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Obesity and health in pregnancies after assisted reproductive technology

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Abstract

Objective: To compare the association of maternal pre-pregnancy body mass index (BMI) with adverse perinatal and maternal outcomes in pregnancies following spontaneous and assisted conception in a large nation-wide cohort.

Design: Population-based cohort study. Data from the Medical Birth Registry of Norway and the Norwegian National Education Database (NUDB) at Statistics Norway.

Setting: Nation-wide registry-based observational study

Patients: A total of 227 765 singleton deliveries; 6 760 after assisted reproductive technology (ART) and 221 005 after spontaneous conception (SC).

Interventions: None.

Main outcome measures: Preterm birth (< 37 weeks), small for gestational age (SGA), large for gestational age (LGA), perinatal death (stillbirth and live birth with death within the first 28 days), hypertensive disorders in pregnancy (HDP; gestational hypertension and preeclampsia), gestational diabetes mellitus, induction of delivery and caesarean section. Associations between maternal pre-pregnancy BMI and outcomes were analysed in logistic regression models, reporting odds ratios and risk differences.

Results: In general, the risks of all the outcomes were higher in ART than in SC across all categories of maternal pre-pregnancy BMI. For all outcomes except SGA, the risk was highest for women with a BMI ≥30 kg/m^2. The risk of perinatal death increased strongly with increasing BMI in both SC and ART, and was higher in ART pregnancies than in SC pregnancies across all categories of maternal BMI. The highest risk of perinatal death was found for women with a BMI ≥30 kg/m2 (0.6% for SC and 1.1% for ART). The risk of HDP increased strongly with increasing BMI in both ART and SC pregnancies. For HDP, the risk difference between women with BMI ≥30 kg/m^2 and BMI 20-24 kg/m^2 was 6.9% and 8.6% for SC and ART pregnancies, respectively.

Conclusions: The associations between maternal BMI and adverse perinatal and maternal outcomes were similar after ART and spontaneous conception, but the absolute risks were higher after ART conception.

Introduction

Overweight and obesity is an increasing problem worldwide. The prevalence of obesity (BMI ≥30 kg/m^2) among women of reproductive age has been estimated to be around 30% in the USA, 20% in the UK and 12% in many other European countries (1, 2).

For women in reproductive age, overweight is associated with anovulation, subfertility and infertility, and miscarriages (3, 4). In overweight women who succeed in becoming pregnant, there is an increased risk of pregnancy complications such as gestational diabetes, hypertensive disorders, gestational hypertension (5), and adverse perinatal outcomes such as preterm birth, SGA and stillbirth (6-8) .

Infertility is also an increasing medical and societal concern, and an increasing number of couples are seeking treatment for infertility (9). Since the start in the late 1970s, assisted reproductive technologies (ART) has become more frequently used, and the share of children born after ART is now between 1.5% and 5% in most European countries (9).

In general, the risk of complications as stillbirth, small for gestational age (SGA) and preterm birth are higher in ART pregnancies than in pregnancies after spontaneous conceptions (SC) (10). Although a substantial proportion of the excess risk in ART pregnancies can be attributed to twin pregnancies and can be prevented by elective single embryo transfer (eSET), the increased risk of adverse perinatal outcomes is also present in singleton ART pregnancies (11). Furthermore, a decrease in occurrence of adverse neonatal outcomes over time in ART pregnancies has been observed, but it is not known whether this development may be attributed to improvements in treatment or by offering treatment to a larger proportion of the population and thus presumably healthier group of infertile couples (12).

Due to the excess risk of adverse pregnancy outcomes for overweight and obese women, most ART clinics do not offer treatment for women with BMI above a certain limit. There is, however, inadequate knowledge about cut-off values, which has resulted in different cut-off values in the different clinics.

Clinical decision-making for women with a high BMI seeking assisted reproduction is further complicated by the fact that it is not known whether the association of maternal weight with adverse pregnancy outcomes is different in women who conceive naturally and women who become pregnant after assisted fertilisation. An improved understanding of the role of overweight in ART pregnancies will provide a better foundation to evaluate whether an upper BMI-limit is advisable for women who seek ART.

The aim of the present study was to estimate and compare the association of maternal pre-pregnancy BMI with adverse perinatal and maternal outcomes in pregnancies following spontaneous and assisted conception in a large nation-wide cohort.

Materials and methods

Study population and design

This study is based on data from the nation-wide Medical Birth Registry of Norway, which comprises information on all deliveries in Norway since 1967. Specifically, the registry collects information on maternal health before and during pregnancy, complications in pregnancy and at birth, perinatal health and mortality, as well as conception method (ART or SC). Information on maternal height and maternal body weight before pregnancy and at delivery has been collected since 2007. The unique identification number of each Norwegian citizen was used to link information from the MBRN to information on maternal education from the Norwegian National Education Database (NUDB) at Statistics Norway.

