Journal Pre-proof

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PII: S0002-9378(20)30218-0

DOI: https://doi.org/10.1016/j.ajog.2020.02.030

Reference: YMOB 13131

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 12 November 2019

Revised Date: 30 January 2020

Accepted Date: 8 February 2020

Please cite this article as: Petersen. SH, Bergh C, Gissler M, Åsvold BO, Romundstad LB, Tiitinen A, Spangmose AL, Pinborg A, Wennerholm U-B, Henningsen A-KA, Opdahl S, Time trends in placenta-mediated pregnancy complications after assisted reproductive technology in the Nordic countries, *American Journal of Obstetrics and Gynecology* (2020), doi: https://doi.org/10.1016/j.ajog.2020.02.030.

Time trends in placenta-mediated pregnancy complications after assisted reproductive technology in the Nordic countries

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Sources of funding:

This work was supported by the Nordic Trial Alliance: a pilot project jointly funded by the Nordic Council of Ministers and NordForsk [grant number 71450], the Central Norway Regional Health Authorities [grant number 46045000], the Nordic Federation of Obstetrics and Gynaecology [grant numbers NF13041, NF15058, NF16026 and NF17043], and by the Research Council of Norway's Centre of Excellence funding scheme [grant number 262700] and the Faculty of Medicine and Health Science, Norwegian University of Science and Technology [grant number 70367047]

Conflicts of Interest: The authors report no conflict of interest.

Condensation: Risk of placenta-mediated pregnancy complications remains higher after assisted reproductive technology, and increases for hypertensive disorders in twin pregnancies and for placenta previa overall.

Short title: Time trends in pregnancy complications after assisted reproductive technology.

AJOG at a glance

Why was this study conducted?

Use of assisted reproductive technology (ART) increases worldwide with improving perinatal outcomes. We aimed to investigate changes in occurrence of placenta-mediated complications in ART pregnancies compared to the background population over three decades.

Key findings

ART pregnancies continue to be at higher risk, despite declining rates of multiple pregnancies. Risk of hypertensive disorders in twin pregnancies is increasing regardless of conception method, while risk of placenta previa has increased more strongly in ART pregnancies. Risk of placental abruption risk has decreased in both populations.

What does this add to what is known?

Recent improvements in perinatal outcomes after ART have not been accompanied by a corresponding improvement in maternal pregnancy health in this population. Increasing risk of placenta previa requires further attention.

Key words:

Preeclampsia, hypertensive disorders in pregnancy, gestational hypertension, placental abruption, placenta previa, assisted reproduction, in vitro fertilization, reproductive medicine, temporal changes, twins.

Abstract

Background: The use of assisted reproductive technology (ART) is increasing worldwide and conception after assisted reproduction currently comprises 3-6% of birth cohorts in the Nordic countries. The risk of placenta-mediated pregnancy complications is higher after ART compared to spontaneously conceived pregnancies. Whether the excess risk of placenta-mediated pregnancy complications in pregnancies following assisted reproduction has changed over time, is unknown.

Objectives: To investigate whether time trends in risk of pregnancy complications (hypertensive disorders in pregnancy, placental abruption and placenta previa) differ for

pregnancies after ART compared to spontaneously conceived pregnancies during three decades of assisted reproduction treatment in the Nordic countries.

Study Design: In a population-based cohort study, with data from national health registries in Denmark (1994-2014), Finland (1990-2014), Norway (1988-2015) and Sweden (1988-2015), we included 6,830,578 pregnancies resulting in delivery. Among these, 146,998 (2.2%) were pregnancies after assisted reproduction (125,708 singleton pregnancies, 20,668 twin pregnancies and 622 of higher order plurality) and 6,683,132 (97.8%) pregnancies were conceived spontaneously (6,595,185 singleton pregnancies, 87,106 twin pregnancies and 1,289 of higher order plurality). We used logistic regression with post-estimation to estimate absolute risks and risk differences for each complication. We repeated analyses for singleton and twin pregnancies, separately. In sub-samples with available information, we also adjusted for maternal body mass index, smoking during pregnancy, previous cesarean section, culture duration and cryopreservation.

Results: The risk of each placental complication was consistently higher in pregnancies following ART compared to spontaneously conceived pregnancies across the study period, except for hypertensive disorders in twin pregnancies, where risks were similar. Risk of hypertensive disorders increased over time in twin pregnancies for both conception methods, but more strongly for pregnancies following ART (risk difference 1.73 percentage points per 5 years, 95% confidence interval 1.35 to 2.11) than for spontaneously conceived twins (risk difference 0.75 percentage points, 95% confidence interval 0.61 to 0.89). No clear time trends were found for hypertensive disorders in singleton pregnancies. Risk of placental abruption decreased over time in all groups (risk difference -0.16 percentage points, 95% confidence interval -0.19 to -0.12 and -0.06 percentage points, 95% confidence interval -0.06 to -0.05 for

pregnancies after assisted reproduction and spontaneously conceived pregnancies, respectively, for singletons and multiple pregnancies combined). Over time, the risk of placenta previa increased in pregnancies after assisted reproduction among both singletons (risk difference 0.21 percentage points, 95% confidence interval 0.14 to 0.27) and twins (risk difference 0.30 percentage points, 95% confidence interval 0.16 to 0.43), but remained stable in spontaneously conceived pregnancies. When adjusting for culture duration, the temporal increase in placenta previa became weaker in all groups of ART pregnancies, whereas adjustment for cryopreservation moderately attenuated trends in ART twin pregnancies.

Conclusions: The risk of placenta-mediated pregnancy complications following ART remains higher compared to spontaneously conceived pregnancies, despite declining rates of multiple pregnancies. For hypertensive disorders in pregnancy and placental abruption, pregnancies after assisted reproduction follow the same time trends as the background population, whereas for placenta previa, risk has increased over time in pregnancies after ART.

