



Reproductive outcomes in women and men conceived by assisted reproductive technologies in Norway: prospective registry based study

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ABSTRACT

OBJECTIVES To determine whether the perinatal outcomes of women or men who were conceived by assisted reproductive technologies are different compared with their peers who were naturally conceived.

DESIGN Prospective registry based study.

SETTING Medical Birth Registry of Norway.

PARTICIPANTS People born in Norway between 1984 and 2002 with a registered pregnancy by the end of 2021.

EXPOSURE People who were conceived by assisted reproductive technologies and have had a registered pregnancy.

MAIN OUTCOME MEASURES Comparing pregnancies and births of people who were conceived by assisted reproductive technologies and people who were naturally conceived, we assessed mean birth weight, gestational age, and placental weight by linear regression, additionally, the odds of congenital malformations, a low 5 min Apgar score (<7), transfer to a neonatal intensive

care unit, delivery by caesarean section, use of assisted reproductive technologies, hypertensive disorders of pregnancy and pre-eclampsia, preterm birth, and offspring sex, by logistic regression. The occurrence of any registered pregnancy from people aged 14 years until age at the end of follow-up was assessed using Cox proportional regression for both groups.

RESULTS Among 1 092 151 people born in Norway from 1984 to 2002, 180 652 were registered at least once as mothers, and 137 530 as fathers. Of these, 399 men and 553 women were conceived by assisted reproductive technologies. People who were conceived by assisted reproductive technologies had little evidence of increased risk of adverse outcomes in their own pregnancies, increased use of assisted reproductive technologies, or any difference in mean birth weight, placental weight, or gestational age. The only exception was for an increased risk of the neonate having a low Apgar score at 5 min (adjusted odds ratio 1.86 (95% confidence interval 1.20 to 2.89)) among women who were conceived by assisted reproductive technologies. Odds were slightly decreased of having a boy among mothers conceived by assisted reproductive technologies (odds ratio 0.79 (95% confidence interval 0.67 to 0.93)). People conceived by assisted reproductive technologies were slightly less likely to have a registered pregnancy within the follow-up period (women, adjusted hazard ratio 0.88 (95% CI 0.81 to 0.96); men, 0.91 (0.83 to 1.01)).

CONCLUSIONS People conceived by assisted reproductive technologies were not at increased risk of obstetric or perinatal complications when becoming parents. The proportion of people conceived by assisted reproductive technologies with a registered pregnancy was lower than among people who were naturally conceived, but a longer follow-up is required to fully assess their fertility and reproductive history.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Use of assisted reproductive technologies is increasing worldwide
- ⇒ Pregnancies conceived by assisted reproductive technologies are at higher risk of several obstetric and perinatal complications
- ⇒ The possible pregnancy risks faced by offspring who were conceived by assisted reproductive technologies and who have their own children have not yet been studied

WHAT THIS STUDY ADDS

- ⇒ Little indication suggests that a woman or man's own mode of conception was associated with an increased risk of pregnancy complications or adverse perinatal outcomes
- ⇒ Men and women who were conceived by assisted reproductive technologies had fewer pregnancies compared with their peers who were naturally conceived, which might be attributable to social factors

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

- ⇒ More in-depth analyses into fertility among women and men conceived by assisted reproductive technologies are needed to ascertain whether these are more likely to experience infertility
- ⇒ No indications suggest that women and men conceived by assisted reproductive technologies have more high risk pregnancies in the absence of other risk factors
- ⇒ Larger studies with a longer follow-up are needed to confirm these reassuring findings and to address risk of adverse pregnancy outcomes at older ages in pregnancies of adults conceived by assisted reproductive technologies

Introduction

The first child conceived by assisted reproductive technologies (ART) in Norway was born in 1984. Since then, more than 50 000 infants have been conceived by ART in Norway, and more than 10 million have been born worldwide.¹ From the earliest development of ART, concerns have arisen about the potential health effects on the offspring.

