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

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Key words
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Abstract

Objective. To study the association of placental weight and placental weight/birthweight ratio with gestational age-specific fetal death. *Design.* Population-based study. *Setting.* Medical Birth Registry of Norway. *Population.* All singleton births in Norway, 1999–2008 (n = 534 892). *Methods.* Gestational age-specific quartiles of placental weight and placental weight/birthweight ratio were estimated, and proportions of fetal deaths and live births within the lowest and highest quartile were compared. The risk of fetal death associated with placental weight/birthweight ratio was estimated as crude and adjusted odds ratios. *Main outcome measures.* Offspring vital status. *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. Adjusted odds ratio of fetal death in preterm deliveries was 1.67 (95% confidence interval 1.44–1.94) for placental weight/birthweight ratio in the lowest quartile and 1.79 (95% confidence interval 1.55–2.08) in the highest quartile. Corresponding odds ratios for deliveries at term were 1.76 (95% confidence interval 1.50–2.06) and 1.18 (95% confidence interval 0.99–1.41). *Conclusions.* Both small and large placentas relative to birthweight were associated with fetal death in preterm births. At term, only small placentas relative to birthweight 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.

Abbreviations: ART, assisted reproductive technology; OR, odds ratio.

Introduction

Fetal death occurs in the Western world in 0.5–1% of all pregnancies lasting longer than 20 weeks (1). A majority of stillbirths are still unexplained, even though a substantial number of studies have been performed on the causes of fetal death (2). The risk of fetal death has been suggested to vary considerably by length of gestation and seems to be particularly high in term and post term pregnancies (3,4). The causes of the increased risk near term are insufficiently understood.

The placenta provides fetal nutrients and oxygen supply to the fetus, and it also produces pregnancy-conserving hormones. A well-functioning placenta is essential

Key Message

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

for a successful pregnancy, and a reduced placental function has been suggested to be one of the mechanisms causing fetal death (5). Since the fetus has an increasing demand for oxygen and nutrition with length of gestation, a relative placental dysfunction may be more closely associated with fetal death in the last part of pregnancy than in early pregnancy.

Placental weight has been suggested as an indicator of placental function, and small placentas may be less functional. We believe that the increased risk of fetal death in term and post term pregnancies may be related to impaired placental function. Thus, the placentas in pregnancies with fetal death at term may be smaller relative to birthweight compared with pregnancies with fetal death at earlier gestation. We studied the association of placental weight, birthweight and placental weight/birthweight ratio with gestational age-specific fetal death. We included all singleton births in Norway at 23 weeks of gestation or beyond, during 1999–2008.

Material and methods

We used data from the Medical Birth Registry of Norway (6). This registry contains information on all births in Norway since 1967. The notification of births to the Medical Birth Registry is compulsory by law and is made by the midwife or attending physician shortly after delivery. Information on placental weight has been reported since 1999.

Our study population comprised all singleton deliveries in Norway during 1999–2008, a total of 567 176 births. Information on gestational length, placental weight and birthweight was missing for 28 812 births and these were therefore excluded from our study sample. We also excluded 2943 births with recorded gestational length of less than 23^{+0} weeks or more than 42^{+6} weeks. Deliveries of offspring with birthweight less than 250 g or above 6500 g, or placental weight less than 25 g or above 2500 g were considered outlying values, and 529 births with such values were excluded. Hence, a total of 534 892 births (94.3%) could be included in our study sample.

Vital status at birth was the outcome variable in this study (fetal death: yes/no). All fetal deaths were included in our study: 78.5% occurred antepartum, 8.0% intrapartum and for 13.5% the time of fetal death was not reported. Gestational length at birth was based on term estimation at routine ultrasound fetal examination in gestational weeks 17–19. This information was available for 97.3% of the pregnancies, and for the remaining, the date of term was based on the first day of last menstrual period. Gestational length at birth was divided into categories of two weeks' intervals. Placental weight was reported in grams. The placentas were weighed fresh with membranes and umbilical cord attached. Birthweight was also reported in grams. We calculated placental weight/birthweight ratios by dividing placental weight by birthweight in grams. Hence, in pregnancies with a low ratio, the placental weight relative to birthweight was low. Placental weight, birthweight and placental weight/birthweight ratio were divided into gestational age-specific quartiles based on the distribution of the total sample. The lowest quartile (smallest 25%) was coded 1 and the highest quartile (largest 25%) was coded 4.