Introduction

Assisted reproductive technology (ART) comprises conception methods where fertilization takes place outside the female body. Risk of placenta-mediated pregnancy complications, including preeclampsia, placental abruption and placenta previa, is higher in pregnancies after ART treatment compared to spontaneously conceived (SC) pregnancies[1,2]. Risk of adverse perinatal outcomes such as preterm birth, low birthweight and perinatal death is also higher[3,4]. This has been attributed partly to the high occurrence of multiple pregnancies after ART treatment. Still, singleton ART pregnancies also carry a higher risk of adverse outcomes

compared to SC singletons[1,2]. The underlying causes of infertility, as well as the ART treatment itself, may both contribute to the higher risk[5-8]. It has been hypothesized that the super-physiological hormone levels seen in ART-cycles may alter early placentation and thereby contribute to adverse outcomes[9].

Worldwide, ART treatment has increased steadily over the past decades, due to increasing availability and success rates in combination with sociodemographic changes with postponement of childbearing[10]. Simultaneously, perinatal outcomes after ART conception have improved and are approaching the levels of the background population, mainly due to reduction of multiple births, but also due to the improved health in ART singletons[11].

It seems likely that the increasing use and success rates of ART would be accompanied by changes in the population of women seeking medical attention for infertility. Women treated with ART today comprise a larger proportion of the total population and may therefore be more comparable to the background population than women treated some decades ago. Conversely, advances in ART[12] over time may also have enabled more severely infertile women to become pregnant. Previous studies indicate that risk of some placenta-mediated pregnancy complications, namely preeclampsia and placental abruption, is declining in the general population[13,14]. Whether this development also concerns ART pregnancies is unknown.

The objective of this study was to investigate whether time trends in occurrence of placenta-mediated pregnancy complications; hypertensive disorders in pregnancy (HDP), placental abruption and placenta previa, differ for ART pregnancies compared to SC pregnancies during three decades of ART treatment in the Nordic countries.

Material and Methods

Study population and data sources

The Committee of Nordic ART and Safety (CoNARTaS) study population comprises all deliveries in Denmark (1994–2014), Finland (1990–2014), Norway (1984–2015) and Sweden (1985–2015). Data were obtained from the nationwide Medical Birth Registries (MBRs) in each country, where detailed information on maternal, fetal and neonatal health for all deliveries is recorded. Individual level data from MBRs can be linked to other data sources through the unique national identity number assigned to all residents in the Nordic countries[15]. ART conception was determined through direct reporting to MBRs (Finland 1990–2014, Norway 1984–2015 and Sweden 1985–2006), in separate notifications of all ART pregnancies at gestational week 6-7 (Norway 1984–2015) or through linkage with cycle-based ART registries (Denmark 1994–2014 and Sweden 2007–2015).

From the MBRs we obtained information on birth year, plurality, birthweight, gestational age, offspring sex, parity, maternal age, smoking status in pregnancy and body mass index (BMI, measured pre-pregnancy or in first trimester). For SC pregnancies, gestational age was estimated based on ultrasound examination or on last menstrual period if information from ultrasound examination was unavailable. For ART pregnancies, gestational age was estimated based on ultrasound examination or on date of embryo transfer and culture duration, according to clinical practice in each country.

Information on pregnancy complications was obtained directly from MBRs in Finland (2004–2014), Norway (1984–2015) and Sweden (1985–2015) and from data linkage with national patient registries (NPRs) in Denmark (1994–2014) and Finland (1989–2014). In the MBRs, complications are reported at delivery with limited information on gestational age at diagnosis. In Norway, the MBR revised the notification form in 1998, changing the reporting of pregnancy complications from free text to checkboxes. For NPR data, diagnoses from each prenatal visit, delivery and postpartum controls were linked to each pregnancy using maternal identity and date of delivery. The Danish NPR comprised data from hospital admissions and outpatient visits in public specialist health care during the entire study period, and from private specialist health care since 2003. The Finnish NPR expanded its data collection in 1998 from hospital admissions only to include also hospital outpatient visits.

Because there were very few ART deliveries during the first years of registration, and among women of young or high reproductive ages, we restricted the study to 1988–2015 and deliveries with maternal age 22-44 years. Thus, a total of 6,830,578 deliveries among 4,160,402 women were eligible.

We excluded 120,628 deliveries with missing information on one or more study variables and 12,944 deliveries with gestational age <22 or ≥45 weeks, birthweight <300 g or ≥6000 g and birthweight for gestational age ≥+6 standard deviations[16]. Multiple pregnancies were excluded when at least one child met the exclusion criteria. Our main analysis sample included 146,998 deliveries after ART and 6,683,580 deliveries of SC pregnancies. Selection of the study population and sub-samples for sensitivity analyses are described in Figure 1.

Outcome variables

Pregnancy complications were registered according to national adaptations of the International Classification of Diseases and related Health Problems (ICD) classification as outlined in Supplemental Table 1.

We considered HDP as a combined outcome including preeclampsia, eclampsia, gestational hypertension, and chronic hypertension with superimposed preeclampsia. We did not consider chronic hypertension as a hypertensive disorder in pregnancy because pre-pregnancy conditions cannot be a consequence of ART. For MBR data, any reporting of relevant ICD codes were considered as events, whereas the following diagnoses were included from NPRs: Diagnoses of HDP registered after 20 weeks gestation, any diagnosis of placental abruption, and any diagnosis of placenta previa in the third trimester or within one month before delivery.

Statistical analyses

We used logistic regression to estimate time trends in occurrence of pregnancy complications within the ART and SC populations. To facilitate interpretation, we used post-estimation commands to calculate absolute risks and risk differences (RDs) with 95% confidence intervals (CIs). We estimated trends over birth year categories (1988-1992, 1993-1997, 1998-2002, 2003-2007, 2008-2012, 2013-2015) and as linear trends across the study period (change per 5 years, continuous variable). We also compared risk of each complication in ART versus SC pregnancies within each period as a measure of whether risks in the two populations converged over time. Analyses were performed on the all pregnancies, and for singletons and twins, separately. We adjusted for parity, maternal age and country. To investigate whether time trends differed between countries, we repeated analyses for each country separately.