Pregnancies conceived by ART have increased risks of complications, including hypertensive disorders of pregnancy, preterm birth, and low birth weight, with some variation by ART method.²⁻⁸ A high proportion of early cohorts of people conceived by ART were part of a multiple birth, which explains some of the obstetric and perinatal outcomes, but not all.²⁻⁴ Whether these risks are increased by causes of subfertility or by the ART treatments is still an ongoing debate.⁹ Although concerns regarding the safety of ART use have to some extent abated,¹⁰ unresolved concerns related to more subtle effects on offspring health through the use of different ART procedures remain. For instance, epigenetic differences at birth have been noted between people conceived naturally and by ART; to what extent these differences have an impact on health or persist into adulthood is unclear.^{11 12}

Since most people conceived by ART have entered childbearing age only recently, little is known about their reproductive outcomes. These individuals might be at increased risk of health problems, such as cancer and poorer cardiometabolic health, which is linked to increased risk of adverse pregnancy outcomes,¹³ but findings are inconsistent.¹⁴⁻¹⁹ Additionally, infertility, the inheritance of which might paradoxically be facilitated through the use of ART, is linked to adverse perinatal outcomes.^{20 21} However, to what extent infertility might be inherited is largely unknown because the underlying causes and genetic predispositions are complex and diverse, and probably differ between couples and over time. Nonetheless, evidence suggests that, for example, a behavioural pattern of delayed age at reproduction is inherited, through social processes across generations,²² and by transmissions of genes associated with age at reproduction.²³ Subfertility has also been linked to an increased risk of miscarriage and subclinical pregnancy loss,^{24 25} which could manifest as apparent reduced fertility rates in the offspring generation. We might also expect increased reproductive issues among offspring conceived by ART because of the higher risk of perinatal complications in these pregnancies and the possibility of negative impacts on reproduction seen among adults born to pregnancies complicated by adverse outcomes.^{26 27} Some studies indicate no differences in hormonal status or pubertal development in female offspring conceived by ART, yet some studies report differences in hormonal status and sperm quality among male offspring conceived by ART, but results are conflicting.²⁸⁻³⁴ Finally, some adverse pregnancy outcomes recur from mother to daughter³⁵⁻⁴² or son;^{36 39 41} although whether this recurrence is also present in those conceived by ART is unknown. To the best of our knowledge, no studies have examined pregnancy outcomes or fertility rates in people who were conceived using ART and their naturally conceived peers.

We describe registered pregnancies and perinatal outcomes of all people born in Norway between 1984 and 2002, according to whether they were conceived using ART or naturally.

Methods

Study design and data sources

We conducted a prospective population based study of all individuals born in Norway between 1984 and 2002 who were alive and living in Norway at the age of 14 years. The first birth after ART use in Norway was in 1984. Our primary data source was the Medical Birth Registry of Norway, which categorised women and men on the basis of their sex registered at birth.⁴³ The birth registry contains information on all Norwegian deliveries and fetal losses after 12 gestational weeks. We used personal identification numbers to link information from an individual's birth record to where they were registered as a mother or father by the end of 2021.

A miscarriage was defined according to Norwegian obstetric guidelines as a fetal loss between gestational weeks 12 and 22 or, if gestational age was missing, a birth weight <500 grams.⁴⁴ Miscarriages and late induced abortions (12-22 gestational weeks) were included as a registered pregnancy in the analyses of ever having a registered pregnancy. However, they were excluded when analysing perinatal outcomes (restricted to births only).

Conception by ART

Fertility clinics in Norway have a mandate to report the use of ART to the birth registry. We defined ART as any use of ART (eg, fresh and frozen embryo transfer and in vitro fertilisation) with and without intracytoplasmic sperm injection. Intrauterine inseminations were not defined as ART, according to the International Committee for Monitoring Assisted Reproductive Technologies guidelines.⁴⁵ Oocyte donation became legal in Norway in January 2021⁴⁶ (after our study period), whereas sperm donation has been allowed during the whole study period.

Obstetric and perinatal outcomes

We assessed the likelihood of having a registered pregnancy in the birth registry. Among those with a registered birth, we also assessed mean birth weight, gestational age, placental weight, the odds of congenital malformations, a low 5 min Apgar score, transfer to a neonatal intensive care unit, delivery by caesarean section, use of assisted reproductive technologies, hypertensive disorders of pregnancy and pre-eclampsia, preterm birth, and offspring sex.