Statistical analyses

We compared mean placental weight, mean birthweight and mean placental weight/birthweight ratio in live births and in pregnancies with fetal death at every two-week interval of gestational length. In term deliveries ($\geq$ 37 weeks of gestation), we also calculated mean placental weight/birthweight ratio within 500-g categories of birthweight. Thereafter, we estimated the proportions of live births and fetal deaths in the lowest and the highest quartile of placental weight, birthweight and placental weight/birthweight within two-week categories of gestational lengths.

Finally, we estimated the crude and the adjusted odds ratios (ORs) of fetal death according to placental weight/birthweight ratio in quartiles, and the second and the third quartile combined were used as the reference group. In multivariable analyses, adjustments were made for maternal age at delivery, preeclampsia, diabetes, smoking, parity and assisted reproductive technology (ART), as these factors may influence the association of placental weight with fetal death. Maternal age at delivery was divided into five-year intervals. Preeclampsia was defined as blood pressure $\geq$ 140/90 and proteinuria with dipstick $\geq$ 1, and diabetes included type 1 or type 2 diabetes mellitus, gestational diabetes or use of anti-diabetic medication during pregnancy. Smokers were defined as occasional or daily smokers at the time of the first antenatal care visit. Parity was defined as previous births after 16 weeks of gestation, and was coded 0 or $\geq$ 1. ART was coded yes or no and included in vitro fertilization, intracytoplasmic sperm injection, the combination of both, or other and unspecified methods of ART. Separate analyses were carried out for preterm deliveries (<37 weeks of gestation) and for term deliveries ($\geq$ 37 weeks of gestation).

The Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. The study was approved by the Norwegian Data Inspectorate and the Publication Committee of the Medical Birth Registry of Norway.

Results

Fetal death occurred in 0.3% of all singleton births at 23 weeks of gestation or beyond in Norway during 1999–2008. The mean length of gestation was 278.7 days (SD 13.1 days) in live births and it was 238.8 days (SD 41.5 days) in pregnancies with fetal death. At any length of gestation, mean placental weight and mean birthweight were higher in pregnancies with live born as compared with stillborn offspring (Table 1). The mean placental weight/birthweight ratio decreased with length of gestation in both pregnancies with live born and stillborn offspring, but the decrease was most pronounced in pregnancies with a stillborn offspring. Overall, the placental weight/birthweight ratio was highest in pregnancies with a stillborn offspring. However, we also performed analyses stratified by birthweight in term deliveries and found an opposite pattern compared with the sample as a whole. At term, the mean placental weight/birthweight ratio was lower in pregnancies with a stillborn offspring, in particular in offspring weighing less than 2500 g (Table 2).

Pregnancies with fetal death were overrepresented in the lowest quartile of placental weight. This was true for deliveries at any gestational length (Figure 1a). In gestational weeks 39–40, 47.3% of pregnancies with fetal death were in the lowest quartile of placental weight. The corresponding proportion in live births was 25.5%. In comparison, in the highest quartile of placental weight, pregnancies with fetal death were underrepresented, and in gestational weeks 39–40, 18.0% of the pregnancies with fetal death were in the highest quartile of placental weight as compared with 25.2% of live births (Figure 1b).

The distribution of birthweights according to vital status at birth displayed similar patterns as placental weight. Pregnancies with fetal death were overrepresented in the lowest quartile of birthweight (Figure 2a) and underrepresented in the highest (Figure 2b). In gestational weeks 39–40, 47.9% of pregnancies with fetal death were in the lowest quartile of birthweight and 16.5% were in the highest quartile.

