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Perinatal outcomes in singletons after fresh IVF/ICSI – a cohort study comparing the Bern IVF Cohort with a tertiary center cohort and the national live birth registry

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Abstract

Research question: How are perinatal outcomes of live born singletons after stimulated and unstimulated in-vitro fertilization different from perinatal outcomes in i) children born in a tertiary center and ii) all children born in Switzerland?

Methods: This cohort study compares the perinatal outcomes of two birth cohorts and the national live birth registry. Relative risks were calculated using modified Poisson regression and clustering for siblings and adjustment for maternal age, parity, and fetal sex

Results: Of the 636,639 live births, 311 were in the Bern IVF Cohort (144 stimulated, 167 unstimulated), 2332 in the tertiary center, and 633,996 in the Swiss Live Birth Registry (SLBR). Perinatal outcomes following IVF did not differ compared to births in the SLBR (relative risk (RR); 95% CI), with the exception of the increased risk of small for gestational age (1.31; 1.01, 1.70, *P* = 0.04; aRR 1.12; 0.87, 1.45, *P* = 0.39). Children born following stimulated IVF had a higher risk of low birthweight (2.17; 1.27, 3.69, *P* < 0.01; aRR 1.72; 1.01, 2.93, *P* = 0.05), and of being small for gestational age (1.50; 1.05, 2.14, *P* = 0.03; aRR 1.31; 0.92, 1.87; *P* = 0.13), whereas children born after unstimulated IVF had no increased risks compared to the SLBR. Higher caesarean rate after IVF was mainly associated with higher maternal age.

Conclusion: Singletons in the Bern IVF Cohort do not show less favorable perinatal outcomes. Gonadotropin stimulation seems to have an effect, because lower risks were associated with unstimulated IVF.

Key words*:* assisted reproduction, natural cycle, IVF/ICSI outcome, gonadotropins, epidemiology

Introduction

Infertility issues affect 8-12% of couples at reproductive age (Vander Borght and Wyns, 2018). In Switzerland, 2-2.5% of newborns are conceived with the support of in vitro fertilization[1] (IVF) technologies (Federal Statistical Office). Higher risk of unfavorable perinatal outcomes in singletons born after IVF, such as reduced gestational age and birthweight as well as preterm birth[2] (PTB), low birthweight[3] (LBW), and small for gestational age[4] (SGA) have been confirmed by several meta-analyses (Pandey et al., 2012). For PTB, the relative risk (RR)[5] after IVF compared to spontaneously conceived singletons was between 1.54- 1.84; (Pandey et al., 2012) and the odds ratio (OR)[6] was 1.55 (Pinborg et al., 2013). Over time, risks were reduced by the development of IVF methods and the rising awareness of safer treatments such as antagonist protocols or lower gonadotropin dosages (Henningsen et al., 2015; Henningsen and Pinborg, 2014) and it remains important to assess perinatal outcomes of more recent cohorts (Berntsen et al., 2019). Many factors related to IVF may be associated with adverse perinatal outcomes (Pontesilli et al., 2021). Gonadotropin stimulation appears to increase the risk of LBW (Mak et al., 2016) or of being born SGA, especially when supraphysiological estradiol levels are reached at trigger day (Kohl Schwartz et al., 2019) or when many oocytes are collected (Sunkara et al., 2015). Gonadotropin stimulation also bears higher risks for the mother for ovarian hyperstimulation syndrome, pregnancy-induced hypertension, gestational diabetes mellitus

[1] IVF: In vitro fertilisation
[2] PTB: Preterm birth
[3] LBW: Low birthweight
[4] SGA: Small for gestational age
[5] RR: Relative risk
[6] OR: Odds ratio
[7] CS: Cesarean sectio
[8] NC-IVF: Natural cycle IVF (unstimulated IVF)
[9] cIVF: stimulated IVF
[10] ODS: Obstetric Data Study (tertiary cohort)
[11] SLBR: Swiss Live Birth Registry
[12] E2: Estradiol
[13] HCG: human chorionic gonadotropin
[14] 95% CI: 95% Confidence Intervals

and seems independently associated with preterm delivery (Pandey et al., 2012). Otherwise, singletons resulting from thawing cycles show significantly lower risks for PTB and LBW but higher risks for large for gestational age and high birthweight (Conforti et al., 2021; Maheshwari et al., 2018; Pontesilli et al., 2021). By postponing the embryo transfer in thawing cycles, the gonadotropins do not directly affect the pregnancy. Epigenetic changes are triggered and DNA methylation is influenced by embryo culture, cryopreservation and laboratory techniques (Berntsen et al., 2019; Pinborg et al., 2016). In addition, age, health, and parental subfertility are associated with higher perinatal risks. The association of longer time to pregnancy, a proxy for subfertility, with PTB (Messerlian et al., 2013) was confirmed by a meta-analysis. In studies with discordantly conceived siblings, differences in birthweight were less pronounced (Goisis et al., 2019; Henningsen et al., 2011) or were not present (Romundstad et al., 2008); this leads to the conclusion that underlying infertility as well plays a role. Cesarean section[7] (CS) is more frequent in deliveries after IVF, with increased RR of 1.54-1.58 (Pandey et al., 2012).