We performed several sensitivity analyses to investigate potential explanations for the observed trends: We repeated analyses for primiparous women. In sub-samples with available information, we adjusted for maternal BMI and smoking. Within the ART population, we also adjusted for embryo cryopreservation (restricted to Denmark, Norway and Sweden) and culture duration (cleavage stage 2-3 days vs blastocyst stage 5-6 days, restricted to Denmark and Sweden). Next, we restricted diagnosis of placenta previa to pregnancies with delivery by cesarean section, which is required in cases of complete obstruction. Furthermore, to investigate the potential impact of a previous cesarean section, a known risk factor for placenta previa subjected to marked time trends, we adjusted for this in a sub-sample of deliveries among parous women whose first delivery was included in the study. Statistical analyses were performed using Stata/MP for Windows, Version 15.0 (StataCorp LLC, College Station, Texas, USA).

Ethical considerations and approvals

Approvals for data retrieval and linkage were obtained in each country. In Denmark and Finland, ethical approval is not required for research solely based on registry data. In Norway, ethical approval was given by the Regional Committee for Medical and Health Research Ethics (REC North, 2010/1909). In Sweden approval was obtained from the Ethical committee in Gothenburg, Dnr 214-12, T422-12, T516-15, T233-16, T300-17, T1144-17, T121-18.

Results

For the total period, deliveries after ART constituted 3.0% of birth cohorts in Denmark, 1.8% in Finland, 2.0% in Norway and 2.0% in Sweden (Table 1). There was a clear increase in

ART deliveries over time from 0.8% of all deliveries in 1988-1997 to 3.4% in 2008-2015, accompanied by a reduction of multiple pregnancies in ART from 26% in 1988-1997 to 8.7% in 2008-2015. The proportion of SC multiple pregnancies remained stable around 1.3%.

Overall, parity was lower (68.0% versus 39.5% primiparous) and mean maternal age higher (33.8 versus 30.3 years) in ART compared to SC pregnancies, whereas BMI was similar between the two groups. ART mothers smoked less (5.7%) than spontaneously conceiving mothers (11.8%). Cesarean sections (30.9% versus 15.4%) and labor inductions (20.7% versus 13.4%) were more common in ART compared to SC pregnancies.

Hypertensive disorders in pregnancy

Risk of HDP in SC pregnancies was 4.4% (Table 2). For all pregnancies (i.e. singletons and multiples combined), risk of HDP was higher in ART compared to SC pregnancies throughout the study period (odds ratio [OR] 1.25, 95% CI 1.23 to 1.28, corresponding to a RD of 1.06 percentage points [*pp*]). In SC pregnancies, risk increased with 0.17 *pp* per 5 years (95% CI 0.16 to 0.18). The increase was stronger in twin compared to singleton pregnancies (RD 0.75 and 0.16 *pp* per 5 years, respectively). When adjusting for maternal smoking and BMI in a sub-sample, time trends were reversed in SC singletons and substantially attenuated in SC twins (Supplemental Table 2). For all ART pregnancies combined, there was no clear time trend. However, in separate analyses of singleton and twin pregnancies, development followed that in SC pregnancies (Figures 2A and 2B), with strongly increasing risk in twin pregnancies (RD 1.73 *pp* per 5 years, 95% CI 1.35 to 2.11) in all countries. Adjustment for maternal smoking and BMI had little influence on trends in ART pregnancies, but adjustment for cryopreservation moderately attenuated trends in ART twin pregnancies (Supplemental Table 2).

Placental abruption

Risk of placental abruption in SC pregnancies was 0.43% (Table 3). Throughout the study period, risk of placental abruption was consistently higher in ART compared to SC pregnancies, both overall (OR 1.95 across the study period, 95% CI 1.83 to 2.07, corresponding to a RD of 0.40 *pp*) and when separating singleton and twin pregnancies. Risk of placental abruption decreased weakly over time in SC pregnancies (RD -0.06 *pp* per 5 years, 95% CI -0.06 to -0.05), with similar trends for singleton and twin pregnancies. In ART pregnancies, the risk decrease was somewhat stronger than in SC pregnancies (RD -0.16 *pp* per 5 years, 95% CI -0.19 to -0.12) and of similar magnitude in singletons and twins. Country specific analyses were compatible with results from pooled analyses (Figures 2C and 2D). In all groups, time trends remained broadly similar after additional adjustment for BMI and smoking (Supplemental Table 3).

Placenta previa

Risk of placenta previa in SC pregnancies was 0.34% (Table 4). Placenta previa was considerably more common in ART compared to SC pregnancies across the study period for all pregnancies combined (OR 3.87, 95% CI 3.70 to 4.04 corresponding to a RD of 0.95 *pp*), and for singleton and twin pregnancies separately. In SC pregnancies, risks did not substantially differ between singletons and twins, whereas for ART pregnancies, risk was somewhat higher for singletons than for twins. In SC pregnancies, risk increased weakly over time for singleton pregnancies (RD 0.03 *pp* per 5 years) but remained stable for twins (Figure 2E). In contrast, risk increased strongly with time in ART pregnancies (RD 0.24 *pp* per 5 years for all pluralities combined, 95% CI 0.18 to 0.30). Trends in ART pregnancies were similar for singletons and twins and were most pronounced in Denmark and Finland (Figure 2F).

In sensitivity analyses, results remained similar when adjusting for smoking and BMI (Supplemental Table 4), when restricting analyses to primiparous women, when restricting diagnoses of placenta previa to those accompanied by cesarean section, and when adjusting for previous cesarean section. When adjusting for culture duration, the temporal increase in placenta previa became weaker in all groups of ART pregnancies.