Information on birth weight in grams was analysed as a continuous variable. Information on placental weight in grams was treated as a continuous outcome. We calculated gestational age from birth registry data using ultrasound dating if the

estimated gestational age at birth was between 22 and 45 completed weeks. If ultrasound data were not available, we used date of last menstrual period with the same time restriction, and for pregnancies conceived using ART, last menstrual period was estimated from date for embryo insertion adjusted to supposed last menstrual period. Preterm delivery was defined as a delivery before 37 completed gestational weeks.

The birth registry also provided information on plurality and on Apgar scores after 5 min, which we defined as low if below 7. The birth registry provided information on whether the newborn had been transferred to a paediatric unit, hereafter called newborn intensive care unit admission, because this unit would be the most common and we could not distinguish these from a common children's hospital ward. Congenital malformations were grouped into a single category (any *v* none). We defined hypertensive disorders of pregnancy as any record of pre-eclampsia, eclampsia, HELLP (haemolysis, elevated liver enzymes, and low platelets), or hypertension diagnosed during pregnancy. Caesarean section was grouped into one outcome because numbers were considered too low to split into acute, planned, or unspecified.

Parents' characteristics

Characteristics of women and men who were registered as parents in the birth registry included age at delivery (in whole years), parity (grouped into 0 or ≥ 1), smoking status at the beginning of pregnancy (women only, grouped into none, daily, occasional, or not consenting to give smoking status). Women who reported smoking at end of pregnancy were categorised as smoking daily. Women who did not consent to provide smoking data (~8.6%) were more similar to people who smoke than people who do not smoke in their other characteristics, such as infant's birth weight and folic acid supplement intake. We, therefore, combined those missing data for the smoking variable with people who smoke in the regression analyses. Maternal marital status was defined as a combined group of married, cohabiting, and registered partner versus other (including single, widowed, separated, and unknown). Maternal folic acid supplement was categorised as "yes" or "no". Maternal body mass index was available from 2006 (70% of index pregnancies (ie, first pregnancy) among women and 75% of partners to the men).

From the parents' own birth records, we extracted information for birth weight, gestational age at birth, maternal country of birth (Norwegian, other or missing), whether or not the parent was part of a multiple birth (yes or no), county of birth, or whether the pregnancy was complicated by a hypertensive disorder of pregnancy.

Statistical analyses

Likelihood of a pregnancy

We compared the likelihood of having a pregnancy among men and women according to whether or not they were conceived using ART by use of Cox proportional hazards regression to estimate the hazard ratio of having a registered pregnancy during follow-up. We used the age of the women and men (in years) as the underlying timescale, and followed up each person from age 14 years until age at conception for a registered pregnancy, emigration, death, or 31 December 2021 for people residing in Norway who had not experienced a pregnancy. We did not have information on emigration or deaths for the year 2021. For missing data for gestational age in cases of miscarriages or stillbirths (0.4% of first pregnancies for women and 0.2% for men), we calculated the mother's and father's age at conception assuming a gestational age of 14 weeks for miscarriages and 22 weeks for stillbirths. All estimates were adjusted for parents' birth year in intervals (1984-89, 1990-93, 1994-97, 1998-2002), and further adjusted for information from the parents' birth records on their mothers' country of birth (Norwegian, other, or missing), and county within Norway (11 counties, a variable associated with availability of ART procedures; see online supplemental eFigure 1 for a directed acyclic graph presentation of the covariates included).

Obstetrical and perinatal outcomes

Our main analysis of pregnancy outcomes was restricted to the first pregnancy born 22 gestational weeks or more to parents born after 1984. In a secondary analysis, we included all registered pregnancies of 22 weeks or more for these parents.

We grouped birth characteristics for mothers, fathers, and their offspring according to whether the parent had been conceived by ART, and calculated means for continuous characteristics and proportions for categorical or binary characteristics.

Each newborn was counted as a separate entry for newborn outcomes, while each pregnancy was counted once for parental characteristics, regardless of number of fetuses. Specifically, the outcomes of pre-eclampsia, hypertensive disorders of pregnancy, caesarean section, and preterm birth were counted only once for pregnancies with multiples (ie, twins, triplets).

