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Cause of stillbirth and pathophysiological pathways in mothers with overweight and obesity

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Abstract

Purpose

Obesity is independently associated with stillbirth, especially in early gestation and late-term gestation. Underlying pathophysiological mechanism causing fetal death is yet not clear. The purpose of this study was to determine the association between maternal body mass index and stillbirth and its importance in potential pathophysiological mechanisms of fetal death.

Methods

In a multicenter prospective cohort study from 2002 to 2008, 1.025 women with a fetal death > 20 weeks of gestation were studied. An extensive diagnostic workup was performed including maternal blood tests, coagulation tests, autopsy and placental examination. Cause of death was classified by a multidisciplinary panel. Odds ratios for each outcome stratified by gestational age were estimated for different maternal BMI classes (underweight BMI < 18.5; overweight BMI 25.0-29.9; obesity BMI > 30.0) compared with normal weight women (BMI 18.5–24.9) by using logistic regression and cause of death was studied.

Results

We analysed 793 women. Obese women significantly more often had pre-existing hypertension, pregnancy induced hypertension or gestational diabetes. Early fetal death (< 37 weeks) in obese women is more often caused by placental bed pathology (OR 4.10, 95% CI 1.79–9.40, P 0.001), and term fetal death by developmental placental pathology (OR 1.93, 95% CI 1.01–3.71, P 0.05).

Conclusion

In obese women there are at least 2 distinct underlying pathophysiological pathways causing fetal death. The underlying mechanisms of these pathways are uncertain and should be investigated in future.

Introduction

Overweight and obesity have been defined by the WHO based on Body Mass Index (BMI). A BMI of 25.0- 29.9 kg/m^2 is classified as overweight; a BMI of 30-39.9 kg/m^2 as obesity and a BMI ≥ 40 kg/m^2 as morbid obesity. In the USA, the prevalence of obesity was 39.8% among adult women.(1) In European countries the same trend is observed, 30–37% of women in reproductive age are overweight or obese.(2) In 2021, 28.0 % of Dutch women are overweighed and 14.7 % are obese.(3) Obesity is associated with stillbirth and the risk increases with increasing BMI.(4–6) Chu et al. performed a meta-analysis including nine studies and found a 1.5 times risk (95% CI 1.1–1.9) of stillbirth among overweight women and 2.1 risk (95% CI 1.6–2.7) in obese women.(7) Jacob et al. reported an increase in stillbirth from OR 1.37 (95% CI 1.02–1.85) in women with overweight up to OR 5.04 (95% CI 1.79–14.07) in pregnant women with BMI ≥ 50. (8) Obese women are more likely to have pre-existing hypertension and diabetes, to develop pregnancy-induced hypertension, preeclampsia, gestational diabetes and fetal macrosomia.(8–13) Even when correcting for these factors, an increased maternal BMI is independently associated with stillbirth, the association is strongest at early gestation and late-term gestation.(9, 10, 14–16) Only a few studies have evaluated the cause of fetal death in relation to maternal BMI.(15, 17–19) In order to be able to prevent fetal death for these women, more insight into these deaths is

needed. Aim of this study was to evaluate the association between maternal BMI and cause of fetal death in a large cohort of stillbirths and to investigate potential causal mechanisms of fetal death related to gestational age.

Methods

We used data of our national study on fetal death (ZOBAS study), performed from 2002 till 2008 in 50 participating secondary and tertiary referral hospitals throughout the Netherlands, with the University Medical Centre in Groningen as the coordinating centre. The study is reported in detail elsewhere.(20) Women with a singleton pregnancy and fetal death diagnosed antepartum after 20 weeks of gestation were included. Pregnancy termination and intrapartum deaths were excluded. Each case of intra-uterine fetal death was evaluated according to an intensive standardized diagnostic work-up protocol. Patient information included maternal baseline characteristics, medical and obstetric history. Several medical tests were performed, including multiple blood tests, coagulation tests, viral serology, microbiologic cultures from mother and fetus, cytogenetic analysis, placental examination and autopsy.