When estimating the distribution of placental weight/birthweight ratio according to vital status at birth, a more complex pattern became apparent. In pregnancies with fetal death, the proportion of pregnancies with a small placenta relative to birthweight increased by length of gestation at delivery (Figure 3a). In gestational weeks 25–26, 28.7% of pregnancies with fetal death had a placenta in the lowest quartile of placental weight/birthweight ratio, in which the placentas were small relative to birthweight. In gestational weeks 39–40, this proportion was 35.9%. The fetal deaths were also overrepresented among pregnancies with a large placenta relative to birthweight, but only in pregnancies with delivery before term (Figure 3b). In gestational weeks 25–26, 36.9% of pregnancies with fetal death were in the highest quartile of the placental weight/birthweight ratio, whereas that was true for only 22.8% with fetal death in gestational weeks 39–40.

The differential associations of placental weight/birthweight ratio with fetal death by length of gestation were also estimated as adjusted ORs (Table 3). In preterm deliveries, the association with placental weight/birthweight ratio displayed a U-shaped pattern, and both small and large placentas relative to birthweight were associated with fetal death. Thus, the adjusted OR of fetal death was 1.67 (95% confidence interval 1.44–1.94) for placental weight/birthweight ratios in the lowest quartile compared with the reference group (second and third quartile combined). For placental weight/birthweight ratios in the highest quartile, the OR was 1.79 (95% confidence interval 1.55–2.08) after adjustments for maternal

Table 1. Mean placental weight, birthweight and placental weight/birthweight ratio in grams according to gestational length in 534 892 births in Norway during 1999–2008.

	n		Mean placental weight (SD)		Mean birthweight (SD)		Mean placental weight/birthweight ratio (SD)	
Gestational weeks	Live births	Fetal deaths	Live births	Fetal deaths	Live births	Fetal deaths	Live births	Fetal deaths
23–24	320	203	271.7 (108.7)	238.0 (107.0)	705.3 (427.4)	529.9 (152.7)	0.41 (0.14)	0.45 (0.17)
25–26	570	122	310.9 (129.2)	274.7 (173.4)	858.7 (398.6)	692.3 (334.9)	0.38 (0.13)	0.40 (0.16)
27–28	906	144	335.2 (123.2)	309.5 (193.9)	1079.3 (422.7)	873.9 (339.5)	0.32 (0.10)	0.35 (0.15)
29–30	1375	117	394.6 (136.3)	382.5 (214.1)	1419.9 (461.9)	1203.3 (452.1)	0.28 (0.08)	0.31 (0.12)
31–32	2496	132	460.7 (143.5)	405.2 (205.5)	1846.4 (488.2)	1576.6 (516.4)	0.25 (0.06)	0.25 (0.07)
33–34	5813	151	531.4 (146.0)	470.1 (169.1)	2320.4 (480.4)	2025.6 (514.3)	0.23 (0.05)	0.23 (0.07)
35–36	17 279	189	597.8 (151.9)	517.7 (206.7)	2829.5 (494.0)	2464.4 (537.7)	0.21 (0.04)	0.21 (0.08)
37–38	93 179	286	647.2 (148.2)	584.8 (184.2)	3304.7 (473.9)	2999.6 (693.0)	0.20 (0.04)	0.20 (0.05)
39–40	271 659	334	676.7 (142.5)	614.0 (193.1)	3615.4 (454.9)	3372.5 (667.6)	0.19 (0.04)	0.18 (0.05)
41–42	139 440	177	712.3 (147.8)	620.1 (174.1)	3863.8 (468.8)	3574.8 (662.4)	0.18 (0.03)	0.17 (0.04)
Total	533 037	1855	673.8 (151.2)	472.0 (229.7)	3563.5 (578.6)	2186.2 (1230.8)	0.19 (0.04)	0.26 (0.14)

Table 2. Mean placental weight/birthweight ratio in live births and in fetal deaths at term (≥37 weeks of gestation) within categories of birthweight.