We used linear regression to compare the mean birth weight, gestational age, and placental weight according to whether the parents were conceived by ART. We used logistic regression to calculate odds ratios according to parental ART status of undergoing a preterm delivery, developing pre-eclampsia, or another hypertensive disorder of pregnancy, delivery by caesarean section (acute, planned, or unspecified), having an infant with any congenital malformation, having a low 5 min Apgar score, transfer to

a neonatal intensive care unit, or having a boy. We also considered the odds of themselves conceiving with ART.

ART procedures have not been practised long enough to observe the whole reproductive period for these people born in 1984 and later. Moreover, the proportion of people conceived by ART among all births has risen steadily over time, which might produce differences between the groups that could confound associations. We analysed the first registered pregnancy for people born after 1984 and present results from two regression models: a crude analysis not adjusting for any covariates; and a model adjusting for offspring sex and for variables with time trends or variations during the study period as potential mediators (online supplemental eFigure 2). These variables at the time of the first pregnancy produced by parents conceived by ART and their peers were age at conception (<25 years, 25-29 years, ≥30 years), year of pregnancy (<2011, 2011-2015, 2016-2018, 2019-2021), smoking status, folic acid supplement, and grandmaternal country of birth (Norwegian, other, or missing). In the analyses of men, both maternal and paternal age at conception were included as covariates. Both regression models were subsequently performed with all registered pregnancies except for the outcome caesarean section, where we further adjusted for parity (0 or ≥1) and clustering due to multiple observations per man and woman.

All analyses were conducted using Stata version 16.0 SE.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. Results of this study will be disseminated to study participants through our public websites, public media, and publicly available newsletters,

and through obstetricians and fertility clinicians reaching the relevant patient community.

Results

Women

531015 liveborn girls were registered between 1984 and 2002 (after excluding neonatal deaths within the first 24 h), of which 526455 were living in Norway at age 14 and with no previous pregnancy (online supplemental eFigure 3a). Of these, 4763 were conceived using ART and 521692 were naturally conceived. After censoring those who moved out of the country, at least one pregnancy was registered for 553 (12%) of the women conceived by ART and 180099 (35%) of the women who were naturally conceived. 465 (84%) of the women who were conceived by ART and had at least one registered pregnancy were conceived by the use of in vitro fertilisation without intracytoplasmic sperm injection. The likelihood of having a registered pregnancy before the end of 2021 was lower in the ART conceived group than the naturally conceived group, with a minimally adjusted hazard ratio of 0.71 (95% confidence interval 0.65 to 0.77) and a further adjusted hazard ratio of 0.88 (0.81 to 0.96) (table 1). No evidence indicated non-proportionality in the adjusted model (P value Schoenfeld residuals of 0.51).

Characteristics at time of the index pregnancy of mothers who were conceived with ART were similar to naturally conceived mothers (table 2). The mothers who were conceived by ART were more likely to have been part of a multiple birth, to have been born after a pregnancy complicated by a hypertensive disorder, and to have had lower birth weight or gestational age at birth, than were naturally conceived mothers (table 2).

We assessed pregnancy outcomes of index pregnancies. Offsprings' birth weight, gestational age, and placental weight were similar in births to both groups of women (table 3). The other outcomes, including preterm delivery, low Apgar score,

Table 1 | Incidence of a first registered pregnancy by mode of conception by sex

Mode of conception type	Number of study participants	Analysis time at risk, years	One registered pregnancy in MBRN, No. (%)	Hazard ratio (95% CI)	
				Minimally adjusted*†	Fully adjusted*‡
Women					
Conceived naturally	521 692	6 109 665	180 099 (34.5)	1 (ref)	1 (ref)
Conceived by ART	4763	46 275	553 (11.6)	0.71 (0.65 to 0.77)	0.88 (0.81 to 0.96)
Men					
Conceived naturally	550 402	6 939 570	137 131 (24.9)	1 (ref)	1 (ref)
Conceived by ART	5083	50 786	399 (7.8)	0.79 (0.71 to 0.87)	0.91 (0.83 to 1.01)

CI=confidence interval; MBRN=Medical Birth Registry of Norway.

