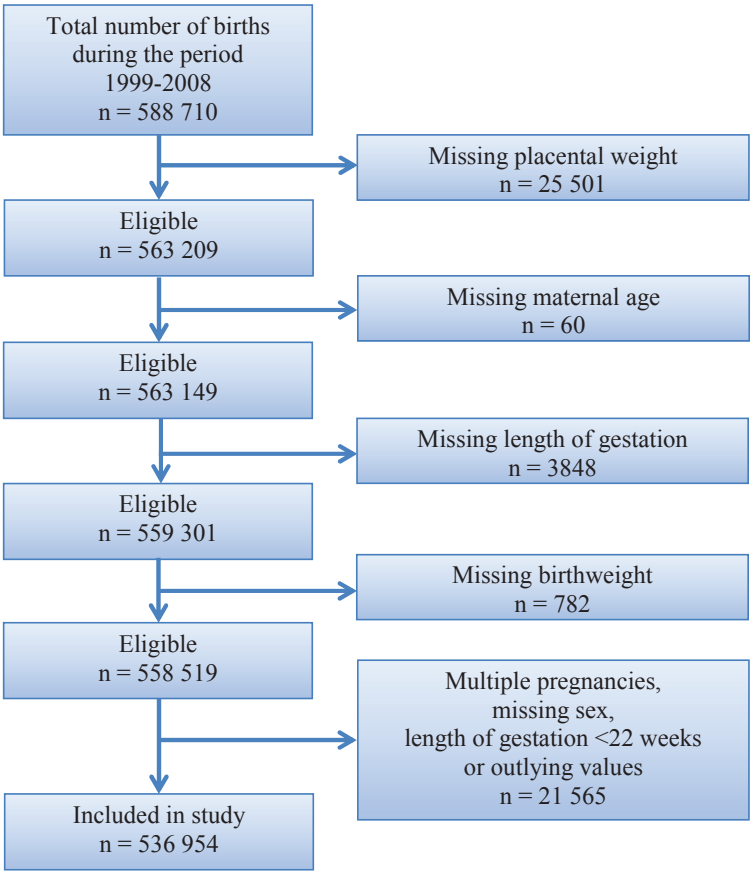


Figure 15. Study sample in Paper III.

4.1.3.4 Main outcome variables

Placental weight. Placental weight was reported in grams. We also calculated placental weight z-scores based on the means and standard deviations of placental weight. A z-score is defined as the actual value minus the mean value, divided by the standard deviation.[138] A z-score of 0 means that the actual placental weight is equal to the mean placental weight. A z-score can be positive or negative, indicating whether it is above or below the mean, and by how many standard deviations. The z-scores used in our study were gestational age- and sex-specific.[113] Placental weight z-scores are thus placental weight percentiles, adjusted for

length of gestation and offspring sex.

Birthweight. Birthweight was measured in grams. Z-scores were calculated, as birthweight also depends on length of gestation and offspring sex.[113,139]

Placental weight/birthweight ratio. Placental weight/birthweight ratios were estimated as described for Paper II.

4.1.3.5 Main explanatory variable

Maternal age. Maternal age was categorised in five-year intervals as described for Paper II.

4.1.3.6 Other study factors

Birthweight. In our analyses of the association of placental weight with maternal age, we adjusted for birthweight, as birthweight is correlated with placental weight[109] and maternal age.[140] Maternal age is positively correlated with both macrosomic and low birthweight infants. Birthweight was divided into 100-gram categories.

Parity, *smoking, preeclampsia* and *diabetes.* All these variables were categorised as described for Paper II.

4.1.3.7 Statistical analyses

Means of placental weight, birthweight and placental weight/birthweight ratio were calculated according to maternal age group. We also estimated the Pearson's correlation coefficient between placental weight and birthweight for each maternal age group. Placental weight and birthweight z-scores were created as described above. The reason for using z-scores rather than crude weight in grams was that placental weight and birthweight vary according to length of gestation and offspring sex,[113,139] and length of gestation also seems to vary with maternal age.[85] The z-scores of placental weight were divided into deciles (ten equal groups if normally distributed), where the lowest decile represented the 10% smallest and the highest decile represented the 10% largest placentas. Also, the z-

scores of birthweight and the placental weight/birthweight ratios in grams were divided into deciles. We estimated the distribution of each decile of placental weight z-score, birthweight z-score and placental weight/birthweight ratio in each maternal age group. Lastly, we estimated crude and adjusted ORs for having a small (lowest decile) or a large (highest decile) placenta according to maternal age. Women below the age of 20 years were used as the reference group in the multivariable model, as we believed that the linear trend of the association of placental weight with maternal age was best presented in this way.

4.2 Ethical aspects

Papers I-III

The Advisory Committee of the Medical Birth Registry of Norway and the Norwegian Data Inspectorate approved our studies. Personally identifiable information was not used in any of the studies.

5 Synopsis of the presented studies

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

Objective: To study the association of fetal death with maternal age by length of gestation.
Methods: In this population-based study, information on pregnancy outcome was obtained from the Medical Birth Registry of Norway. We studied all ongoing pregnancies after 16 completed weeks of gestation during the period 1967-2006 (n = 2 182 756).
Results: The risk of fetal death was 1.4 times higher in women aged 40-44 years than in women aged 20-24 years in mid-pregnancy, but was 2.8 times higher at term. In term pregnancies, the relative importance of maternal age increased with additional weeks of pregnancy. In gestational weeks 42-43, the crude risk was 5.1 times higher in mothers aged 40 years or older. During the period 1987-2006, the elevated risk of fetal death in older mothers at term was attenuated.
Conclusion: Women aged 40 years or older had the highest risk of fetal death throughout pregnancy, and particularly in term and postterm pregnancies. Improved obstetric care may explain the attenuated risk associated with maternal age in recent years.

Paper II: Fetal death and placental weight/birthweight ratio: a population study.

Objective: To study the association of placental weight and placental weight/birthweight ratio with gestational age-specific fetal death.
Methods: In this population-based study of all singleton births in Norway during the period 1999-2008 (n = 534 892), we estimated gestational age-specific quartiles of placental weight and placental weight/birthweight ratio, and compared the proportions of fetal deaths and live births in the lowest and highest quartiles. The risk of fetal death associated with placental weight/birthweight ratio was estimated as crude and adjusted ORs.
Results: Pregnancies with fetal death were overrepresented in the lowest quartile of placental weight and placental weight/birthweight ratio in term and preterm deliveries. In

preterm deliveries, fetal deaths were also overrepresented in the highest placental weight/birthweight ratio. The adjusted OR for fetal death in preterm deliveries was 1.67 (95% CI 1.44-1.94) for placental weight/birthweight ratio in the lowest quartile, and 1.79 (95% CI 1.55-2.08) in the highest quartile. Corresponding ORs for term deliveries were 1.76 (95% CI 1.50-2.06) and 1.18 (95% CI 0.99-1.41).

Conclusion: Both small and large placentas relative to birthweight were associated with fetal death in preterm births. At term, only small placentas were associated with fetal death. Understanding the mechanisms behind the increased risk of adverse pregnancy outcomes in pregnancies with disproportionate placental weight/birthweight ratio may be important for prevention of fetal deaths.

Paper III: The association of maternal age with placental weight: a population-based study of 536 954 pregnancies.

Objective: To study the association of maternal age with placental weight, birthweight and placental weight/birthweight ratio.

Methods: In this population-based study of all singleton births in Norway during the period 1999-2008 (n = 536 954), we calculated z-scores of placental weight and birthweight and divided them into deciles. The proportions of births with a small or a large placenta were calculated within each maternal age group. Also the ORs of having a small (lowest decile) or a large (highest decile) placenta according to maternal age were estimated, with and without adjustment for birthweight in grams, parity, smoking, preeclampsia and diabetes.

Results: The mean placental weight increased with maternal age, and was 647.1 grams in women below the age of 20 years, and 691.3 grams in women aged 45 years or older. Among the oldest group of women (≥45 years), 15.8% of the placentas were in the highest decile of placental weight z-score, whereas this was true for just 7.0% of the women below the age of 20 years (p <0.001, Wald test). Using women younger than 20 years of age as the reference group, the OR for having a placenta in the highest decile of placental weight z-score was 2.50 (95% CI 1.92-3.26) for women aged 45 years or older after adjustment for offspring birthweight, parity, maternal smoking, preeclampsia and diabetes.

Conclusion: We found an association between increased placental weight and maternal age, and this finding may be important in understanding the causes of adverse events associated with high maternal age.

6 General discussion

6.1 Main results

6.1.1 Paper I

Fetal death occurred in 1.04% of all births after 16 completed weeks of gestation during the period 1967-2006. Women aged 40 years or older had the highest absolute risk of fetal death at all lengths of gestation, but the increased risk was most pronounced in gestational weeks 16-22 and at term. In term pregnancies, the relative importance of maternal age increased with additional weeks of pregnancy. In the more recent study period (1987-2006), the increased risk of fetal death at term and postterm was attenuated.