Comment

Main findings

In this registry-based cohort with nationwide data from four countries across almost three decades, we found a higher risk of placenta-mediated pregnancy complications in ART pregnancies compared to the background population of SC children throughout the study period. For placenta previa, risk increased substantially over time in ART pregnancies, in contrast to a weakly increasing risk in the background population. For HDP, ART pregnancies followed the trends of the background population, with weakly increasing occurrence in singletons and strongly increasing occurrence in twins. Risk of placental abruption decreased over time in all groups.

Results

Recent meta-analyses of observational studies show positive associations between ART conception and gestational hypertension, preeclampsia, placental abruption and placenta previa[1,17]. Our results are largely consistent with these studies, apart from lower risk of HDP in ART twin pregnancies compared to SC twin pregnancies.

We are not aware of previous studies investigating time trends in pregnancy complications following ART conception. However, some studies of time trends in the general population

exist for these complications. In contrast to the weakly increasing rates of HDP in the general population that we observed from 1988 to 2015, Roberts et al.[14] reported declining rates of gestational hypertension and preeclampsia in several Western populations, including Denmark, Norway and Sweden, during the shorter time span from 1997 to 2007. Causes of the increasing incidence of HDP in twin pregnancies are unknown, but are not likely due to increasing gestational age, since mean gestational age did not increase in twin pregnancies across time in our study, in line with the previously reported stable occurrence of preterm birth for twin pregnancies[11].

Ananth et al.[13] reported declining rates of placental abruption in singleton pregnancies in several Western populations, including the Nordic countries, from 1978 to 2008. They hypothesized that this might be due to changes in smoking. Our results are consistent with their study, but additionally show that risk of placental abruption has declined regardless of conception methods and multiplicity, suggesting that the development might be driven by reduction in risk factors common to all subgroups. However, smoking seemed not to explain this development, since adjustment for smoking had very little influence on trends, both for ART and SC pregnancies.

An Australian cohort study showed that the risk of placenta previa in the general population increased from 0.69% to 0.87% in the years 2001–2009[18], while a Swiss population-based cohort study showed an increase in the yearly incidence of placenta previa from 0.3% to 0.5% between 1993 and 2014[19]. Although our results support an overall increasing trend, the increase of placenta previa in the background population was much weaker. The increase in risk in ART pregnancies was considerably stronger, a finding not previously reported. Consistent with expectations from a Swedish study showing higher risk of placenta previa

after blastocyst transfer[20] in a sub-sample of our Swedish study population, the increasing risk of placenta previa over time attenuated moderately after adjustment for culture duration.

Clinical implications

When considering all ART pregnancies combined, risk of all complications declined considerably and approached that in the background population during the study period, mainly due to declining occurrence of multiple pregnancies, a major risk factor for adverse outcomes, after ART conception. Elective single embryo transfer (eSET) policies in the Nordic countries have led to substantial reductions in multiple pregnancies after ART, thereby also reducing risk of adverse outcomes in ART pregnancies. Thus, our results further emphasize the importance of eSET.

The increasing risk of placenta previa in ART pregnancies is a matter of concern and could only partly be explained by the concurrent increase in blastocyst culture. Whether other treatment-related and thus potentially modifiable factors are involved, or whether changes in characteristics of the ART population contribute to this trend, is not yet known.

Furthermore, informing clinicians and infertile couples that ART pregnancies are still at higher risk of placenta-mediated pregnancy complications despite increasing success rates and improving neonatal outcomes in ART[11,21], is important.

Research implications

Future studies should investigate underlying causes for the increasing occurrence of HDP in twin pregnancies. In addition, reasons behind the increasing incidence of placenta previa in ART pregnancies warrant further investigation.

Strengths and limitations

A key strength of this study is the large study sample with data on all deliveries in four Nordic countries over three decades, which enabled precisely estimated time trends in most analyses. Nonetheless, there were few events in the ART population in the earliest study period and that power was limited also in some sensitivity analyses.

Another strength is that we could adjust for potential confounders such as parity, maternal age and country, as well as BMI, smoking and cesarean section in subsamples. Still, we cannot exclude residual confounding by unmeasured factors such as causes for infertility or from misclassification of self-reported information such as smoking status.

In the Nordic countries, ART treatment is strongly subsidized, ensuring that the couple's financial situation is not a major determinant of ART conception. In combination with nationwide data sources with a very low proportion of missing data, this suggests that selection bias should be minimal. Furthermore, practically all pregnant women attend the publicly financed antenatal care program. In consequence, opportunities to detect pregnancy complications should not differ between the two conception methods, and the overall validity of such diagnoses is acceptable in all countries[22-26]. However, it is possible that women who conceive through ART have a lower threshold for seeking medical attention during pregnancy, and detection bias thus cannot be excluded.

Occurrence of pregnancy complications was generally higher when extracted from patient registries (Denmark, Finland) than from MBRs only (Norway, Sweden). Changes in registration and coding practice over time may also have influenced the observed trends but should not affect ART and SC pregnancies differently.

Conclusions

Risk of placenta-mediated pregnancy complications following ART conception is higher than for SC pregnancies in the Nordic countries. For HDP and placental abruption, ART pregnancies follow the same trends as the background population. Risk of HDP is increasing in both ART and SC twin pregnancies. Placenta previa risk has increased strongly over time in ART pregnancies.

