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The associations between artificial reproductive technologies (ART) and newborn size, as well as perinatal risk factors among singleton births in Vienna, Austria.

Sylvia Kirchengast[1] · Beda Hartmann[2]

[1]Department of Evolutionary Anthropology, University of Vienna, Austria
[2]Clinic Donaustadt, Department of Gynecology and Obstetrics, Vienna, Austria

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Correspondence to:

Sylvia Kirchengast
email: sylvia.kirchengast@univie.ac.at

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Abstract

Background The use of assisted reproductive technologies (ART) such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) has increased markedly during the last four decades. ART, however, is still discussed critically, as there is no consensus on whether these treatments have a negative effect on fetal growth or increase the risk of preterm birth, low birth weight, and perinatal complications.

Objectives The aim of this study is the analysis of association patterns between ART (IVF or ICSI) and newborn size, preterm birth rate, and the mode of delivery.

Sample and Methods In this single-center medical record-based study data concerning the conception mode (spontaneous versus IVF or ICSI), preterm birth, newborn sex and size, child presentation, delivery mode, labor induction as well as parity, maternal age, body height, weight, and gestational weight gain of 5867 singleton-term births taking place in Vienna from 2015 to 2023 were included. 178 newborns (3.0%) were conceived by IVF or ICSI.

Results ART (IVF or ICSI) increased the risk of preterm birth by a factor of 3.4, and the risk of emergency cesarean section by a factor 2.3. ART was not independently associated with newborn size as well as breech presentation. The most important factor for newborn size was the gestational week of delivery, but also maternal parameters such as body height, gestational weight gain, and age.

Conclusion Preterm birth is a major cause of small newborn size and complications at birth. Therefore, ART can also be interpreted with caution as an indirect risk factor for small newborn size with all its long-term consequences.

Take-home message for students Assisted reproductive technologies increase the risk of preterm birth significantly, and therefore the risk of small newborn size.

Introduction

From a biological perspective, successful reproduction is a fundamental basis for the existence of life and the driving force of evolution (Dunbar 1995). Not reproducing successfully is therefore interpreted as a pathological problem or as an adaptive reaction to adverse environmental conditions. Those who do not reproduce are eliminated from the game of evolution. The study of reproduction is therefore a focus in biological research. Of special interest is human reproduction, because *Homo sapiens* is the only living being that consciously separates sexuality and reproduction by developing effective contraceptive methods, and thus decides whether and when to reproduce. Therefore, human reproduction and family planning are not only of intrinsic interest to biology but also to representatives of other disciplines, such as sociology, psychology, cultural anthropology, and medicine, such as obstetrics and public health. In the second half of the 20th century, the fight against global overpopulation but also the aim to reduce high rates of maternal as well as neonatal morbidity and mortality in many middle- and low-income countries resulted in the search for efficient means of disseminating effective family planning methods (Prata 2009). On the other hand, infertility, and involuntary childlessness are increasingly seen as dramatic public health problems (The Lancet Global Health 2022).

According to Lancet Global Health (The Lancet Global Health 2022) has been estimated that currently 48 million couples and 186 million individuals worldwide live with infertility. According to a recent report by the World Health Organization (WHO 2023), approximately 17.6% or one in six people have experienced infertility at some stage in their lives, globally. Childlessness is often associated with devastating social and psychological impacts, but it is also associated with economic burden. Mainly affected women, but also couples are confronted with negative consequences of childlessness such as stigmatization, anxiety, depression, and low self-esteem., This is particularly true in societies where the offspring is the guarantee of social status and provides social security in old age (WHO 2023). Therefore, infertility or involuntary childlessness is not only a medical but also a multidisciplinary problem. From a biomedical viewpoint, infertility is defined as a disease of the male or female reproductive system characterized by the failure to conceive successfully after 12 months or more of regular unprotected sexual intercourse (WHO 2023). The reasons for infertility are manifold, it may result from several pathological conditions affecting the male or the female reproductive system, but also from lifestyle parameters such as the voluntary postponement of reproduction typical of recent high-income states (WHO 2023). The mean age at first birth has increased dramatically during the last 50 years, in most of the high-income countries the mean age of first-time mothers is currently older than 30 years. With increasing female age, however, the number of ovulatory cycles decreases and so does the probability of successful conception (Dunson et al. 2002). Consequently, the use of artificial reproductive technologies (ART) gains in importance. 45 years ago, Louise Brown, the first child conceived in vitro, was born. This first successful application of in-vitro fertilization was a medical sensation and was interpreted as a game changer in the treatment of infertile couples. Currently, assisted reproduction techniques (ART), such as in vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI), are established standard procedures in the treatment of infertility and are used widely to help involuntarily childless couples (Chang et al. 2020; Wyns et al. 2022).