6.1.2 Paper II

Independent of length of gestation at delivery, placental weight was lower in pregnancies with fetal death compared to pregnancies with live-born offspring. In both preterm and term deliveries, small placentas relative to birthweight were associated with fetal death. However, in preterm deliveries, also large placentas relative to birthweight were associated with fetal death.

6.1.3 Paper III

Mean placental weight and also placental weight relative to birthweight increased by maternal age.

6.2 Methodological considerations

6.2.1 Strengths and limitations of the studies

The Medical Birth Registry of Norway includes information on all births in Norway with close to 100% completeness. We have thus been provided with high quality population-based data, which allow for the generalisability of the findings. A major advantage of our

studies is the large sample size. This size generally assures tight CIs and minimises the likelihood of type-II error. The large sample size also makes it possible to study rare events such as fetal death.

There are some limitations of our studies. For studying differences between some subgroups of women, the statistical power may be limited. As an example, only a few women aged 40 years or older experienced fetal death in postterm pregnancies, and therefore the CIs around the risk estimates in these analyses were wide. Other limitations of the studies are presented and discussed in each paper, but will also be systematically discussed below.

Bias refers to systematic errors resulting in incorrect estimations of the association between an exposure and an outcome. Bias can be classified into three categories: selection bias, information bias and confounding.

6.2.2 Selection bias

Selection bias occurs when the association between the exposure and the outcome differs between participants and non-participants in the source population, that is if the study sample is not representative of the study population.[141] We included all births in Norway during the study period. It is therefore unlikely that we have a skewed selection of study participants in any of our studies, and selection bias affecting the internal validity can be widely excluded. The possible altered selection to pregnancy and delivery over time, and resultant changes in the composition of women who give birth, are discussed in the interpretation of the results (6.3.1).

Selection bias affecting the external validity of our studies may be discussed. The results that we obtained in a Norwegian setting may not be valid in other countries with different genetic and demographic compositions, different causes of fetal death, or with different obstetric care practices.

Skewed selection of the study sample primarily affects prevalence estimates.[141] Our aims were mainly to study the associations between exposure and outcome. Under certain circumstances, estimates of associations are also affected, in the sense that the association

is reversed, for example becomes positive rather than negative. We have no reason to believe that a skewed selection of our study samples has biased the direction of our estimates.

6.2.3 Information bias

Information bias occurs when the collected information is erroneous.[141] Although the validity of many of the variables reported to the Medical Birth Registry may be uncertain,[142] several studies have been performed to validate different diagnoses, and have confirmed that the information in the registry is of generally good quality.[143-146] For instance, the diagnosis of unexplained antepartum fetal death was validated against data obtained from hospital records and from autopsy data.[145] In this validity study, singletons with a gestational length of 28 weeks or above, or with a birthweight of 1000 grams or above, that were delivered at Haukeland Hospital in Bergen or at Aker Hospital in Oslo, were included. The reported specificity was 88-93%, and the sensitivity was 76-78%, therefore the authors concluded that the variable was sufficiently valid for use in epidemiological studies.

Information bias may also be defined as systematic differences in the way data on exposure or outcome are obtained. It can be divided into differential and non-differential misclassification.[141] Non-differential misclassification is not related to other variables, while differential misclassification changes according to the values of other study variables.[141] Hence, if differential misclassification is present, the erroneous values of the exposure may be linked to the outcome, leading to an erroneous direction of the estimated association. In this thesis, I will only emphasise possible differential misclassifications. If the misclassification is non-differential, our results have not been affected.

6.2.3.1 Differential misclassification

Paper I. There could be a possible differential misclassification of induced abortions as fetal deaths during the period 1986-December 1998. Our estimates of a higher risk of fetal death in gestational weeks 16-22 may have been biased if the prevalence of erroneously registered fetal deaths differed by maternal age. There were probably few induced abortions after 16 completed weeks of gestation before the introduction of routine

ultrasonographic screening in 1986, since a large percentage of these induced abortions are due to malformations,[147] and malformations are discovered by ultrasonographic examinations. Since December 1998, all induced abortions have been registered separately and were excluded from our analyses. Since older women are probably overrepresented among those having induced abortions due to anomalies, this bias would affect older women in particular. If induced abortions have been misclassified as fetal deaths, the increased risk of fetal death in gestational weeks 16-22 among older women during the period 1967-2006 could be overestimated.

The reporting of all live births and fetal deaths to the Medical Birth Registry is compulsory by law. However, the reporting of fetal deaths at 16-22 weeks of gestation is probably less established than that of fetal deaths at higher lengths of gestation. Therefore, we cannot exclude the possibility that early fetal deaths have been underreported. Live births reported to the Medical Birth Registry are matched with births registered in the Central Person Registry to ensure completeness of registration. However, there is no such system to ensure the completeness of registration of fetal deaths. Thus, underreporting of fetal deaths in general may occur. We have no reason to believe that a possible underreporting of fetal deaths is differential according to maternal age. However, in such a scenario, our results may have been biased.

Misclassification of the date of term could also have biased the results presented in Paper I. Date of term was based on the first day of the last menstrual period until December 1998. After December 1998, the Medical Birth Registry also started to record the date of term based on routine ultrasonographic screening performed at 17-19 weeks of gestation. Term estimates before December 1998 may be more inaccurate, particularly in women with irregular menstrual cycles, or with uncertain date of the last menstrual period.[148] Length of gestation may have been overestimated for some women before the introduction of ultrasonographic screening.[149,150] It is not known whether such misclassification is independent of maternal age. If the misclassification is non-differential according to maternal age, our results have not been biased.

A third issue could be the new notification form, which was introduced by the Medical Birth Registry in December 1998. The new form contains pre-coded answer alternatives, and could cause more frequent reporting of certain exposures or conditions, such as

preeclampsia or diabetes. Reporting of these variables is probably independent of maternal age, but this is not known for sure. If systematic differences did exist in the reporting of study variables according to maternal age, or according to vital status at birth, this may have resulted in over- or underestimations of the associations found in our studies.

Paper II. A misclassification of the main explanatory variables (placental weight, birthweight and placental weight/birthweight ratio) could have occurred if delayed cord clamping, which increases the blood volume in the newborn and decreases the blood volume in the placenta,[151] took place in live births only. This may have caused lower placental weight/birthweight ratios in live births compared to pregnancies with fetal death. Hence, the low placental weight/birthweight ratio in pregnancies with fetal death may have been underestimated, and the association of a high ratio with fetal death may have been overestimated. Whether delayed cord clamping was a common procedure in Norwegian maternity wards during the study period is not known.

It is also not known whether fetal death influences the weight of the placenta, or the infant after delivery, and thus if the placental weight/birthweight ratio changes as a function of death. After fetal death, the placenta undergoes morphological changes with increasing syncytial knots, fibrosis of the villous stroma, thickening of the trophoblastic basement membrane and villous stromal oedema.[152] These changes are probably related to the cessation of fetal blood flow. A marked reduction in maternal blood flow through the placenta[153] and a stagnation of maternal blood in the intervillous space after fetal death have also been observed.[152] All these factors could potentially influence placental weight after fetal death, but birthweight may also change due to morphological changes that occur in the fetus after death. Fetal weight may increase as a consequence of tissue oedema,[154] or decrease because of atrophy and autolysis.[155] If the placental weight/birthweight ratio changes as a function of fetal death, our findings may be biased due to differential misclassification. If the placental weight/birthweight ratio increases while the fetus is dead *in utero*, our finding of a large placenta relative to birthweight in preterm fetal deaths may have been an overestimate, and our observation of a small placenta relative to birthweight in preterm and term fetal deaths may have been an underestimate. On the other hand, if the placental weight/birthweight ratio decreases as a function of death, the opposite may have been the case. However, it is unlikely that the U-shaped association of placental weight/birthweight ratio with fetal death in preterm deliveries can be explained by

morphological changes in the placenta or the fetus after death.

Paper III. Differential misclassification may have occurred if the weighing procedures of the placenta differed according to maternal age. Infants born to older mothers are more often delivered by caesarean section,[82,91] and in a caesarean delivery the placenta is removed immediately. Conversely, after a vaginal birth, the delivery of the placenta is delayed, and the leakage of blood from the placenta during this delay may cause lower placental weight. This could cause an overestimate of large placentas among older women. However, our findings remained almost unchanged when analyses were conducted after exclusion of women with caesarean delivery.