Our primary outcome was cause of fetal death. We stratified our primary outcome by gestational age periods which were categorized as 1) 22 + 0–27 + 6 weeks of gestation, 2) 28 + 0–31 + 6 weeks of gestation, 3) 32 + 0–36 + 6 weeks of gestation and 4) ≥ 37 + 0 weeks of gestation. Gestational age was calculated from the last menstrual period and confirmed by early ultrasonography.

Cause of death was classified by a multidisciplinary team according to the Tulip classification.(21) The Tulip classification allows unambiguous classification of underlying cause and mechanism of perinatal mortality with a low percentage of unknown causes. The classification consists of six main causes: (1) congenital anomaly, (2) placenta, (3) prematurity, (4) infection, (5) other, and (6) unknown. Within the Tulip classification only one underlying cause of death can be allocated. Subgroups of placental cause of death were defined as described previously. (21) Placental bed pathology involves inadequate spiral artery remodelling and/or spiral artery pathology leading to uteroplacental vascular insufficiency such as placental abruption (a clinical diagnosis supported by placental examination) or significant infarction (in preterm cases, any placental infarction; in term cases, extensive infarction of > 10% of the placental area). Placental bed pathology as a cause was allocated if the percentage of infarctions in the parenchyma in relation to the weight of the placenta was regarded likely to cause death. In a term placenta of appropriate weight, at least 30% infarctions was regarded plausible to cause death. Developmental pathology is a morphologic abnormality due to abnormal development such as villus immaturity (placental maturation defect with microscopy revealing deficient formation of syncytiovascular membranes and was considered as a cause of death after 36 weeks of gestation) or placental hypoplasia (a too low placenta: birth weight ratio or in combination with an absolute too low placental weight less than the 10th percentile). Parenchyma pathology is an acquired disorder of the villi or intervillous space such as fetal thrombotic vasculopathy, massive perivillous fibrin deposition, villitis of unknown origin, Intervillositis or fetomaternal haemorrhage without obvious cause. Localization pathology is placenta praevia. Umbilical cord complication was classified if there was clinical and/or pathological evidence of an umbilical cord complication, sufficient to explain obstruction and/or disruption of the blood flow. Placental pathology not otherwise specified is a combination of placental causes when no choice could be made as to which was first in the chain of events leading to death.

Ethnic origin was ascribed by the woman's healthcare provider and classified as Caucasian, Negroid, Mediterranean, Asian or other. Maternal height and weight were recorded at the first visit for antenatal care. Body Mass Index was calculated (kg/m^2) and used to define maternal weight groups according to WHO definition: 1) underweight (BMI < 18.5), 2) normal weight (BMI 18.5–24.9), 3) overweight (BMI 25.0-29.9) and 4) obese (BMI ≥ 30.0).(22) Diseases associated with obesity in pregnancy such as diabetes, hypertension and preeclampsia were registered. Hypertensive

disorders were defined as pre-existing hypertension (pre-pregnancy systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 95), gestational hypertension (same references values) and preeclampsia (gestational hypertension and proteinuria ≥ 300mg in a 24-hour urine collection). Fetal growth percentiles for birth weight by gestational age were calculated according the Kloosterman growth charts. (23) Small for gestational age (SGA) was defined as birth weight < 10th percentile; large for gestational age (LGA) as birth weight > 90th percentile.(23)

Maternal blood samples for testing C-reactive protein (mg/l), glycated haemoglobin (%), random glucose (mmol/l), thyroid stimulating hormone (TSH, mE/l) and free thyroxin (pmol/l) were determined in the treating hospital. Test results were compared to local laboratory reference values and if exceeding these were regarded as abnormal.

Statistical analyses

Baseline characteristics were compared between women with different BMI groups using normal weight women as reference category. Categorical variables were expressed as counts and percentages and continuous variables as a mean with standard deviation or median and ranges, with exact 95% confidence intervals (CIs) when appropriate.

We calculated the prevalence of pregnancy complications and laboratory test abnormalities stratified by gestational age. We compared these estimates by univariate logistic regression modelling, using normal weight women (BMI 18.5–24.9) as the reference category and expressing associations as odds ratios with a 95% confidence interval. In additional analyses, we performed multi-variable binary logistic regression analyses for abnormal laboratory testing to adjust for potential maternal diseases or pregnancy complications.