The Bern IVF Cohort was established to assess obstetric, perinatal, and long-term outcomes of children born after different types of IVF treatments, stimulated and unstimulated IVF, performed in one centre with standardized laboratory and embryo culture conditions. Unstimulated, natural cycle IVF[8] (NC-IVF) is based on the concept of natural follicular recruitment and the selection of one oocyte whereas in gonadotropin stimulated IVF[9] (cIVF) polyfollicular oocyte growth is common (von Wolff, 2019). NC-IVF can serve as a model for natural ovulatory development and the comparison to cIVF is allowing to assess the effect of gonadotropin stimulation on perinatal outcomes (Kohl Schwartz et al., 2019). The aim of this study was first, to compare perinatal outcomes of the Bern IVF Cohort with outcomes in i) a cohort of births in a tertiary center (Bern University Hospital: the Obstetrics Data Study[10] (ODS)), and ii) all children born in Switzerland during the same period of time (Swiss Live Birth Registry[11] (SLBR)); and second, to address the effect of gonadotropin stimulation by comparing cIVF and NC-IVF to the children born in Switzerland.

Materials and methods

The Bern IVF Cohort

The Bern IVF Cohort includes couples treated in the Division of Gynecological Endocrinology and Reproductive Medicine at the Bern University Hospital with a pregnancy following fresh embryo transfer within IVF treatment. Data was collected using research electronic data capture (REDCap) tools at the Clinical Trials Unit, University of Bern. REDCap is a secure, web-based platform designed to support data collection for research (Harris et al., 2019, 2009). All women independent of any health condition with a birth between November 2010 and August 2018 were included (n=349). Women with incomplete data on gestational age and birthweight (n=2), with multiple births (n=33) and in case of perinatal death (n=3) were excluded. (Figure I).

The Obstetrics Data Study

In the ODS of the Department of Obstetrics and Gynecology at the University Hospital of Bern a cohort of women were recruited during their first-trimester routine ultrasound visit and followed until delivery. In this study, data on mode of conception, pregnancy, and delivery was collected. Women with a singleton born alive were included in the analysis. All women independent of preexisting chronic conditions or disorders were included. Only women treated by IVF, ovarian stimulation, or insemination (n=255), miscarriages, perinatal deaths (n=55), women who refused further use of their medical data for research (n=354), and cases with missing information on gestational age or birthweight (n=18) were excluded from analysis (Figure I).

The Swiss Live Birth Registry

In the SLBR of the Federal Statistical Office, routine data for all infants born alive in Switzerland were collected. Only core information for mothers (age, nationality, profession, parity) and infants (gestational age, birthweight, length, sex, siblings) was collected; no medical data on the health of the mother, the newborn or information on conception, the course of the pregnancy and delivery were

available. All live births registered between November 2010 and August 2018 were included. Birth with missing valid identifiers (n=6943), multiple births (n= нпЮптнý a gestational age below 22 weeks or birthweight below 500g (n=541), mothers age above 45 years at delivery (n=960), and missing information on gestational age and birthweight (n=2479) were excluded from the analysis. The gestational age of 22 weeks is according to Swiss legislation on differentiation between miscarriage and stillbirth.

In-vitro fertilization treatment in the Bern IVF Cohort

Women with regular menstrual cycles (26-32 days) could chose the treatment according to their preference, as NC-IVF requires a regular cycle. In women undergoing NC-IVF, the cycles were monitored by ultrasound and measurement of estradiol[12] (E2) and luteinizing hormone. When follicle diameter reached at least 16mm and E2 was greater than or equal to 700pmol/L, the women received a trigger shot of 5000 IU human chorionic gonadotropin[13] (HCG) to induce ovulation. Oocyte retrieval took place 36 hours later without anesthesia (A. S. Kohl Schwartz et al., 2020). To reduce the risk of premature ovulation, either 25mg clomiphene citrate from cycle day seven onwards (von Wolff *et al.*, 2014) or 400mg ibuprofen three times daily beginning 48 hours before oocyte pick-up was taken by the woman (A S Kohl Schwartz et al., 2020).

For cIVF, 75 IU ç 350 IU gonadotropin per day were administered. Either an antagonist or an agonist (short or long downregulation) protocol was performed. In cIVF treatment, the stimulation was monitored by ultrasound and serum E2 level measurements. When more than two of the leading follicles reached a diameter of at least 18mm with corresponding E2 concentration, ovulation was triggered by injecting HCG by the women themselves. We retrieved oocytes 36 hours later under conscious sedation (Al-Inany et al., 2016; Kolibianakis et al., 2006)

Oocytes were fertilized by standard intracytoplasmic sperm injection (ICSI) or IVF. Consistent standard conditions for embryo culture applied to both groups. Fresh embryos were transferred at cleavage-

stage on culture day two or three with ultrasound guidance. The women received luteal phase support with up to 200mg micronized progesterone administered twice daily if necessary (von Wolff *et al.*, 2017). Switzerland did not allow longer embryo culture until 2017 and supernumerary zygotes were vitrified.