6.2.4 Confounding

Confounding factors are variables that correlate with both the main outcome and the main explanatory variable, and thus confuse the effects if not accounted for in the data analyses.[141] The potential confounding factors for each paper were chosen *a priori* on the basis of findings from previous studies. Even though we adjusted for factors associated with the main outcome and the main explanatory variable, insufficient control for confounders may remain. Potential bias caused by confounding has been discussed in each paper. Nevertheless, I would like to highlight a few factors that may have confounded our results.

Maternal disease. In Paper I, we were criticised for the choice of confounding factors, as the occurrence of several maternal conditions increases with age. We wanted to see if the risk of fetal death differed throughout pregnancy in different age groups, and also if the gestational age-specific risk of fetal death according to maternal age changed during the study period (1967-2006). In epidemiological studies, the rule of thumb is not to make adjustments for factors on the causal pathway. We considered diabetes and hypertension to be a part of the biological process of aging, and therefore did not adjust for these variables. The fact that we adjusted for preeclampsia can be debated, since preeclampsia can also be seen as a consequence of aging. However, preeclampsia is also more frequent in first-time mothers.[16]

BMI. The lack of information on BMI in the Medical Birth Registry is problematic since

BMI influences the risk of fetal death.[19,156] BMI may also be associated with maternal age[157] and with placental weight.[158] In addition, the overall BMI in the population changes over time.[157] Thus, BMI could be a potential confounding factor in our studies.

In Papers I and II, we studied gestational age-specific fetal death. It is unlikely that BMI had a differential impact on fetal death according to length of gestation. Thus, BMI is probably not a source of confounding in these studies.

Our findings of large placentas in older mothers in Paper III may have been overestimated if high BMI is associated with high placental weight, and the oldest women have the highest BMI. However, population studies in Norway suggest that younger women have higher BMI compared to women aged 40 years or older.[157] It is therefore unlikely that BMI has confounded the results of this study.

Congenital anomalies and chromosomal abnormalities. Fetal malformations and karyotypic abnormalities are more common with advanced maternal age[93, 94] and contribute to an increased risk of fetal death.[30] It is conceivable that the presence of anomalies varies by length of gestation at delivery. The higher prevalence of congenital anomalies and chromosomal abnormalities in offspring of older women could therefore explain the higher fetal death rate among older women in Paper I, but it is not likely to explain the steep increase in risk in older women in postterm pregnancies. In an American study, which is contextually similar to Paper I, births with congenital anomalies were excluded.[159] However, the exclusion of these births was criticised, as the quality of the registration of anomalies in American birth certificates is poor, and the possibility to detect and exclude anomalous births is therefore limited.[160] The validity of anomalies reported in the Medical Birth Registry of Norway is not known. Nevertheless, in additional data analyses, we excluded births with recorded anomalies from our study population, but no significant differences in the associations of gestational age-specific fetal death with maternal age were found.

Ethnicity. During the period 1967-2006, a demographic change took place in Norway, which led to the current overrepresentation of immigrants particularly among younger women giving birth. Non-Western immigrants account for approximately 50% of all deliveries in Oslo among women below the age of 25 years.[161] Migrant women also have a

higher risk of fetal death.[162] Therefore, the lack of adjustment for ethnicity could have caused an underestimation of the maternal age-related difference in the risk of fetal death. However, the gestational age-specific fetal death rates have probably not been affected.

Smoking. We adjusted for smoking in Papers II and III, but not in the Paper I, as data on smoking habits have only been recorded in the Medical Birth Registry since December 1998.

ART. We adjusted for ART in Paper II only. ART is associated with large placentas and with high placental weight/birthweight ratios, but these associations were unknown until 2012.[137]

Socioeconomic status. Parental income, education and occupation are not reported to the Medical Birth Registry of Norway. The results of Papers I and II could be confounded if the association of socioeconomic status with maternal age differs according to length of gestation. We have no reason to believe that this is the case. Changes in the risk of fetal death across our study period could possibly have been confounded by changes in maternal socioeconomic status over time. This issue will be thoroughly discussed in the interpretation of the results (6.3.1).

Low socioeconomic status is associated with a high placental weight/birthweight ratio.[51] Our findings of large placentas among older women in Paper III could be overestimated if low socioeconomic status is associated with high maternal age.

6.3 Interpretation of the results

6.3.1 The increased risk of fetal death in older mothers

In Paper I, we found that women with advanced age at childbearing had an increased risk of fetal death throughout pregnancy. The increased risk in older mothers was pronounced in gestational weeks 16-22, but was particularly high in term and postterm pregnancies.

- *Why do older mothers have an increased risk of fetal death in gestational weeks 16-22?*

One possible explanation for the increased risk of fetal death in gestational weeks 16-22 could be that older women have a higher cumulative risk of having received treatment with cervical cone excision compared to younger women. Cervical cone excision increases the risk of cervical insufficiency, which may lead to miscarriage or premature delivery.[99] Premature delivery can cause intrapartum fetal death as a consequence of fetal immaturity.[39]

The fetal death rate in gestational weeks 16-22 has increased and now seems to exceed the fetal death rate at term.[11] Thus, increased knowledge of the causes of fetal deaths in gestational weeks 16-22 is important in our attempts to prevent fetal death. The excess risk in older mothers, as shown in our study, may be one contribution to the goal of increasing our knowledge in this area.

- *Why do older mothers have a particularly high risk of fetal death in term and postterm pregnancies?*

The causes of the particularly high risk of fetal death in term and postterm pregnancies of older mothers are not known. A lower uteroplacental perfusion, and thus reduced placental function by maternal age, has been suggested.[89] The importance of a well-functioning placenta may increase with length of gestation since the fetal demand for oxygen and nutrition increases during pregnancy.[100] If the placental function of older mothers is impaired, fetuses of older mothers may be particularly vulnerable in the last part of pregnancy.

The second aim of Paper I was to study changes in the risk of fetal death according to maternal age in term and postterm pregnancies from the period 1967-1986 to the period 1987-2006. The overall risk of fetal death decreased, and the decrease was particularly pronounced in pregnancies of older mothers.

- *How can the reduction in the risk of fetal death in term pregnancies of older mothers from the period 1967-1986 to the period 1987-2006 be explained?*

Antenatal and obstetric care. We believe that the introduction of new diagnostic technology has played an important role in reducing the risk of fetal death. Ultrasonographic examinations in pregnancy have enhanced the assessment of fetal growth, CTG has enabled the diagnosis of fetal distress, and a more consistent use of the partogram has improved the monitoring of labour progression. The identification of pregnancies with a high risk of fetal death has thereby improved over time. Of all fetal deaths in 1967, 19.2% occurred at 40 weeks of gestation or above. Corresponding figures for 1986 and 2006 were 12.4% and 8.3%, respectively (data not shown). These findings support our theory of timely intervention as the main explanation behind the reduced fetal death rates in recent years.

Ultrasonographic examinations in pregnancy have enabled more appropriate estimations of term, and thereby a more accurate identification of postterm pregnancies. The number of postterm deliveries in Norway has decreased, probably due to timely induction of labour. The proportion of infants that are born in gestational week 42 has decreased from 9.4% in 1967 to 4.7% in 2011.[10] Corresponding figures for births in gestational week 43 or later were 4.4% in 1967 and 0.1% in 2011. At the same time, the labour induction rate has almost doubled, from 10.4% in 1967 to 19.1% in 2011.[10] It is not known whether labour was induced before gestational week 42 in older women in particular. However, the overall labour induction rates have been higher in older compared to younger women in recent years.[163]

The low fetal death rate among older mothers in recent years could reflect a change over time in selection to pregnancy and childbirth at a more advanced age. A study using data from the Norwegian Mother and Child Cohort, showed that women who were pregnant with their first baby at an advanced age during the period 1999-2008 were more often unemployed, had a lower educational level, less contact with family and friends, were single, and more often overweight or obese compared to first-time mothers aged 25-32 years.[164] In the Norwegian Mother and Child Cohort study, only 38.5% of women eligible for inclusion chose to participate. It is therefore uncertain whether the results from this cohort study of first-time mothers may be generalised to all mothers aged 40 years or

older.[165]

To explore whether changes in the composition of childbearing women could contribute to the decline in fetal death rates in general, and to the changes in age-related risks in particular, we performed supplementary analyses using data from the Medical Birth Registry for the period 1967-2011. We studied changes in the proportion of older women with risk factors for fetal death, such as nulliparity and multiparity, low socioeconomic status, non-Western ethnicity and maternal medical disorders.

Nulliparity and multiparity. We estimated the proportions of women aged 40 years or older who were nulliparous and multiparous, according to year of delivery (Figure 16). The proportion of nulliparous women increased, whereas the proportion of multiparous women (para ≥4) aged 40 years or older decreased. However, both nulliparity and multiparity are associated with an increased risk of fetal death.[19,44-46] These findings alone can therefore not support the evidence that older mothers have had a lower risk of fetal death in recent years, compared to the risk they had in the beginning of the period.