*Hazard ratios of having a pregnancy before 2020 in women and men born after 1984. Fetal losses and stillbirths after gestational week 12 are included in the analysis. People entered the risk set at age 14 years and were censored at age of death or emigration (data only available through 2020), or age at the end of the study period (31 December 2021).

†The hazard ratios were adjusted for year of birth categorically (1984-1989, 1990-1993, 1994-1997, 1998-2002).

‡The hazard ratios were adjusted for year of birth (categorically), grandmaternal country of birth (Norwegian, other, or missing), grandmaternal age at birth (continuous), and county of birth (categorically).

Table 2 | Characteristics of mothers born between 1984 and 2002 at the time of their first registered pregnancy*

Characteristic	Naturally conceived mothers	ART conceived mothers
Pregnancies	179 036	549
Children	181 305	560
Age at conception, mean (SD)	25.6 (4.1)	25.1 (3.6)
Parity		
0†	176 078 (98.3)	541 (98.6)
≥1	2958 (1.7)	8 (1.5)
Smoking at beginning of pregnancy		
No	139 164 (77.7)	476 (86.7)
Daily or occasional	24 675 (13.8)	43 (7.8)
No consent	15 197 (8.5)	30 (5.5)
Pre-pregnancy BMI, mean (SD)	24.4 (4.9)	24.5 (4.8)
Missing BMI	49 616 (27.7)	78 (14.2)
Folic acid supplement during pregnancy	144 594 (80.8)	476 (86.7)
Marital status		
Married/registered/cohabiting	159 184 (88.9)	492 (89.6)
Other	19 852 (11.1)	57 (10.4)
Multiple birth	2257 (1.3)	10 (1.8)
Stillbirth index pregnancy	590 (0.3)	<5 (0.2)
Mother of the woman's country of birth		
Norway	148 193 (82.8)	457 (83.2)
Other	9720 (5.4)	26 (4.7)
Missing	21 123 (11.8)	66 (11.9)
Hypertensive disorder of pregnancy in mother of the woman	8086 (4.5)	46 (8.4)
Birth weight in grams, mean (SD)	3460 (541)	2936 (791)
Birth weight in grams among singletons only, mean (SD)	3478 (525)	3327 (629)
Gestational age in days, mean (SD)	281.6 (13.7)	269.2 (22.1)
Gestational age in days among singletons only, mean (SD)	282.0 (13.2)	278.3 (15.7)
Part of multiple birth	3574 (2.0)	227 (41.3)

Data are number, number (%), unless otherwise specified. BMI=body mass index. SD=standard deviation.

*Miscarriages and induced abortions between week 12 and 22 are excluded from the analysis. We had no information on miscarriages before week 12.

†First pregnancy.

pre-eclampsia or other hypertensive disorders of pregnancy, conceiving with ART, having a newborn with a congenital malformation, admission to a newborn intensive care unit, or delivery by caesarean section, were also similar between groups (figure 1A). The associations did not change substantially after

adjusting for possible confounders. Risk for a low 5 min Apgar score among offspring of women who were conceived using ART mothers was increased (adjusted odds ratio 1.86 (1.20 to 2.89)); although, this finding was based on small numbers (n=21). The odds of having a boy were lower among the ART

Table 3 | Linear regression models comparing birth weight, gestational age, and placental weight by parental mode of conception by sex

Outcome	Conceived naturally	Conceived by ART	Difference between study groups (95% CI)	
			Unadjusted	Adjusted *
Women				
Birth weight, gram [‡]	3426 (589)	3439 (589)	13 (-36 to 62)	3 (-51 to 56)
Placental weight, grams [‡]	649 (154)	640 (146)	-9 (-22 to 4)	-4 (-18 to 11)
Gestational age, days [§]	278.2 (14.5)	278.9 (13.3)	0.3 (-0.9 to 1.6)	0.2 (-1.2 to 1.6)
Men				
Birth weight, gram [‡]	3441 (587)	3463 (552)	22 (-35 to 79)	8 (-49 to 65)
Placental weight, grams [‡]	650 (153)	640 (147)	-10 (-25 to 6)	-7 (-22 to 9)
Gestational age, days [§]	278.1 (14.2)	277.7 (13.5)	-0.2 (-1.6 to 1.3)	-0.2 (-1.7 to 1.2)

