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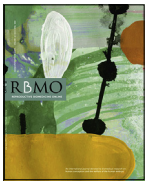

ARTICLE

Perinatal outcomes in singletons after fresh IVF/ICSI: results of two cohorts and the birth registry

BIOGRAPHY

Vera Mitter is a pharmacist and epidemiologist. She successfully finished her PhD in 2020 on outcomes of reproductive medicine at the Bern University Hospital in Switzerland. Now she works as a Postdoc at the Centre for Fertility and Health at the Norwegian Institute of Public Health in Oslo, Norway.

Vera Ruth Mitter[1,2,*], Pascale Fasel[1,3], Claudia Berlin[4], Sofia Amylidi-Mohr[5], Beatrice Mosimann[5], Marcel Zwahlen[4], Michael von Wolff[1], Alexandra Sabrina Kohl Schwartz[1,6]

KEY MESSAGE

Singletons born after IVF/ICSI did not show adverse perinatal outcomes when controlled for maternal age, parity and childs sex 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 did not.

ABSTRACT

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

Methods: This cohort study compared 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 childs sex.

Results: Of the 636,639 live births, 311 were in the Bern IVF Cohort (144 stimulated, 167 unstimulated), 2332 in the tertiary centre and 633,996 in the Swiss Live Birth Registry (SLBR). Perinatal outcomes following IVF did not differ compared with births in the SLBR (adjusted relative risk [aRR]; 95% confidence interval [CI]), with the exception of the increased risk of small for gestational age (1.31; 1.01 to 1.70, $P = 0.04$; aRR 1.12; 0.87 to 1.45, $P = 0.39$). Children born following stimulated IVF had a higher risk of low birthweight (2.17; 1.27 to 3.69, $P < 0.01$; aRR 1.72; 1.01 to 2.93, $P = 0.05$), and of being small for gestational age (1.50; 1.05 to 2.14, $P = 0.03$; aRR 1.31; 0.92 to 1.87; $P = 0.13$), whereas children born after unstimulated IVF had no increased risks compared with 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 favourable perinatal outcomes. Gonadotrophin stimulation seems to have an effect, because lower risks were associated with unstimulated IVF.

[1] Division of Gynaecological Endocrinology and Reproductive Medicine, Inselspital, Bern University Hospital, University of Bern, Bern 3010, Switzerland
[2] Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo 0213, Norway
[3] Department of Medical Genetics, Inselspital, Bern University Hospital, University of Bern, Bern 3010, Switzerland
[4] Institute of Social and Preventive Medicine, University of Bern, Bern 3010, Switzerland
[5] Department of Obstetrics and Gynaecology, Inselspital, Bern University Hospital, University of Bern, Bern 3010, Switzerland
[6] Cantonal Hospital Lucerne, Women's Hospital, Division of Reproductive Medicine and Gynaecological Endocrinology, Lucerne 6000, Switzerland