	Live births			Fetal deaths		
Birthweight	*n*	Placental weight/birthweight ratio	95%CI	*n*	Placental weight/birthweight ratio	95%CI
<2500	5005	0.219	0.214–0.224	89	0.202	0.188–0.216
2500–2999	45 523	0.192	0.192–0.193	178	0.193	0.186–0.200
3000–3499	155 967	0.189	0.188–0.189	245	0.186	0.180–0.191
3500–3999	189 419	0.187	0.187–0.187	173	0.175	0.169–0.180
4000–4499	88 491	0.187	0.187–0.187	66	0.177	0.168–0.187
4500–4999	20 175	0.188	0.188–0.189	32	0.183	0.163–0.202
≥5000	2698	0.190	0.189–0.192	14	0.189	0.157–0.222
Total	504 278	0.188	0.188–0.188	797	0.186	0.183–0.189

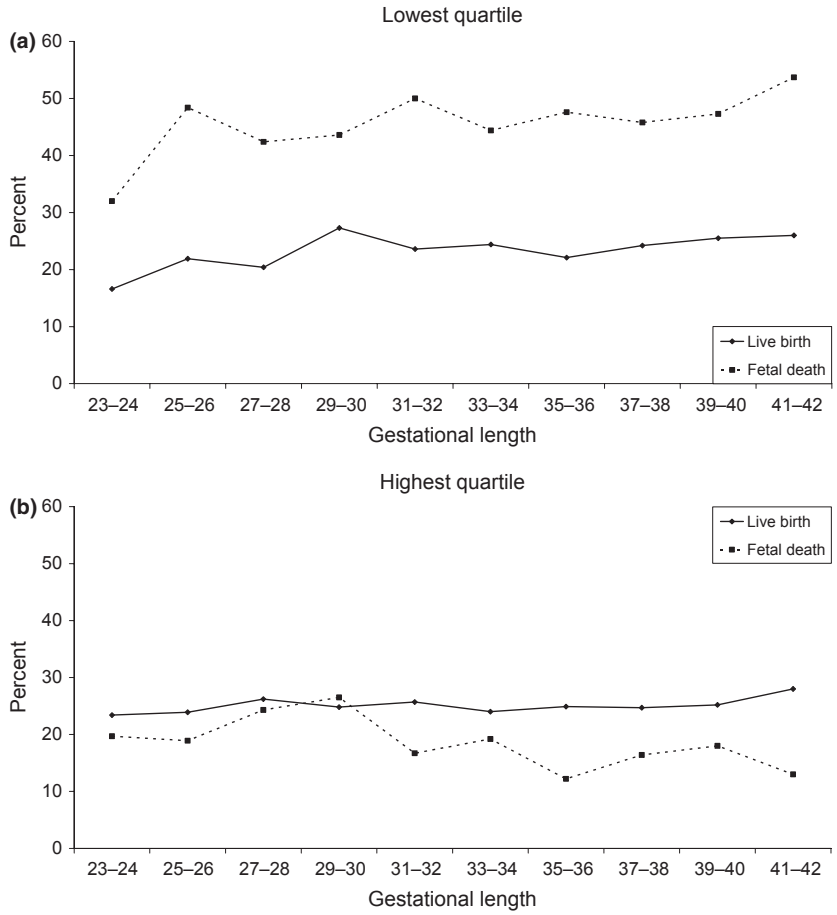

Figure 1. Placental weight in the lowest (a) and the highest (b) quartile according to gestational length among live births and fetal deaths in Norway in 1999–2008 (*n* = 534 892).

age, preeclampsia, diabetes, smoking, parity and ART. In term deliveries, only small placental weight/birthweight ratios were associated with fetal death, and the adjusted OR was 1.76 (95% confidence interval 1.50–2.06) comparing the lowest quartile of placental weight/birthweight ratio with the reference group. For the highest quartile, the adjusted OR of fetal death was 1.18 (95% confidence interval 0.99–1.41). We did separate analyses with additional adjustment for cesarean delivery (yes/no). Also, we excluded from the study sample offspring with recorded