Despite the success of IVF and ICSI these techniques are still discussed as risk factors for gestational diabetes, hypertension, preeclampsia, placenta previa (Zhu et al. 2016), perinatal morbidity (Kalra and Molinaro 2008; Wennerholm and Bergh 2020; Zheng et al. 2018) and fetal growth restriction, resulting in a higher rate of very low birth weight and low birth weight (Heo et al. 2019; Lieberman et al. 2006; Tough et al. 2000) and an increased number of small-for-gestational-age newborns (Schieve et al. 2007), preterm birth (Aboulghar and Aboulghar 2021), and several obstetric problems, such as breech presentation of increased risk for cesarean section (Chen et al. 2023; Helmerhorst et al. 2004; Koudstaal et al. 2000; Malchau et al. 2014; Noli et al. 2019; Pandey et al. 2012; Portal et al. 2021; Romundstad et al. 2009; Schieve et al. 2007; Slavov 2020; Sullivan-Pyke et al. 2017; Zádori et al. 2003). It is still unclear whether these problems are directly related to ART use (Berntsen et al. 2019; Romundstad et al. 2008; Stern et al. 2015; Valenzuela-Alcaraz et al. 2016), because these adverse effects are mainly associated with multiple pregnancies, which are more common after ART treatment, but also with increased maternal age, preterm birth, or nulliparity (Romundstad et al. 2009). Therefore, many studies ended with the demand for further research, although Graham et al. (2023) pointed out that the results of short- and long-term outcome studies after controlling for multiple gestations and preterm delivery suggest that ART is a safe procedure, with low risks. In our present study, we tried to contribute to clarifying this issue and analyzed the neonatal and perinatal outcomes of singleton pregnancies resulting from IVF or ICSI, which took place in Vienna, Austria. In detail, we tested the following two hypotheses:

- Singleton pregnancies resulting from IVF or ICSI are associated with an increased risk of fetal growth restriction resulting in smaller newborn size.
- Singleton pregnancies resulting from IVF or ICSI are associated with an increased risk of preterm birth, lower APGAR scores, acidosis, breech presentation and cesarean sections.

Material and methods

Data set

In this single-center and medical record-based study, we analyzed the association patterns between the mode of conception (spontaneously versus artificial reproductive technology (ART) and newborn size as well as obstetrical risk factors (preterm birth, breech presentation, cesarean section, labor induction) among 5867 singleton births taking place between 2015 and 2023 at the Donaustadt Clinic in Vienna, Austria. We included only singleton pregnancies resulting from spontaneous conceptions and pregnancies resulting from IVF or ICSI. Therefore, we excluded all cases of multiple births, pregnancies resulting from hormonal treatment or homologous insemination, chromosomal anomalies, and congenital malformations. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Vienna (responsible for Public Hospitals) (Protocol number: EK 19–274-VK 18 March 2020).