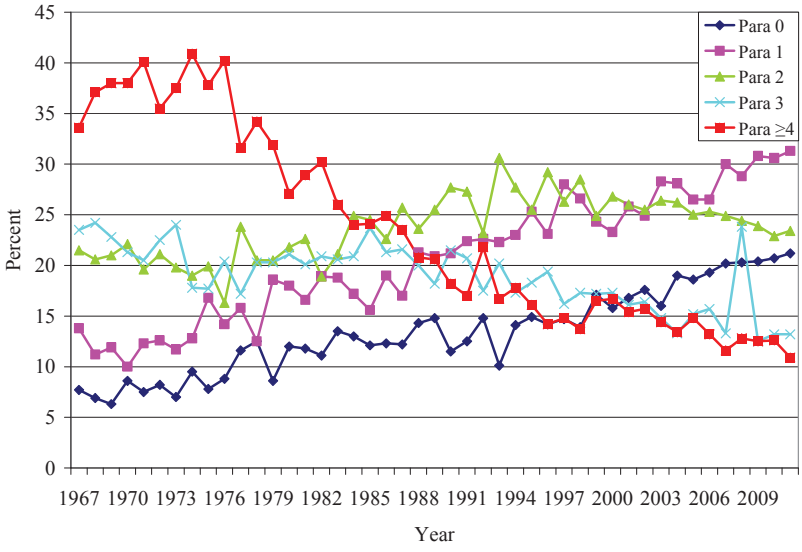


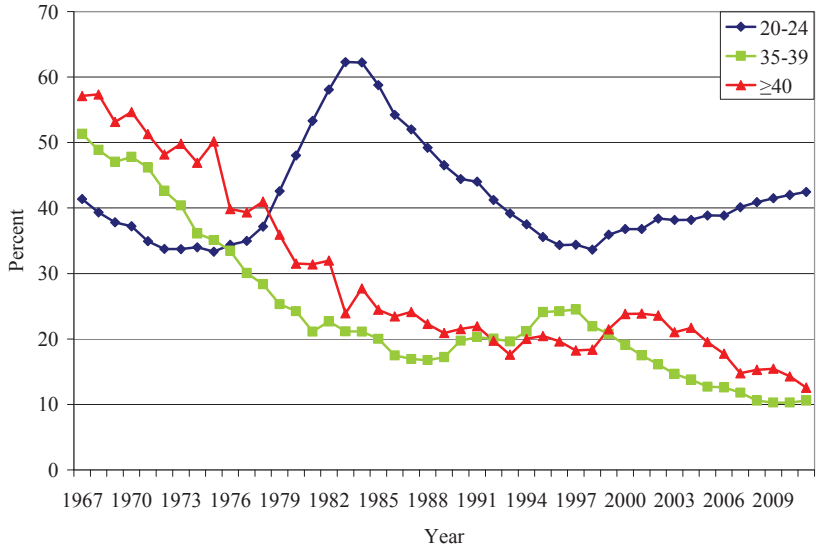
Figure 16. Proportions of nulliparous and multiparous women aged 40 years or older at delivery during the period 1967-2011.

Socioeconomic status. Low socioeconomic status has been associated with an increased risk of fetal death,[51] and the socioeconomic conditions of women living in Norway improved during our study period.[166,167] The increase in socioeconomic status has been relatively larger among older compared to younger women, and could possibly explain the decrease in relative risk of fetal death among older women in term pregnancies in recent years.

To explore whether older women have had an increase in socioeconomic status in particular, additional analyses were performed using data from the Medical Birth Registry combined with data from Statistics Norway (REK 2012-1433). For these analyses, we received help from senior researcher Lars Monkerud and Professor Jostein Grytten at the University of Oslo. Jostein Grytten is the principal investigator for several studies using these data.

Changes in the age-dependent proportion of pregnant women with compulsory school education only were calculated (Figure 17A). We also calculated the age-dependent proportion of pregnant women among the families with the 10% lowest yearly income during the period 1967-2011. Family income was defined as the income of the pregnant woman and her partner (Figure 17B).

A



B

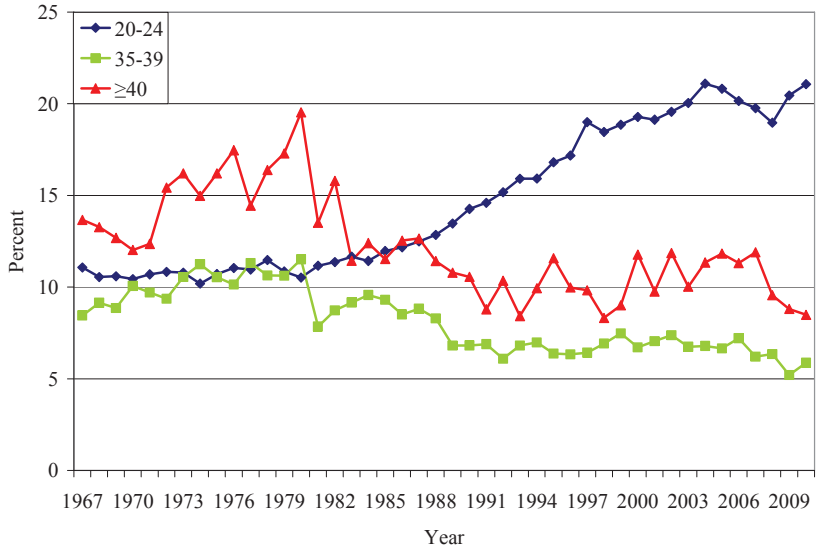


Figure 17. A) Proportions of women with compulsory school education only, and **B)** proportions of women with the 10% lowest family income according to maternal age (20-24 years, 35-39 years and ≥40 years) and year of delivery during the period 1967-2011.

During the period 1967-2011, the overall proportion of women aged 40 years or older with compulsory education only decreased (Figure 17A). At the same time, the relative difference in educational level between women aged 20-24 years old and women aged 40 years or older increased. Thus, the educational level was higher in older as compared to younger women towards the end of the study period compared to the figures from 40 years ago.

During the same period, the overall proportion of older women with low family income decreased, and the relative difference in family income between younger and older women increased (Figure 17B). Thus, family income was higher in older as compared to younger women towards the end of the study period compared to the figures from 40 years ago. We cannot exclude the possibility that a higher educational level and a higher family income among older women have had an impact on the reduction in fetal death rates in this group of women in recent years.

On the other hand, there are studies that have suggested that low socioeconomic status has not been an important risk factor for fetal death in term pregnancies in recent years. In Paper I, we studied changes in the relative risk of fetal death in term pregnancies according to maternal age from the period 1967-1986 to the period 1987-2006. There is no information available on social disparity in fetal death at term for the first part of our study period. However, a study from 2013, which included all pregnancies among Norwegian-born women during the period 1999-2004, suggested that low maternal educational level is not associated with fetal death at 37 weeks of gestation or above.[168] The findings from the aforementioned study suggest that a higher increase in educational level in older as compared to younger women does not explain the more pronounced decrease in fetal death risk in older women over time.

Decades ago, women with a high educational level, or with a highly educated spouse, had a greater chance of being delivered by caesarean section compared to women with lower education. In recent years, caesarean section has been equally available to all women living in Norway, regardless of their educational level.[169] Thus, obstetric interventions may have played a greater role in the prevention of fetal death in women with low educational level.

Ethnicity. It is well known that non-Western immigrants have an increased risk of fetal

death.[162] Therefore, the proportion of immigrants among childbearing women could influence the fetal death rate.

Forty years ago, very few women from non-Western countries gave birth in Norway. In the first part of our study period (1967-1986), non-Western immigrants contributed to less than 3% of all births, compared to up to 14% in the last part of the study period (1987-2006). If non-Western ethnicity is an important risk factor for fetal death, an increased rather than a decreased fetal death rate would be expected. In our supplementary analyses, we found the increase in deliveries among non-Western immigrants to be less pronounced in older as compared to younger women (Figure 18). However, this relatively small difference cannot explain the large reduction over time in fetal death rates at term among older women.