Main outcomes

All three datasets provided information on primary outcomes, birthweight, and gestational age. Birthweight percentiles were calculated for each live born singleton according to the formula provided by Nicolaides *et al.*, 2018. Data on birth length was available in the Bern IVF Cohort and the SLBR. Delivery mode was compared between the Bern IVF Cohort and the ODS. CS is defined as secondary if labor had already started (presence of contractions, bleeding, or rupture of membranes). The reasons for CS were categorized into maternal, fetal, or emergency (see Table A2).

Covariates

Information on maternal age at delivery (continuous), parity (primiparous vs multiparous), and fetal sex was available in all datasets. Additional information from the Bern IVF Cohort and the ODS on smoking during pregnancy (yes or no) and on maternal body mass index (BMI as kg/m^2, continuous) measured in early pregnancy were used.

Statistical analyses

First, primary perinatal outcomes were compared, and second, the mode of delivery and reasons for CS were described. For the comparison among the three data sets, adjustments were made for maternal age, parity and fetal sex (Model I). For the comparison between the Bern IVF Cohort and the ODS, adjustments were additionally made for maternal BMI and smoking during pregnancy (Model II). Continuous outcomes such as birthweight, gestational age, length, and birthweight percentiles were assessed using uni- and multivariable linear regression. For associations with binary outcomes such as LBW (<2500g), PTB (<37 gestational weeks), SGA (<10^{th} percentile), and CS, modified Poisson

regression was used, reporting RR and 95% Confidence Intervals[14] (95% CI) (Zou, 2004). To account for singletons born to the same mother, maternal identifiers were used as cluster-robust variance estimates. For the assessment of the impact of gonadotropin stimulation, singletons born after cIVF were compared to those born after NC-IVF but both subgroups were also compared to the SLBR. The proportion of missing data was very low: in the Bern IVF Cohort, two participants were lost to follow-up (<0.01%); in the ODS, 18 (<0.1%) and in the SLBR, 2479 (<0.005%) were excluded due to missing data on birthweight or gestational age (Figure I). Interpretation of birthweight as an outcome has been the subject of debate, as it correlates closely with gestational age. Perinatal epidemiologists recommend not to adjust birthweight for gestational age, but rather to assess birthweight in ăƚyƎfŜűƨyã ōƨǋyˁ l·ű űŜǋY όҗoт ƎŜăűl·űƚƨyl·f ǿŜŜʅăύ separately, which was done for sensitivity analysis (Wilcox, 2001). A p-value of <0.05 was considered as statistically significant. For data analysis, STATA 16.0 (StataCorp LLC, Texas, USA) was used.

Ethics Approval

The Bern IVF Cohort and the comparison with other cohorts (KEK Bern, 2015-00235, last amendment August 2018) and the ODS study (KEK Bern, 2019-01828, June 2020) were approved by the cantonal ethics committee.

Results

In the analysis, 636,639 deliveries were included. Figure I presents the exclusions and the final study populations: the Bern IVF cohort (N=311), the tertiary center ODS (N=2,332); and the SLBR (N= 633,996). Mothers in the Bern IVF Cohort were on average 3.6 years (95% CI 3.2, 4.1) older and more often primiparous than non IVF-mothers; and compared to the ODS, they smoked less and had a lower BMI (Table 1).

Gestational age and birthweight

Mean gestational age was comparable in the Bern IVF and the SLBR singletons but lower in the ODS singletons (Table 2). Singletons in the Bern IVF Cohort and the SLBR had comparable risks for PTB, which were higher for ODS singletons (Table 3). The unadjusted mean birthweight was lower in the Bern IVF children than in the SLBR, but this difference disappeared when the comparison was restricted to children born at term or after adjustment (Table 2). All covariates of Model I were strongly associated with birthweight and explained most of the difference between the Bern IVF Cohort and the SLBR: maternal age per year increase (-3.0g, 95% CI -3.4, -2.8; *P* < 0.01); multiparity (139.1g, 95% CI 136.7, 141.5; *P* < 0.01), and male sex (132.7g, 95% CI 130.3, 135.2; *P* < 0.01). Delivery by CS was strongly associated with lower birthweight, lower birthweight at term, and lower gestational age in conditional analysis.

Birthweight percentile

The mean birthweight percentiles did not differ but were below the 50th percentile for all 3 cohorts (Table 2). The Bern IVF Cohort and the ODS singletons had an increased risk of being born SGA compared to the SLBR (Table 3). When limited to children born at term, the risk for SGA is similar of ODS singletons (RR 1.07, 95% CI 0.95, 1.20; *P* = 0.24) and of IVF singletons (RR 1.27, 95% CI 0.96, 1.70; *P* = 0.10) both compared to SLBR.

Mode of delivery

Despite a higher prevalence of risk factors in the ODS women, mothers in the Bern IVF Cohort delivered more often by CS (42.1% vs 36.0%; *P* = 0.03; RR 1.17, 95% CI 1.01, 1.36; *P* = 0.04) (Table 5). This association disappeared after adjustment (Model I): maternal age (aRR 1.03, 95% CI 1.02, 1.04; *P* < 0.01) and sex of the child (aRR for girls: 0.86, 95% CI 0.78, 0.96; *P* < 0.01) were associated, but parity (multiparous: aRR 0.96, 95% CI 0.87, 1.06; *P* = 0.43) was not. Primary CS was more frequent in the Bern

IVF Cohort (Table 5). Delivery by CS was strongly associated with lower birthweight, lower birthweight at term, and lower gestational age in conditional analysis.

