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Temporal changes in fetal death risk in pregnancies with preeclampsia: Does offspring birthweight matter? A population study

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ABSTRACT

Objectives: To study the associations of preeclampsia with fetal death risk within percentiles of offspring birthweight, and whether these associations have changed during 1967–2014.
Study design: In this population study, we included all singleton pregnancies in the Medical Birth Registry of Norway during 1967–2014 (n = 2 607 199). Odds ratios (ORs) for fetal death associated with preeclampsia were estimated within percentiles of birthweight by applying logistic regression analyses. We estimated ORs for the study period as a whole, and for the years 1967–1983 and 1984–2014.
Results: During the study period as a whole, preeclampsia increased the risk of fetal death, OR 2.73 (95% CI 2.57–2.89), and the fetal death risk associated with preeclampsia differed across percentiles of offspring birthweight. The overall risk of fetal death decreased during our study period, and the decrease was most prominent in preeclamptic pregnancies with low offspring birthweight (<1 percentile). Thus, in recent years, the risk of fetal death in pregnancies with low offspring birthweight was lower in preeclamptic than in non-preeclamptic pregnancies, OR 0.22 (95% CI 0.12-0.41). Only in pregnancies with offspring birthweight within the 10–90 percentiles, the risk of fetal death associated with preeclampsia remained significantly increased throughout the study period.
Conclusions: The decline in fetal death risk was most prominent in preeclamptic pregnancies with low offspring birthweight. The introduction of a national screening program for preeclampsia in the 1980s, and identification of growth restricted offspring by fetal ultrasonography, may explain our findings.

Introduction

Preeclampsia is characterized by maternal hypertension and proteinuria, and is a leading cause of maternal mortality worldwide [1]. Preeclampsia is also associated with complications such as fetal growth restriction and fetal death [2,3].

In pregnancies with preeclampsia, the prevalence of fetal growth restriction is increased [4,5], and it is well known that fetal growth restriction is associated with increased risk of fetal death [6,7]. Thus, if fetal growth restriction is diagnosed in a preeclamptic pregnancy, the offspring may be delivered to prevent intrauterine death. Most infants born to preeclamptic mothers have birthweight appropriate for gestational age, and birthweight may also be increased in pregnancies with preeclampsia [8,9]. Reliable knowledge about the risk of fetal death in normal, and in large for gestational age offspring in pregnancies with preeclampsia is important for clinical decisions about intervention in such pregnancies.

During the last decades, the fetal death rate has declined significantly in the Western world [10], and the decline has been more prominent in preeclamptic as compared to non-preeclamptic pregnancies [11,12]. It is not known whether the decline in fetal death rate in preeclamptic pregnancies has differed by offspring birthweight.

Therefore, we studied the temporal changes in fetal death risk in pregnancies with and in pregnancies without preeclampsia within categories of offspring birthweight. We included all singleton pregnancies in Norway during the years 1967–2014.

Materials and methods

We used data from the Medical Birth Registry of Norway. This registry includes information about all births in Norway from 16^{+0} weeks of gestation and beyond since 1967 [13]. The reporting of births to the Medical Birth Registry is compulsory by law and is performed by the midwife or the doctor attending the delivery.

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Study population

We aimed at including all singleton pregnancies in Norway during the years 1967–2014 ($n = 2\ 747\ 844$) (Fig. 1). We excluded pregnancies with missing information about gestational age of the offspring at birth and pregnancies with gestational age at birth less than 23^{+0} weeks. We also excluded pregnancies with missing offspring birthweight, offspring sex or maternal age. Of the remaining, we excluded pregnancies with outlying values on gestational age at birth ($\geq 46^{+0}$ weeks) or offspring birthweight (<250 g or >6500 g). A total of 2 607 199 pregnancies could be included in our data analyses.