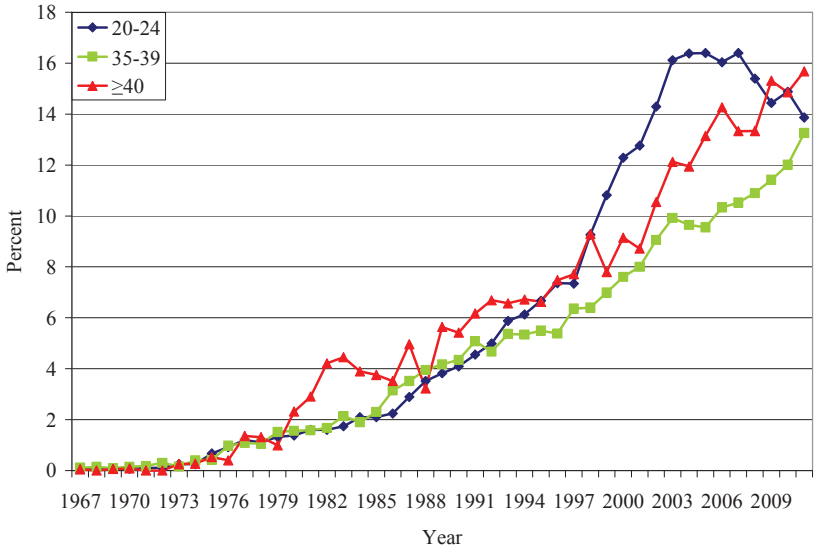
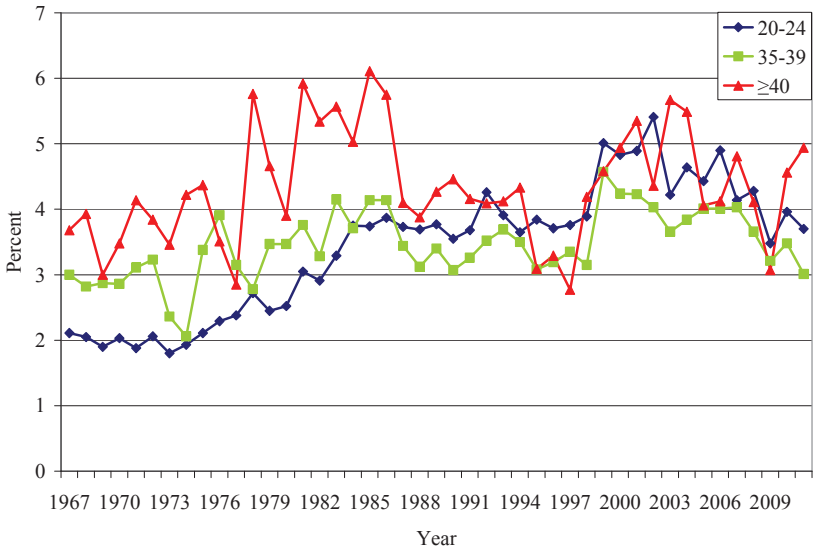


Figure 18. Proportions of non-Western immigrants among childbearing women, according to maternal age (20-24 years, 35-39 years and ≥40 years) and year of delivery during the period 1967-2011.

Maternal medical disorders. In supplementary analyses, we also calculated changes in the age-dependent proportions of pregnant women with preeclampsia (Figure 19A), chronic hypertension (Figure 19B), gestational diabetes (Figure 20A) and diabetes mellitus (Figure 20B) during the period 1967-2011.

A



B

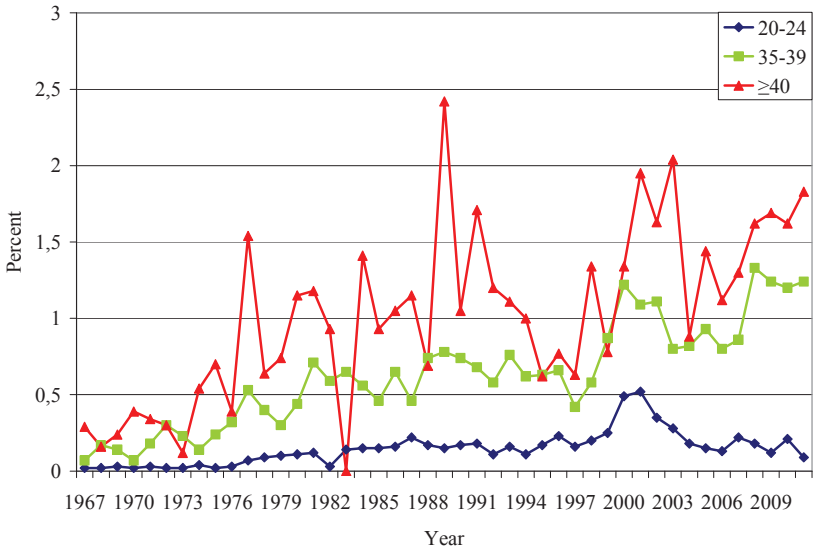
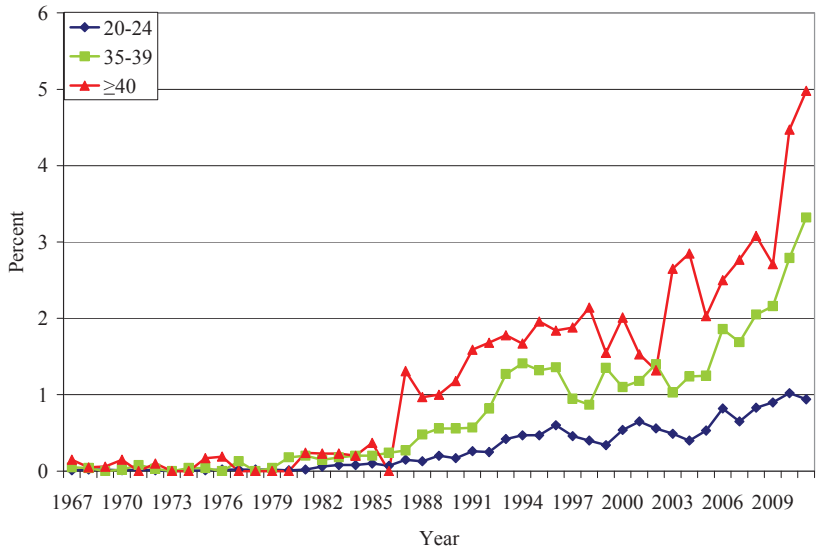


Figure 19. A) Proportions of women with preeclampsia, and **B)** proportions of women with chronic hypertension according to maternal age (20-24 years, 35-39 years and ≥40 years) and year of delivery during the period 1967-2011.

A



B

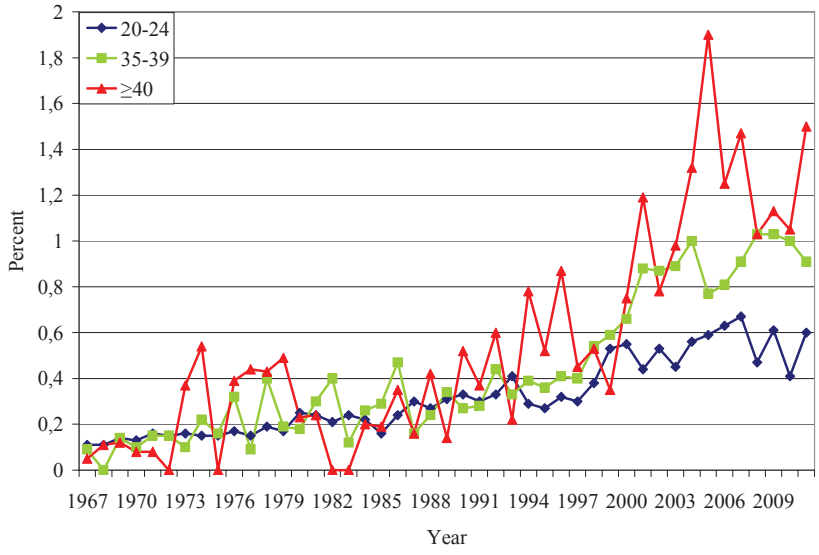


Figure 20. A) Proportions of women with gestational diabetes, and **B)** proportions of women with diabetes mellitus according to maternal age (20-24 years, 35-39 years and ≥40 years) and year of delivery during the period 1967-2011.

The absolute proportion of women aged 40 years or older with preeclampsia was relatively stable during the period 1967-2011. However, the relative difference in the risk of developing preeclampsia between younger and older women decreased (Figure 19A). The prevalence of other maternal medical disorders associated with an increased risk of fetal death, such as chronic hypertension, gestational diabetes and diabetes mellitus, increased during the study period (Figures 19B, 20A-B). The distribution of these conditions according to maternal age also changed, with an increased proportion of women aged 40 years or older having chronic hypertension, gestational diabetes and diabetes mellitus. Therefore, is not likely that the overall reduction in the risk of fetal death can be explained by improved maternal health. On the contrary, the overall reduction in the risk of fetal death among women aged 40 years or older may be even more prominent than indicated by crude fetal death rates, since there has been an increase in several maternal medical disorders over time, and the increase seems to be higher in older as compared to younger women. Thus, the estimated decrease in fetal death we observed in older women may represent an underestimate. However, improved reporting of maternal disease over time as a source for biased reasoning cannot be ruled out.