Comparison between stimulated cIVF and unstimulated NC-IVF

Gestational age and birthweight or risk for LBW and SGA did not differ between singletons born after cIVF and NC-IVF. Gestational age of either cIVF or NC-IVF did not differ compared to births registered in the SLBR. Birthweight of children born after cIVF was on average 114g lower (95% CI -212g, -17g; *P* = 0.02) compared to the SLBR, but in children born after NC-IVF it was similar (-13g, 95% CI -92g, 65g; *P* = 0.74). This difference was attenuated in children born at term (cIVF 82g, 95% CI -167g, 4g; *P* =; NC-IVF: -17g, 95% CI -88g, 53g; *P* = 0.63) or after adjustment in Model I (Table A1). CIVF was also associated with higher risks of being born with LBW or SGA, whereas children after NC-IVF had no increased risks compared to the SLBR (Table 4).

Discussion

In comparison to single births in the SLBR, singletons of the Bern IVF Cohort showed no differences in gestational age and birthweight percentiles and no increased risks for LBW or PTB. On the other hand, they showed a lower mean birthweight and a higher risk for SGA. There were no differences in the Bern IVF Cohort in comparison with the ODS. IVF mothers were older and more often primiparous. Gonadotropin stimulation influenced birthweight and intrauterine growth: singletons born after cIVF had a lower mean birthweight and increased risks of LBW and of being SGA compared to the SLBR, whereas singletons born after NC-IVF were similar to SLBR singletons.

Strengths

The strengths of this study are the detailed and complete information on conception, infertility treatment, course of pregnancy, and perinatal outcomes in the Bern IVF Cohort collected. The study

included the use of the population-based SLBR, as comparison group. This study contributes to the limited literature on perinatal outcomes of children born after NC-IVF.

Limitations

The sample size of the Bern IVF Cohort is limited, that is why we focus on the reporting of 95% CI for all comparisons. Characteristics of women choosing NC-IVF and of those choosing cIVF might be different. In Switzerland, IVF treatment is not subsidized; this impedes randomized controlled trials (von Wolff *et al.*, 2019). The ODS data was collected in a tertiary center with a neonatology unit. Patients are referred in case of pregnancy complications or for second opinions. The ODS consists primarily of a high-risk population; selection bias is an issue. The SLBR includes all children born alive, independent of how long they survived after birth. Therefore, it includes perinatal deaths occurring within the first week of life. The SLBR data include the deliveries in the Bern IVF Cohort and part of the deliveries in the ODS. Deliveries could not be linked in the cohorts to anonymized SLBR data to identify duplicates. The SLBR also contains pregnancies conceived after fertility treatment in Switzerland or abroad. However, the proportion of both cohorts compared to the SLBR is too small to affect mean outcome measures.

Interpretations of findings

The different demographic characteristics of parents undergoing IVF (older age, lower parity) have been shown in other countries; it is possible that these characteristics reflect the shift to older childbearing age and the delay of diagnosis of parental infertility (Goisis et al., 2020). On the other hand, the IVF mothers in this study had fewer pregnancy complications and a healthier lifestyle compared to ODS mothers; this might positively affect perinatal outcomes ó!ØðI·ℕ Ŝű I·fŒΣ нлнмT DÑyűKŜℕ et al., 2021; Khashan and Kenny, 2009).

With regard to perinatal outcomes, the results of our study are reassuring. Findings of previous meta-analysis (Pandey et al., 2012) could not be confirmed. In our study, gestational age and birthweight percentiles were not lower and risks for PTB and LBW were not increased after IVF. A lower crude mean birthweight and an increased risk of SGA in IVF children (Kohl Schwartz et al., 2019) could only be confirmed in unadjusted analysis. PTB and intrauterine growth restriction both reduce birthweight and SGA is a consequence of intrauterine growth restriction, which sometimes requires induction of labor or CS. Also in our study, delivery by CS was associated with LBW and PTB. Maternal age and parity are other independent risk factors associated with perinatal outcomes. Our results are explained partly by the higher age and lower parity of IVF mothers (Lean et al., 2017). Intrauterine growth may be affected by IVF, but maternal factors seemed more important in our study. Endometrial receptivity (Bonagura et al., 2008; Devroey et al., 2004) or vanishing twins are other possible explanations for which we could not control (Pinborg et al., 2007).

A separate study in Switzerland found that mainly regional differences influence birthweight; maternal age influenced gestational age, but surprisingly, regional differences in CS rates were not associated with differences in birthweight or gestational age (Skrivankova et al., 2019).

Birthweight percentiles below 50 were observed for all three populations. The birthweight percentiles that were used, based on children born in England and were not adjusted for sex of the infant (Nicolaides et al., 2018). They were not completely transferable to Swiss singletons. The lower birthweight percentiles of the Swiss cohorts may reflect a different distribution of parental characteristics. Birthweight percentiles developed in the USA specific for IVF singletons did find very little differences to the US population standards (Dickey et al., 2016). The similar mean birthweight percentiles are reassuring for our IVF population.