Study factors

Our main outcome measure was fetal death (yes/no). Fetal death was defined as no sign of life at birth in offspring born in pregnancy week 23^{+0} or beyond. A total of 65.5% of the fetal deaths were reported to have occurred antepartum, 11.4% intrapartum, and for 23.1% the time of death was not reported. Induced abortions are not performed in pregnancy week 23^{+0} or beyond, according to the Norwegian Act on Induced Abortion (https://lovdata.no/dokument/NL/lov/1975-06-13-50).

Preeclampsia (yes/no) included pregnancies with preeclampsia and/or eclampsia. Preeclampsia was defined as blood pressure $\geq$140/90 mmHg and proteinuria with dip-stick $\geq$1, whereas eclampsia was defined as preeclampsia with maternal seizures. This definition of preeclampsia has been used in Norway throughout our study period.

Birthweight was reported in grams. Since offspring birthweight varies by gestational age, and gestational age at birth may vary by maternal preeclampsia status, we made adjustment for gestational age at birth by using birthweight z-scores in our data analyses [14]. We calculated z-scores by using means and standard deviations of birthweight by gestational week in the study sample as a whole [15]. Z-scores were calculated separately for male and female offspring. The distribution of z-scores was grouped into percentiles as follows: <1, 1–2.5, 2.5–10, 10–90, 90–97.5, 97.5–99 and >99 percentile of birthweight.

During the years 1967–1999, gestational age at birth was calculated from the date of the last menstrual period. After 1999, the gestational age at birth estimate was based on fetal size at routine fetal ultrasonographic examination in pregnancy week 17-19. Such examination was performed for 97.3% of all pregnancies after 1999.

Statistical analyses

We calculated the absolute risk of fetal death (in percent) in pregnancies with and in pregnancies without preeclampsia. The absolute risk was calculated for the study sample as a whole, and within categories of offspring birthweight (categories described above). The relative risk of fetal death in pregnancies with preeclampsia compared to pregnancies without preeclampsia was estimated as crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) in the sample as a whole, and within categories of offspring birthweight. Non-preeclamptic pregnancies were used as the reference group within each birthweight category. We made adjustments for maternal age (in years at the time of delivery), parity (previous deliveries in pregnancy week 16^{+0} or beyond, coded 0 or $\geq$1) and maternal diabetes (type 1 or type 2 diabetes mellitus, gestational diabetes, or use of anti-diabetic medication during pregnancy, coded yes or no).

We repeated the above analyses for births during the years: 1967–1983 and 1984–2014, and in supplementary analyses, we further sub-grouped the year of birth into: 1967–1973, 1974–1983, 1984–1993, 1994–2003 and 2004-2014. To test for consistency of