KEYWORDS

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*Corresponding author. E-mail address: vera.mitter@insel.ch (V. R. Mitter). https://doi.org/10.1016/j.rbmo.2021.12.007
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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 IVF technologies (Federal Statistical Office, https://www.bfs.admin.ch/bfs/en/home/statistics/health/state-health/reproductive-health/assisted-reproductive-technology.html). Higher risk of unfavourable perinatal outcomes in singletons born after IVF, such as reduced gestational age and birthweight as well as preterm birth (PTB), low birthweight (LBW) and small for gestational age (SGA), have been confirmed by several meta-analyses (*Pandey et al., 2012*). For PTB, the relative risk (RR) after IVF compared with naturally conceived singletons was between 1.54 and 1.84 (*Pandey et al., 2012*), and the odds ratio (OR) was 1.55 (*Pinborg et al., 2013*). Over time, risks have been reduced by the development of IVF methods and the rising awareness of safer treatments such as antagonist protocols or lower gonadotrophin dosages (*Henningsen and Pinborg, 2014*; *Henningsen et al., 2015*) 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*). Gonadotrophin stimulation appears to increase the risk of LBW (*Mak et al., 2016*) or of being born SGA, especially when supraphysiological oestradiol concentrations are reached at trigger day (*Kohl Schwartz et al., 2019*) or when many oocytes are collected (*Sunkara et al., 2015*). Gonadotrophin stimulation also bears higher risks for the mother for ovarian hyperstimulation syndrome, pregnancy-induced hypertension and gestational diabetes mellitus, and appears to be 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 gonadotrophins do not directly affect the pregnancy (*Asserhøj et al., 2021*). 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 also plays a role. Caesarean section is more frequent in deliveries after IVF, with an 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), performed in one centre with standardized laboratory and embryo culture conditions. Unstimulated, natural cycle IVF (NC-IVF) is based on the concept of natural follicular recruitment and the selection of one oocyte whereas in gonadotrophin-stimulated IVF (sIVF), polyfollicular oocyte growth is common (*von Wolff, 2019*). NC-IVF can serve as a model for natural ovulatory development and the comparison to sIVF allows assessment of the effect of gonadotrophin 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 centre (Bern University Hospital: the Obstetrics Data Study [ODS]), and (ii) all children born in Switzerland during the same period (Swiss Live Birth Registry [SLBR]); and second, to address the effect of gonadotrophin stimulation by comparing sIVF and NC-IVF to the children born in Switzerland registered in the SLBR.

MATERIALS AND METHODS

The Bern IVF Cohort

The Bern IVF Cohort includes couples treated in the Division of Gynaecological Endocrinology and Reproductive Medicine at the University Hospital of Bern with a pregnancy following fresh embryo transfer within IVF treatment. Data were 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., 2009*, *2019*). 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 1).

The Obstetrics Data Study (ODS)

In the ODS of the Department of Obstetrics and Gynaecology at the University Hospital of Bern a cohort of women were recruited during their first trimester routine ultrasound visit and followed until delivery. This study collected data on mode of conception, pregnancy and delivery, and women with a singleton born alive were included in the analysis. All women, independent of pre-existing chronic conditions or disorders, were included (n = 3014). 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 1).

The Swiss Live Birth Registry (SLBR)

The SLBR of the Federal Statistical Office collects routine data for all infants born alive in Switzerland. 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 (n = 669,390). Births with missing valid identifiers (n = 6942), multiple births (n = 24,472), a gestational age below 22 weeks or birthweight below 500 g (n = 541), mother's 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 differentiating between miscarriage and stillbirth.

IVF treatment in the Bern IVF Cohort

Women with regular menstrual cycles (26–32 days) could choose the treatment according to their preference, as NC-IVF requires a regular cycle. In