Three cohort studies assessed the effect of gonadotropin stimulation in comparison to NC-IVF (Mak et al., 2016). In a Japanese IVF registry study, data of 8224 singletons after fresh cIVF were compared to 610 after NC-IVF. The adjusted ORs (aOR) for LBW were 1.60-1.72 for agonist and antagonist protocols (Nakashima et al., 2013). In a IVF registry study from the UK data on 98,667 stimulated and 262 unstimulated fresh cycles were included and a trend towards higher odds was shown only for LBW (aOR 1.58, CI 0.96, 2.58) and PTB (aOR 1.43, 95% CI 0.91, 2.26) (Sunkara et al., 2016). In a small US study with 174 stimulated and 190 unstimulated IVF cycles birthweight was reduced by 163g; the proportion of LBW babies was 1.0% in NC-IVF and 8.6% in cIVF. This could be explained by a substantially higher proportion of very preterm deliveries (<32 gestational weeks) in the cIVF group (6.3 vs 0.5%) (Mak et al., 2016). A meta-analysis on NC-IVF showed an increased risk for PTB (RR 1.32, 95% CI 1.05, 1.66) but not for LBW (RR 2.98, 95% CI 0.54, 16.29) after stimulated IVF (Kamath et al., 2018). Decreased risks of PTB and LBW following the transfer of frozen embryos could not only be related to cryopreservation, but to the fact that no gonadotropins are used in the cycle before the transfer (Conforti et al., 2021). Research comparing fresh NC-IVF with natural thawing cycles could bring more light on the specific impact of cryopreservation on perinatal outcomes.

In our study, lower mean birthweight, reduced gestational age, or higher risks for PTB and LBW in cIVF compared to NC-IVF were not found. However, lower birthweight and higher risks for LBW and SGA in the cIVF births compared to the SLBR were identified, whereas the perinatal outcomes of NC-IVF were similar to the SLBR. The risk of LBW remained higher after adjustment (Model I), but the risk of SGA was attenuated. It can be concluded that cIVF seems to be associated with slightly higher risks; maternal age and parity can explain it only partially. However, the risk difference is much lower in our study than in other studies (Mak et al., 2016). The gonadotropin dosage and the individual ovarian response seem to be associated with birthweight and SGA (Pereira et al., 2017, 2015). Superovulation and supraphysiological E2 levels are both associated with adverse outcomes, as they risk to affect the

endometrium, implantation, placentation, and intrauterine growth disproportionately more (Sunkara et al., 2015). An impact on the expression of endometrial genes was shown by an analysis of endometrial biopsy tissue in cIVF and NC-IVF women, which is critical to tissue remodeling and placentation (Senapati et al., 2018). Another explanation might be the healthier lifestyle of the mothers in the Bern IVF Cohort.

Several studies reported higher rates of CS or assisted vaginal delivery in IVF children (Pandey et al., 2012). A higher risk of operative and assisted vaginal delivery in term births of IVF pregnancies was reported by an Italian study, despite the absence of risk factors, but fewer prolonged labors (Vannuccini et al., 2018). The highest CS rates in IVF term singletons was reported by an Australian birth register study (Sullivan et al., 2010). Conception by IVF seemed to influence the decisions of the gynecologists and parents regarding pregnancy follow-up, diagnostic interventions, and delivery mode was concluded by both studies. Pregnancies after IVF are often followed up more closely and are subject to more diagnostic interventions; this may possibly lead to primary CS (Srebnik et al., 2013). ¢Kλă LJKŜy₴YˆŜy₴yˇø l·ă ₦Ŝ₮Ŝ₦₦ŜŘ ű₴ l·ă ûKŜ ά£J₦ŜŎλ₴dză ō1·ōè Ŝ₮₮ŜŎűε (Minkoff and Berkowitz, 2005). In an American study, a higher incidence of pregnancy complications and higher maternal age were the main reasons for increased CS rates after IVF. Subfertile women also had a higher CS rate than fertile women did. Maternal age, subfertility, and associated underlying medical conditions were concluded to be responsible, rather than a different management or the άprecious baby effectε (Stern et al., 2018). In our study, the higher rate of CS in IVF deliveries was not seen after adjustment for maternal age, parity, and fetal sex. Probably different characteristics of IVF mothers were reflected by our data: this is not surprising, as the women in the ODS had a higher incidence of pregnancy complications and represent a high-risk population. However, the higher rate of primary CS in IVF women might be an indication for avoiding risk during delivery. The CS rates in ODS and Bern IVF Cohort deliveries are higher than the 32% CS rate in Switzerland (Federal Statistical Office). It should be noted that CS rates

are also highly influenced by cultural perceptions and regional differences such as urbanization. Therefore, it is difficult to conclude whether pregnancies and deliveries are subject to necessary medical interventions or whether obstetricians and parents are especially careful in cases where it was challenging to achieve the pregnancy. But as delivery mode in primiparous women influences delivery mode in subsequent pregnancies and a CS also affects the success of further ART treatment, it would be especially important to avoid unnecessary CS in primiparous, low-risk term IVF pregnancies (Vissers et al., 2020). Further studies on CS in pregnancies conceived by IVF or after a longer time to conception would contribute to the understanding of underlying factors.