We calculated maternal BMI before pregnancy as maternal weight at the start of pregnancy in kilograms divided by maternal height in meters squared.

Perinatal outcomes comprised preterm birth (<37 weeks), small for gestational age (SGA), large for gestational age (LGA) and perinatal death. For SC pregnancies, gestational age was defined according to ultrasound investigation performed in the second trimester or from the date of the last menstrual period if ultrasound had not been performed. In ART pregnancies, gestational age was calculated from the date of oocyte retrieval or from ultrasound examination if the date of oocyte retrieval was not available. We used Marsal's formulas to calculate cut-off values for growth deviation, and defined SGA and LGA as birthweight <-2 and >+2 standard deviations, respectively, according to week of gestation and foetal sex (13). Perinatal death was defined as stillbirth and live birth with death within day 28 after birth.

Maternal complications included hypertensive disorders in pregnancy (HDP), gestational diabetes mellitus (GDM), induction of delivery and caesarean section, all registered by separate check boxes in the notification form, but with the possibility of adding specific codes in an open text field. Hypertensive disorders in in pregnancy included gestational hypertension and preeclampsia (International Classification of Diseases, Tenth Revision, ICD-10: O11, O16, O140-142, O149, O150-152, O159). Gestational diabetes mellitus included only diabetes discovered in pregnancy (ICD-10: O24.4, O24.9, as well as E13 or E14 if listed as detected in pregnancy). For induction of labour, we combined the different modes of induction (oxytocin, prostaglandins, amniotomy and other) and considered them as one outcome. For caesarean sections, we treated elective, emergency and unspecified caesarean sections as one outcome.

A total of 531 732 singleton pregnancies leading to delivery between 2007 and 2015 were eligible for our study. We excluded 289 243 pregnancies with missing information on maternal height and/or pre-pregnancy weight (*n*=271 856) and education (*n*= 17 387). We further excluded 873 pregnancies with missing information about the child (unknown sex: *n*=68; birth weight: *n*=105; gestational age/length: *n*=700), and 13 851 pregnancies with impossible or extreme values (pregnancies with gestational age <22+0 or >44+0 weeks: *n*=171; maternal age <22 or >44 years: *n*=13 627; birthweight below -6 SD (*n*=20) or above +6 SD (*n*=33) from the mean according to Marsal's formulas. Thus, the study population consisted of 6 760 ART and 221 005 SC singleton deliveries. In total, 227 765 singleton deliveries were included in the study. For the maternal outcomes (HDP, GDM, induction and caesarean section), data from 2015 were not available and the analyses were therefore restricted to deliveries between 2007 and 2014 (n=190 603).

Statistical analyses

We categorized maternal pre-pregnancy BMI as <20 kg/m^2, 20-24 kg/m^2, 25-29 kg/m^2 and >30 kg/m^2. We used logistic regression to estimate odds ratios (OR's) with 95 % confidence intervals (CIs) according to categories of maternal pre-pregnancy BMI and conception method, taking correlations within mothers into account. To increase interpretability, we also used the results of the logistic regression to estimate adjusted absolute risk differences with 95% CIs. In all analyses, we adjusted for maternal age (22-29, 30-34, 35-39, 40-44 years), parity (0, 1, 2, ≥3) and education (education level up to high school, lower college or university degree, higher college or university degree). In separate analyses, we also adjusted for maternal smoking at the start of pregnancy (no/yes) and for year of birth (one-year categories).

To evaluate whether the association of each adverse outcome with BMI differed between ART and SC, we carried out likelihood ratios tests with inclusion of product terms between BMI and conception method. Due to the high number of pregnancies with missing information on maternal BMI, we compared other maternal and pregnancy characteristics between pregnancies with and without reported pre-pregnancy BMI.

All statistical analyses were conducted using Stata statistical software, version 13 and 14 (StataCorp LP, TX USA).

Ethics

The study was approved by the Regional Committees for Medical and Health Research Ethics (REK 2010/1909).

Results

In total, 6 760 ART and 221 005 SC singleton pregnancies were analysed. Baseline characteristics are described in Table 1. Parity differed markedly between the included SC and ART pregnancies, where 40 % of SC mothers and 62 % of ART mothers were nulliparous. ART mothers were also older than SC mothers and more likely to have a caesarean section (18% vs 13% in SC). Mean birth weight was lower for ART pregnancies with a corresponding higher proportion of SGA. Women who gave birth after ART were more often non-smokers than women who gave birth after SC, but the mean maternal pre-pregnancy BMI and mean weight increase in pregnancy was similar in SC and ART pregnancies, as was distribution across BMI categories.