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Figure captions:

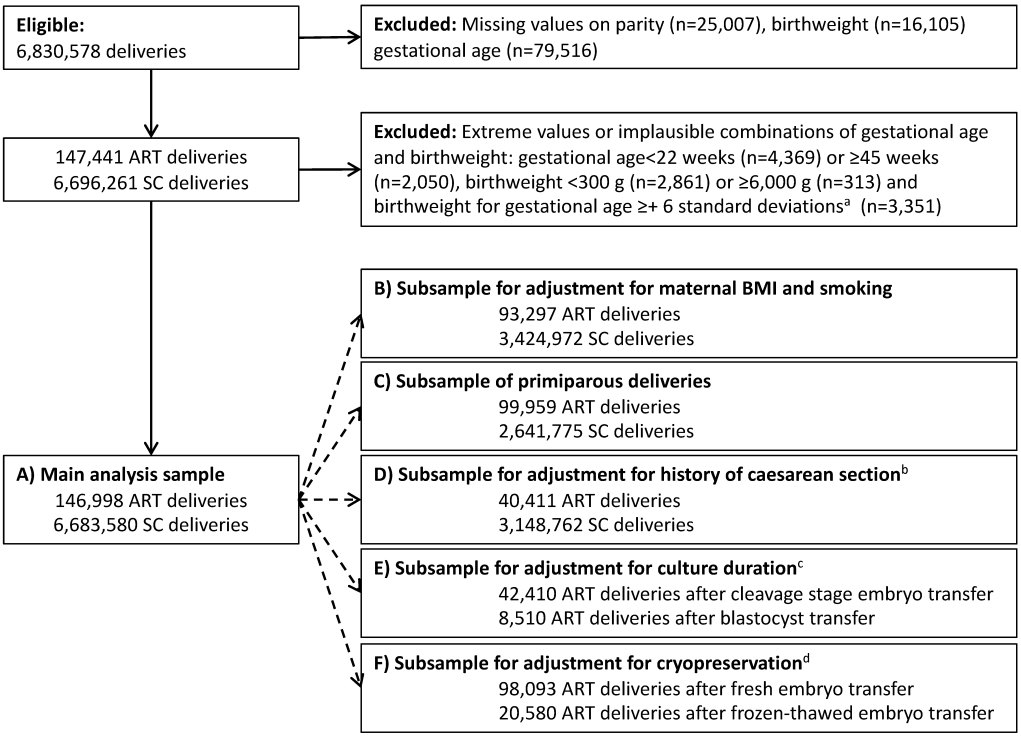
- FIGURE 1**: Selection of the study population and sub-samples for sensitivity analyses**. *ART*, assisted reproductive technology, *SC*, spontaneous conception, *BMI*, body mass index. Solid line arrows pointing to the right indicate exclusions, dashed line arrows pointing to the right indicate sub-sample selection.
- FIGURE 2**: Time trends in risk if placenta-mediated pregnancy complications according to conception method, plurality and country**. *ART*, assisted reproductive technology, *HDP*, hypertensive disorders in pregnancy. Estimates are adjusted for parity and maternal age.

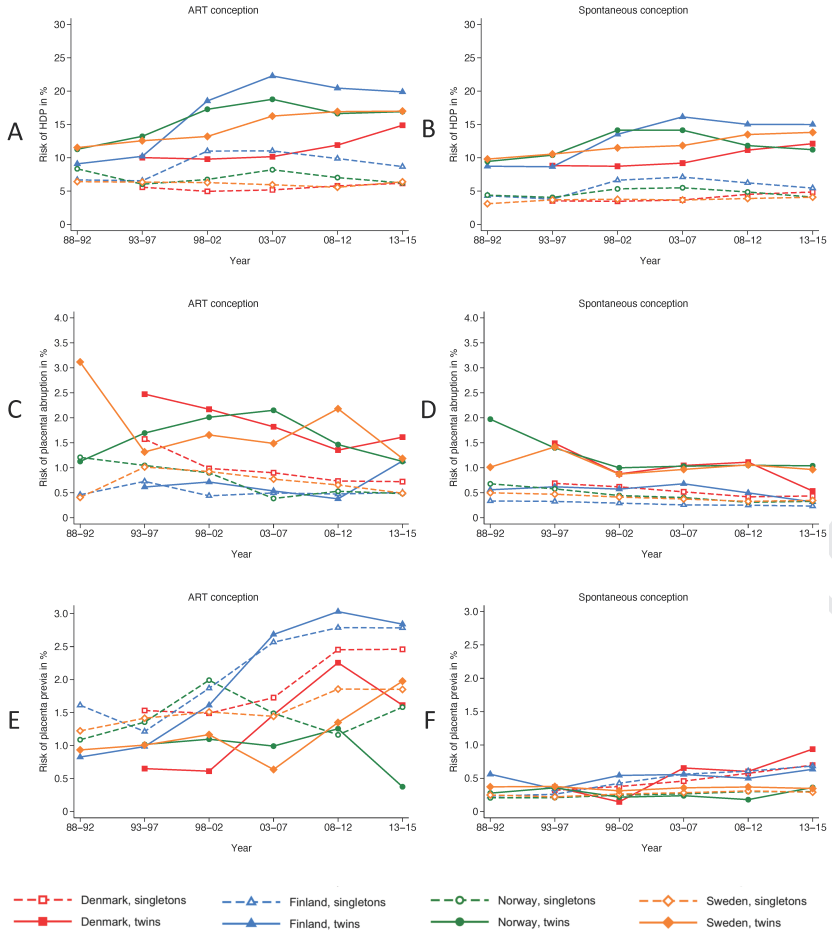
[a]**Using z-scores from Marsal et. al where the authors developed growth curves based on ultrasonography from Swedish centers and made exclusive curves according to offspring sex**

[b]**Deliveries among parous women whose first delivery was included in the main analysis sample and thus had information on delivery mode in all previous deliveries**