Conclusion

Overall, children of the Bern IVF Cohort did not show impaired perinatal outcomes because of fertility treatment. However, the gonadotropin stimulation might have an additional effect on intrauterine growth and birthweight. The risk for low birthweight and small for gestational age was increased after stimulated IVF in the unadjusted analysis and the risk for low birthweight in the adjusted analysis in comparison to SLBR. An analysis that includes nationwide data on all IVF children would be important to verify these findings.

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Author biography

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Key message: Singletons born after IVF/ICSI did not show adverse perinatal outcomes when controlled for maternal age and parity but singletons born after stimulated IVF had higher risks of low birthweight and small for gestational age compared to the Swiss Live Birth Registry, whereas singletons born after unstimulated IVF had not.

Figure legend

Figure 1: Description of sample selection by population

cIVF: stimulated in-vitro fertilization

NC-IVF: unstimulated, natural cycle in-vitro fertilization

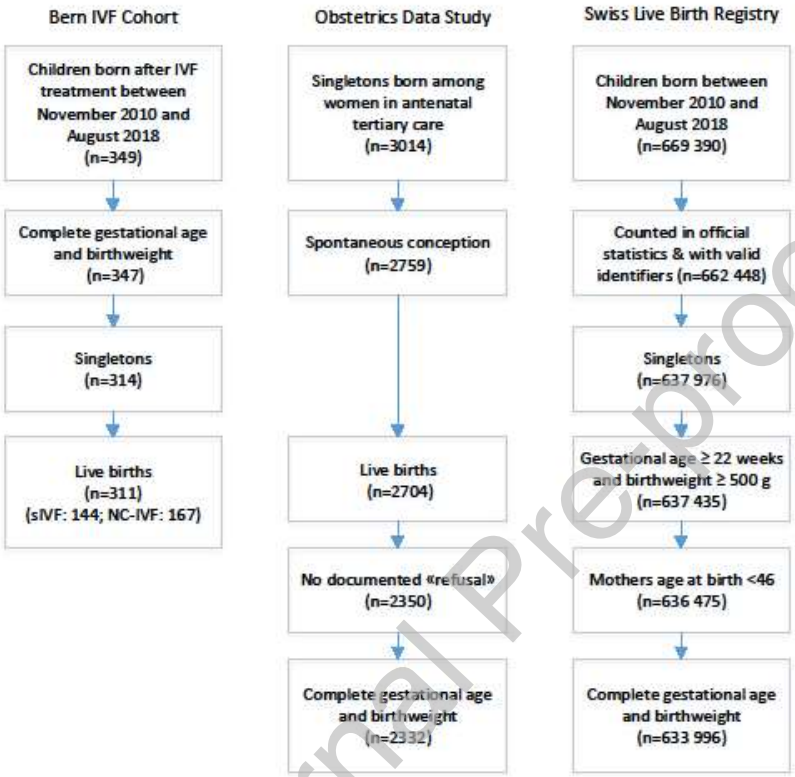

Table 1. Baseline characteristics by population

	Bern IVF Cohort (N = 311)	Obstetric Data Study (N = 2332)	Swiss Live Birth Registry (N = 633 996)
Maternal age at delivery (years)			
Mean age (SD)	35.0 (4.0)	31.3 (5.3)	31.4 (5.0)
Maternal parity			
Primiparous	237 (76.2%)	1134 (48.6%)	312 292 (49.3%)
Multiparous	74 (23.8%)	1198 (51.4%)	321 704 (50.7%)
Maternal body mass index (BMI)*			
<18.5 kg/m^2	21 (6.8%)	102 (4.4%)	na
18.5-24.9 kg/m^2	224 (72.0%)	1419 (60.8%)	na
25-29.9 kg/m^2	51 (16.4%)	517 (22.2%)	na
ж0л]ƎкY^2	12 (3.9%)	294 (12.6%)	na
Missing	3 (1.0%)	0 (0.0%)	na
Smoking during pregnancy			
No	272 (87.5%)	2128 (91.3%)	na
Yes	11 (3.5%)	204 (8.7%)	na
Missing	28 (9.0%)	0 (0.0%)	na
Sex of child			
Male	165 (53.1%)	1186 (50.9%)	326 020 (51.4%)
Female	146 (46.9%)	1145 (49.1%)	307 976 (48.6%)
Missing	0 (0.0%)	1 (0.0%)	0 (0.0%)

Abbreviations: N: number; SD: standard deviation, na: not available, kg: kilogram, m^2: square meter

*BMI: body mass index, measured before or during first trimester of pregnancy

Table 2: Birthweight, height at birth, gestational age, and birthweight percentile by population