Maternal parameters

The following maternal somatic parameters were documented: maternal age (in years), body height (in cm), and body weight at the beginning and at the end of pregnancy (in kg). Trained personnel measured height to the nearest 0.1cm at the first prenatal visit, usually during the 8th gestational week. Pre-pregnancy weight was recorded by an interview using the retrospective method. Body weight was measured to the nearest 0.1kg on a balance beam scale, at the first prenatal visit around the 8th week of gestation. Maternal weight was measured again before delivery (i. e. at the end of pregnancy). The pregnancy weight gain was calculated by subtracting pre-pregnancy weight from body weight before delivery. In addition, the pre-pregnancy BMI (kg/m^2) was calculated. A detailed description of the methods applied is presented in an earlier paper (Kirchengast and Hartmann 2021).

Obstetric characteristics

The data set contained information regarding the following obstetrical parameters: previous births, previous abortions, duration of pregnancy (preterm birth versus term birth), induction of labor (yes or no), mode of delivery (spontaneous vaginal delivery, planned cesarean section, unplanned or emergency cesarean section), fetal presentation at birth (cephalic presentation, breech presentation, others) and the pH value (to one decimal place) of the arterial umbilical cord blood, which allows an accurate, reproducible and objective evaluation of the oxygen deficiency during birth (Mogos et al. 2019).

Newborn parameters

Immediately after birth, the following newborn parameters were recorded: sex, birth weight (in g) using a digital infant scale, birth length (in cm) using a standard measurement board for infants, and head circumference (in cm) using a standard tape. All measurements were taken by a trained midwife. Newborn size was used as a proxy of intrauterine growth. According to the recommendations of the WHO (WHO 2004), a birth weight between 1500g and 2499g was defined as low birth weight (LBW) and a birth weight below 1500g was defined as very low birth weight (VLBW). APGAR scores have been recorded 1, 5, and 10 minutes after birth (Apgar 1953).

Statistical analysis

The statistical analysis was carried out with IBM SPSS version 27. After computing descriptive statistics, student t-tests were performed to test group differences between newborns conceived spontaneously and those conceived via ART with respect to their statistical significance. To evaluate the risk of preterm birth, cesarean section, breech presentation, and low birth weight, the odds ratios were calculated for ART-conceived newborns compared to spontaneously conceived ones with the respective 95% confidence interval. To test for an association between conception mode and preterm birth, labor induction, the mode of delivery, fetal presentation as well as newborn weight status, Pearson Chi^2 tests were performed. A linear regression analyses was computed to test the independent associations between ART, maternal age, body height, pre-pregnancy BMI, gestational weight gain, previous births, as well as gestational week of delivery and newborn size. Binary logistic regression analyses were calculated to test the effect of ART, independent of gestational weight gain, maternal age, body height, gestational week of birth, as well as previous births on several obstetrical characteristics, such as breech presentation, low birth weight, preterm birth, planned cesarean section, emergency caesarean section. A p-value of 0.05 was considered as significant.

Results

Sample characteristics

The data set contained 5867 singleton live births. 178 of these births (3.0%) originated from IVF (n=129; 2.2%) or ICSI (n=49, 0.8%). 5431 births corresponded to the definition of term birth (37 gestational weeks), while 436 were classified as preterm (<37 gestational weeks). The IVF/ICSI rate among term birth was 2.6% and among preterm births, the IVF/ICSI rate was 7.8%.

IVF/ICSI and maternal as well as newborn characteristics

Table 1 demonstrates maternal and newborn somatic characteristics for spontaneous conceptions and ART separately. In the first step, the whole data set including preterm births was considered. Mothers conceiving via IVF or ICSI were significantly older, taller, and heavier than mothers conceiving spontaneously. The newborns conceived via IVF or ICSI, however, were significantly lighter, shorter, and showed a significantly lower head circumference than their spontaneously conceived counterparts. Furthermore, they had significantly higher rates of very low birth weight (3.8% vs. 0.8%) and low birth weight (7.9% vs. 4.4%). The APGAR scores 1, 5, and 10 minutes after births were always significantly lower among IVF or ICSI offspring. No significant differences in the sex ratio between spontaneously and ART-conceived newborns could be observed. The number of male newborns was always higher than that of female newborns.