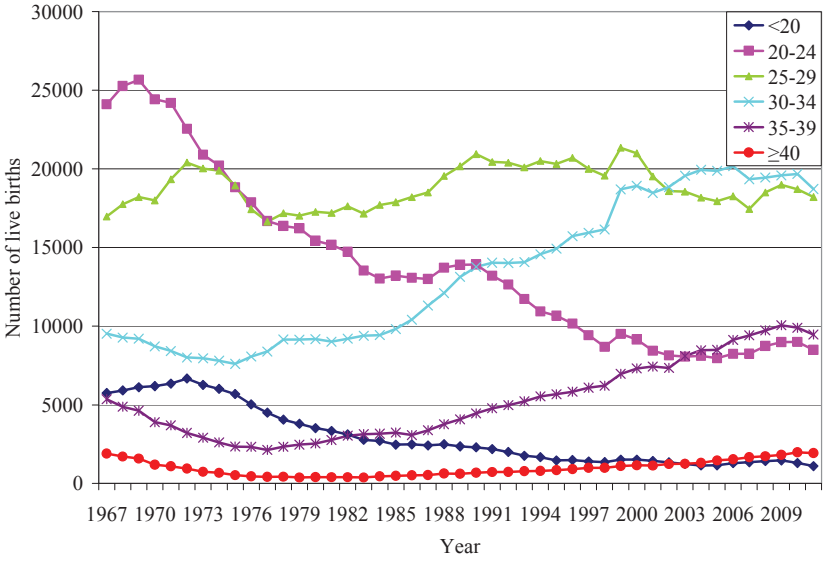
- *Has the proportion of fetal deaths attributable to high maternal age changed over time?*

The population-attributable risk of fetal death indicates the importance of a given causal factor, and suggests the number of fetal deaths that could be potentially prevented if this factor was removed. Maternal age is no causal factor of fetal death. However, in large reviews, population-attributable risks have also been estimated for risk factors that do have a significant association with fetal death.[17] Therefore, we calculated the total number of fetal deaths that may be attributed to high maternal age.

In our study population, 55 out of a total of 938 fetal deaths (5.9%) could be attributed to high maternal age in 1967. Corresponding figures were 6/442 (1.4%) in 1986 and 10/388 (2.6%) in 2006. Because of the low number of women giving birth at the age of 40 years or above in Norway, high maternal age has little impact on the total number of fetal deaths, or on fetal death rates in the general population.

The figures below (Figures 21-22) show the number of live births, fetal deaths and the overall changes in age-specific fetal death rates at 22 weeks of gestation or above over time.

A



B

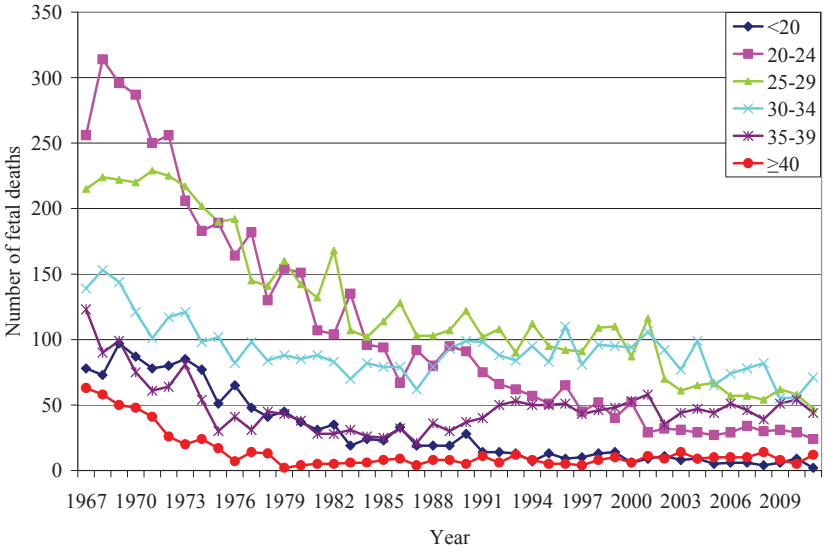


Figure 21. A) Number of live births, and **B)** number of fetal deaths at 22 weeks of gestation or above according to maternal age and year of delivery in Norway during the period 1967-2011.

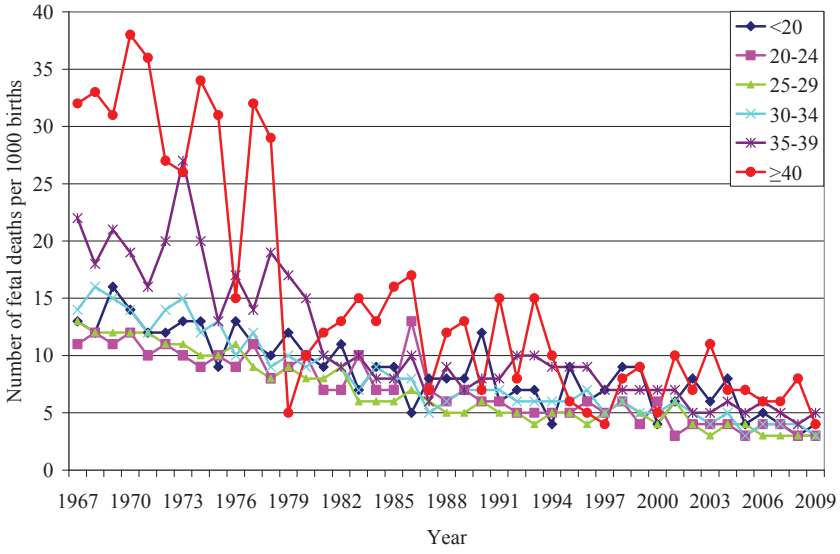


Figure 22. Changes in fetal death rates at 22 weeks of gestation or above according to maternal age and year of delivery in Norway during the period 1967-2011.

6.3.2 Placental size in pregnancies with fetal death

In Paper II, we found small placentas and small placentas relative to birthweight to be associated with fetal death in preterm and term pregnancies.

However, in preterm pregnancies, large placentas relative to birthweight were also associated with an increased risk of fetal death (Figure 23). It is not surprising to find that small placentas and low placental weight/birthweight ratios are associated with fetal death, as small placentas probably have a reduced capacity to supply the fetus with oxygen and nutrition.[110,111]