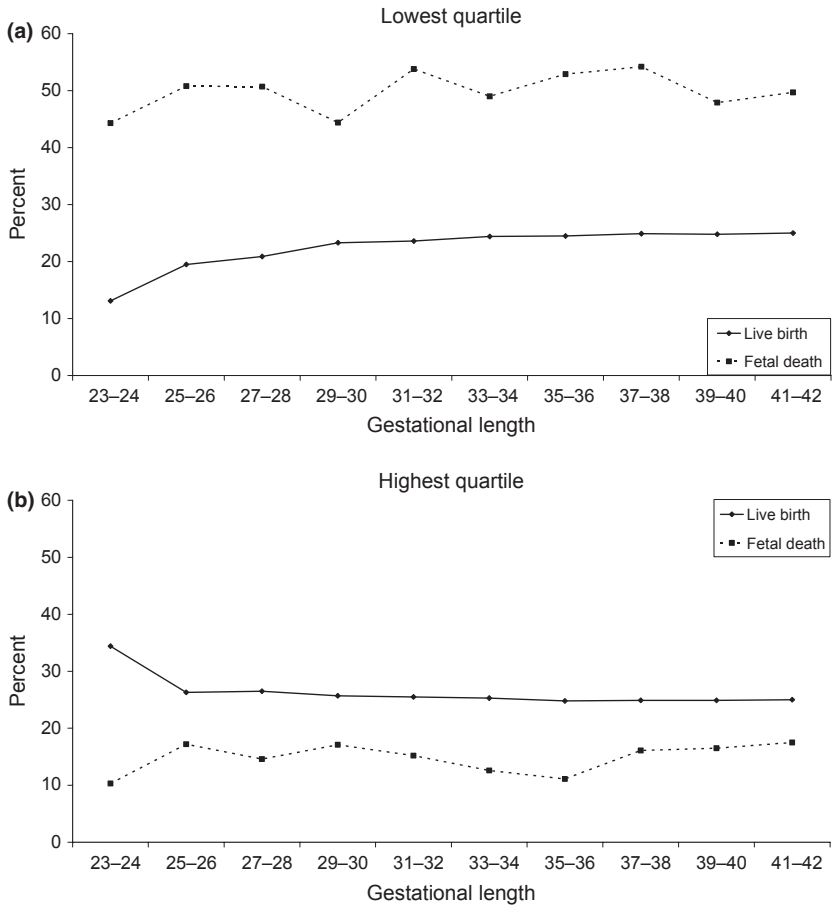

Figure 2. Birthweight in the lowest (a) and the highest (b) quartiles according to gestational length among live births and fetal deaths in Norway in 1999–2008 (n = 534 892).

congenital malformations (2.1%). The associations of fetal death with placental weight remained essentially unchanged in these analyses (data not shown).

Discussion

In this study of more than half a million pregnancies in Norway during 1999–2008, we found fetal deaths to be associated with small placentas and also with low placental weight relative to birthweight. In fetal deaths before term, high placental weight relative to birthweight was also associated with fetal death.

Our results may be misleading if placental weight relative to birthweight changes as a consequence of fetal death. However, little information exists on changes in placental weight or birthweight when the fetus lies dead in utero. Fetal weight may increase as a consequence of tissue edema (7). On the other hand, weight reduction due to atrophy and autolysis may also occur (8). The time from intrauterine death until delivery is normally short (9), thus it is unlikely that death influences birthweight significantly. The placenta undergoes morphological changes after fetal death with increases in syncytial knots and fibrosis of the villous stroma. These changes are probably related to the cessation of fetal vascular perfusion (10). A reduction in maternal placental blood flow after fetal death has also been described (11); however, this probably has only a modest effect on placental weight. The U-shaped association of placental weight/birthweight ratio with fetal death in preterm deliveries can not be explained by changes in placental or offspring weight as a function of death. On the contrary, if there are differential changes in weight according to vital status, this association may have been underestimated.