In the second step, only term births were considered (table 1). Mothers conceiving via IVF or ISCI were still significantly older and taller, but not significantly heavier than spontaneously conceiving ones. Among IVF or ICSI term births, insignificantly more girls were born. The newborns of the two groups, however, did not differ significantly in size, in contrast, the IVF or ICSI-conceived newborns were slightly heavier, longer, and had a higher head circumference. Consequently, the significant differences in newborn size are not observable among term births. Concerning the APGAR scores, only the APGAR score 1 minute after birth was still significantly lower among IVF or ICSI newborns.

The results of linear regression analyses considering the whole sample corroborated these observations. As presented in table 2, birth weight, birth length, and head circumference were significantly positively associated with maternal body height, prepregnancy body mass index, gestational weight gain, the number of previous births, and significantly associated with the gestational week when the delivery took place. Maternal age was significantly positively associated the head circumference only. Artificial reproductive technology (IVF or ICSI), however, was not independently significantly related to newborn size.

IVF/ICSI and obstetrical risk factors

Table 3 presents obstetrical characteristics according to conception mode of the whole sample and the term birth sample separately. Considering all births (including preterm ones), the pregnancies resulting from IVF or ICSI ended significantly earlier and the preterm birth rate was significantly higher. Furthermore, first-time mothers, labor induction, a history of previous abortions, planned as well as emergency cesarean sections and breech presentation occurred significantly more often in IVF or ICSI pregnancies. No significant differences occurred for the pH value of the arterial umbilical cord blood or the presence of acidosis. Considering the term birth sample only, pregnancies resulting from IVF or ICSI showed also significantly higher rates of first-time mothers, labor induction, as well as planned and emergency cesarean sections. No significant group differences occurred regarding gestational week of delivery, history of previous abortions, breech presentation, and pH value of the arterial umbilical cord blood.

Binary logistic regression models were calculated to show the independent effect of ART on pregnancy and perinatal complications. As presented in table 4, ART (IVF or ICSI) represented an independent risk factor for preterm birth (OR 3.4; 95% CI 2.09-4.73), the need for labor induction (OR 1.5, 95% CI 1.09-2.07) planned (OR 2.54 95% CI 1.27-2.47) as well as emergency cesarean section (OR 2.29 95% CI 1.49-3.52). Breech presentation and low birth weight, however, were not independently associated with ART.

Discussion

The improvement of reproductive health is a major goal in global public health initiatives. For a long time, the focus of these efforts was on reducing maternal and infant mortality rates, improving medical care during pregnancy and childbirth, reducing dangerous abortions, as well as dissemination of safe and effective contraceptives, and the reduction of sexually transmitted

Table 1 Maternal and newborn characteristics according to conception mode (spontaneous versus assisted conception) for the whole sample and term birth only.

	whole sample					Term birth only (≥37 gestational week)				
Variable	spontaneous		ICSI or IVF			spontaneous		ICSI or IVF		
N	5689		178			5287		144		
	mean n	SD %	mean n	SD %	p-value	mean n	SD %	mean n	SD %	p-value
Maternal age (years)	30.9	5.4	35.1	5.6	<0.001	30.9	5.3	35.1	5.7	<0.001
Body height (cm)	165.2	6.3	166.7	6.3	0.002	165.3	6.3	166.7	6.2	0.006
PP weight (kg)	66.9	15.1	69.0	15.6	0.036	66.9	15.1	67.9	14.0	0.182
PPBMI (kg/m2)	24.5	5.3	24.8	5.5	0.216	24.5	5.3	24.4	4.7	0.472
EPW (kg)	80.7	15.1	81.8	15.8	0.172	80.8	15.0	81.5	14.6	0.298
GWG (kg)	13.8	8.7	12.8	8.2	0.080	13.8	8.4	13.5	5.7	0.278
Birth weight (g)	3391.8	551.6	3248.4	728.9	<0.001	3471.5	455.2	3493.9	464.5	0.280
Newborn weight status										
VLBW <1500g	48	0.8%	7	3.9%	<0.001					
LBW 1500 – 2500 g	250	4.4%	14	7.9%	<0.001	81	1.5%	2	1.4%	0.267
Birth length	50.7	2.7	49.9	3.8	<0.001	51.1	2.1	51.2	1.9	0.221
Head circumference	34.3	1.8	33.9	2.4	0.010	34.5	1.5	34.7	1.4	0.063
Newborn sex										
male	2946	51.8%	90	50.6%	0.748	2740	51.8%	71	49.3%	0.550
female	2743	48.2%	88	49.4%		2547	48.2%	73	50.7%	
APGAR score 1 min	8.9	0.9	8.5	1.5	<0.001	9.0	0.9	8.8	1.1	0.002
APGAR score 5 min	9.8	0.7	9.6	1.0	<0.001	9.8	0.6	9.8	0.6	0.109
APGAR score 10 min	9.9	0.3	9.8	0.6	<0.001	9.9	0.3	9.9	0.3	0.370