In both ART and SC pregnancies, we found a moderately strong, U-shaped association of maternal BMI with risk of preterm birth, and the risk was higher in ART pregnancies than in SC pregnancies across all categories of maternal BMI (Table 2, Figure 1a). The highest risk of preterm birth was found for women with a BMI ≥30 kg/m^2, (5.9% for SC and 9.5% for ART pregnancies). A similar pattern was observed for SGA, but the risk for SGA was highest for women with a BMI <20 kg/m^2 (4.6% for SC and 5.7% for ART pregnancies). We found no clear evidence of heterogeneity between ART and SC in association of BMI with risk of neither preterm birth nor SGA.

After ART, the crude risk of LGA increased strongly with increasing maternal BMI from 1.8% for women with BMI <20 kg/m^2 to 9.4% for women with BMI ≥30 kg/m^2. In SC pregnancies, the corresponding risks were 1.5% and 9.3%, respectively. We found no evidence of heterogeneity between ART and SC for these associations.

Similarly, for perinatal death, the risk increased strongly with increasing BMI in both SC and ART, and was higher in ART pregnancies than in SC pregnancies across all categories of maternal BMI (Figure 1b and Table 2). The highest risk of perinatal death was found for women with a BMI ≥30 kg/m2 (0.6% for SC and 1.1% for ART). There was no clear evidence of heterogeneity between ART and SC in association of BMI with risk of perinatal death.

The risk of maternal complications (HDP and GDM) and increased strongly and consistently with increasing BMI in both ART and SC pregnancies (Figure 1c and 1d, Table 3). For HDP, the risk difference between women with BMI ≥30 kg/m^2 and BMI 20-24 kg/m^2 was 6.9% and 8.6% for SC and ART pregnancies, respectively. We found no evidence of heterogeneity between ART and SC in association of BMI with risk of HDP. Even though women with spontaneous conception and a BMI ≥30 kg/m^2 had a higher OR for GDM than women with ART pregnancies and a BMI ≥30 kg/m^2 (OR 6.36 versus 3.72, respectively, p-value for interaction 0.002), the absolute increase in risk was similar in both groups (6.2% for SC and 5.8% for ART pregnancies).

The risks of induction of labour and caesarean section also increased with increasing BMI in both conception groups. The absolute increase in risk was similar in both groups, with a difference in risk of around 10% for obese women compared to women with normal weight, and we found no evidence of heterogeneity for the associations.

Adjustment for parity, maternal age and education did not substantially influence the estimates, nor did adjustment for smoking status and birth year (the latter results are not shown). In a sensitivity analysis of risk of GDM, we also excluded 1574 pregnancies where the mother had pre-pregnancy diabetes mellitus, but associations remained practically unchanged (not shown).

A comparison of pregnancies with and without BMI information indicated no substantial differences between these two groups on maternal age, education, parity, gestational age, birth weight, HDP, GDM, induction, caesarean section or ART conception. However, the proportion of missing BMI decreased markedly during the study period (86% in 2007 versus 26% in 2015). The risk of perinatal death was somewhat higher in pregnancies with missing BMI compared to those with available information on BMI (0.6% versus 0.4%). The proportion of pregnancies with missing information on maternal smoking was also higher in pregnancies with missing information on BMI (25% versus 0.5%).

Discussion

In this large population-based study of 6 760 singleton ART and 221 005 singleton SC pregnancies, we found no substantial differences between ART and SC pregnancies in the association of maternal BMI with risk of major foetal and maternal outcomes. A high maternal pre-pregnancy BMI was associated with a higher risk of preterm birth, SGA, LGA, perinatal death, hypertensive disorders, GDM, induction of delivery and caesarean section, in pregnancies following both SC and ART. Still, the absolute risk of complications was higher in ART compared to SC pregnancies within all categories of maternal BMI. With the exception of SGA, the risk was highest for women with BMI ≥30 kg/m2.

Our results are in accordance with those from numerous previous studies comparing risk of adverse pregnancy outcomes according to maternal pre-pregnancy BMI (7, 8, 14). In a study of more than 1.5 million singleton births in Sweden from 1992 to 2010, the risk of all degrees of preterm birth increased with increasing maternal overweight/obesity, but also underweight women had a higher risk of preterm birth compared to women with a normal BMI (15).