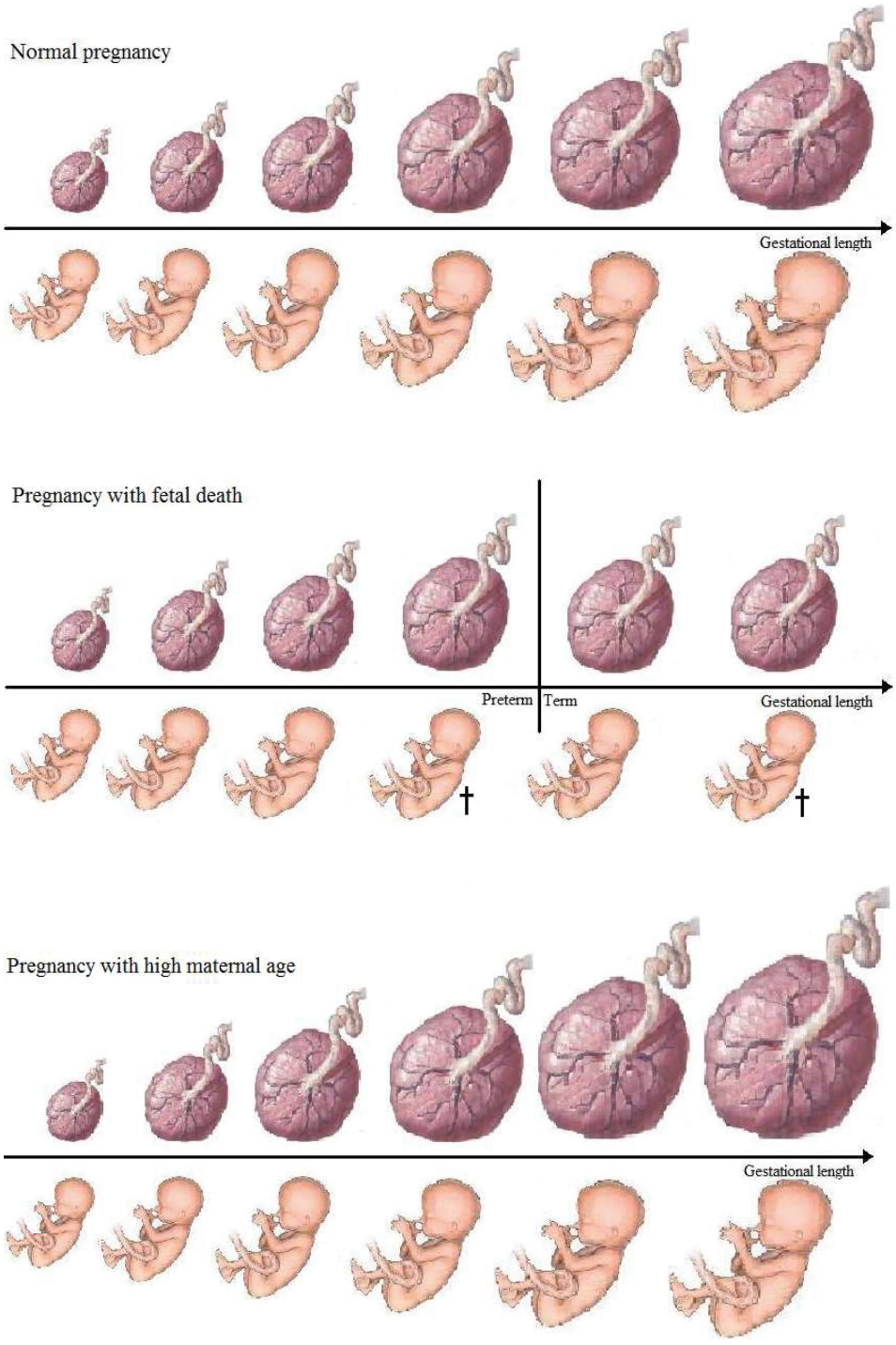


Figure 23. Placental weight relative to birthweight in normal pregnancies as compared to pregnancies with fetal death and pregnancies with high maternal age at childbirth.

- *Why are large placentas relative to birthweight associated with preterm fetal death?*

A high placental weight/birthweight ratio can represent three different situations:

i) Enlargement of the placenta and a normal-sized or small infant.
ii) A normal-sized placenta and a small infant.
iii) A small placenta and a relatively smaller infant.

In supplementary analyses of preterm births with a high placental weight/birthweight ratio, we found the mean birthweight of stillborn to be lower compared to the birthweight of live-born infants at the same length of gestation. The placental weight of stillborn infants was, however, in many cases equivalent to or even higher than the placental weight of live-born. In preterm fetal deaths with a normal-sized placenta and a small infant, death may have occurred due to fetal causes, such as chromosomal abnormalities and congenital anomalies. It is unclear why a large placenta relative to birthweight is associated with preterm fetal deaths, and we can only speculate on possible explanations. Could a relatively large placenta be an indicator of the fetus' failure to thrive? Large placentas relative to birthweight have also been found in other high-risk pregnancies, such as pregnancies with diabetes[130] or preeclampsia,[129] ART pregnancies[137] and pregnancies of mothers with low socioeconomic status.[134] In addition, high placental weight/birthweight ratios have been associated with induction of labour,[158] acute and elective caesarean sections,[118,158] spontaneous preterm birth,[158] postterm delivery,[158] delivery of low birthweight infants,[158] and excess postpartum haemorrhage.[170] The relative enlargement of the placenta in these pregnancies can be an adequate biological response to increase the chance of fetal survival, but in some pregnancies the enlargement may not be sufficient for the fetus to survive.

Small placentas have been assessed as dysfunctional.[110,111] However, the function of large placentas is unknown. A relatively large placenta may itself require a lot of oxygen and nutrition, and therefore have a lower capacity to nourish the fetus.

- *Why are large placentas relative to birthweight associated with preterm fetal deaths only?*

There may be differential causes of fetal death before and at term, and placental dysfunction, measured as a small placenta, may play the greatest role in term fetal deaths. On the other hand, conditions associated with a relatively large placenta may more often cause preterm fetal death. For instance, infections have been suggested to be a more important cause of fetal death in the second trimester than at term,[27,33,34] and inflammatory changes may cause enlargement of the placenta.[171]

An alternative explanation is that only the healthiest pregnancies will last until term. Hence, a dysfunctional pregnancy, indicated by a high placental weight/birthweight ratio, may be more likely to result in preterm delivery. It is also possible that pregnancies with a high risk of fetal death are delivered before term to prevent such an event. In many high-risk pregnancies associated with a high placental weight/birth weigh ratio, such as pregnancies with preeclampsia or diabetes,[129,130] labour is often induced.[172] Thus, preterm induction of labour may prevent fetal deaths that would otherwise have occurred at term. The reduced fetal death rate at term in recent years,[11] particularly in pregnancies with preeclampsia[18] or diabetes,[173] but also in pregnancies of older mothers, supports the hypothesis that timely intervention in high-risk pregnancies prevents fetal deaths.

Reduced peripheral chorionic villous vascularisation has been seen in second trimester fetal deaths.[174] Reduced vascularisation and thereby reduced blood flow causes fetal hypoxia.[174] It is conceivable that placental growth is a long-term form of compensation for fetal hypoxia through increased angiogenesis.[175,176] In some cases, compensation by placental growth may not be sufficient, and the fetus dies. This hypothesis is more thoroughly explained in the following, since hypoxia could also be the answer to our next question.

6.3.3 Placental size in pregnancies with high maternal age

In Paper III, we found that older mothers had larger placentas and higher placental weight/birthweight ratios compared to younger mothers.

- *Why do older mothers have larger placentas and larger placentas relative to birthweight compared to younger women?*

It is conceivable that the fetal oxygen supply is lower in older than in younger mothers because of a higher prevalence of vascular degenerative changes in older mothers, such as atheromatosis and arteriosclerosis.[177] Through degenerative changes in the uterine spiral arteries, the uteroplacental blood flow is reduced and circulating intervillous blood is decreased.[178] A reduction in intervillous blood flow may cause a reflectory increase in vascular resistance and thus decreased fetoplacental circulation.[178] Thus, degenerative changes in the uteroplacental vessels may impair the transfer of oxygen from the placenta to the fetus. The placenta may adapt to the relative hypoxia by compensatory placental growth.[179,180] Generally, hypoxia is known to initiate angiogenesis in the placenta by regulating levels of different angiogenic factors, such as VEGF,[181,182] and increased angiogenesis may cause placental enlargement.[175,176] An enlargement of the placenta has also been seen in other pregnancies with reduced oxygenation of the fetus, such as pregnancies with maternal anaemia,[179,183] maternal smoking[180] and pregnancies of women living in high altitudes.[184] Thus, a high placental weight/birthweight ratio may be an indicator of suboptimal conditions for the fetus.

In some high-risk pregnancies, such as pregnancies with preeclampsia or intrauterine growth restriction, more proliferative and less invasive trophoblasts have been seen.[181] This leads to a relatively shallow invasion of uterine spiral arteries and increased uteroplacental resistance.[181] The consequences are long-term compromised uteroplacental perfusion, and thus reduced transport of oxygen and nutrients.[181] Compensatory placental growth due to hypoxia may again be the result. It is not known whether the trophoblasts are less invasive in older mothers. However, a decline in apoptotic cells and an increased number of proliferative cells in placental trophoblasts have been suggested,[185] and could be another explanation for the large placentas observed in older women.

- *Is a relatively large placenta in older women beneficial or detrimental?*

At present, more research is needed to answer this question. However, we believe that a large placenta may represent a well-functioning placenta making an effort to save a pregnancy that is threatened due to lack of oxygen. Relative hypoxia, resulting in increased angiogenesis and thereby placental growth may be crucial in older mothers for the pregnancy to succeed. If the woman cannot compensate with an increased production of VEGF, placental growth will be restricted, and the pregnancy may result in miscarriage or fetal death. On the contrary, if the fetus survives, and the compensatory mechanisms are well-functioning, placental enlargement may occur. This is consistent with our hypothesis, suggesting that for some older women, compensatory placental growth may be necessary to achieve a successful pregnancy.

It is, however, also conceivable that a large placenta is an indicator of a well-functioning pregnancy. There may be a differential selection by age of pregnancies that continue until birth of a live infant. Hence, only healthy pregnancies with a large, well-functioning placenta are successful in older women, whereas pregnancies with dysfunctional and small placentas more often end in miscarriage or fetal death (Figure 23). Younger women may have a better biological capacity to successfully deliver a live infant even when the placenta is small and less functional.

6.4 Clinical implications

Our first study may have important clinical implications for pregnancy among older women. Older mothers have an increased risk of fetal death in term and postterm pregnancies. Although a considerable reduction in the fetal death risk in older mother has taken place in recent years, their risk is still increased as compared to the risk in younger mothers. More aggressive efforts to electively deliver, or to induce labour among older women at term and beyond may warrant discussion, but timing of labour induction in postterm pregnancies is a controversial issue.[186-188] Different countries and even different hospitals have dissimilar clinical routines regarding time of induction. Austria and Belgium have a liberal attitude towards induction at, or shortly after term, whereas in Scandinavian countries, a larger proportion of pregnancies that continue beyond term is managed

expectantly.[189] In some countries, such as France and Canada, it has been suggested to systematically induce labour at 41 weeks of gestation rather than having an expectant approach.[189] Our study has shown that there barely is any increased risk of fetal death in postterm pregnancies in Norway since the introduction of ultrasonographic examinations in pregnancy. The reduction in the risk of fetal death from the period 1967-1986 to the period 1987-2006, particularly in term and postterm pregnancies, indicates that improved maternity care has already been implemented, allowing for detection of high-risk pregnancies and thereby timely intervention. The exception may be in pregnancies of women aged 40 years or older. Based on the results of our studies, it is our opinion that in women aged 40 years or older, labour should be induced in gestational week 41. For younger women, the risk of fetal death in postterm pregnancies is so small that changes in the present recommendations of induction of labour may cause more harm than good.