The timing of cord clamping after delivery may influence placental weight relative to birthweight, since delayed clamping increases the blood volume in the newborn (12). Hence, delayed cord clamping in live born offspring only could have caused an underestimation of the

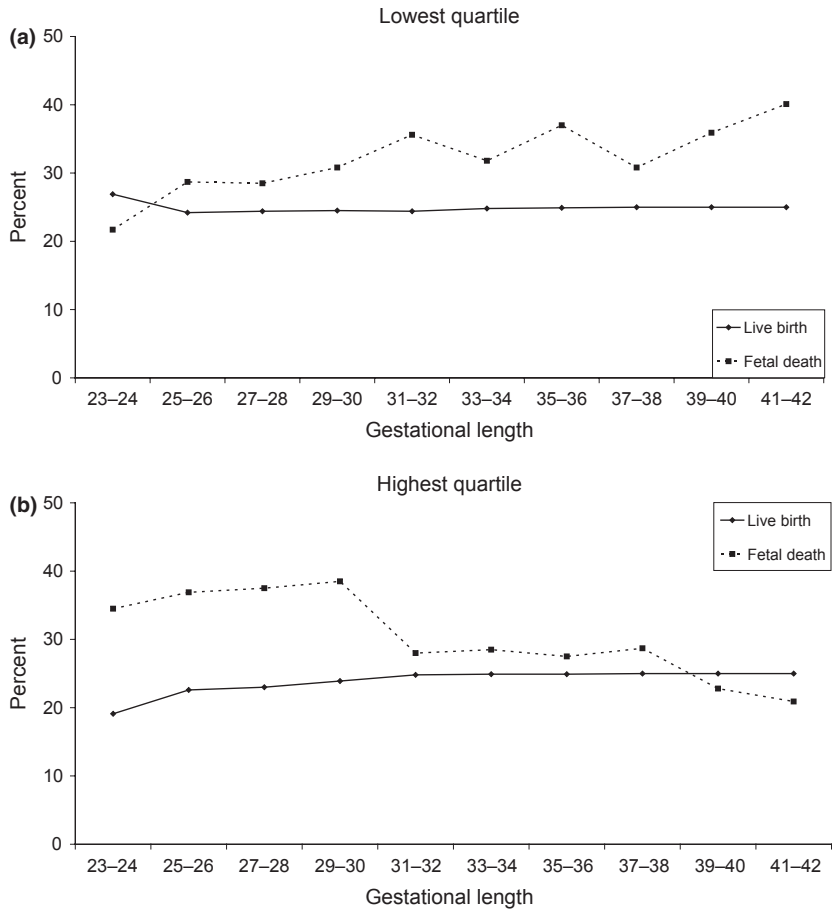

Figure 3. Placental weight/birthweight ratio in the lowest (a) and the highest (b) quartile according to gestational length among live births and fetal deaths in Norway in 1999–2008 (n = 534 892).

Table 3. The odds ratio of fetal death according to placental weight/birthweight ratio in 534 892 births in Norway during 1999–2008. Placental weight/birthweight ratio is presented in gestational length specific quartiles.

Placental weight/ birthweight ratio in quartiles	*n* live births	*n* fetal deaths	OR	95%CI	OR[a]	95%CI
	Gestational weeks 23–36					
Lowest	7135	321	1.67	1.44–1.94	1.67	1.44–1.94
Middle (2nd and 3rd)	14 520	391	1.00		1.00	
Highest	7104	346	1.81	1.56–2.10	1.79	1.55–2.08
Total	28 759	1058				
	Gestational weeks 37–42					
Lowest	125 978	279	1.73	1.47–2.03	1.76	1.50–2.06
Middle (2nd and 3rd)	252 225	323	1.00		1.00	
Highest	126 075	195	1.21	1.01–1.44	1.18	0.99–1.41
Total	504 278	797				

[a]Adjustments made for maternal age, preeclampsia, diabetes, smoking, parity and assisted reproductive technology.
CI, confidence interval; OR, odds ratio.

association of low placental weight/birthweight ratios with fetal death, but also an overestimation of the association with a high ratio.