	N cases (%)	Crude[a] (95% CI)	*P*-value	Adjusted[b] (95% CI) Model I	*P*-value	Adjusted[c] (95% CI) Model II	*P*-value
Birthweight (g)							
IVF	311 (100)	3270 (3208, 3333)	0.06	3448 (3387, 3510)	0.68	3438 (3348, 3528)	0.32
ODS	2332 (100)	3280 (3258, 3301)	<0.01	3410 (3389, 3432)	<0.01	3402 (3336, 3469)	Ref
SLBR	633 996 (100)	3330 (3329, 3332)	Ref	3461 (3457, 3465)	Ref	na	
Birthweight at term (at least 37 gestational weeks)							
IVF	291 (93.6)	3336 (3280, 3391)	0.10	3534 (3480, 3588)	0.87	3509 (3432, 3586)	0.36
ODS	2186 (93.7)	3344 (3325, 3365)	<0.01	3500 (3481,3519)	<0.01	3480 (3422, 3537)	Ref
SLBR	600 701 (94.8)	3382 (3381, 3384)	Ref	3538 (3535, 3542)	Ref	na	
Height at birth (cm)							
IVF	302 (97.1)	49.41 (49.09, 49.73)	0.45	50.41 (50.09, 50.72)	0.76	na	na
SLBR	633 945 (100)	49.54 (49.53, 49.55)	Ref	50.45 (50.43, 50.48)	Ref	na	na
Gestational age (days)							
IVF	311 (100)	275.33 (273.94, 276.72)	0.29	274.53 (273.14, 275.93)	0.22	275.67 (273.56, 277.78)	0.71
ODS	2332 (100)	274.96 (274.45, 275.46)	<0.01	274.28 (273.77, 274.79)	<0.01	275.97 (274.39, 277.55)	Ref
SLBR	633 996 (100)	276.08 (276.05, 276.11)	Ref	275.41 (275.31, 275.51)	Ref	na	
Birthweight percentile[d]							
IVF	311 (100)	45.51 (42.15, 48.86)	0.30	na	na	na	na
ODS	2332 (100)	45.43 (44.23, 46.62)	<0.01	na	na	na	na
SLBR	633 996 (100)	47.27 (47.19, 47.35)	Ref	na	Ref	na	na

[a] Crude measures reflect the average outcome of a child born to a mother age 30 at delivery

[b] Adjusted for: maternal age at delivery (years); maternal parity (primiparous vs multiparous), and sex of child. Average reflects a primiparous mother of age 30 years with a male child.

[c] Adjusted for: maternal age at delivery (years), body mass index (kg/m^2) and parity (primiparous vs multiparous), sex of child, smoking during pregnancy (yes vs no). Average reflects a non-smoking, primiparous mother of age 30 years with BMI 20, having a male child.

[d] Birthweight percentiles according to Nicolaides *et al.*, 2018; standardization of birthweight adjusted for gestational age

Abbreviations: IVF: Bern IVF Cohort; ODS: Obstetric Data Study; SLBR: Swiss Live Birth Registry; CI: Confidence Interval; g: grams; cm: centimeter; na: not available; kg: kilogram; m: meter; Ref: Referfence

Table 3: Relative risk for preterm birth, low birthweight and small-for-gestational-age by population

	N cases (%)	RR (95% CI)	*P*-value	Adjusted[a] RR (95% CI) Model I	*P*-value	Adjusted[b] RR (95% CI) Model II	*P*-value
Low birthweight (<2500 grams)							
IVF	20 (6.4%)	1.43 (0.92, 2.24)	0.11	1.14 (0.73, 1.79)	0.56	0.90 (0.53, 1.53)	0.71
ODS	135 (5.8%)	1.29 (1.09, 1.52)	<0.01	1.29 (1.10, 1.53)	<0.01	1.00 (Reference)	Ref
SLBR	нуΩппс όпΦр̂ ̂ ύ	1.00 (Reference)	Ref	1.00 (Reference)	Ref	na	na
Low birthweight in term born children (at least 37 gestational weeks)							
IVF	9 (3.1%)	1.64 (0.81, 3.34)	0.17	1.29 (0.64, 2.63)	0.22	1.16 (0.51, 2.68)	0.78
ODS	49 (2.2%)	1.19 (0.90, 1.57)	0.22	1.19 (0.90, 1.57)	0.48	1.00 (Reference)	Ref
SLBR	ммΩонт όмΦф̂ ̂ ύ	1.00 (Reference)	Ref	1.00 (Reference)	Ref	na	na
Preterm birth (<37 gestational weeks)							
IVF	20 (6.4%)	1.22 (0.80, 1.87)	0.35	1.02 (0.67, 1.55)	0.94	0.95 (0.57, 1.60)	0.85
ODS	146 (6.3%)	1.19 (1.02, 1.40)	0.03	1.20 (1.02, 1.40)	0.03	1.00 (Reference)	Ref
SLBR	ооΩнфр όрΦо̂ ̂ ύ	1.00 (Reference)	Ref	1.00 (Reference)	Ref	na	na
Small-for-gestational-age (<10th birthweight percentile)							
IVF	49 (15.8%)	1.31 (1.01, 1.70)	0.04	1.12 (0.87, 1.45)	0.39	1.01 (0.75, 1.36)	0.95
ODS	313 (13.4%)	1.11 (1.00, 1.24)	0.04	1.12 (1.01, 1.45)	0.04	1.00 (Reference)	Ref
SLBR	тсΩпоп (12.1%)	1.00 (Reference)	Ref	1.00 (Reference)	Ref	na	na

[a] Adjusted for: maternal age at delivery (years); maternal parity (primiparous vs multiparous) and sex of child.