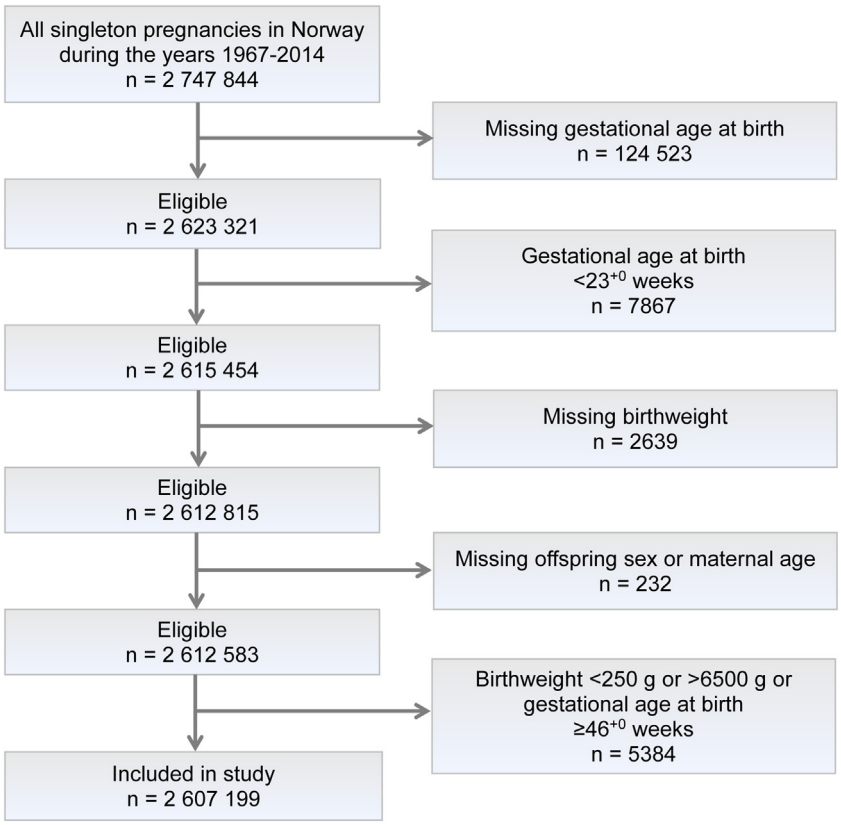

Fig. 1. Flow chart of the study sample.

Table 1
Characteristics of the study sample, 2 607 199 singleton pregnancies in Norway during the period 1967–2014.

	Preeclampsia		Fetal death		
Characteristics	Yes	No	Yes	No	Total
Maternal age (years, mean)	27.7	27.8	27.8	27.8	27.8
Number of previous deliveries (mean)	0.6	0.9	1.1	0.9	0.9
Gestational age of offspring at birth (days, mean)	270.8	280.6	240.1	280.5	280.3
Offspring birthweight (grams, mean)	3154.2	3537.7	2040.4	3535.7	3526.5
Offspring birthweight z-score (mean)	−0.262	0.008	−0.794	0.005	0.000
Total number of pregnancies (% of total)	76 066 (2.9)	2 531 133 (97.1)	16 105 (0.6)	2 591 094 (99.4)	2 607 199 (100)

our findings, we studied pregnancies with delivery in pregnancy week 28^{+0} or beyond separately. In these analyses, only fetal deaths that were reported to have occurred antepartum were used as outcome.

All statistical analyses were conducted by using IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY, USA).

Ethical approval

Use of the Medical Birth Registry of Norway for research is approved by the Norwegian Data Inspectorate. The advisory committee for the Medical Birth Registry has recommended this study (Reference number 07/944/236).

Results

A total of 16 105 fetal deaths occurred during the years 1967–2014, representing 0.6% of all births from 23^{+0} weeks of gestation and beyond (Table 1). Preeclampsia occurred in 76 066 pregnancies (2.9% of all pregnancies). Mean birthweight was 3154.2 g in pregnancies with preeclampsia, and 3537.7 g in pregnancies without preeclampsia (Student's *t*-test, $P < 0.001$). Preeclamptic pregnancies were on average 9.8 days shorter than non-preeclamptic pregnancies (Student's *t*-test, $P < 0.001$).

During the study period as a whole, the absolute risk of fetal death was higher in preeclamptic compared to non-preeclamptic pregnancies (1.6% *vs* 0.6%) (Table 2). The crude OR for fetal death associated with preeclampsia was 2.73 (95% CI 2.57–2.89).

The absolute risk of fetal death was highest in pregnancies with the lowest offspring birthweight (<1 percentile) (Table 2, Fig. 2), and in these pregnancies there was little difference in fetal death risk in pregnancies with preeclampsia compared to pregnancies without preeclampsia (7.0% *vs* 6.3%, crude OR 1.12, 95% CI 0.96–1.32). In pregnancies with offspring birthweight within the 10–90 percentiles, fetal death occurred in 1.2% of pregnancies with preeclampsia, and in 0.5% of pregnancies without preeclampsia (crude OR 2.45, 95% CI 2.26–2.65). In pregnancies with the highest offspring birthweight (>99

Table 2
Risk of fetal death according to presence of preeclampsia within percentiles of birthweight. Risks are presented as absolute risks (percent) and crude and adjusted odds ratios with 95% confidence intervals. Non-preeclamptic pregnancies represent the reference group. Results are presented for all singleton pregnancies in Norway during the total study period 1967–2014, during the years 1967-83 and during the years 1984–2014.