[c]**Data from Denmark (2011-2014), Norway (2011-2015) and Sweden (2006-2015)**

[d]**Data from Denmark (1994-2014), Norway (1988-2015) and Sweden (1988-2015)**


Eligible:
6,830,578 deliveries
Excluded: Missing values on parity (n=25,007), birthweight (n=16,105) gestational age (n=79,516)
147,441 ART deliveries
6,696,261 SC deliveries
Excluded: Extreme values or implausible combinations of gestational age and birthweight: gestational age<22 weeks (n=4,369) or ≥45 weeks (n=2,050), birthweight <300 g (n=2,861) or ≥6,000 g (n=313) and birthweight for gestational age ≥+ 6 standard deviations[a] (n=3,351)
A) Main analysis sample
146,998 ART deliveries
6,683,580 SC deliveries
B) Subsample for adjustment for maternal BMI and smoking
93,297 ART deliveries
3,424,972 SC deliveries
C) Subsample of primiparous deliveries
99,959 ART deliveries
2,641,775 SC deliveries
D) Subsample for adjustment for history of caesarean section[b]
40,411 ART deliveries
3,148,762 SC deliveries
E) Subsample for adjustment for culture duration[c]
42,410 ART deliveries after cleavage stage embryo transfer
8,510 ART deliveries after blastocyst transfer
F) Subsample for adjustment for cryopreservation[d]
98,093 ART deliveries after fresh embryo transfer
20,580 ART deliveries after frozen-thawed embryo transfer


A
ART conception
Risk of HDP in %
Year
B
Spontaneous conception
Risk of HDP in %
Year
C
ART conception
Risk of placental abruption in %
Year
D
Spontaneous conception
Risk of placental abruption in %
Year
E
ART conception
Risk of placenta previa in %
Year
F
Spontaneous conception
Risk of placenta previa in %
Year
88–92
93–97
98–02
03–07
08–12
13–15
Denmark, singletons
Denmark, twins
Finland, singletons
Finland, twins
Norway, singletons
Norway, twins
Sweden, singletons
Sweden, twins

Supplemental Table 1. Overview of coding systems in use in the Nordic countries during the study period and selection of codes from each system.

	International Classification of Diseases and related Health Problems (ICD) classification version		
	ICD-8	**ICD-9**	**ICD-10**
Year in use			
Denmark	-	-	1994-2014
Finland	-	1989-1995	1996-2014
Norway	1988-1998	-	1999-2015
Sweden	-	1988-1996	1997-2015
Diagnostic codes			
Hypertensive disorders in pregnancy	637	642.3-7	O11, 013-16
Placental abruption	632.1	641.2	O45
Placenta previa	632.0	641.0, 641.1	O44

Supplemental Table 2. Time trends in hypertensive disorders in pregnancies conceived after assisted reproductive technology (ART) and spontaneous conception. Estimates of time trends are risk differences in percentage points.

Analysis sample	Model	Cases/ Deliveries	RD[a] (95% CI)	Cases/ Deliveries	RD[a] (95% CI)
All pregnancies			**ART**		**Spontaneous conception**
B) BMI & smoking	Basic model[b]	6,928/ 93,295	-0.26 (-0.44 to -0.08)	149,946/ 3,424,972	0.06 (0.04 to 0.08)
B) BMI & smoking	Basic model[b] + smoking[c]		-0.27 (-0.45 to -0.09)		0.03 (0.01 to 0.05)
B) BMI & smoking	Basic model[b] + BMI[d]		-0.29 (-0.46 to -0.11)		-0.10 (-0.12 to -0.08)
B) BMI & smoking	Basic model[b] + smoking[c] + BMI[d]		-0.31 (-0.49 to -0.13)		-0.13 (-0.15 to -0.11)
C) Primiparous	Basic model[e]	8,979/ 99,974	-0.02 (-0.15 to 0.12)	172,609/ 2,641,775	0.29 (0.27 to 0.31)
E) Culture duration	Basic model[b]	3,658/ 53,230	0.04 (-0.05 to 0.13)		
E) Culture duration	Basic model[b] + culture duration[f]		0.00 (-0.09 to 0.10)		
F) Cryopreservation	Basic model[b]	8,737/ 121,987	-0.03 (-0.05 to -0.03)		
F) Cryopreservation	Basic model[b] + cryopreservation[g]		-0.05 (-0.08 to -0.03)		
Singletons			**ART**		**Spontaneous conception**
B) BMI & smoking	Basic model[b]	5,401/ 82,867	0.07 (-0.18 to 0.25)	144,510/ 3,380,732	0.05 (0.03 to 0.07)
B) BMI & smoking	Basic model[b] + smoking[c]		0.07 (-0.11 to 0.26)		0.03 (0.01 to 0.04)
B) BMI & smoking	Basic model[b] + BMI[d]		0.05 (-0.14 to 0.23)		-0.10 (-0.12 to -0.09)
B) BMI & smoking	Basic model[b] + smoking[c] + BMI[d]		0.03 (-0.15 to 0.22)		-0.14 (-0.16 to -0.12)
C) Primiparous	Basic model[e]	6,578/ 85,404	0.23 (0.09 to 0.37)	166,549/ 2,607,276	0.28 (0.26 to 0.30)
E) Culture duration	Basic model[b]	3,019/ 49,285	0.07 (-0.02 to 0.16)		
E) Culture duration	Basic model[b] + culture duration[f]		0.05 (-0.04 to 0.14)		
F) Cryopreservation	Basic model[b]	6,349/ 104,085	0.02 (0.00 to 0.04)		
F) Cryopreservation	Basic model[b] + cryopreservation[g]		0.00 (-0.03 to 0.02)		
Twins			**ART**		**Spontaneous conception**
B) BMI & smoking	Basic model[b]	1,496/ 10,240	1.52 (0.83 to 2.22)	5,375/ 43,690	0.50 (0.24 to 0.75)
B) BMI & smoking	Basic model[b] + smoking[c]		1.47 (0.76 to 2.17)		0.41 (0.15 to 0.67)
B) BMI & smoking	Basic model[b] + BMI[d]		1.46 (0.76 to 2.16)		0.29 (0.03 to 0.55)
B) BMI & smoking	Basic model[b] + smoking[c] + BMI[d]		1.39 (0.68 to 2.10)		0.19 (-0.07 to 0.45)
C) Primiparous	Basic model[e]	2,340/ 14,093	1.95 (1.46 to 2.43)	5,963/ 33,856	1.19 (0.92 to 1.46)
E) Culture duration	Basic model[b]	632/ 3,896	0.03 (-0.51 to 0.58)		
E) Culture duration	Basic model[b] + culture duration[f]		-0.14 (-0.69 to 0.41)		
F) Cryopreservation	Basic model[b]	2,334/ 17,164	0.30 (0.21 to 0.38)		
F) Cryopreservation	Basic model[b] + cryopreservation[g]		0.23 (0.14 to 0.31)		