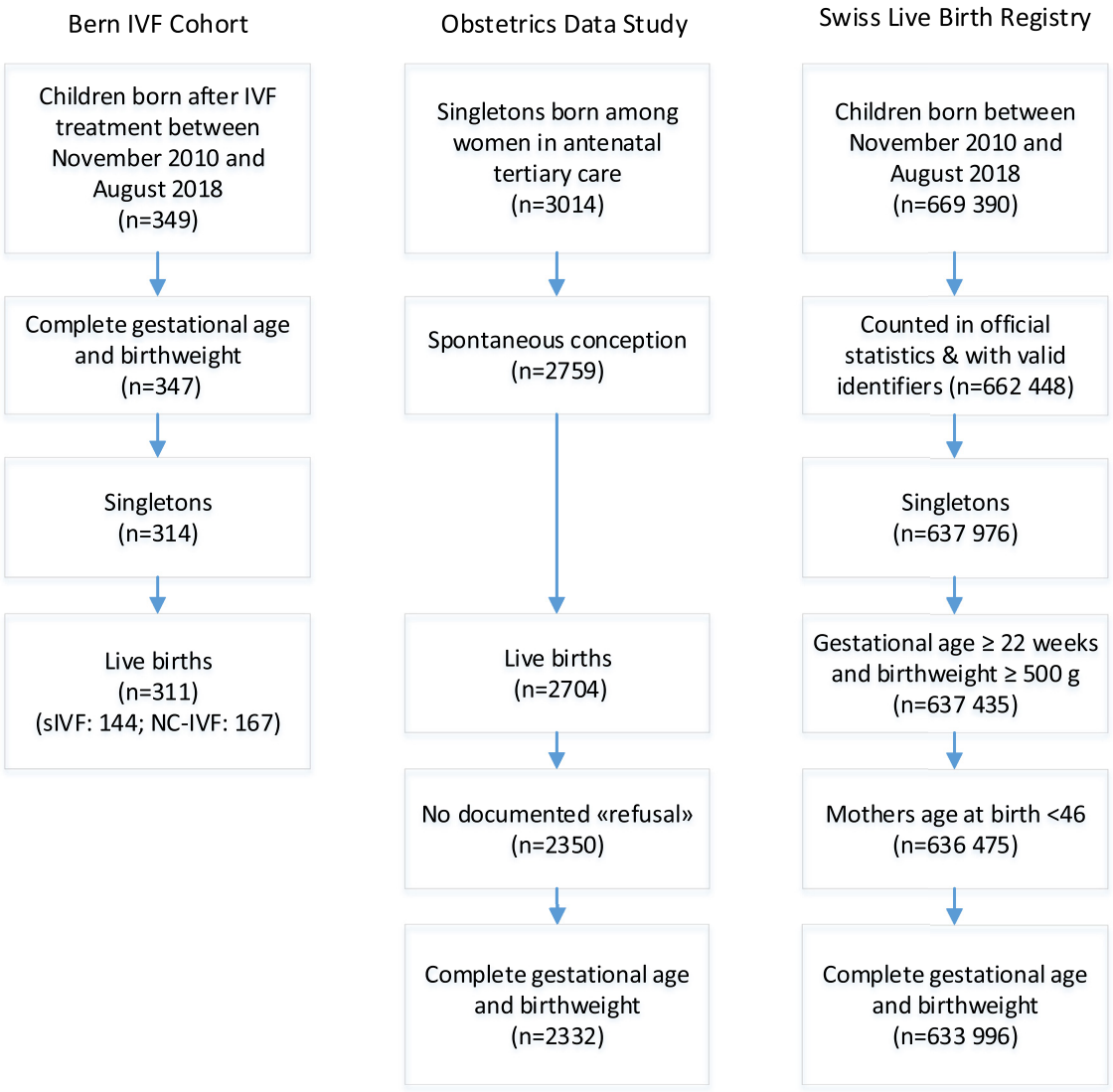

FIGURE 1 Description of sample selection by population. sIVF = stimulated IVF; NC-IVF = unstimulated, natural cycle IVF.

women undergoing NC-IVF, the cycles were monitored by ultrasound and measurement of oestradiol and Luteinizing hormone (LH). When follicle diameter reached at least 16 mm and oestradiol was ≥700 pmol/l, the women received a trigger shot of 5000 IU human chorionic gonadotrophin (HCG) to induce ovulation. Oocyte retrieval took place 36 h later without anaesthesia (*Kohl Schwartz et al., 2020a*). To reduce the risk of premature ovulation, either 25 mg clomiphene citrate from cycle day 7 onwards (*von Wolff et al., 2014*) or 400 mg ibuprofen three times daily beginning 48 h before oocyte retrieval was taken by the woman (*Kohl Schwartz et al., 2020b*).

For sIVF, 75–350 IU gonadotrophin per day were administered and either an antagonist or an agonist (short or long down-regulation) protocol was performed. In sIVF treatment, the stimulation was monitored by ultrasound and serum oestradiol concentration measurements. When more than two of the leading follicles reached a diameter of at least 18 mm with corresponding oestradiol concentration, ovulation was triggered by injecting HCG by the women themselves. Oocytes were retrieved 36 h 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 2 or 3 with ultrasound guidance. The women received luteal phase support with up to 200 mg micronized progesterone administered twice daily if necessary (*von Wolff et al., 2017*). Switzerland did not allow longer embryo culture before 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 were available in the Bern IVF Cohort and the SLBR. Delivery mode was compared between the Bern IVF Cohort and the ODS. Caesarean section is defined as secondary if labour had already started (presence of contractions, bleeding or rupture of membranes). The reasons for Caesarean section were categorized into maternal, fetal or emergency (see Supplementary Table 1).