The distributions of causes of fetal death by gestational age for different BMI groups were analysed in a similar manner. A two-tailed $P < 0.05$ was considered to indicate statistical significance. Data were analysed using the Statistical Package for Social Science version 20.0.

Results

In our national study on fetal death we analysed .1025 women and their intra-uterine fetal death. The women were grouped based on maternal body mass index (BMI): 2.3 % of the women was underweight, 37.1 % normal weight, 23.5 % overweight and 14.4 % was obese. For 232 women (22.6%), BMI was missing, and they had to be excluded from further analyses. The baseline characteristics of these women with missing values were comparable to those of normal weight women. (Data not shown)

Table 1 shows the results of the baseline characteristics for the remaining 793 women within different BMI groups. Underweight women were younger (95% CI; 1.10 to 5.38, *P* 0.003) and smoked more frequently (OR 3.25, 95% CI; 1.37 to 7.72, *P* 0.007). Compared with normal weight women, obese women were more likely to smoke (OR 1.84, 95% CI; 1.19 to 2.85, *P* 0.006), to have pre-existing hypertension (OR 3.57, 95% CI; 1.76 to 7.24, *P*< 0.001) and fetal death occurred more often after 37 weeks of gestation (OR 1.80, 95% CI; 1.21 to 2.70, *P* 0.004).

Table 1
Characteristics of the patient population

CHARACTERISTICS											
		BMI <18.5		**BMI 18.5–24.9**		**BMI 25.0-29.9**		**BMI > 30.0**		**Total**	
		n = 24 (2.3)		n = 380 (37.1)		n = 241 (23.5)		n = 148 (14.4)		n = 793 (100.0)	
Age	*mean (95% CI) in years*	**27**	**(24.7–29.3) ***	30.2	(29.7–30.7)	30.7	(30.0-31.3)	30.7	(29.8–31.5)		
Ethnicity	Caucasian	19	(79.2)	298	(78.4)	181	(75.1)	111	(75.0)	609	(76.8)
	Negroid	2	(8.3)	12	(3.2)	14	(5.8)	5	(3.4)	33	(4.2)
	Mediterranean	0	(0.0)	36	(9.5)	31	(12.9)	21	(14.2)	88	(11.1)
	Asian	1	(4.2)	12	(3.2)	2	(0.8)	1	(0.7)	16	(2.0)
	Other	2	(8.3)	22	(5.8)	13	(5.4)	10	(6.8)	47	(5.9)
Parity	Primiparous	17	(70.8)	206	(54.2)	120	(49.8)	80	(54.1)	423	(53.3)
	Multiparous	7	(29.2)	174	(45.8)	121	(50.2)	68	(45.9)	370	(46.7)
ART in recurrent pregnancy		1	(4.2)	25	(6.6)	17	(7.1)	11	(7.4)	54	(6.8)
Gestational age	20 + 0–27 + 6 weeks	7	(29.2)	127	(33.4)	84	(34.9)	**30**	**(20.3) ***	248	(31.3)
	28 + 0–36 + 6 weeks	10	(41.7)	153	(40.3)	87	(36.1)	60	(40.5)	310	(39.1)
	> 37 + 0 weeks	7	(29.2)	100	(26.3)	70	(29.0)	**58**	**(39.2) ***	235	(29.6)
Smoking		**10**	**(41.7) ***	72	(18.9)	57	(23.7)	**44**	**(29.7) ***	183	(23.1)
Alcohol		1	(4.2)	17	(4.5)	9	(3.7)	4	(2.7)	31	(3.9)
Thyroid disease		0	(0.0)	7	(1.8)	3	(1.2)	1	(0.7)	11	(1.4)
Pre-existing diabetes		0	(0.0)	2	(0.5)	4	(1.7)	3	(2.0)	9	(1.1)
Pre-existing hypertension		0	(0.0)	15	(3.9)	8	(3.3)	**19**	**(12.8) ***	42	(5.3)

Results are given in n(%) unless otherwise specified. BMI: body mass index. ART: assistant reproductive technology. Women with a BMI < 18.5, 25.0–29.9 and BMI > 30 are compared with normal weight women (BMI 18.5–24.9). * significant difference with a p-value < 0.05.