To our knowledge, only a few studies on the association of fetal death with placental weight have been published. One study, including 5882 preterm deliveries, reported a

higher risk of adverse pregnancy outcomes in both pregnancies with small and those with large placentas (13). In another study of 59 969 term deliveries, only small placentas relative to birthweight were associated with fetal death (14). These results are in agreement with our findings. However, another hospital-based study including 84 294 births, reported no significant association of fetal-to-placental weight ratio with unexplained fetal death (15).

Small placentas may have a reduced capacity to supply the fetus with sufficient oxygen and nutrition. Thus, if the fetus is programmed to be large, a small placenta, for instance due to insufficient implantation, may be increasingly unable to provide oxygen and nutrition to the growing fetus. The increased risk for fetal death in pregnancies with low placental weight/birthweight ratio supports such hypothesis.

The association of a high placental weight/birthweight ratio with fetal death is more difficult to explain. One possible explanation is that the placentas are dysfunctional and therefore the growth of the fetus may be restricted, leading to death in some cases. Also inflammatory changes may cause enlargement of the placenta (16), and infections are likely to be a more important cause of fetal death in mid-pregnancy than at term (17,18). Infectious causes of fetal death are common in developing countries. However, also in the Western world it is assumed that between 10 and 25% of fetal deaths are caused by infection (17).

In second trimester fetal deaths, a reduced peripheral chorionic villous vascularization has been found (19). Reduced blood flow and thereby hypoxia in the placenta might initiate compensatory mechanisms through increased angiogenesis and thereby placental growth (20,21). Large placentas relative to birthweight have also been reported in other high risk pregnancies, such as pregnancies with high maternal age (22), pregnancies with diabetes, preeclampsia (23) and in pregnancies after ART (24). It is conceivable that enlargement of the placenta is an adequate biological response to a threatened fetus, but in some of these pregnancies, compensatory placental growth may not be sufficient to ensure fetal survival. The high placental weight/birthweight ratio in live born offspring weighing less than 2500 g at term supports the hypothesis that a compensatory enlarged placenta in threatened pregnancies is a biological response to increase the chances of fetal survival.

A high placental weight/birthweight ratio was not associated with fetal death in deliveries at term. This lack of association could possibly be explained by high risk pregnancies not reaching term. For instance, pregnancies with a high placental weight/birthweight ratio and a high risk of fetal death, such as pregnancies with maternal diabetes and preeclampsia (23,25) are often delivered preterm. Thus, delivery preterm may have prevented fetal deaths associated with a high placental weight/birthweight ratio that otherwise would have occurred at term. There has been a more than 70% reduction in the fetal death rate in Norway in the last 40 years (26) and this reduction has in particular been reported in pregnancies with preeclampsia (27) and with diabetes (28). It is also possible that pregnancies with a high placental weight/birthweight ratio are overrepresented among spontaneous preterm deliveries; however, such an association is difficult to study, since we do not have any information on the placental weight/birthweight ratio in pregnancies without preterm delivery.

The introduction of modern technology in obstetric care has probably been important in decreasing the fetal death rate at term (26). Offspring with increased risk of fetal death may have been identified through calculating the pulsatility index at ultrasonographic examination, since a high pulsatility index is associated with decreased placental volume (29) and placental insufficiency (30). Whether modern diagnostic methods also identify threatened pregnancies with a large placenta relative to offspring is not known.

We found both small and large placentas relative to birthweight to be associated with fetal death in preterm deliveries. At term, only small placentas relative to birthweight were associated with fetal death. Our findings encourage further studies on the increased risk of adverse pregnancy outcomes in pregnancies with a disproportionate placental weight/birthweight ratio. Understanding the mechanisms behind such disproportion may be important for prevention of fetal deaths.

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