[a]Per 5 years in sample B-D and per year in sample E-F. [b]Basic model includes adjustment for parity, maternal age and country. [c]Smoking (yes/no) [d]BMI: <20, 20-24, 25-29, ≥30 kg/m^2. [e]Adjusted for maternal age and country. [f]Cleavage stage vs blastocyst transfer. [g]Fresh vs frozen embryo transfer. ART: Assisted reproductive technology, RD: Risk difference, CI: Confidence interval, BMI: Body mass index.

Supplemental Table 3. Time trends in placental abruption in pregnancies conceived after assisted reproductive technology (ART) and spontaneous conception. Estimates of time trends are risk differences in percentage points.

Analysis sample	Model	Cases/ Deliveries	RD[a] (95% CI)	Cases/ Deliveries	RD[a] (95% CI)
All pregnancies		**ART**		**Spontaneous conception**	
B) BMI & smoking	Basic model[b]	683/ 93,295	-0.11 (-0.16 to -0.05)	12,454/ 3,424,972	-0.02 (-0.03 to -0.02)
B) BMI & smoking	Basic model[b] + smoking[c]		-0.10 (-0.15 to -0.04)		-0.01 (-0.02 to -0.00)
B) BMI & smoking	Basic model[b] + BMI[d]		-0.11 (-0.16 to -0.05)		-0.02 (-0.03 to -0.02)
B) BMI & smoking	Basic model[b] + smoking[c] + BMI[d]		-0.10 (-0.15 to -0.05)		-0.01 (-0.02 to -0.00)
C) Primiparous	Basic model[e]	816/ 99,974	-0.14 (-0.18 to -0.10)	11,079/ 2,641,775	-0.06 (-0.06 to -0.05)
E) Culture duration	Basic model[b]	384/ 53,230	-0.05 (-0.08 to -0.02)		
E) Culture duration	Basic model[b] + culture duration[f]		-0.05 (-0.09 to -0.02)		
F) Cryopreservation	Basic model[b]	1,073/ 121,987	-0.04 (-0.04 to -0.03)		
F) Cryopreservation	Basic model[b] + cryopreservation[g]		-0.03 (-0.04 to -0.02)		
Singletons		**ART**		**Spontaneous conception**	
B) BMI & smoking	Basic model[b]	532/ 82,867	-0.07 (-0.12 to -0.02)	12,046/ 3,380,732	-0.02 (-0.03 to -0.02)
B) BMI & smoking	Basic model[b] + smoking[c]		-0.06 (-0.11 to -0.00)		-0.01 (-0.02 to -0.01)
B) BMI & smoking	Basic model[b] + BMI[d]		-0.07 (-0.12 to -0.02)		-0.02 (-0.03 to -0.02)
B) BMI & smoking	Basic model[b] + smoking[c] + BMI[d]		-0.06 (-0.11 to -0.00)		-0.01 (-0.02 to -0.01)
C) Primiparous	Basic model[e]	592/ 85,404	-0.11 (-0.15 to -0.06)	10,779/ 2,607,276	-0.06 (-0.06 to -0.05)
E) Culture duration	Basic model[b]	317/ 49,282	-0.04 (-0.07 to -0.01)		
E) Culture duration	Basic model[b] + culture duration[f]		-0.05 (-0.08 to -0.02)		
F) Cryopreservation	Basic model[b]	763/ 104,085	-0.02 (-0.03 to -0.02)		
F) Cryopreservation	Basic model[b] + cryopreservation[g]		-0.02 (-0.03 to -0.02)		
Twins		**ART**		**Spontaneous conception**	
B) BMI & smoking	Basic model[b]	149/ 10,240	-0.07 (-0.31 to 0.17)	405/ 43,690	-0.05 (-0.12 to 0.02)
B) BMI & smoking	Basic model[b] + smoking[c]		-0.07 (-0.31 to 0.17)		-0.04 (-0.11 to 0.03)
B) BMI & smoking	Basic model[b] + BMI[d]		-0.07 (-0.31 to 0.17)		-0.06 (-0.13 to 0.01)
B) BMI & smoking	Basic model[b] + smoking[c] + BMI[d]		-0.07 (-0.32 to 0.17)		-0.05 (-0.12 to 0.02)
C) Primiparous	Basic model[e]	217/ 14,093	-0.07 (-0.24 to 0.10)	293/ 33,856	-0.03 (-0.10 to 0.04)
E) Culture duration	Basic model[b]	66/ 3,896	-0.15 (-0.35 to 0.05)		
E) Culture duration	Basic model[b] + culture duration[f]		-0.13 (-0.33 to 0.01)		
F) Cryopreservation	Basic model[b]	303/ 17,164	-0.03 (-0.07 to -0.00)		
F) Cryopreservation	Basic model[b] + cryopreservation[g]		-0.03 (-0.06 to -0.00)		

[a]Per 5 years in sample B-D and per year in sample E-F. [b]Basic model includes adjustment for parity, maternal age and country. [c]Smoking (yes/no) [d]BMI: <20, 20-24, 25-29, ≥30 kg/m^2. [e]Adjusted for maternal age and country. [f]Cleavage stage vs blastocyst transfer. [g]Fresh vs frozen embryo transfer.