Table 2 shows the prevalence of pregnancy complications within different BMI groups and stratified by gestational age. Underweight women more often had a small for gestational age fetus after 37 weeks of gestation (OR 5.68, 95% CI; 1.17 to 27.5, *P* 0.03). In early gestation (20 + 0–27 + 6 weeks), pregnancies in obese women were more often complicated by gestational hypertension (OR 4.26, 95% CI; 1.51 to 11.9, *P* 0.006) and preeclampsia/HELLP syndrome (OR 3.28, 95% CI; 1.07 to 10.1, *P* 0.038). Between 28 + 0 weeks and 36 + 6 weeks of gestation, obese women were still

more likely to have gestational hypertension (OR 3.96, 95% CI; 1.63 to 9.61, *P* 0.002) than normal weight women. In this period the prevalence of preeclampsia/HELLP syndrome in obese women was also higher but not statistically significant (OR 2.28, 95% CI; 0.89 to 5.82, *P* 0.08). After 37 + 0 weeks of gestation, obese women more often had a large for gestational age fetus (OR 3.85, 95% CI; 1.57 to 9.43, *P* 0.003) and gestational diabetes (OR 3.49, 95% CI; 1.11 to 10.9, *P* 0.03).

Table 2
Pregnancy complications in women with a stillbirth stratified by maternal BMI and gestational age.

PREGNANCY COMPLICATIONS in women with a stillbirth related to maternal BMI										
	BMI <18.5		BMI 18.5–24.9		BMI 25.0-29.9		BMI > 30.0		Total	
	n = 24		n = 380		n = 241		n = 148		n = 793	
Fetus SGA										
20–28 weeks	4/7	(57.1)	41/127	(32.3)	36/84	(42.9)	12/30	(40.0)	93/248	(37.5)
28–37 weeks	6/10	(60.0)	49/153	(32.0)	27/87	(31.0)	24/60	(40.0)	106/310	(34.2)
> 37 weeks	**4/7**	**(57.1)***	19/100	(19.0)	12/70	(17.1)	11/58	(19.0)	46/235	(19.6)
Fetus LGA										
20–28 weeks	0/7	(0.0)	1/127	(0.8)	1/84	(0.8)	0/30	(0.0)	2/248	(0.8)
28–37 weeks	1/10	(10.0)	12/153	(7.8)	11/87	(12.6)	8/60	(13.3)	32/310	(10.3)
> 37 weeks	0/7	(0.0)	9/100	(9.0)	9/70	(12.9)	**16/58**	**(27.6)***	34/235	(14.5)
Gestational diabetes										
20–28 weeks	0/7	(0.0)	0/127	(0.0)	1/84	(1.2)	0/30	(0.0)	1/248	(0.4)
28–37 weeks	0/10	(0.0)	0/153	(0.0)	0/87	(0.0)	3/60	(5.0)	3/310	(1.0)
> 37 weeks	0	(0.0)	5/100	(5.0)	3/70	(4.3)	**9/58**	**(15.5)***	17/235	(7.2)
Gestational hypertension										
20–28 weeks	0/7	(0.0)	10/127	(7.9)	4/84	(4.8)	**8/30**	**(26.7)***	22/248	(8.9)
28–37 weeks	0/10	(0.0)	10/153	(6.5)	7/87	(8.0)	**13/60**	**(21.7)***	30/310	(9.7)
> 37 weeks	1/7	(14.3)	5/100	(5.0)	5/70	(7.1)	4/58	(6.9)	15/235	(6.4)
Preeclampsia / HELLP syndrome										
20–28 weeks	0/7	(0.0)	9/127	(7.1)	8/84	(9.5)	**6/30**	**(20.0)***	23/248	(9.3)
28–37 weeks	0/10	(0.0)	11/153	(7.2)	6/87	(6.9)	9/60	(15.0)	26/310	(8.4)
> 37 weeks	0/7	(0.0)	4/100	(4.0)	1/70	(1.4)	1/58	(1.7)	6/235	(2.6)

Results are given in n (%). BMI: body mass index. SGA: small for gestational age. LGA: large for gestational age. Women with a BMI < 18.5, 25.0–29.9 and BMI > 30 are compared with normal weight women (BMI 18.5–24.9) for each gestational age group. Significant difference with a p-value < 0.05.