[b] Adjusted for: maternal age at delivery (years), body mass index (kg/m^2) and parity (primiparous vs multiparous); sex of child, smoking during pregnancy (yes vs no).

Abbreviations: IVF: Bern IVF Cohort; ODS: Obstetric Data Study; SLBR: Live Birth Registry; N: number of cases; RR: Relative Risk, CI: Confidence Interval; na: not available; Ref: Reference

Table 4: Relative risk for preterm birth, low birthweight and small for gestational age in stimulated (cIVF) and unstimulated IVF (NC-IVF)

	N cases (%)	Unadjusted RR (95% CI)	*P*-value	Adjusted[a] RR (95% CI) Model I	*P*-value	Adjusted[b] RR (95% CI) Model II	*P*-value
Low birthweight (<2500 grams)							
cIVF	14 (9.7%)	2.17 (1.27, 3.69)	<0.01	1.72 (1.01, 2.93)	0.05	2.61 (1.02, 6.72)	<0.05
NC-IVF	6 (3.6%)	0.80 (0.36, 1.76)	0.58	0.64 (0.29, 1.41)	0.27	1.00 (Reference)	Ref
SLBR	ну⌂ппс (4.5%)	1.00 (Reference)	Ref	1.00 (Reference)	Ref	na	na
Low birthweight in term-borns (at least 37 gestational weeks)							
cIVF	6 (4.5%)	2.39 (0.97, 5.88)	0.06	1.92 (0.78, 4.72)	0.15	2.61 (1.02, 6.72)	0.21
NC-IVF	3 (1.9%)	1.01 (0.33, 3.09)	0.99	0.78 (0.25, 2.41)	0.67	1.00 (Reference)	Ref
SLBR	мм⌂онт (1.9%)	1.00 (Reference)	Ref	1.00 (Reference)	Ref	na	na
Preterm birth (<37 gestational weeks)							
cIVF	11 (7.6%)	1.45 (0.82, 2.57)	0.20	1.18 (0.67, 2.08)	0.57	1.21 (0.51, 2.87)	0.66
NC-IVF	9 (5.4%)	1.03 (0.54, 1.94)	0.94	0.87 (0.46, 1.64)	0.67	1.00 (Reference)	Ref
SLBR	оо⌂нфр (5.3%)	1.00 (Reference)	Ref	1.00 (Reference)	Ref	na	na
Small-for-gestational-age (<10th birthweight percentile)							
cIVF	26 (18.1%)	1.50 (1.05, 2.14)	0.03	1.31 (0.92, 1.87)	0.13	1.28 (0.75, 2.17)	0.36
NC-IVF	23 (13.8%)	1.14 (0.78, 1.67)	0.50	0.96 (0.66, 1.40)	0.84	1.00 (Reference)	Ref
SLBR	тс⌂поп (12.1%)	1.00 (Reference)	Ref	1.00 (Reference)	Ref	na	na

[a] Adjusted for: maternal age at delivery (years); maternal parity (primiparous vs multiparous) and sex of child.

[b] Adjusted for: maternal age at delivery (years) and parity (primiparous vs multiparous); sex of child, smoking during pregnancy (yes vs no).

Abbreviations: IVF: In-vitro Fertilization, cIVF: stimulated IVF; NC-IVF: natural (non-stimulated) IVF; SLBR: Swiss Live Birth Registry; N: number of cases; RR: Relative Risk, CI: Confidence Interval; na: not available; Ref: Reference

Table 5: Pregnancy complications and delivery mode

	Bern IVF Cohort (N = 311)	Obstetric Data Study (N = 2332)
Maternal hypertension during pregnancy		
No	310 (99.7%)	2284 (97.9%)
Yes	1 (0.3%)	48 (2.1%)
Maternal gestational diabetes		
No	295 (94.9%)	1901 (81.5%)
Yes	16 (5.1%)	429 (18.4%)
Missing	0 (0.0%)	2 (0.1%)
Maternal pre-eclampsia		
No	306 (98.4%)	2282 (97.9%)
Yes	5 (1.6%)	50 (2.1%)
Mode of delivery		
Vaginal spontaneous	138 (44.4%)	1258 (53.9%)
Vaginal instrumental	42 (13.5%)	235 (10.1%)
Cesarean section	131 (42.1%)	838 (36.0%)
Missing	0 (0.0%)	1 (0.0%)
For women with cesarean section only	*N=131*	*N=838*
Type of cesarean section		
Primary	68 (51.9%)	402 (48.0%)
Secondary	61 (46.6%)	433 (51.7%)
Missing	2 (1.5%)	3 (0.4%)
Reason for cesarean section		
Maternal reason	61 (46.6%)	511 (61.0%)
Fetal reason	62 (47.3%)	299 (35.7%)
Emergency	4 (3.1%)	24 (2.9%)
Missing	4 (3.1%)	4 (0.5%)

Abbreviations: N: number; SD: standard deviation,