Covariates

Information on maternal age at delivery (continuous), parity (primiparous versus 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 Caesarean section were described. To compare the three datasets, adjustments were made for maternal age, parity and childs 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 (<2500 g), PTB (<37 gestational weeks), SGA (<10th percentile) and Caesarean section, modified Poisson regression was used, reporting RR and 95% CI (*Zou, 2004*). To account for singletons born to the same mother, maternal identifiers were used as cluster-robust variance estimates. To assess the impact of gonadotrophin stimulation, singletons born after sIVF were compared with those born after NC-IVF, but both subgroups were also compared with 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 1). 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 singletons born at term (≥37 gestational weeks) separately, which was done for the sensitivity analysis (*Wilcox, 2001*). A *P*-value <0.05 was considered to be statistically significant. STATA 16.0 (StataCorp LP, College Station, TX, USA) was used.

Ethical 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

The analysis included 636,639 deliveries. FIGURE 1 presents the exclusions and the final study populations: the Bern IVF Cohort (*n* = 311), the tertiary centre ODS (*n* = 2332) and the SLBR (*n* = 633,996). Mothers in the Bern IVF Cohort were on average 3.6 years (95% CI 3.2 to 4.1 years) older and more often primiparous than non-IVF mothers; and compared with 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 Cohort and the SLBR singletons but lower in the ODS singletons ($P < 0.001$) (TABLE 2). Singletons in the Bern IVF Cohort and the SLBR had comparable risks for PTB, which were higher for ODS singletons ($P = 0.03$) (TABLE 3). The unadjusted mean birthweight was lower in the Bern IVF Cohort 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

TABLE 1 BASELINE CHARACTERISTICS BY POPULATION

Characteristic	Bern IVF Cohort (*n* = 311)	Obstetric Data Study (*n* = 2332)	Swiss Live Birth Registry (*n* = 633,996)
Maternal age at delivery (years, mean ± 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 BMI (kg/m^2)			
<18.5	21 (6.8)	102 (4.4)	N/A
18.5–24.9	224 (72.0)	1419 (60.8)	N/A
25–29.9	51 (16.4)	517 (22.2)	N/A
≥30	12 (3.9)	294 (12.6)	N/A
Missing	3 (1.0)	0 (0.0)	N/A
Smoking during pregnancy			
No	272 (87.5)	2128 (91.3)	N/A
Yes	11 (3.5)	204 (8.7)	N/A
Missing	28 (9.0)	0 (0.0)	N/A
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 (0.04)	0 (0.0)

Data are presented as *n* (%) unless otherwise stated.

BMI = body mass index, measured before or during first trimester of pregnancy; N/A = not available.

TABLE 2 BIRTHWEIGHT, HEIGHT AT BIRTH, GESTATIONAL AGE AND BIRTHWEIGHT PERCENTILE BY POPULATION

	Cases (*n*, %)	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)	<0.001	3410 (3389, 3432)	<0.001	3402 (3336, 3469)	Ref
SLBR	633,996 (100)	3330 (3329, 3332)	Ref	3461 (3457, 3465)	Ref	N/A	
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)	<0.001	3500 (3481,3519)	<0.001	3480 (3422, 3537)	Ref
SLBR	600,701 (94.8)	3382 (3381, 3384)	Ref	3538 (3535, 3542)	Ref	N/A	
Height at birth (cm)[d]							
IVF	302 (97.1)	49.41 (49.09, 49.73)	0.45	50.41 (50.09, 50.72)	0.76	N/A	na
SLBR	633,945 (99.99)	49.54 (49.53, 49.55)	Ref	50.45 (50.43, 50.48)	Ref	N/A	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)	<0.001	274.28 (273.77, 274.79)	<0.001	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	N/A	
Birthweight percentile[e]							
IVF	311 (100)	45.51 (42.15, 48.86)	0.30	N/A	N/A	N/A	N/A
ODS	2332 (100)	45.43 (44.23, 46.62)	0.003	N/A	N/A	N/A	N/A
SLBR	633,996 (100)	47.27 (47.19, 47.35)	Ref	N/A	Ref	N/A	N/A