A retrospective cohort study of primi-parous women delivering singleton babies in Aberdeen from 1976 to 2005 investigated obstetric and perinatal outcomes according to maternal pre-pregnancy BMI (16). In that study, high BMI was associated with an increased risk of preeclampsia, macrosomia, induction of delivery and caesarean section. For preterm birth, an association was present only for birth before 33 weeks of gestation. In contrast with our results, a higher risk of stillbirth was found only for overweight women, whereas a higher risk of low birthweight (<2500 g) was found only for underweight women.

We found an increasing risk of perinatal death with increasing BMI. This is consistent with findings in other studies. In a meta-analysis on maternal obesity and the risk of stillbirth, maternal overweight and obesity increased the risk of perinatal death compared to normal weight (17). A recent sibling study from Sweden indicates that this association may be independent of genetic factors and early environment (18). In that study, the associations of BMI with risk of stillbirth and infant death were stronger within pairs of sisters than in the general population.

The risk of pregnancy complications in relation to maternal pre-pregnancy BMI was investigated in a Finnish population-based study of deliveries between 2006 and 2010 (5). They found that the risk of GDM started to increase already in the lower range of normal

BMI, and when using the WHO classifications of BMI, they concluded that the risk of GDM was increased in overweight and obese women compared to normal weight women. Similar findings were reported for preeclampsia, where they found an increased risk for overweight and obese women without pre-existing diabetes or hypertension.

In a meta-analysis of maternal obesity and the risk of caesarean section, the authors estimated that overweight and obese women have about two and three times higher risk of caesarean delivery, respectively (19). They also found that even among women with no medical conditions, overweight and obese women had a higher risk of caesarean section than normal weight women.

We are aware of only one previous study investigating whether the impact of BMI on adverse pregnancy outcomes vary according to conception method. Machtinger et al conducted a hospital-based cohort study and compared 464 ART and 1171 SC singleton pregnancies within categories of maternal BMI (20). Specifically, they studied placental ischaemic disorders, preeclampsia, SGA, GDM, preterm delivery, caesarean section, gestational age at delivery, and birthweight <2500 g and >4000 g. After adjusting for maternal age, parity, race, smoking, pre-gestational diabetes and chronic hypertension, the authors found that for most outcomes, the risk in ART pregnancies was similar or lower than in SC pregnancies with similar maternal BMI. However, for placental ischaemic disorders, preeclampsia and SGA, risk was higher after IVF among normal weight women. This is in contrast with our findings that ART pregnancies had a higher risk of most complications also within BMI categories. We speculate that differences in study design may underlie the different results, since Machtinger et al used different sampling procedures for ART and SC pregnancies, whereas our study was population-based for both groups.

Strengths of our study include the population-based design and the high data quality in the MBRN. Prenatal care programs are free of charge and provided by the public health care system, and reporting to the MBRN is routine procedure and mandatory by law (21). Both prenatal care and reporting to MBRN is independent of conception method. Because women with ART pregnancies follow the same prenatal care programs as the general population, it seems unlikely that our findings may be the result of differences in reporting. The reimbursement of costs related to fertility treatment in Norway ensures that the decision to choose ART treatment is based on medical indications rather than the couple's private economy.

The main limitation of our study is the high proportion of pregnancies with missing information on maternal pre-pregnancy BMI. However, the comparison of pregnancies with and without such information suggest that year of birth was a major predictor for missingness. Since registration of BMI was included in the MBRN from 2007, we believe that this pattern of missingness simply reflects that time is needed before changes in registration practice reach their maximal compliance. Thus, we do not suspect that missing information on BMI has resulted in any substantial selection bias. It is also reassuring that BMI missingness was not associated with conception method.

Due to the associations of overweight and obesity with infertility (3), it seems likely that ART conception would result from a high BMI for a subgroup of the women in this study (i.e. an intermediate step between BMI and the studied complications). In consequence, we cannot exclude the possibility that other factors affecting both the need for ART treatment and the risk of adverse pregnancy outcomes, may have confounded the results(22). However, the distributions of maternal pre-pregnancy BMI were very similar in ART and SC pregnancies.

When treated with ART, women who are obese have lower chances of achieving pregnancy compared to women with a normal weight (23, 24). Our study includes only women who had a successful treatment, and our study population was limited to pregnancies lasting more than 22 weeks, and pregnancies ending before 12 weeks are not reported to the MBRN. Although we found no clear differences in the impact of obesity in ART and SC pregnancies, obese women with ART pregnancies had a high absolute risk of most adverse outcomes. Our results therefore support that a continued restrictive clinical decision-making for obese infertile women may be important to prevent additional risks. Thus, the clinical guidance should focus on optimizing lifestyle factors before initiating fertility treatment

In conclusion, maternal overweight and obesity was associated with adverse perinatal and maternal outcomes fin both ART and spontaneously conceived pregnancies. Still, the absolute risks were generally higher after ART compared to those conceived after spontaneous conception regardless of maternal BMI, supporting a continued restrictive practice for offering fertility treatment.