Table 3 shows the prevalence of abnormal laboratory tests within different BMI groups and stratified by gestational age. Significantly more overweight women had elevated C-reactive protein levels between 20 + 0 until 27 + 6 weeks of

gestation (OR 2.61, 95% CI; 1.42 to 4.8, *P* 0.002) and 28 + 0 until 36 + 6 weeks of gestation (OR 2.32, 95% CI; 1.30 to 4.12, *P* 0.004). In the group of obese women abnormal C-reactive protein was significantly more prevalent in each gestational age period (20 + 0 until 27 + 6 weeks: OR 2.63, 95% CI; 1.11 to 6.19, *P* 0.027; 28 + 0n until 36 + 6 weeks: OR 2.89, 95% CI; 1.45 to 5.76, *P* 0.003; >37 + 0 weeks: OR 5.39, 95% CI; 1.94 to 14.9, *P* 0.001). Adjustment for infection as cause of fetal death did not influence these results. Increased glycated haemoglobin was observed significantly more in obese women after 37 + 0 weeks of gestation (OR 3.85, 95% CI; 1.50 to 9.84, *P* 0.005), even after adjustment for gestational diabetes (adjusted OR 3.29, 95% CI; 1.25 to 8.65, *P* 0.016).

Table 3

Prevalence of abnormal laboratory test results in women with a stillbirth stratified by maternal BMI and gestational age

LABORATORY TESTING in women with a stillbirth related to maternal BMI											
		BMI <18.5 n = 24		BMI 18.5–24.9 n = 380		BMI 25.0-29.9 n = 241		BMI > 30.0 n = 148		Total n = 793	
	N tested										
C-reactive protein (mg/l) ↑											
20–28 weeks	220	2/7	(28.6)	41/115	(35.7)	**42/71**	**(59.2) ***	**16/27**	**(59.3) ***	101/220	(45.9)
28–37 weeks	266	5/8	(62.5)	55/132	(41.7)	**48/77**	**(62.3) ***	**33/49**	**(67.3) ***	141/266	(53.0)
> 37 weeks	196	1/4	(25.0)	53/87	(60.9)	40/58	(69.0)	**42/47**	**(89.4) ***	136/196	(69.4)
HbA1c (%) ↑											
20–28 weeks	221	0/6	(0.0)	0/112	(0.0)	3 /76	(3.9)	0/27	(0.0)	3/221	(1.4)
28–37 weeks	273	0/9	(0.0)	5/134	(3.7)	4/74	(5.4)	5/56	(8.9)	14/273	(5.1)
> 37 weeks	213	0/7	(0.0)	8/88	(9.1)	8/64	(12.5)	**15/54**	**(27.8) ***	31/213	(14.6)
Random glucose (mmol/l) ↑											
20–28 weeks	227	2/7	(28.6)	21/117	(17.9)	12/75	(16.0)	5/28	(17.9)	40/227	(17.6)
28–37 weeks	284	0/9	(0.0)	18/137	(13.1)	15/80	(18.8)	12/58	(20.7)	45/284	(15.7)
> 37 weeks	213	0/6	(0.0)	16/91	(17.6)	13/65	(20.0)	16/51	(31.4)	45/213	(21.1)
TSH (mE/l) ↑											
20–28 weeks	234	1/5	(20.0)	3/122	(2.5)	3/78	(3.8)	1/29	(3.4)	8/234	(3.4)
28–37 weeks	287	1/9	(11.1)	8/142	(5.6)	5/80	(6.2)	4/56	(7.1)	18/287	(6.3)
> 37 weeks	211	0/7	(0.0)	9/91	(9.9)	5/63	(7.9)	4/50	(8.0)	18/211	(8.5)

Results are given in n (%). BMI: body mass index. SGA: small for gestational age. LGA: large for gestational age. Women with a BMI < 18.5, 25.0–29.9 and BMI > 30 are compared with normal weight women (BMI 18.5–24.9) for each gestational age group. * Significant difference with a p-value < 0.05.