Data are mean (standard deviation), unless otherwise specified. CI=confidence interval

*Adjusted for maternal age at conception (<25 years, 25-29 years, ≥30 years), year of birth index pregnancy (categorically, <2011, 2011-15, 2016-18, 2019-20), offspring sex, smoking (none v combined smoking and missing), folic acid supplement (yes v no), grandmaternal country of birth (Norway, other, or missing). Also adjusted for paternal age at conception (<25 years, 25-29 years, ≥30 years) in the analyses of men.

†Missing information on birth weight for 0.03% (n=54, women) and 0.02% (n=31, men) of the newborns, these were excluded from the analyses.

‡Missing information on placental weights for ~2% (n=3656, women and n=2624, men) of newborns, these were excluded from the analyses.

§Missing information on gestational age for 0.3% (n= 455, women) and 0.2% (n= 281, men) of pregnancies, these were excluded from the analyses.

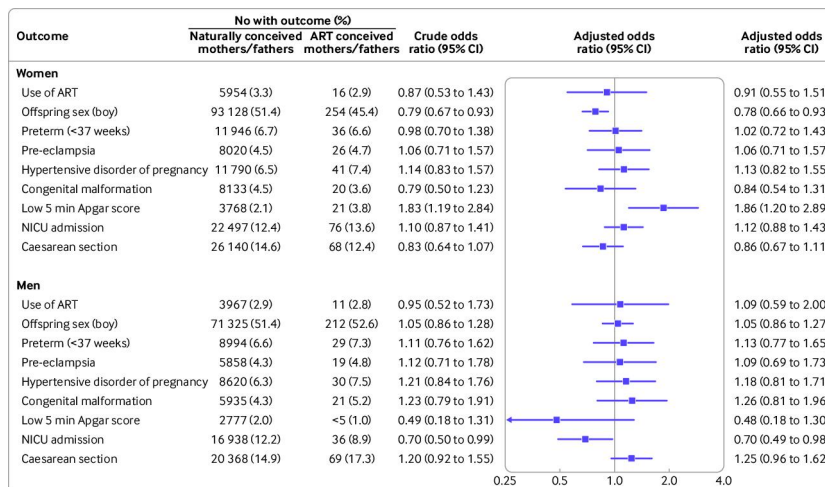


Figure 1 | The odds ratios of pregnancy outcomes in women and men who were conceived by ART compared with women and men who were naturally conceived. We have excluded people with missing information from the analyses. These proportions were 0.3% (n=469, women) and 0.1% (n=204, men) for newborn intensive care unit admission, <0.01% for offspring sex (n=14, women and n=9, men), and ~0.04% for Apgar scores (n=66, women and n=50, men). Odds ratios were adjusted for maternal age at conception (<25 years, 25-29 years, ≥30 years), year of birth index pregnancy (categorically, <2011, 2011-15, 2016-18, 2019-21), offspring sex, smoking (none status v smoking or not consented to provide information on smoking), use of folic acid supplement (yes v no), and grandmaternal country of birth (Norwegian or other). Also adjusted for paternal age at conception (<25 years, 25-29 years, ≥30 years) in the analyses of men. ART=assisted reproductive technologies; NICU=neonatal intensive care unit

conceived mothers (adjusted odds ratio 0.78 (0.66 to 0.93)).

Results were similar when including subsequent pregnancies (online supplemental eTables 1 and 2).

Men

Among 561 136 liveborn boys born between 1984 and 2002, 555 485 were registered as living in Norway at age 14 years (online supplemental eFigure 3b). Of these, 5083 were conceived by ART and 550 402 were naturally conceived. 399 (8%) men conceived using ART and 137 131 (25%) who were naturally conceived fathered at least one pregnancy. Of the men who were ART conceived and fathered at least one pregnancy, 343 (86%) were conceived by the use of in vitro fertilisation without intracytoplasmic sperm injection. The likelihood of contributing a registered pregnancy before the end of 2021 was lower among men conceived by ART, with an unadjusted hazard ratio of 0.79 (95% confidence interval 0.71 to 0.87) and an adjusted hazard ratio of 0.91 (0.83 to 1.01) (table 1). No indication suggested non-proportionality in the adjusted model (P value Schoenfeld residuals of 0.64).