There are no immediate clinical implications of our studies on placental weight, since placental weight is measured after delivery. However, the studies may have potential future importance. The association of a high placental weight/birthweight ratio with fetal death is new and original, and may add important pieces to the puzzle of understanding the causes of fetal death. Measuring placental volume may, in the future, be as important for the evaluation of fetal well-being, as fetal biometry is today. Particularly, the placental weight/birthweight ratio may be an important clinical marker of a high-risk pregnancy.

7 Future perspectives

The risk of fetal death has decreased by almost 70% in Norway during the last four decades.[11] However, increasing prevalence of maternal obesity, diabetes mellitus and also demographic changes in the Western world will probably make it difficult to further reduce the fetal death rate.[190] High maternal age at delivery has become a public health issue, since high maternal age is associated with maternal morbidity, poor obstetric outcomes and high rates of obstetric interventions. More knowledge about the mechanisms behind this increased risk is needed.

New technology has probably had a great impact on the reduction of fetal death rates, particularly among older women. High-risk pregnancies can be identified, timely interventions performed, and fetal deaths prevented. Recently, the number of antenatal care visits in Norway has been reduced,[191] and low-risk delivery units with less diagnostic technology have been established.[192] It remains to be seen whether this alteration of a well-functioning antenatal and obstetric care system will lead to increased fetal death rates. If so, the oldest women are the most likely to be affected.

The role of placental weight as an indicator of poor obstetric outcome is insufficiently understood. Our findings of large placentas and high placental weight/birthweight ratios in high-risk pregnancies reveal new questions. A deeper understanding of the mechanisms behind this increased ratio and further knowledge about the factors that influence placental growth are needed. High placental weight/birthweight ratios have been associated with short-term adverse perinatal oucome,[117,118] but also with long-term complications, such as hypertension and cardiovascular disease in adulthood.[120,121] Infants who have compensated *in utero* because of a suboptimal environment, but have managed to maintain a good birthweight, seem to have undergone physiologic stress that may affect their future health.[110] It has also been suggested that women delivering an infant with a large placenta have an increased risk of developing invasive epithelial ovarian cancer later in life.[193] Hence, changes in placental growth during pregnancy could be associated with altered fetal programming and may have long-term implications for the health of the next generation, but may also influence the health of the mother.

8 Conclusions

In this thesis, which was based on large population-based studies, we found that:

- High maternal age at delivery was associated with an increased risk of fetal death, particularly in term and postterm pregnancies. However, the increased risk of fetal death in older mothers was attenuated in the more recent study period (1987-2006).

- Small and large placentas relative to birthweight were associated with fetal death in preterm pregnancies, whereas only small placentas relative to birthweight were associated with fetal death at term.

- High maternal age was associated with large placentas and also with high placental weight/birthweight ratios.

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APPENDIX

I

II

III

Notification forms
Medical Birth Registry of Norway
1967 - December 1998 and
December 1998 – present

Registreringsskjema fra 1967-1998

STATENS HELSETILSYN
Postboks 8128 Dep.
0032 OSLO

Medisinsk registrering av fødsel

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

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

Barnet	Barnet var 1 ☐ Levende født 2 ☐ Dødfødt foster	Født dag, mnd., år	Klokkeslett	Personnr.	Skriv ikke her
	1 ☐ Enkel 2 ☐ Tvilling 3 ☐ Trilling 4 ☐ Firling		Kjønn 1 ☐ Gutt 2 ☐ Pike		
	Etternavn, alle fornavn (bare for levendefødte)				
	Fødested. Navn og adresse på sykehuset/fødehjemmet		Kommune		
Faren	Etternavn, alle fornavn		Født dag, mnd., år	Bostedskommune	
Moren	Etternavn, alle fornavn. Pikenavn			Født dag, mnd., år	
	Bosted. Adresse		Kommune		
	Ekteskapelig status 1 ☐ Ugift 6 ☐ Samboende 2 ☐ Gift 3 ☐ Enke 4 ☐ Separert 5 ☐ Skilt			Ekteskapsår (gifte)	
	Antall tidligere fødte (før denne fødselen)	Levende fødte	Av disse i live	Dødfødte	
	Er moren i slekt med faren? 1 ☐ Nei 2 ☐ Ja. Hvilket slektskapsforhold:				
Morens helse før svangerskapet	1 ☐ Normal 2 ☐ Sykdom (spesifiser):				
			Siste menstruasjons første blødningsdag		
Morens helse under svangerskapet	1 ☐ Normal 2 ☐ Komplikasjoner (spesifiser):				
Ble fødselen provosert	1 ☐ Nei 2 ☐ Ja				
Inngrep under fødselen	1 ☐ Nei 2 ☐ Ja (spesifiser):				
	Inngrepet utført av 1 ☐ Lege 2 ☐ Jordmor				
Komplikasjoner i forbindelse med fødselen	1 ☐ Nei 2 ☐ Ja (spesifiser):				
Fostervann, placenta og navlesnor	1 ☐ Normalt 2 ☐ Patologisk (spesifiser):				
Barnets tilstand	Bare for levende fødte. Tegn på asfyksi? 1 ☐ Nei 2 ☐ Ja		Apgarscore etter 1 min.	etter 5 min.	
	For levende fødte og dødfødte. Tegn på medfødt anomali, på skade eller sykdom? 1 ☐ Nei 2 ☐ Ja. Hvilke:				
	Lengde (i cm)	Hode-omkr. (i cm)	Vekt (i g)	For døde innen 24 timer Livet varte i	Timer	Min
	For dødfødte. Døden inntrådte 1 ☐ Før fødselen 2 ☐ Under fødselen Dødsårsak: Seksjon? 1 ☐ Nei 2 ☐ Ja					
Alvorlige arvelige lidelser i slekten	1 ☐ Nei 2 ☐ Ja Sykdommens art og hos hvilke slektninger:					

50 000. 5.96. SSM GRAFISK

Sted (sykehusets stempel) | Dato | Jordmor | Lege

IK - 1002.

MFR

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

Se utfyllingsinstruks for blanketten på baksiden

Sosial- og helsedirektoratet

A – Sivile opplysninger

Institusjonsnr: | Institusjonsnavn

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

Mors fulle navn og adresse

Pikenavn (etternavn):

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

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

Mors bokommune

Fars fødselsdato | Fars fulle navn

Mors fødselsnr:

B – Om svangerskap og mors helse

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

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

Ultralyd utført? ☐ Nei ☐ Ja UL termin:

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

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

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

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

Spesifikasjon av forhold før eller under svangerskapet: B

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

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

Røyking og yrke
Forutsetter mors samtykke – se rettledning på baksiden
☐ Skriftlig orientering gitt til mor ☐ Samtykker ikke for røykeoppl.

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

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

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

Mors yrke

Bransje:

C – Om fødselen

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

Fødselstart: ☐ Spontan ☐ Indusert ☐ Sectio

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

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

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

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

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

Spesifikasjon av forhold ved fødselen/andre komplikasjoner C

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

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

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

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

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

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

D – Om barnet

Fødselsdato | **Klokken**

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

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

Barnets vekt: | Hode-omkrets:

Total lengde: | Eventuelt sete–issemål:

Apgar score: 1 min | 5 min

Barnet var: ☐ Levendefødt ☐ Dødfødt/sp.abort Oppgi dødsårsak i «D»

For dødfødte: ☐ Død før fødsel ☐ Død under fødselen ☐ Ukjent dødstidspunkt

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

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

Død senere (dato): | **Klokken**

Overfl. barneavd. ☐ Nei ☐ Ja Dato:

Overfl. til

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

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

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

Icterus behandlet: ☐ Lysbehandlet ☐ Utskifting

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

Tegn til medfødte misdannelser: ☐ Nei ☐ Ja

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

☐ **Kryss av hvis skjema er oppfølgingsskjema**

Jordmor v/fødsel:

Jordmor v/utskrivning:

Lege:

Lege barsel/barneavd:

Utskrivningsdato

Mor:

Barn:

Protokollnr.: /

IS-1002 23011. 07.06. Andvord Grafisk.