LABORATORY TESTING in women with a stillbirth related to maternal BMI											
Free thyroxin (pmol/l) ↓											
20–28 weeks	226	0/5	(0.0)	8/118	(6.8)	5/74	(6.8)	1/29	(3.4)	14/226	(6.2)
28–37 weeks	278	1/9	(11.1)	15/137	(10.9)	7/78	(9.0)	3/54	(5.6)	26/278	(9.4)
> 37 weeks	200	2/7	(28.6)	14/90	(15.6)	11/59	(18.6)	9/44	(20.5)	36/200	(18.0)
Results are given in n (%). BMI: body mass index. SGA: small for gestational age. LGA: large for gestational age. Women with a BMI < 18.5, 25.0–29.9 and BMI > 30 are compared with normal weight women (BMI 18.5–24.9) for each gestational age group. * Significant difference with a p-value < 0.05.											

Cause of death was determined for all fetal deaths and classified according to the Tulip classification; Table 4 shows the results within different BMI groups and stratified by gestational age. Overweight women were more likely to have a fetal death caused by a congenital anomaly (OR 4.29, 95% CI; 1.28 to 14.4, *P* 0.018). When we studied these individual cases more in detail, we observed different types of congenital anomalies, making it difficult to establish an association with maternal weight. In this group there were 3 cases of trisomy 21, 2 cases of trisomy 18, 1 case of congenital neoplasm, 2 cases with a congenital heart defect and 1 case with multiple organ anomalies.

Table 4
Cause of fetal death stratified by maternal BMI and gestational age

CAUSE OF DEATH in women with a stillbirth related to maternal BMI										
	BMI <18.5		**BMI 18.5–24.9**		**BMI 25.0-29.9**		**BMI > 30.0**		**Total**	
	n = 24		n = 380		n = 241		n = 148		n = 793	
Congenital anomaly										
20–28 weeks	1/7	(14.3)	7/127	(5.5)	3/84	(3.6)	1/30	(3.3)	12/248	(4.8)
28–37 weeks	0/10	(0.0)	4/153	(2.6)	**9/87**	**(10.3)***	4/60	(6.7)	17/310	(5.5)
> 37 weeks	0/7	(0.0)	2/100	(2.0)	1/70	(1.4)	3/58	(5.2)	6/235	(2.6)
Placenta bed pathology										
20–28 weeks	4/7	(57.1)	34/127	(26.8)	32/84	(38.1)	**18/30**	**(60.0)***	88/248	(35.5)
28–37 weeks	6/10	(60.0)	56/153	(36.6)	36/87	(41.4)	29/60	(48.3)	127/310	(41.0)
> 37 weeks	2/7	(28.6)	16/100	(16.0)	12/70	(17.1)	9/58	(15.5)	39/235	(16.6)
Placental pathology: development										
20–28 weeks	0/7	(0.0)	8/127	(6.3)	4/84	(4.8)	0/30	(0.0)	12/248	(4.8)
28–37 weeks	1/10	(10.0)	27/153	(17.6)	11/87	(12.6)	4/60	(6.7)	43/310	(13.9)
> 37 weeks	1/7	(14.3)	39/100	(39.0)	29/70	(41.4)	**32/58**	**(55.2)***	101/235	(43.0)
Placental pathology: parenchyma										
20–28 weeks	0/7	(0.0)	5/127	(3.9)	1/84	(1.2)	1/30	(3.3)	7/248	(2.8)
28–37 weeks	0/10	(0.0)	4/153	(2.6)	2/87	(2.3)	1/60	(1.7)	7/310	(2.3)
> 37 weeks	0/7	(0.0)	2/100	(2.0)	2/70	(2.9)	0/58	(0.0)	4/235	(1.7)
Placental pathology: Localisation										
20–28 weeks	0/7	(0.0)	0/127	(0.0)	0/84	(0.0)	0/30	(0.0)	0/248	(0.0)
28–37 weeks	1/10	(10.0)	0/153	(0.0)	0/87	(0.0)	0/60	(0.0)	1/310	(0.3)
> 37 weeks	0/7	(0.0)	0/100	(0.0)	0/70	(0.0)	0/58	(0.0)	0/235	(0.0)
Umbilical cord complication										
20–28 weeks	0/7	(0.0)	2/127	(1.6)	7/84	(8.3)	1/30	(3.3)	10/248	(4.0)
28–37 weeks	1/10	(10.0)	13/153	(8.5)	3/87	(3.4)	1/60	(1.7)	18/310	(5.8)