Legend: To test group differences, t-tests were computed. For categorical variables, 2 tests were applied.

Abbreviations: PP weight = pre-pregnancy weight, PPBMI = pre-pregnancy body mass index, EPW = end of pregnancy weight, GWG = gestational weight gain, VLBW = very low birth weight, LBW = low birth weight.

diseases (Mascarenhas et al. 2012). Another reproductive health problem that has increasingly become the focus of public health research is infertility. Although difficult to reconstruct, it can be assumed that infertility rates have increased in recent decades. According to Sun et al. (Sun et al. 2019), the age-standardized prevalence rate of infertility increased by 0.370% per year for females and 0.291% per year for males globally from 1990 to 2017.
On the one hand, this increase is due to changes in environmental pollution such as pesticides or endocrine disruptors (bisphenol, plasticizers, phthalates), and on the other hand, to changes in living conditions such as psychological and somatic stress, obesity, but also a postponement of reproduction into the fourth and fifth decade of life (Bala et al. 2021). These changes affect both men and women. Over the last 40 years, anovulation and hormonal disturbances have increased in human females, while among males the quantity and quality of sperm has decreased significantly, resulting in one in 20 men being affected by reduced fertility (Levine et al. 2017). Globally, about 15% of couples of reproductive ages are affected (Gerrits et al. 2017). This has led to an increasing use of artificial reproductive technologies (ART) in recent years, with

Table 2 The impact of ART, obstetric parameters and maternal parameters on newborn size

		R2	Reg coeff	p-value	95% CI
Birth weight					
	ART (IVF or ICSI)	0.71	27.39	0.375	-33.14 – 87.94
	Number of previous births		46.69	<0.001	39.62 – 59.76
	Maternal age		-0.42	0.675	-2.45 – 1.59
	Maternal body height		13.09	<0.001	11.48 – 14.72
	Gestational weight gain		5.04	<0.001	3.79 – 6.28
	Pre-pregnancy body mass index		11.68	<0.001	9.63 – 13.74
	Gestational week		190.54	<0.001	185.27 – 195.81
Birth length					
	ART (IVF or ICSI)	0.69	0.01	0.959	0.29 – 0.31
	Number of previous births		0.15	<0.001	0.09 – 0.19
	Maternal age		0.01	0.131	-0.01 – 0.02
	Maternal body height		0.57	<0.001	0.49 – 0.65
	Gestational weight gain		0.12	<0.001	0.01 – 0.02
	Pre-pregnancy body mass index		0.03	<0.001	0.02 – 0.04
	Gestational week		0.94	<0.001	0.91 – 0.97
Head circumference					
	ART (IVF or ICSI)	0.59	0.09	0.435	-0.13 – 0.31
	Number of previous births		0.15	<0.001	0.12 – 0.19
	Maternal age		0.02	<0.001	0.01 – 0.02
	Maternal body height		0.03	<0.001	0.03 – 0.04
	Gestational weight gain		0.01	<0.001	0.01 – 0.02
	Pre-pregnancy body mass index		0.03	<0.001	0.02 – 0.03
	Gestational week		0.52	<0.001	0.49 – 0.54

Legend: linear regression analyses
Abbreviations: ART = artificial reproductive technology; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection

an annual increase of between 5 and 10% (WHO 2023). These technologies are not only expensive and are only financed to a limited extent by social insurance, but – mainly in the case of IVF and ICSI – are also considered as independent risk factors for numerous complications during pregnancy and birth, including preterm birth, breech presentation, increased rates of cesarean section and fetal growth restriction (Graham et al. 2023; Heo et al. 2019).