Fathers conceived by ART were more likely to have been part of a multiple birth or part of a pregnancy complicated by a hypertensive disorder, and more likely to have had lower birth weight or gestational age at birth (table 4). At the time of their index pregnancy, the characteristics were generally similar to those of naturally conceived fathers (table 4).

When assessing their first registered pregnancy in the birth registry, offspring of men conceived by ART had similar birth weight, gestational age, and placental weight to the offspring of naturally conceived men (table 3). The odds were similar for partner's having a preterm delivery, infants with a congenital malformation or a low Apgar score, partner's pre-eclampsia or other hypertensive disorders of pregnancy, admission to newborn intensive care unit, partner's caesarean section, having a male baby, and conceiving with ART (figure 1B). These associations did not change substantially after adjusting for possible confounders. Results were also similar when including subsequent pregnancies (online supplemental eTables 1 and 3).

Discussion

Main findings

In this registry based study of all pregnancies to men and women born between 1984 and 2002 in Norway, parents who were conceived by ART or by natural conception had pregnancies with similar rates of complications and outcomes. A smaller proportion of men and women who were conceived by ART had a registered pregnancy before the end of 2021; although, this difference was strongly attenuated by adjustments, suggesting that the remaining differences might be due to residual confounding. Surprisingly, we noted a lower odds of giving birth to a boy among the women conceived by ART. False positive results are common with sex ratios (especially in the absence of a prior hypothesis),⁴⁷ yet, we cannot exclude a possible true difference. If this finding is replicated in

Table 4 | Characteristics of fathers born between 1984 and 2002 at the time of their first registered pregnancy*

Characteristic	Naturally conceived fathers	ART conceived fathers
Pregnancies	136 977	399
Children	138 709	403
Age at conception, mean (SD)	27.0 (4.0)	25.8 (3.5)
Maternal (partner) parity		
0†	122 336 (89.3)	368 (92.2)
≥1	14 641 (10.7)	31 (7.8)
Maternal (partner) smoking at beginning of pregnancy		
No	109 213 (79.7)	342 (85.7)
Daily or occasional	16 566 (8.9)	29 (7.3)
Missing	11 198 (8.2)	28 (7.0)
Maternal (partner) pre-pregnancy BMI, mean (SD)	24.4 (4.8)	24.5 (5.0)
Missing BMI	31 284 (22.8)	58 (14.5)
Maternal (partner) folic acid supplement during pregnancy	112 205 (81.9)	350 (87.7)
Marital status		
Married/registered/cohabiting	123 441 (90.1)	357 (89.5)
Other	13 536 (9.9)	42 (10.5)
Multiple birth	1719 (1.3)	<5 (1.0)
Stillbirth index pregnancy	389 (0.3)	<5 (0.2)
Mother of the father's country of birth		
Norway	112 628 (82.2)	334 (83.7)
Other	7 256 (5.3)	14 (3.5)
Missing	17 093 (12.5)	51 (12.8)
Hypertensive disorder of pregnancy in mother of the father	6627 (4.8)	46 (11.5)
Birth weight in grams, mean (SD)	3599 (571)	3029 (805)
Birth weight in grams among singletons only, mean (SD)	3618 (555)	3445 (667)
Gestational age in days, mean (SD)	280.6 (14.0)	267.7 (22.1)
Gestational age in days among singletons only, mean (SD)	281.0 (13.5)	278.2 (15.6)
Part of a multiple birth	2700 (2.0)	170 (42.6)

Data are number, number (%), unless otherwise specified. BMI=body mass index

*Miscarriages and induced abortions between week 12 and 22 are excluded from the analysis. We had no information on miscarriages before week 12.