CAUSE OF DEATH in women with a stillbirth related to maternal BMI										
> 37 weeks	1/7	(14.3)	11/100	(11.0)	5/70	(7.1)	1/58	(1.7)	18/235	(7.7)
Placental pathology NOS *										
20–28 weeks	0/7	(0.0)	3/127	(2.4)	4/84	(4.8)	0/30	(0.0)	7/248	(2.8)
28–37 weeks	0/10	(0.0)	8/153	(5.2)	1/87	(1.1)	3/60	(5.0)	12/310	(3.9)
> 37 weeks	0/7	(0.0)	15/100	(15.0)	8/70	(11.4)	7/58	(12.1)	30/235	(12.8)
Infection										
20–28 weeks	0/7	(0.0)	4/127	(3.1)	1/84	(1.2)	0/30	(0.0)	5/248	(2.0)
28–37 weeks	0/10	(0.0)	2/153	(1.3)	4/87	(4.6)	2/60	(3.3)	8/310	(2.6)
> 37 weeks	1/7	(14.3)	0/100	(0.0)	3/70	(4.3)	0/58	(0.0)	4/235	(1.7)

Table 4
continued

	BMI ‹18.5		**BMI 18.5–24.9**		**BMI 25.0-29.9**		**BMI > 30.0**		**Total**	
	n = 24		n = 380		n = 241		n = 148		n = 793	
Other										
20–28 weeks	0/7	(0.0)	14/127	(11.0)	6/84	(7.1)	1/30	(3.3)	21/248	(8.5)
28–37 weeks	0/10	(0.0)	13/153	(8.5)	7/87	(8.0)	2/60	(3.3)	22/310	(7.1)
> 37 weeks	0/7	(0.0)	0/100	(0.0)	0/70	(0.0)	0/58	(0.0)	0/235	(0.0)
Unknown										
20–28 weeks	2/7	(28.6)	50/127	(39.4)	26/84	(31.0)	8/30	(26.7)	86/248	(34.7)
28–37 weeks	1/10	(10.0)	26/153	(17.0)	14/87	(16.1)	14/60	(23.3)	55/310	(17.7)
> 37 weeks	2/7	(28.6)	15/100	(15.0)	10/70	(14.3)	6/58	(10.3)	33/235	(14.0)

Results are given in n (%). BMI: body mass index. * NOS: not otherwise specified, combination of placenta pathologies. Women with a BMI < 18.5, 25.0–29.9 and BMI > 30 are compared with normal weight women (BMI 18.5–24.9) for each gestational age group. * Significant difference with a p-value < 0.05.

In early gestation (20 + 0–27 + 6 weeks), fetal death in obese women was often caused by placental bed pathology (OR 4.10, 95% CI; 1.79 to 9.40, *P* 0.001). In additional multivariate analyses, we found that this was strongly related to a higher incidence of hypertensive disorders and smoking (adjusted OR 2.27, 95% CI; 0.84 to 5.97, *P* 0.09). After 37 weeks of gestation, obese women more often had developmental placental pathology as cause of fetal death (OR 1.93, 95% CI; 1.01 to 3.71, *P* 0.05) than normal weight women, which was associated with gestational diabetes and large for gestational age fetus (adjusted OR 1.82, 95% CI; 0.93 to 3.58, *P* 0.08).

Discussion

We studied risk factors and causes of fetal death related to maternal BMI and thereby evidence for an underlying mechanism of stillbirth in overweight and obese women. Based on our results, we could not establish a gestational-age

specific cause of fetal death which was only associated with maternal BMI, but we were able to observe 2 different pathways causing fetal death in obese women. In early gestation, obese women have more often placenta bed pathology. The underlying mechanism appears to be related to a higher prevalence of hypertensive disorders, which possible leads to an early onset uteroplacental insufficiency. After 37 weeks of gestation, fetal death in obese women is more often caused by a disorder of placental development. Villus immaturity is a defective formation of syncytial-vascular membranes (SVM) in tertiary villi. In placental hypoplasia there is a disorder of the placental growth which causes a too low placenta/birth weight ratio or in combination with an absolute too low placental weight (< 10th percentile). The absence of SVM and lagging placental growth is thought to cause placental dysfunction in term pregnancy, when demands on placental function are increased. Gestational diabetes seems to be strong associated with the potential underlying mechanism in this group of women