		Preeclampsia					
		Yes		No			
Birthweight percentiles	Total (n)	Fetal death % (n)	Live birth % (n)	Fetal death % (n)	Live birth % (n)	cOR (95% CI)	aOR* (95% CI)
During the total study period, 1967–2014							
<1	26 085	7.0 (182)	93.0 (2425)	6.3 (1472)	93.7 (22 006)	1.12 (0.96-1.32)	1.13 (0.96-1.32)
1–2.5	39 280	4.0 (105)	96.0 (2547)	1.9 (679)	98.1 (135 949)	2.18 (1.77-2.69)	2.22 (1.80-2.75)
2.5–10	194 965	2.5 (230)	97.5 (8959)	1.1 (2063)	98.9 (183 713)	2.29 (1.99-2.62)	2.27 (1.97-2.61)
10–90	2 086 067	1.2 (658)	98.8 (53 641)	0.5 (10 127)	99.5 (2 021 641)	2.45 (2.26-2.65)	2.40 (2.22-2.60)
90–97.5	195 468	0.3 (13)	99.7 (4974)	0.2 (347)	99.8 (190 134)	1.43 (0.82-2.49)	1.15 (0.66-2.02)
97.5–99	39 277	0.6 (8)	99.4 (1266)	0.2 (91)	99.8 (37 912)	2.63 (1.28-5.44)	2.13 (1.01-4.47)
>99	26 057	1.2 (13)	98.8 (1045)	0.5 (117)	99.5 (24 882)	2.65 (1.49-4.71)	2.05 (1.13-3.70)
Total	2 607 199	1.6 (1209)	98.4 (74 857)	0.6 (14 896)	99.4 (2 516 237)	2.73 (2.57-2.89)	2.63 (2.48-2.79)
During 1967–1983							
<1	13 739	12.5 (172)	87.5 (1199)	8.7 (1071)	91.3 (11 297)	1.51 (1.27-1.80)	1.50 (1.26-1.79)
1–2.5	17 623	8.7 (90)	91.3 (950)	2.6 (434)	97.4 (16 149)	3.53 (2.78-4.47)	3.45 (2.71-4.39)
2.5–10	81 466	6.6 (187)	93.4 (2653)	1.5 (1171)	98.5 (77 455)	4.66 (3.98-5.47)	4.28 (3.64-5.03)
10–90	733 127	2.8 (383)	97.2 (13 200)	0.7 (5150)	99.3 (714 394)	4.03 (3.62-4.47)	3.74 (3.36-4.16)
90–97.5	61 053	0.4 (5)	99.6 (1242)	0.3 (173)	99.7 (59 633)	1.39 (0.57-3.38)	1.15 (0.47-2.82)
97.5–99	11 812	1.3 (4)	98.7 (306)	0.4 (46)	99.6 (11 456)	3.26 (1.17-9.10)	2.65 (0.92-7.63)
>99	7 653	3.2 (8)	96.8 (239)	0.7 (50)	99.3 (7356)	4.93 (2.31-10.50)	4.31 (1.98-9.39)
Total	926 473	4.1 (849)	95.9 (19 789)	0.9 (8095)	99.1 (897 740)	4.76 (4.43-5.11)	4.34 (4.04-4.67)
During 1984–2014							
<1	12 346	0.8 (10)	99.2 (1226)	3.6 (401)	96.4 (10 709)	0.22 (0.12-0.41)	0.22 (0.12-0.41)
1–2.5	21 657	0.9 (15)	99.1 (1597)	1.2 (245)	98.8 (19 800)	0.76 (0.45-1.28)	0.76 (0.45-1.28)
2.5–10	113 499	0.7 (43)	99.3 (6306)	0.8 (892)	99.2 (106 258)	0.81 (0.60-1.10)	0.81 (0.60-1.11)
10–90	1 352 940	0.7 (275)	99.3 (40 441)	0.4 (4977)	99.6 (1 307 247)	1.79 (1.58-2.02)	1.74 (1.54-1.97)
90–97.5	134 415	0.2 (8)	99.8 (3732)	0.1 (174)	99.9 (130 501)	1.61 (0.79-3.27)	1.28 (0.62-2.63)
97.5–99	27 465	0.4 (4)	99.6 (960)	0.2 (45)	99.8 (26 456)	2.45 (0.88-6.83)	1.92 (0.67-5.48)
>99	18 404	0.6 (5)	99.4 (806)	0.4 (67)	99.6 (17 526)	1.62 (0.65-4.04)	1.29 (0.51-3.28)
Total	1 680 726	0.6 (360)	99.4 (55 068)	0.4 (6801)	99.6 (1 618 497)	1.56 (1.40-1.73)	1.49 (1.34-1.66)