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Tables and figures

Table 1. Description of the study population

	Spontaneous conception	ART conception
Number of observations (%)	221 005 (97.03)	6760 (2.97)
Mean maternal age, years (SD)	30.3 (4.7)	33.1 (4.3)
Parity (%)		
0	88 205 (39.9)	4174 (61.8)
1	83 507 (37.8)	2065 (30.6)
2	35 948 (16.3)	407 (6.0)
≥3	13 345 (6.0)	114 (1.7)
Maternal education		
High school or lower	99 337 (45.0)	2433 (36.0)
College/university lower level	89766 (40.6)	3055 (45.2)
College/university higher level	31 902 (14.4)	1272 (18.8)
Mean pre-pregnancy BMI, kg/m² (SD)	24.4 (4.8)	24.3 (4.3)
BMI groups, kg/m² (%)		
<20	30 427 (13.8)	890 (13.2)
20-24	114 197 (51.7)	3 496 (51.7)
25-29	49 089 (22.2)	1 618 (23.9)
≥30	27 292 (12.4)	756 (11.2)
Mean weight increase, kg (SD)	14.3 (7.4)	14.1 (7.3)
N missing (%)	115 567 (52.3)	4 024 (59.5)
Birth year (%)		
2007-2009	45 003 (20.4)	1 181 (17.5)
2010-2012	73 214 (33.1)	2 150 (31.8)
2013-2015	102 788 (46.5)	3 429 (50.7)
Mean birth weight, grams (SD)	3 546.8 (551.8)	3 443.4 (623.4)
SGA[1] (%)	6 954 (3.2)	311 (4.6)
LGA[1] (%)	9 484 (4.3)	276 (4.1)
Gestational age, weeks (%)		
<28	494 (0.2)	50 (0.7)
28+0 - 31+6	882 (0.4)	59 (0.9)
32+0 - 36+6	8774 (4.0)	400 (5.9)
≥37	210 855 (95.4)	6251 (92.5)
Perinatal death[2] (%)	815 (0.4)	45 (0.7)
Smoking (%)		
Non-smoker	170 857 (77.3)	5 751 (85.1)
Smoke before start of pregnancy	33 185 (15.0)	607 (9.0)
No consent to registration of smoking status	15 949 (7.2)	377 (5.6)
Missing	1014 (0.5)	25 (0.4)
Hypertensive disorders (%)	8 223 (3.7)	352 (5.2)
Gestational diabetes mellitus (%)	4 602 (2.1)	(198 (2.9)
Induction of delivery (%)	29 404 (13.3)	1 197 (17.7)
Caesarean section (%)	28 999 (13.1)	1 242 (18.4)

[1]SGA and LGA are defined as birthweight <-2 and >+2 standard deviations, respectively, according to week of gestation and foetal sex.
[2]Defined as still birth and live birth with death within the first 28 days.

Table 2. Perinatal outcomes according to maternal pre-pregnancy body mass index and mode of conception