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

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

[d] No data available about height at birth, was not collected in ODS.

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

BMI = body mass index; CI = confidence interval; IVF = Bern IVF Cohort; N/A = not available; ODS = Obstetric Data Study; SLBR = Swiss Live Birth Registry.

associated with birthweight and explained most of the difference between the Bern IVF Cohort and the SLBR: maternal age per year increase (–3.0 g, 95% CI –3.4 to –2.8; $P < 0.001$); multiparity (139.1 g, 95% CI 136.7 to 141.5; $P < 0.001$) and male sex (132.7 g, 95% CI 130.3 to 135.2; $P < 0.001$).

Birthweight percentile

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

Mode of delivery

Despite a higher prevalence of risk factors in the ODS women, mothers in the Bern IVF Cohort delivered significantly more often by Caesarean section (42.1% versus 36.0%; $P = 0.03$; RR 1.17, 95% CI 1.01 to 1.36; $P = 0.04$) (TABLE 5). This association disappeared after adjustment (Model I and Model II): maternal age (aRR 1.03, 95% CI 1.02 to 1.04; $P < 0.001$) and sex of the child (aRR for girls 0.86, 95% CI 0.78 to 0.96; $P = 0.005$) were associated, but parity (multiparous: aRR 0.96, 95% CI 0.87 to 1.06; $P = 0.43$) and smoking (aRR 1.00, 95% CI 1.00 to 1.01; $P = 0.59$) were not. Primary Caesarean section was more frequent in the Bern IVF Cohort (TABLE 5). Delivery by Caesarean section was significantly associated with PTB ($P = 0.004$) and with LBW ($P < 0.001$) and, when restricted to term births, with LBW ($P < 0.001$) in conditional analysis (Model I).

Comparison between stimulated sIVF and unstimulated NC-IVF

Gestational age and birthweight or risk for LBW and SGA did not differ between singletons born after sIVF and NC-IVF (TABLE 4). Gestational age of either sIVF or NC-IVF did not differ compared with births registered in the SLBR. Birthweight of children born after sIVF was on average 114 g lower (95% CI –212 to –17 g; $P = 0.02$) compared with the SLBR, but in children born after NC-IVF it was similar (–13 g, 95% CI –92 to 65 g; $P = 0.74$). This difference was attenuated in children born at term (sIVF –82 g, 95% CI –167 to 4 g; $P = 0.06$; NC-IVF: –17 g, 95% CI –88 to 53 g; $P = 0.63$) or after adjustment in Model I (Supplementary Table 2). sIVF 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

TABLE 3 RELATIVE RISK FOR PRETERM BIRTH, LOW BIRTHWEIGHT AND SMALL FOR GESTATIONAL AGE BY POPULATION

	Cases (*n*, %)	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 g)							
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)	0.002	1.29 (1.10, 1.53)	0.002	1.00 (reference)	Ref
SLBR	28,446 (4.5)	1.00 (reference)	Ref	1.00 (reference)	Ref	N/A	N/A
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	11,327 (1.9)	1.00 (reference)	Ref	1.00 (reference)	Ref	N/A	N/A
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	33,295 (5.3)	1.00 (reference)	Ref	1.00 (reference)	Ref	N/A	N/A
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	76,434 (12.1)	1.00 (reference)	Ref	1.00 (reference)	Ref	N/A	N/A

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

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

BMI = body mass index; CI = confidence interval; IVF = Bern IVF Cohort; N/A = not available; ODS = Obstetric Data Study; SLBR = Swiss Live Birth Registry.