cOR, crude odds ratio; *aOR*, adjusted odds ratio; *CI*, confidence interval.
* Adjusted for gestational age at birth, offspring sex, maternal age, parity and maternal diabetes.

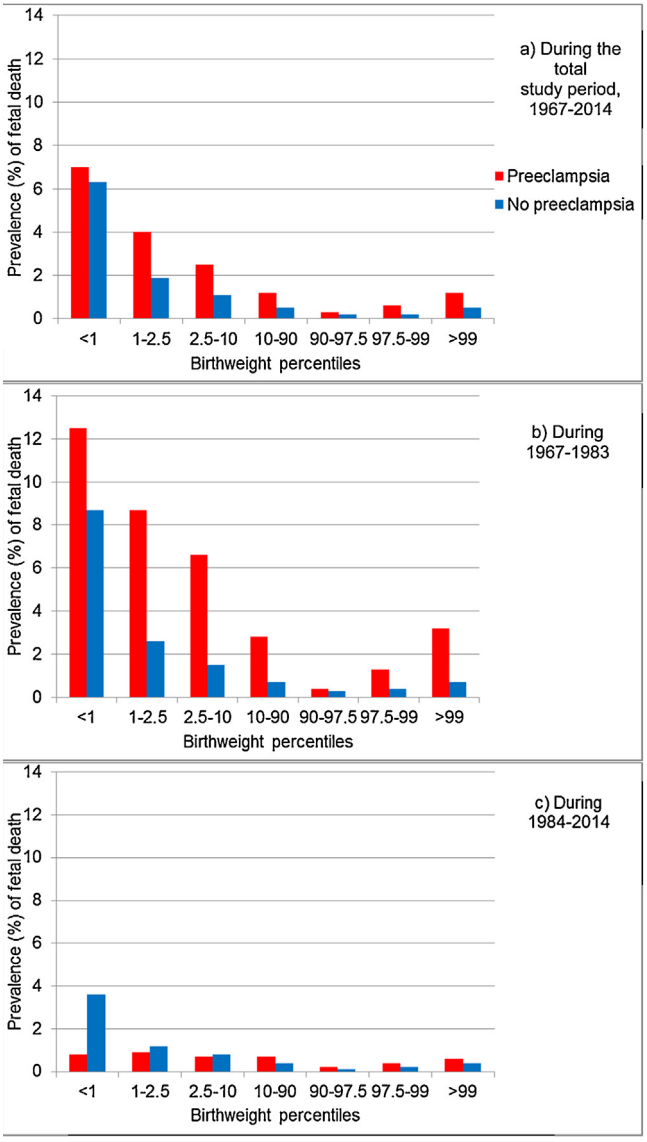

Fig. 2. Prevalence (%) of fetal death in pregnancies with and in pregnancies without preeclampsia within birthweight percentile categories in Norway during the years. a) 1967–2014, b) 1967–1983 and c) 1984–2014.

percentile, fetal death occurred in 1.2% of pregnancies with preeclampsia, and in 0.6% of non-preeclamptic pregnancies (crude OR 2.65, 95% CI 1.49–4.71).

Changes over time

During the years 1967–1983, the prevalence of preeclampsia was 2.2% (Table 2). Fetal death occurred in 4.1% of all pregnancies with preeclampsia, and in 0.9% of non-preeclamptic pregnancies (crude OR 4.76, 95% CI 4.43–5.11).