This study focuses on association patterns between ART and newborn parameters, but also obstetrical risk factors such as breech presentation, labor induction and cesarean section in an Austrian sample. Since the two most frequently described consequences of ART, namely preterm birth, and fetal growth restriction, can be seen in connection with the more frequent multiple pregnancies among ART, only singleton births were included in the present study.

The first hypothesis tested was related to the intrauterine growth process. We first showed that even among singleton pregnancies, IVF or ICSI newborns were significantly smaller than their spontaneously conceived counterparts. Furthermore, the proportion of very low birth weight (<1500g) and low birth weight (1500–2500g) newborns was significantly higher in the ART group. These observations are initially in line with the results of numerous other studies, which also described an increased risk for very low and low birth weight among ART pregnancies (Camarano et al. 2012; D'Angelo et al. 2011; Hayashi et al. 2012; Heo et al. 2019; McDonald et al. 2009; Pandey et al. 2012; Schieve et al. 2007; Wang et al. 2005; Yu et al. 2022). Several of these studies met some criticism because multiple pregnancies have been included, which increases per se the risk of preterm birth and fetal growth restriction (Wang et al. 2021).

Table 3 Obstetric characteristics according to conception mode (spontaneous versus assisted conception) for the whole sample and term birth only.

Variable	spontaneous		ICSI or IVF			spontaneous		ICSI or IVF		
N	5689		178			5287		144		
	mean	SD	mean	SD	p-value	mean	SD	mean	SD	p-value
Preterm birth (<37 weeks)	402	7.1%	34	19.1%	<0.001					
Gestational week	39.1	1.9	38.2	2.8	<0.001	39.4	1.2	39.3	1.1	0.178
Labor induction	1455	25.6%	63	35.4%	0.003	1322	25.0%	56	38.9%	<0.001
First-time mothers	1846	32.4%	10.1	56.7%	<0.001	1697	31.1%	78	54.2%	<0.001
Previous abortions	2042	35.9%	77	43.3%	<0.001	1872	35.4%	62	43.1%	0.059
Cesarean section										
Planned CS	431	7.6%	32	18.0%	<0.001	345	6.5%	21	14.6%	<0.001
Emergency CS	492	8.6%	38	7.2%	<0.001	405	7.7%	25	17.4%	<0.001
Breech presentation	264	4.6%	21	11.8%	<0.001	204	3.9%	7	4.8%	0.070
Ph- arterial umbilical blood	7.3	0.1	7.3	0.1	0.479	7.25	0.25	7.25	0.9	0.303

Legend: To test group differences, t-tests were computed. For categorical variables, 2 tests were applied.
Abbreviations: CS = cesarean section; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection

In the present study, however, only singleton pregnancies were considered. Another point of criticism of the assumption that ART is independently associated with lower intrauterine growth is the increased rate of preterm birth among ART pregnancies. Birth before the 37th week of gestation is undoubtedly a risk factor for smaller newborn size. Therefore, in the present study, only term births were considered in the second step. Considering term births only, however, no significant differences in newborn size between ART and spontaneously conceived newborns

Table 4 The associations between ART and obstetrics and maternal parameters, and newborn parameters among term births.)