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. Gonadotrophin stimulation influenced birthweight and intrauterine growth: singletons born after sIVF had a lower mean birthweight and increased risks of LBW and of being SGA compared with the SLBR, whereas

TABLE 4 RELATIVE RISK FOR PRETERM BIRTH, LOW BIRTHWEIGHT AND SMALL FOR GESTATIONAL AGE IN STIMULATED (sIVF) AND UNSTIMULATED IVF (NC-IVF)

	Cases (*n*, %)	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 g)							
sIVF	14 (9.7)	2.17 (1.27, 3.69)	0.004	1.72 (1.01, 2.93)	0.05	2.61 (1.02, 6.72)	0.046
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	28,446 (4.5)	1.00 (reference)	Ref	1.00 (reference)	Ref	N/A	N/A
Low birthweight in term-borns (at least 37 gestational weeks)							
sIVF	6 (4.5)	2.39 (0.97, 5.88)	0.06	1.92 (0.78, 4.72)	0.15	2.64 (0.59, 11.87)	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	11,327 (1.9)	1.00 (reference)	Ref	1.00 (reference)	Ref	N/A	N/A
Preterm birth (<37 gestational weeks)							
sIVF	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	33,295 (5.3)	1.00 (reference)	Ref	1.00 (reference)	Ref	N/A	N/A
Small for gestational age (<10th birthweight percentile)							
sIVF	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	76,434 (12.1)	1.00 (reference)	Ref	1.00 (reference)	Ref	N/A	N/A

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

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

CI = confidence interval; N/A = not available; NC-IVF = natural (non-stimulated) IVF; RR = relative risk; sIVF = stimulated IVF; SLBR = Swiss Live Birth Registry.

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)
Caesarean section	131 (42.1)	838 (36.0)
Missing	0 (0.0)	1 (0.04)
For women with Caesarean section only	*n* = 131	*n* = 838
Type of Caesarean section		
Primary	68 (51.9)	402 (48.0)
Secondary	61 (46.6)	433 (51.7)
Missing	2 (1.5)	3 (0.4)
Reason for Caesarean 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)

singletons born after NC-IVF were similar to SLBR singletons.

The strengths of this study are the detailed and complete information collected on conception, infertility treatment, course of pregnancy and perinatal outcomes in the Bern IVF Cohort. The study included the use of the population-based SLBR as comparison group and it contributes to the limited literature on perinatal outcomes of children born after NC-IVF.

The sample size of the Bern IVF Cohort is limited, which is why the focus is on the reporting of 95% CI for all comparisons. Characteristics of women choosing NC-IVF and of those choosing sIVF might be different. In Switzerland, IVF treatment is not subsidized; this impedes randomized controlled trials (*von Wolff et al., 2019*). The ODS data were collected in a tertiary centre with a neonatology unit, to which 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, and so 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 anonymised 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 with the SLBR is too small to affect mean outcome measures.

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 with ODS mothers; this might positively affect perinatal outcomes (*Avşar et al., 2021*; *Günther et al., 2021*; *Khashan and Kenny, 2009*).

With regard to perinatal outcomes, the results of the current study are reassuring; findings of a previous meta-analysis (*Pandey et al., 2012*) could not be confirmed. In this 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 labour or Caesarean section. Also in this study, delivery by Caesarean section was associated with LBW and PTB. Maternal age and parity are other independent risk factors associated with perinatal outcomes. The current 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 this study. Endometrial receptivity (*Bonagura et al., 2008*; *Devroey et al., 2004*) or vanishing twins are other possible explanations that could not be controlled for (*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 Caesarean section 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 used were 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 difference

from the US population standards (*Dickey et al., 2016*). The similar mean birthweight percentiles are reassuring for this IVF population.