In pregnancies with the lowest offspring birthweight (<1 percentile), fetal death occurred in 12.5% of pregnancies with preeclampsia, and in 8.7% of non-preeclamptic pregnancies (crude OR 1.51, 95% CI 1.27–1.80) (Table 2, Fig. 2). In pregnancies with offspring birthweight within the 10–90 percentiles, fetal death occurred in 2.8% of pregnancies with preeclampsia, and in 0.7% of pregnancies without preeclampsia (crude OR 4.03, 95% CI 3.62–4.47). Similar figures were seen in pregnancies with the highest offspring birthweight (>99 percentile), (3.2% *vs* 0.7%, crude OR 4.93, 95% CI 2.31–10.50).

During the years 1984–2014, the absolute risk of fetal death was greatly reduced compared to the years 1967–1983, particularly in preeclamptic pregnancies (Table 2). Thus, during the years 1984–2014, fetal death occurred in 0.6% of pregnancies with preeclampsia, and in 0.4% of pregnancies without preeclampsia (crude OR 1.56, 95% CI 1.40–1.73). The prevalence of preeclampsia during these years was 3.3%.

The reduction in fetal death risk was most prominent in pregnancies with the lowest offspring birthweight (<1 percentile), and in these pregnancies, the risk of fetal death during the years 1984–2014 was lower in preeclamptic pregnancies compared to non-preeclamptic pregnancies (0.8% *vs* 3.6%, crude OR 0.22, 95% CI 0.12-0.41) (Table 2, Fig. 2). Only in pregnancies with offspring birthweight within the 10–90 percentiles, the risk of fetal death was significantly higher in pregnancies with preeclampsia compared to non-preeclamptic pregnancies (0.7% *vs* 0.4%, crude OR 1.79, 95% CI 1.58–2.02). In pregnancies with the highest offspring birthweight (>99 percentile), fetal death occurred in 0.6% of pregnancies with preeclampsia, and in 0.4% of non-preeclamptic pregnancies (crude OR 1.62, 95% CI 0.65–4.04).

The overall decline in fetal death risk occurred gradually during our study period (Supplementary material, Table S1). However, in pregnancies with preeclampsia and offspring birthweight <1 percentile, there was a distinct decline from 1974–1983 to 1984–1993. In 1974–1983, fetal death occurred in 8.3% of pregnancies with preeclampsia, and in 7.5% of pregnancies without preeclampsia (crude OR 1.13, 95% CI 0.84–1.52). In the next decade, 1984–1993, the corresponding figures were 0.7% and 3.9% (crude OR 0.17, 95% CI 0.06-0.45). After 1994, the point OR estimate for fetal death has been lower in pregnancies with preeclampsia compared to pregnancies without preeclampsia in pregnancies with offspring birthweight < 10 percentile.

We repeated our main analyses among pregnancies with delivery in pregnancy week 28^{+0} and beyond, and we used antepartum fetal death as outcome measure (54.6% of all fetal deaths in our main analyses). The results remained essentially unchanged (Supplementary material, Table S2).

Discussion

Main findings

In this population study of more than 2.5 million singleton pregnancies in Norway, the risk of fetal death associated with preeclampsia declined during the years 1967–2014, particularly in pregnancies with very small for gestational age offspring.

Strengths and limitations

The major strength of our study is the large sample size, which has provided statistical power to study temporal changes in fetal death risk in preeclamptic and non-preeclamptic pregnancies within categories of birthweight. We included all singleton pregnancies in Norway. It is therefore unlikely that a skewed selection of study participants has biased our results.

The definition of fetal death has remained unchanged over time. Also, the definition of preeclampsia has not changed notably in Norway during the study period [16]. Thus, it is unlikely that changes in the definitions of our main study factors have influenced our estimates.