ART: Assisted reproductive technology, RD: Risk difference, CI: Confidence interval, BMI: Body mass index.

Supplemental Table 4. Time trends in placenta previa in pregnancies conceived after assisted reproductive technology (ART) and spontaneous conception. Estimates of time trends are risk differences in percentage points.

Analysis sample	Model	Cases/ Deliveries	RD[a] (95% CI)	Cases/ Deliveries	RD[a] (95% CI)
All pregnancies			**ART**		**Spontaneous conception**
B) BMI & smoking	Basic model[b]	1,759/ 93,295	0.23 (0.13 to 0.34)	12,492/ 3,424,972	0.03 (0.02 to 0.03)
B) BMI & smoking	Basic model[b] + smoking[c]		0.22 (0.11 to 0.32)		0.03 (0.02 to 0.04)
B) BMI & smoking	Basic model[b] + BMI[d]		0.24 (0.14 to 0.34)		0.03 (0.02 to 0.03)
B) BMI & smoking	Basic model[b] + smoking[c] + BMI[d]		0.22 (0.12 to 0.32)		0.03 (0.03 to 0.04)
C) Primiparous	Basic model[e]	1,584/ 99,974	0.25 (0.18 to 0.31)	6,993/ 2,641,775	0.03 (0.02 to 0.03)
D) History of cesarean section	Basic model[b]	847/ 40,421	0.25 (0.10 to 0.38)	11,668/ 3,148,760	0.04 (0.03 to 0.05)
D) History of cesarean section	Basic model[b] + history of cesarean section		0.24 (0.10 to 0.40)		0.04 (0.03 to 0.04)
E) Culture duration	Basic model[b]	986/ 53,230	0.06 (0.00 to 0.10)		
E) Culture duration	Basic model[b] + culture duration[f]		0.03 (-0.02 to 0.08)		
F) Cryopreservation	Basic model[b]	1,993/ 121,987	0.04 (0.03 to 0.05)		
F) Cryopreservation	Basic model[b] + cryopreservation[f]		0.05 (0.04 to 0.06)		
Singletons			**ART**		**Spontaneous conception**
B) BMI & smoking	Basic model[b]	1,588/ 82,867	0.24 (0.13 to 0.35)	12,302/ 3,380,732	0.03 (0.02 to 0.03)
B) BMI & smoking	Basic model[b] + smoking[c]		0.22 (0.11 to 0.34)		0.03 (0.02 to 0.04)
B) BMI & smoking	Basic model[b] + BMI[d]		0.24 (0.13 to 0.35)		0.03 (0.02 to 0.03)
B) BMI & smoking	Basic model[b] + smoking[c] + BMI[d]		0.23 (0.11 to 0.34)		0.03 (0.03 to 0.04)
C) Primiparous	Basic model[e]	1,402/ 85,404	0.22 (0.15 to 0.30)	6,874/ 2,607,276	0.03 (0.02 to 0.03)
D) History of cesarean section	Basic model[b]	771/ 34,972	0.18 (0.03 to 0.33)	11,503/ 3,107,064	0.04 (0.04 to 0.05)
D) History of cesarean section	Basic model[b] + history of cesarean section		0.17 (0.02 to 0.33)		0.04 (0.03 to 0.04)
E) Culture duration	Basic model[b]	930/ 49,285	0.06 (0.00 to 0.11)		
E) Culture duration	Basic model[b] + culture duration[f]		0.03 (-0.02 to 0.08)		
F) Cryopreservation	Basic model[b]	1,787/ 104,085	0.03 (0.02 to 0.05)		
F) Cryopreservation	Basic model[b] + cryopreservation[f]		0.04 (0.03 to 0.06)		
Twins			**ART**		**Spontaneous conception**
B) BMI & smoking	Basic model[b]	170/ 10,240	0.08 (-0.22 to 0.37)	189/ 43,690	-0.00 (-0.06 to 0.05)
B) BMI & smoking	Basic model[b] + smoking[c]		0.05 (-0.25 to 0.35)		0.01 (-0.04 to 0.06)
B) BMI & smoking	Basic model[b] + BMI[d]		0.08 (-0.22 to 0.37)		0.00 (-0.05 to 0.06)
B) BMI & smoking	Basic model[b] + smoking[c] + BMI[d]		0.05 (-0.25 to 0.35)		0.01 (-0.04 to 0.07)
C) Primiparous	Basic model[e]	178/ 14,093	0.29 (0.14 to 0.44)	118/ 33,856	0.03 (-0.01 to 0.08)
D) History of cesarean section	Basic model[b]	75/ 5,360	0.34 (0.04 to 0.65)	164/ 41,196	0.00 (-0.04 to 0.05)

D) History of cesarean section	Basic model[b] + history of cesarean section		0.34 (0.04 to 0.65)		0.00 (-0.05 to 0.05)
E) Culture duration	Basic model[b]	56/ 3,896	0.01 (-0.17 to 0.20)		
E) Culture duration	Basic model[b] + culture duration[f]		0.00 (-0.20 to 0.20)		
F) Cryopreservation	Basic model[b]	202/ 17,164	0.05 (0.02 to 0.07)		
F) Cryopreservation	Basic model[b] + cryopreservation[g]		0.05 (0.02 to 0.08)		

[a]Per 5 years in sample B-D and per year in sample E-F. [b]Basic model includes adjustment for parity, maternal age and country. [c]Smoking (yes/no) [d]BMI: <20, 20-24, 25-29, ≥30 kg/m^2. [e]Adjusted for maternal age and country. [f]Cleavage stage vs blastocyst transfer. [g]Fresh vs frozen embryo transfer.

ART: Assisted reproductive technology, RD: Risk difference, CI: Confidence interval, BMI: Body mass index.