Three cohort studies assessed the effect of gonadotrophin stimulation in comparison to NC-IVF. In a Japanese IVF registry study, data from 8224 singletons after fresh sIVF were compared with 610 after NC-IVF. The adjusted odds ratios (aOR) for LBW were 1.60–1.72 for agonist and antagonist protocols (*Nakashima et al., 2013*). In an 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, 95% CI 0.96 to 2.58) and PTB (aOR 1.43, 95% CI 0.91 to 2.26) (*Sunkara et al., 2016*). In a small US study with 174 stimulated and 190 unstimulated IVF cycles, birthweight was reduced by 163 g; the proportion of LBW babies was 1.0% in NC-IVF and 8.6% in sIVF. This could be explained by a substantially higher proportion of very preterm deliveries (<32 gestational weeks) in the sIVF group (6.3 versus 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 to 1.66) but not for LBW (RR 2.98, 95% CI 0.54 to 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 gonadotrophins are used in the cycle before the transfer (*Conforti et al., 2021*). Research comparing fresh NC-IVF with natural thawing cycles could shed more light on the specific impact of cryopreservation on perinatal outcomes.

In the current study, lower mean birthweight, reduced gestational age or higher risks for PTB and LBW in sIVF compared with NC-IVF were not found. However, lower birthweight and higher risks for LBW and SGA in the sIVF births compared with the SLBR were identified, whereas the perinatal outcomes of NC-IVF were similar to the SLBR. The risk of LBW remained higher after adjustment (**TABLE 4**, Model I), but the risk of SGA was attenuated. It can be concluded that sIVF seems to be associated with slightly higher risks; maternal age and parity can only partially explain it. However, the risk difference is much lower in this study than in other studies (*Mak et al., 2016*). The gonadotrophin dosage and the individual ovarian response seem to be associated with birthweight and SGA (*Pereira et al., 2015*, *2017*). Superovulation and supraphysiological oestradiol concentrations are both associated with adverse outcomes, as they risk affecting 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 sIVF and NC-IVF women, which is critical to tissue remodelling and placentation (*Senapati et al., 2018*). Another explanation might be the healthier lifestyle of the mothers in the Bern IVF Cohort.

Several studies have reported higher rates of Caesarean section 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 labours (*Vannuccini et al., 2018*). The highest Caesarean rates in IVF term singletons were reported by an Australian birth register study (*Sullivan et al., 2010*). Conception by IVF seemed to influence the decisions of the gynaecologists and parents regarding pregnancy follow-up, diagnostic interventions and delivery mode, as 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 Caesarean section (*Srebnik et al., 2013*). This phenomenon was referred to as the 'precious baby effect' (*Minkoff and Berkowitz, 2005*). In an American study, a higher incidence of pregnancy complications and higher maternal age were the main reasons for increased Caesarean section rates after IVF. Subfertile women also had a higher Caesarean section 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 'precious baby effect' (*Stern et al., 2018*). In the current study, the higher rate of Caesarean section in IVF deliveries was not seen after adjustment for maternal age, parity and child sex. It is probable that different characteristics of IVF mothers were reflected by these 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 Caesarean section in IVF women might be an indication for avoiding risk during delivery. The Caesarean section rates in the ODS and Bern IVF Cohort deliveries are higher than the 32% Caesarean section rate in Switzerland (Federal Statistical Office, https://www.bfs.admin.ch/bfs/de/home/statistiken/kataloge-datenbanken/karten.assetdetail.4262550.html). It should be noted that Caesarean section 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 Caesarean section also affects the success of further ART treatment, it would be especially important to avoid unnecessary Caesarean sections in primiparous, low-risk term IVF pregnancies (*Vissers et al., 2020*). Further studies on Caesarean section in pregnancies conceived by IVF or after a longer time to conception would contribute to the understanding of underlying factors.

Overall, children of the Bern IVF Cohort did not show impaired perinatal outcomes because of fertility treatment. However, the gonadotrophin stimulation might have an additional effect on intrauterine growth and birthweight. The risk for low birthweight and SGA 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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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2021.12.007.

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