The likelihood of reporting fetal deaths and preeclampsia to the Medical Birth Registry may have changed during our study period. For instance, in the first part of our study period, it is possible that preeclampsia was more likely to be reported if fetal death had occurred. However, we found little difference in the prevalence of preeclampsia according to offspring vital status in pregnancies

with very small offspring in the first part of our study period among pregnancies with very small offspring. This observation does not support differential reporting or diagnosing of pre-eclampsia.

We made supplementary analyses of pregnancies with delivery in pregnancy week 28^{+0} or beyond. In these analyses, we excluded pregnancies where fetal death had occurred intrapartum or the time of fetal death was not reported, since fetal death during labor may be unrelated to preeclampsia. The results remained essentially the same.

We made adjustments for risk factors of preeclampsia that have increased in prevalence over time, such as high maternal age, being a first time mother and maternal diabetes [2], but the estimated associations of preeclampsia with fetal death remained essentially unchanged. We also made adjustment for differences in gestational age at birth by using birthweight z-score.

The occurrence of fetal death could possibly influence birthweight [17,18]. Nevertheless, it is unlikely that such changes are differential by maternal preeclampsia status, birthweight or year of birth.

Interpretation

During the first part of our study period (1967–1983), we found that preeclampsia increased the risk of fetal death within all categories of offspring birthweight. Although the absolute risk of fetal death was highest in very small for gestational age offspring, the relative risk of fetal death associated with preeclampsia was highest in pregnancies with normal or high offspring birthweight. This finding suggests that there are other factors than fetal growth restriction that cause fetal death in preeclamptic pregnancies.

There has been an overall decline in fetal death rate during the past decades [21], and this decline has been most prominent in pregnancies with preeclampsia [11,12]. Interestingly, we found that the temporal decline in fetal death rate was particularly pronounced in preeclamptic pregnancies with small for gestational age offspring. In fact, the risk of fetal death in small for gestational age offspring was lower in preeclamptic than in than non-preeclamptic pregnancies in the last part of our study period. Only in pregnancies with offspring birthweight within the 10–90 percentiles, we found a persistent increased risk of fetal death in pregnancies with preeclampsia throughout the study period.

Identification of high risk pregnancies and timely intervention are preconditions for prevention of fetal death. Preeclampsia is a well-known risk factor for fetal death, and in 1984, a public screening program for preeclampsia was implemented in primary antenatal health care in Norway. At least ten routine clinical examinations were recommended [22], and antenatal and obstetric health care is free of charge. It is assumed that virtually all pregnant women who live in Norway follow the program [23,24]. Women with clinical signs of preeclampsia are referred to hospitals with specialized obstetric health care for further clinical examinations.

Both small and large for gestational age offspring are known to be at increased risk of fetal death [19,20], and ultrasonography has made it possible to identify pregnancies with abnormal fetal growth. Fetal ultrasonography was gradually introduced in Norway after 1975, and by 1985, almost all deliveries in the country (96%) took place in maternity wards where ultrasonographic examinations could be performed [25]. Since women with preeclampsia are routinely referred to obstetric health care, abnormal fetal growth is more likely to be diagnosed in these pregnancies than in non-preeclamptic pregnancies. In non-preeclamptic pregnancies, fetal ultrasonographic examinations are not routinely performed, except for in pregnancy week 17–19, which is prior to the occurrence of preeclampsia. Interestingly, after 1984, we found a marked decrease in fetal death risk in preeclamptic pregnancies with a small for gestational age offspring. This marked decrease strongly suggests that the introduction of screening for pre-eclampsia, in combination with fetal ultrasonographic examinations, have been important for preventing fetal death in small for gestational age offspring.

Conclusion

In this study of all pregnancies in Norway, we found that the risk of fetal death associated with preeclampsia was greatly reduced during the years 1967–2014, particularly in pregnancies with a small for gestational age offspring. In pregnancies with a normal weight offspring, the risk of fetal death in pregnancies with preeclampsia is still higher than in non-preeclamptic pregnancies. This increased risk may not be sufficiently acknowledged, and it is likely that there still is a potential for further prevention of fetal death in preeclamptic pregnancies with normal offspring birthweight.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgements

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eurox.2019.100009.

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