	Odds Ratio	*p*-value	95% CI
Preterm birth <37 gestational week)			
ART (IVF or ICSI)	3.41	<0.001	2.09 – 4.73
Number of previous births	1.05	0.295	0.96 – 1.15
Maternal age	1.01	0.836	0.98 – 1.02
Maternal body height	0.98	0.006	0.96 – 0.99
Gestational weight gain	0.97	<0.001	0.96 – 0.08
Breech presentation			
ART (IVF or ICSI)	1.43	0.189	0.84 – 2.44
Number of previous births	0.65	<0.001	0.56 – 0.78
Maternal age	1.05	0.003	1.01 – 1.06
Maternal body height	1.04	0.005	1.00 – 10.5
Gestational weight gain	1.00	0.839	0.99 – 1.02
Gestational week	0.739	<0.001	0.71 – 0.77
Birth induction			
ART (IVF or ICSI)	1.50	0.014	1.09 – 20.07
Number of previous births	0.87	<0.001	0.82 – 0.93
Maternal age	1.02	0.003	1.00 – 10.3
Maternal body height	0.99	0.730	0.99 – 1.01
Gestational weight gain	0.99	0.165	0.99 – 1.01
Gestational week	1.09	<0.001	1.05 – 1.13
Planned CS			
ART (IVF or ICSI)	2.54	<0.001	1.27 – 2.47
Number of previous births	1.00	0.889	0.92 – 1.12
Maternal age	1.01	<0.001	1.03 – 1.08
Maternal body height	0.99	0.433	0.98 – 1.01
Gestational weight gain	1.01	0.047	1.00 – 1.02
Gestational week	0.64	<0.001	0.61 – 0.67
Emergency CS			
ART (IVF or ICSI)	2.29	<0.001	1.49 – 3.52
Number of previous births	0.62	<0.001	0.55 – 0.69
Maternal age	1.07	<0.001	1.05 – 1.09
Maternal body height	0.94	<0.001	0.93 – 0.96
Gestational weight gain	1.00	0.697	0.99 – 1.01
Gestational week	0.81	<0.001	0.78 – 0.84
Low birth weight (<2500g)			
ART (IVF or ICSI)	1.03	0.992	0.45 – 2.44
Number of previous births	0.84	0.025	0.72 – 0.98
Maternal age	0.98	0.124	0.95 – 1.00
Maternal body height	0.96	<0.001	0.93 – 0.98
Gestational weight gain	0.99	0.831	0.98 – 1.02
Gestational week	0.32	<0.001	0.29 – 0.35

Legend: binary regression analyses
Abbreviations: ART = artificial reproductive technology, CS = cesarean section; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection

occurred. On the contrary, the ART-conceived newborns were even insignificantly larger than spontaneously conceived ones. A similar effect was described by Yu et al. (Yu et al. 2022) who found an increased risk of macrosomia in IVF-conceived newborns. In our sample, the mothers of ART who conceived non-preterm newborns were older but also taller and had experienced a significantly higher gestational weight gain in comparison to their spontaneously conceiving counterparts. These somatic characteristics of via ART conceiving mothers may have positively affected fetal growth and resulted in slightly heavier and longer newborns. Consequently, the frequently described smaller newborn size among ART newborns may be due to a higher rate of multiple pregnancies following ART or maybe due to the higher rate of preterm birth. This conclusion was corroborated by the results of linear and binary logistic regression analyses which showed that neither birth weight and birth length nor head circumference of the newborn and the risk of low birth weight were statistically significantly associated with ART independently. The somatic characteristics of the newborn were independently associated with maternal somatic characteristics, such as body height, pre-pregnancy weight, but most importantly with the gestational week in which the birth occurred. Thus, in our study, the use of ART is not an independent risk factor for growth restriction. Indirectly, however, there is an association between ART and lower newborn size, as newborn size is significantly associated with the gestational week in which the birth takes place. The duration of pregnancy, however, is significantly shorter in ART pregnancies and the rate of preterm birth is also significantly higher in ART pregnancies. Consequently, ART is associated with a smaller newborn size, even if the relationship is based on the duration of pregnancy.