		Spontaneous conceptions (SC)					ART conceptions					ART versus SC[1]	
		Risk[2], %	Risk difference, % (95% CI)[3]		Odds ratio (95% CI)[3]		Risk[2], %	Risk difference, % (95% CI)[3]		Odds ratio (95% CI)[3]		Odds ratio (95 % CI)[3]	
Preterm birth <37 weeks *($P_{LR\text{-}test}$ 0.91)*													
BMI (kg/m^2)	<20	4.7	0.5	(0.3 to 0.8)	1.13	(1.06 to 1.20)	7.3	0.7	(-1.3 to 2.6)	1.11	(0.83 to 1.47)	1.63	(1.25 to 2.13)
	20-24	4.2	0	(Ref)	1	(Ref)	6.8	0	(Ref)	1	(Ref)	1.54	(1.34 to 1.77)
	25-29	4.7	0.5	(0.3 to 0.7)	1.11	(1.06 to 1.17)	8.3	1.2	(-0.4 to 2.9)	1.20	(0.95 to 1.50)	1.61	(1.33 to 1.94)
	≥30	5.9	1.5	(1.1 to 1.8)	1.36	(1.28 to 1.45)	9.5	2.2	(0.0 to 4.4)	1.35	(1.02 to 1.79)	1.47	(1.36 to 1.89)
Small for gestational age *($P_{LR\text{-}test}$ 0.54)*													
BMI (kg/m^2)	<20	4.6	1.5	(1.2 to 1.8)	1.53	(1.43 to 1.63)	5.7	1.2	(-0.5 to 2.8)	1.28	(0.92 to 1.77)	1.06	(0.79 to 1.42)
	20-24	3.0	0	(Ref)	1	(Ref)	4.5	0	(Ref)	1	(Ref)	1.17	(0.99 to 1.39)
	25-29	2.6	-0.4	(-0.6 to -0.2)	0.87	(0.82 to 0.93)	3.9	-0.6	(-1.8 to 0.5)	0.86	(0.64 to 1.16)	1.12	(0.86 to 1.45)
	≥30	3.1	0.0	(-0.3 to 0.2)	0.99	(0.91 to 1.07)	5.3	0.6	(-1.1 to 2.3)	1.14	(0.80 to 1.63)	1.33	(0.95 to 1.87)
Large for gestational age *($P_{LR\text{-}test}$ 0.77)*													
BMI (kg/m^2)	<20	1.5	-1.6	(-1.7 to -1.4)	0.50	(0.45 to 0.55)	1.8	-1.1	(-2.2 to -0.1)	0.61	(0.36 to 1.05)	1.59	(0.95 to 2.64)
	20-24	3.1	0	(Ref)	1	(Ref)	2.9	0	(Ref)	1	(Ref)	1.20	(0.98 to 1.47)
	25-29	6.0	2.6	(2.4 to 2.9)	1.90	(1.80 to 2.00)	5.4	2.2	(1.0 to 3.5)	1.80	(1.33 to 2.42)	1.09	(0.87 to 1.36)
	≥30	9.3	5.7	(5.4 to 6.1)	3.02	(2.86 to 3.20)	9.4	6.0	(3.9 to 8.1)	3.23	(2.35 to 4.46)	1.21	(0.94 to 1.56)
Perinatal death[4] *($P_{LR\text{-}test}$ 0.66)*													
BMI (kg/m^2)	<20	0.3	-0.03	(-0.1 to 0.04)	0.91	(0.73 to 1.15)	0.5	-0.1	(-0.6 to 0.4)	0.83	(0.28 to 2.44)	1.72	(0.62 to 4.80)
	20-24	0.3	0	(Ref)	1	(Ref)	0.5	0	(Ref)	1	(Ref)	1.50	(0.94 to 2.40)
	25-29	0.4	0.05	(-0.01 to 0.1)	1.15	(0.96 to 1.37)	0.9	0.4	(-0.2 to 0.9)	1.72	(0.85 to 2.45)	1.94	(1.11 to 3.40)
	≥30	0.6	0.2	(0.1 to 0.3)	1.64	(1.36 to 1.99)	1.1	0.7	(-0.2 to 1.5)	2.27	(0.99 to 5.20)	1.54	(0.73 to 3.24)

[1]SC pregnancies are the reference group. [2]Unadjusted. [3]Adjusted for maternal age, education and parity. [4]Defined as stillbirth and live birth with death within 28 days.

Table 3. Maternal outcomes according to maternal pre-pregnancy body mass index and mode of conception[1]