Previous studies on cause of fetal death and maternal BMI were not able to establish a final pathological pathway. Norh et al. examined pregnancy outcome among 54.505 pregnant women in the Danish National Birth cohort and observed a higher risk of stillbirth after 28 weeks of gestation caused by placental dysfunction or an unexplained reason in overweight and obese women. Placental dysfunction was defined as fetal growth restriction, infarction of the placenta without fetal growth restriction and placental abruption, and women with diabetes, preeclampsia and other hypertensive disorders were excluded.(15) Tennant et all analysed a cohort of 40.000 singleton pregnancies and found higher rates of pre-eclampsia among stillbirths of obese women.(18)

In our cohort we found significant elevated levels of C-reactive protein and glycated haemoglobin in obese women. This points in the direction of insulin resistance and low-grade inflammation, two important markers of the metabolic syndrome. The metabolic syndrome includes abdominal obesity, insulin resistance and dyslipidemia.(24) Hyperlipidemia reduces prostacyclin secretion and enhances peroxidase production, which may contribute to an increased endothelial dysfunction and vasoconstriction.(9),(25),(26) It is also associated with low-grade inflammation with elevated levels of circulating inflammatory markers as C-reactive protein.(24),(27),(28),(29) One of our hypotheses is that a combination of impaired microvascular endothelial function, vasoconstriction and a low-grade inflammation as a result of the metabolic syndrome, may contribute to the onset of villus immaturity and hypoplasia which results in decreased placental function later on in pregnancy when the fetus is demanding more eventually resulting in hypoxemia and fetal death. Yao et all showed that planned earlier delivery by 38 weeks in gestation minimizes perinatal mortality complicated by maternal morbid obesity. (30) Unfortunately, we were not able to study other markers related to the metabolic syndrome such as inflammatory factors interleukin-6, interleukin-8 and tumor necrosis factor-α, factors for dyslipidemia as cholesterol or insulin levels.(24)

The main strength of this study is the size of the cohort and the standardized approach in which fetal death was evaluated. We also acknowledge some limitations and potential weaknesses in our study. First, our study was not a case-control study and therefore it is not possible to determine differences between abnormal placental findings in stillbirths and live births in overweight or obese women. Second, maternal height, and in some cases, weight are self-reported. It is known that pregnant women over report their height and underreport their weight. This can result in an underestimation of the maternal BMI. (31) Such misclassification can lead to an underestimation of the true effect of obesity.

Conclusion

The underlying mechanism of stillbirth in obese women is complex and presumably multifactorial. Our study shows that in obese women there are at least two distinct underlying pathophysiological pathways, which are causing placental bed pathology in early gestation and placental development disorders in term gestation. In the further search

for prevention of stillbirth in obese women we should focus on determining the exact underlying mechanism of these pathways so we can develop specific interventions to reduce the risk of stillbirth in overweight and obese women. Till then, we have to help women to prevent weight gain before pregnancy in healthy women and should encouraged overweight and obese women to lose weight and adopt a healthy lifestyle before getting pregnant. Pregnancy in overweight or obese women should be considered as a high risk pregnancy. Intensive follow-up with frequent antenatal checks are advised with screening for hypertensive disorders and diabetes. It is also necessarily to monitoring the fetal growth by ultrasound.

Declarations

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Competing interests

The authors declare no conflict of interest

Author contributions

JW Nijkamp was responsible for acquisition and analysis of data and for writing the first draft of the paper and revising. FJ Korteweg and A Timmer contributed to critical aspects of the conduct of research, interpreted data and revised the article. JJHM Erwich conceived the research idea, contributed to critical aspects of the conduct of research, interpreted data, revised the article and was responsible for supervising. H Groen was responsible for interpretation of data and revising the article. All authors gave their final approval.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the institutional review board of the UMCG. The boards of all participating hospitals provided local approval.

Consent to participate

All women who agreed to participate in this study gave written informed consent.

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