The first hypothesis of the present study can thus be considered partially verified. This also applies to the second hypothesis of this study. We were able to show that, as expected, the preterm birth rate, and the need for labor induction, were significantly positively associated with ART pregnancies. This is also in line with the results of Cavoretto et al. (2008) and Pandey et al. (2012). Furthermore, the risk of planned as well as emergency cesarean section was also significantly increased in ART pregnancies in our study. This corresponds to the results of other authors (Helmerhorst et al. 2004; Jackson et al. 2004; Lodge-Tulloch et al. 2021; Pandey et al. 2012). It must be emphasized that the increased risk of cesarean section was also related to the increased rate of preterm birth. In the present study, we were able to show that in the case of preterm birth, the risk for an emergency cesarean section (CS) was increased by a factor of 3.8, and that for a planned CS by a factor of 4.2. Nevertheless, the present studies showed that the risk of planned and emergency cesarean deliveries was increased in ART pregnancies regardless of gestational week, maternal age, or maternal height. In contrast, no increased risk of breech presentation or low pH-values of the umbilical arterial blood was observed in the present study. These results are partly in accordance with those of several other studies (Berntsen et al. 2019; Helmerhorst et al. 2004; Koudstaal et al. 2000; Malchau et al. 2014; Pandey et al. 2012; Slavov 2020; Wyns et al. 2022; Zádori et al. 2003) but in contrast to the recently published study by Chen et al. (Chen et al. 2023), who reported a significant association between ART and breech presentation.

Preterm birth and a significantly increased risk of CS birth remain the most serious obstetrical consequences of ART in this sample. The precise mechanisms of how ART affects fetal growth and pregnancy duration, and the mode of delivery are not yet fully understood. The causes are difficult to pinpoint. Numerous studies point out that ART itself is only an indicator of other medical problems that made per se ART necessary (Kondapalli and Perales-Puchalt 2013; Stern et al. 2015). Sunkara et al. (Sunkara et al. 2021) reported higher preterm birth rates after ART among women suffering from ovulatory disorders, tubal disorders, and endometriosis than among women suffering from idiopathic infertility. The risk of low birth weight in contrast was only higher among women suffering from ovulatory disorders and tubal disorders but not among those suffering from endometriosis (Sunkara et al. 2021). No effect on newborn size was found among ART pregnancies when infertility was caused by male factors. Therefore, we can assume that female infertility factors such as Polycystic ovary syndrome (PCOS), tubal factors, and inflammatory processes have a negative impact on pregnancy and fetal growth. Another problem may be the advanced maternal age among women who undergo infertility treatment. In our study, maternal age in the ART group was significantly higher than in the group of spontaneous conceptions. Advanced maternal age represents an independent risk factor for adverse pregnancy outcomes. It is well documented that with increasing maternal age the risk of cesarean section, the need for labor induction, but also preterm birth rates increase even among spontaneously conceiving mothers (Bergholt et al. 2020; Fuchs et al. 2018; Kocourková et al. 2019).

Conclusion

To sum it up, at first glimpse, ART seems not to have a negative impact on fetal growth and consequently newborn size. ART, however, increased the risk of preterm birth by a factor of 3.4 and preterm birth is a major cause of small newborn size and complications at birth. Therefore, ART can also be interpreted with caution as an indirect risk factor for small newborn size with all its long-term consequences. Considering the rising infertility rates among couples of reproductive age worldwide, these findings are of particular concern. We can assume that increasing infertility rates will also increase the use of ART with all associated consequences and risks. Therefore, from a public health viewpoint, it still makes sense to examine the relationships between ART and fetal growth as well as obstetric parameters.

Limitations

We are aware that our study has several limitations, which should be mentioned. A major limitation is the fact, that despite the large sample size (n= 5869) the number of ART pregnancies is still low (n=178). Furthermore, we have no information regarding the pathological basis of infertility, because the data set used in this medical record-based study did not contain information concerning the etiology of infertility. A further limitation is that we have no information regarding life circumstances, socioeconomic factors, and individual stress levels, which might affect intrauterine growth, the course of pregnancy, and delivery itself.

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