	Spontaneous conceptions (SC)					ART conceptions					ART versus SC[2]	
	Risk[3], %	Risk difference, % (95% CI)[4]		Odds ratio (95% CI)[4]		Risk[3], %	Risk difference, % (95% CI)[4]		Odds ratio (95% CI)[4]		Odds ratio (95 % CI)[4]	
Hypertensive disorders *($P_{LR\text{-}test}$ 0.32)*												
BMI (kg/m^2) <20	2.1	-0.7	(-0.9 to -0.5)	0.78	(0.71 to 0.85)	2.9	-1.6	(-3.1 to 0.0)	0.68	(0.45 to 1.04)	1.17	(0.78 to 1.75)
20-24	2.7	0	(Ref)	1	(Ref)	4.3	0	(Ref)	1	(Ref)	1.29	(1.09 to 1.54)
25-29	4.6	2.4	(2.1 to 2.6)	1.79	(1.69 to 1.90)	5.7	1.8	(0.2 to 3.4)	1.39	(1.06 to 1.82)	1.02	(0.82 to 1.27)
≥30	8.4	6.9	(6.5 to 7.4)	3.46	(3.26 to 3.68)	11.1	8.6	(5.7 to 11.5)	2.96	(2.21 to 3.97)	1.04	(0.82 to 1.31)
Gestational diabetes mellitus *($P_{LR\text{-}test}$ 0.002)*												
BMI (kg/m^2) <20	0.7	-0.4	(-0.5 to -0.2)	0.72	(0.62 to 0.83)	0.3	-1.9	(-2.7 to -1.2)	0.18	(0.06 to 0.58)	0.35	(0.11 to 1.11)
20-24	1.1	0	(Ref)	1	(Ref)	2.0	0	(Ref)	1	(Ref)	1.44	(1.12 to 1.85)
25-29	2.8	1.9	(1.7 to 2.1))	2.57	(2.37 to 2.79)	4.5	2.9	(1.6 to 4.3)	2.33	(1.65 to 3.28)	1.34	(1.04 to 1.71)
≥30	6.7	6.2	(5.9 to 6.6)	6.36	(5.88 to 6.88)	7.1	5.8	(3.6 to 7.9)	3.72	(2.55 to 5.41)	0.94	(0.71 to 1.25)
Induction of labour *($P_{LR\text{-}test}$ 0.54)*												
BMI (kg/m^2) <20	9.7	-2.3	(-2.7 to -1.8)	0.82	(0.78 to 0.85)	12.7	-4.3	(-7.3 to -1.3)	0.74	(0.59 to 0.93)	1.21	(0.98 to 1.48)
20-24	11.7	0	(Ref)	1	(Ref)	16.6	0	(Ref)	1	(Ref)	1.34	(1.22 to 1.47)
25-29	15.3	4.2	(3.7 to 4.6)	1.37	(1.32 to 1.41)	19.4	3.6	(0.9 to 6.3)	1.24	(1.01 to 1.45)	1.18	(1.04 to 1.34)
≥30	20.3	10.1	(9.5 to 10.7)	1.96	(1.89 to 2.03)	25.0	10.7	(6.7 to 14.6)	1.78	(1.46 to 2.17)	1.17	(0.98 to 1.38)
Caesarean section *($P_{LR\text{-}test}$ 0.29)*												
BMI (kg/m^2) <20	9.6	-1.9	(-2.4 to -1.5)	0.84	(0.80 to 0.88)	15.3	-0.3	(-3.7 to 3-0)	0.98	(0.79 to 1.22)	1.30	(1.07 to 1.59)
20-24	11.5	0	(Ref)	1	(Ref)	16.3	0	(Ref)	1	(Ref)	1.12	(1.02 to 1.24)
25-29	15.2	4.1	(3.7 to 4.5)	1.37	(1.33 to 1.42)	21.1	5.1	(2.4 to 7.9)	1.35	(1.15 to 1.58)	1.14	(1.00 to 1.30)
≥30	20.1	9.6	(8.9 to 10.2)	1.93	(1.85 to 2.00)	25.7	10.1	(6.1 to 14.0)	1.74	(1.42 to 2.13)	1.05	(0.88 to 1.25)

[1]Data not available for 2015. [2]SC pregnancies are the reference group. [3]Unadjusted. [4]Adjusted for maternal age, education and parity

Table 4. Characteristics of pregnancies with and without available information on maternal pre-pregnancy body mass index (BMI)

	Information on BMI available	Missing information on BMI
Number of observations (%)	227 765 (49.1)	236 553 (51.0)
ART conceptions (%)	5 595 (2.9)	5 852 (2.6)
Maternal education		
High school or lower	101 770 (44.7)	102 245 (43.2)
College/university lower level	92 821 (40.8)	97 723 (41.3)
College/university higher level	33 174 (14.6)	26 585 (15.5)
Mean maternal age, years (SD)	30.4 (4.7)	30.6 (4.7)
Parity (%)		
0	92 379 (40.1))	92 024 (38.9)
1	85 572 (37.6)	89 976 (38.0)
2	36 355 (16.0)	39 063 (16.5)
≥3	13 459 (5.9)	15 490 (6.6)
Birth year (%)		
2007	6 791 (13.6)	43 106 (86.4)
2008	18 858 (36.4)	32 989 (63.6)
2009	20 535 (38.7)	32 493 (61.3)
2010	21 808 (41.2)	31 118 (58.8)
2011	24 528 (46.7)	27 977 (53.3)
2012	29 028 (55.3)	23 436 (44.7)
2013	32 494 (63.8)	18 427 (36.2)
2014	36 561 (71.9)	14 258 (28.1)
2015	37 162 (74.5)	12 749 (25.5)
Gestational age, weeks (%)		
<28	544 (0.2)	921 (0.4)
28+0 - 31+6	941 (0.4)	1 315 (0.6)
32+0 - 36+6	9 174 (4.0)	10 189 (4.3)
≥37	217 106 (95.3)	224 128 (94.7)
Mean birth weight, gram (SD)	3 543.7 (554.4)	3 527.0 (574.2)
Smoking (%)		
Non-smoker	176 608 (77.5)	109 649 (46.4)
Smokes before start of pregnancy	33 792 (14.8)	21 561 (9.1)
No consent to registration of smoking status	16 326 (7.2)	46 726 (19.8)
Missing	1039 (0.5)	58 617 (24.8)
Perinatal death (%)	860 (0.4)	1 326 (0.6)
Hypertensive disorders[1] (%)	8 575 (4.5)	11 865 (5.3)
Gestational diabetes mellitus[1] (%)	4 800 (2.5)	4 032 (1.8)
Induction of delivery[1] (%)	30 601 (16.1)	33 967 (15.2)
Caesarean section[1] (%)	30 241 (15.9)	36 762 (16.4)