†First pregnancy.

future studies, some possible explanations could be selection mechanisms occurring at the fertilisation or implantation stages or sex differences in the later probability to avoid miscarriage. We also observed an increased odds of a low 5 min Apgar score among newborns born to women who were conceived by ART, and this finding should be followed up in later studies.

Strengths and limitations

A major strength of this study was our access to all births, including all births conceived by ART, in Norway since the earliest birth by ART in 1984. Additionally, we had the ability to link information from parents' own birth with the outcomes of pregnancies they produce, while accounting for differences in baseline characteristics.

Limitations of this study include the small number of pregnancies produced by people conceived by ART, which provides limited statistical power to examine rare outcomes or to detect small true differences. This challenge is true in particular for the binary outcomes. Additionally, we had no information on deaths or emigrations during the year 2021, limiting the complete assessment of the study population during this year when assessing the likelihood of having a registered pregnancy according to

mode of conception. Residual confounding might be present in the analyses assessing the likelihood of having a registered pregnancy in the birth registry by end of follow-up. Specifically, we did not have information on socioeconomic status in the parent generation, which might have affected both the use of ART to conceive and the later likelihood of having a registered pregnancy among the offspring (eFigure 1). Additionally, due to low numbers of parents who were conceived by ART, smokers and people not consenting to provide information status on smoking in pregnancy were grouped into one category in regression analyses. Furthermore, given that all parents were born in Norway, this study represents a relatively homogeneous population, and we cannot be certain of the generalisability to a more ethnically diverse population.

Time does not yet allow for complete follow-up of the reproductive history of offspring conceived by ART, therefore, difficult questions of selection bias and interpretation remain. The people included in this study, in particular the men, were generally younger than the mean age at first birth in Norway.⁴³ Possible increased risks of adverse perinatal outcomes related to either infertility or medical conditions such as cardiometabolic health conditions could, in theory, become apparent

only at an older age of pregnancy, which we are unable to investigate at present. The reduced rate of first registered pregnancies for men and women conceived by ART could be caused by an increased risk of unrecorded miscarriages before 12 weeks, which constitute most miscarriages.⁴⁸ Selection into pregnancy could be further affected by various factors, such as unmeasured socioeconomic differences, varying fertility wishes, or differences in chronic conditions. Furthermore, we could not separate subfecundity from social factors that determine the decision to conceive. For example, daughters of older mothers are more likely to not have a child,⁴⁹ but they do not to have lower fecundability.^{50 51} Differences in the preferred age to start having children might differ between families, and people conceived by ART would tend to come from parents who had started trying to reproduce at relatively older ages.⁵² Adjustment for their mother's age at time of birth substantially closed the gap between pregnancy rate in offspring between the groups. Although we can only speculate at this point, we might take further reassurance about the fertility of offspring conceived by ART from the fact that subfertile couples have an increased risk of adverse pregnancy outcomes^{21 53} and we find little evidence of increased risk of adverse pregnancy outcomes in people conceived by ART. Future studies of the fecundability of ART offspring should be able to answer this question more definitively. We find limited evidence that the pregnancies of women and men conceived by ART should be followed up as high risk in the absence of other risk factors, acknowledging that the cohorts conceived by ART are still relatively young. Continuing follow-up of these cohorts will be necessary to confirm their healthy reproduction throughout their reproductive years.

Conclusions

Men and women who were conceived by ART and become parents do not appear to be at increased risk of adverse pregnancy outcomes. People conceived by ART were less likely to conceive, although the differences were attenuated in analyses adjusted for their own mother's country of birth, age, and place of residence. Larger studies with a longer follow-up time and a more direct assessment of time to pregnancy will help to provide a comprehensive view of fertility among offspring conceived by ART. Meanwhile, these early results are reassuring for the increasing number of adolescents and young adults who were conceived by ART and are entering their reproductive years.

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Contributors EOC, MCM, SEH, and AJW conceived and designed the study. SEH obtained access to data. EOC conducted data analysis and drafted the initial version of the manuscript. AJW, SEH, MCM, and HIH provided important insight during the data analysis. All authors contributed in the interpretation of the data and critically revised the manuscript. All authors had full access to the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. EOC is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no other meeting the criteria have been omitted. Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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