[1]Not available for deliveries in 2015

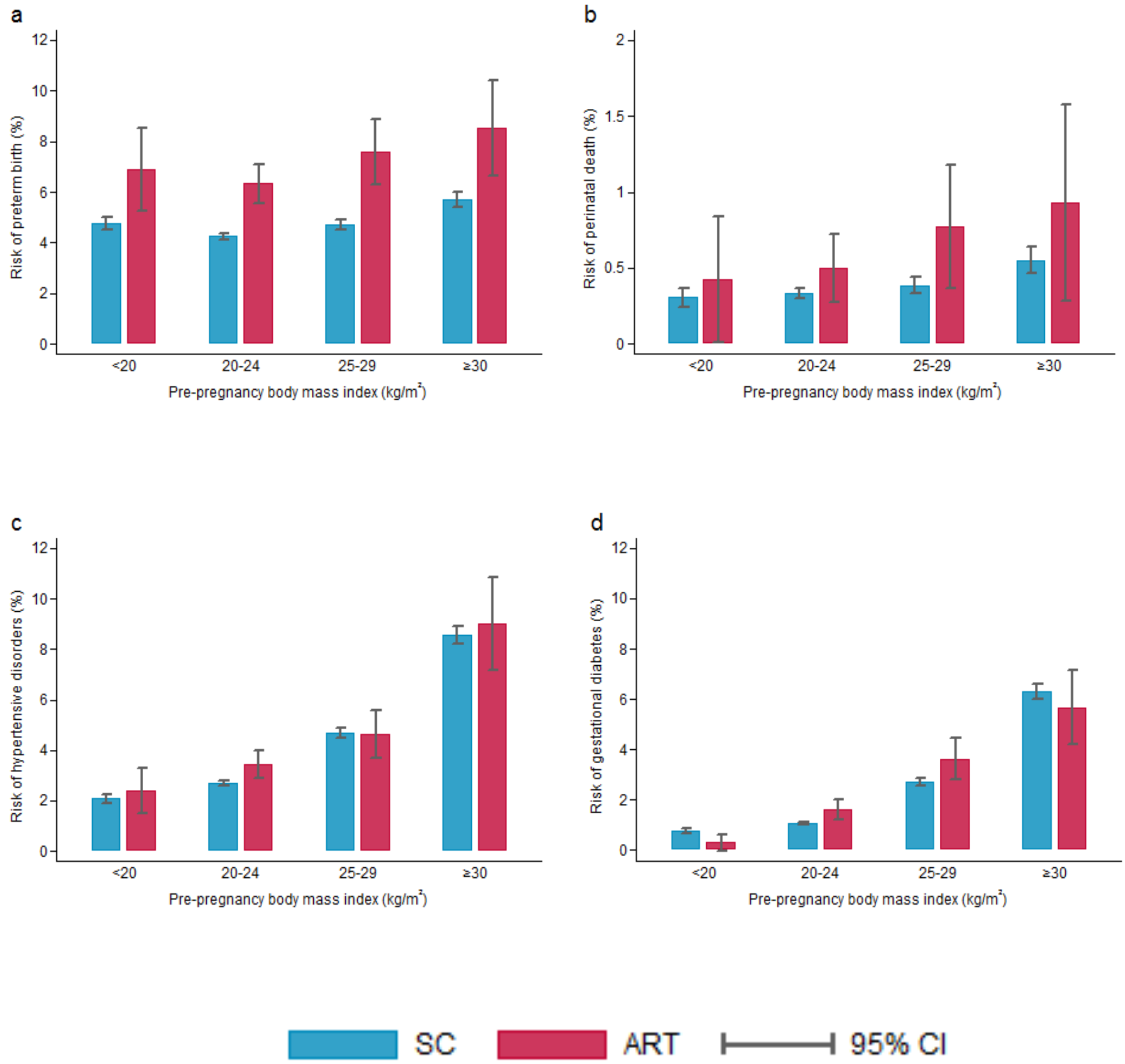

Figure 1. Risk of selected perinatal and maternal outcomes according to mode of conception and maternal pre-pregnancy body mass index. a) Preterm birth, b) Perinatal death, c) Hypertensive disorders in pregnancy and d) Gestational diabetes mellitus.