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## Article

# A Comparison of Preterm Birth Rate and Growth from Birth to 18 Years Old between in Vitro Fertilization and Spontaneous Conception of Twins

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**Abstract**

The aim of the present study was to compare the rate of preterm birth (PTB) and growth from birth to 18 years between twins conceived by in vitro fertilization (IVF) and twins conceived by spontaneous conception (SC) in mainland China. The retrospective cohort study included 1164 twins resulting from IVF and 25,654 twins conceived spontaneously, of which 494 from IVF and 6338 from SC were opposite-sex twins. PTB and low birth weight (LBW), and growth, including length/height and weight, were compared between the two groups at five stages: infancy (0 year), toddler period (1−2 years), preschool (3−5 years), primary or elementary school (6−11 years), and adolescence (10−18 years). Few statistically significant differences were found for LBW and growth between the two groups after adjusting for PTB and other confounders. Twins born by IVF faced an increased risk of PTB compared with those born by SC (adjusted odds ratio [a*OR*] 8.21, 95% confidence interval [CI] [3.19, 21.13], $p < .001$ in all twins and a*OR* 10.12, 95% CI [2.32, 44.04], $p = .002$ in opposite-sex twins). Twins born by IVF experienced a similar growth at five stages (0−18 years old) when compared with those born by SC. PTB risk, however, is significantly higher for twins conceived by IVF than those conceived by SC.

**Keywords:** In vitro fertilization; spontaneous conception; preterm birth; growth; low birth weight

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Since the first live birth of in vitro fertilization (IVF) in the UK in 1978 (Steptoe & Edwards, 1978), assisted reproductive technology (ART) has continued to advance during the past 40 years. ART, which mainly includes IVF and intracytoplasmic sperm injection (ICSI), is currently the preferred treatment for more than 70 million couples suffering from infertility worldwide (Ombelet et al., 2008). Global utilization of ART was approximately 2.0 million cycles and 0.5 million babies in 2011, estimated by data extracted from 2560 ART clinics of 65 countries (Adamson et al., 2018). Infants born from ART contribute to a substantial number of the total newborns, for example, 3.3% in Australia (Hansen et al., 2012), 4.2% in Israel (Farhi et al., 2013), 1.5% in Japan (Fujii et al., 2010) and 1.7−2.2% in Europe (Calhaz-Jorge et al., 2016). Although ART has gained widespread application in clinical work, there is growing concern regarding the potential risks of the technique.

It has been found that children conceived from ART may exhibit vulnerability to more health risks than spontaneously conceived children, which can be partially explained by the higher percentage of multiple births brought by ART. The percentage of multiple-birth infants conceived from ART is higher than that of spontaneous conceptions (SCs). According to ART statistics from the USA in 2016, compared with all infants born in the total birth population, the percentage of multiple-birth infants was higher among infants conceived from ART (31.5% vs. 3.4%, respectively), of which approximately 30.4% were twins (Sunderam et al., 2019). Similarly, in mainland China in 2016, the percentage of twinning births from IVF was around 27.9%, and the rate after ICSI was around 27.2% (Bai et al., 2020). Multiple births pose substantial risks for both mothers and infants, including obstetric complications and adverse perinatal outcomes. For instance, the percentage of preterm births (PTBs) was 17.11%

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in singletons, 65.69% in twins and 95.51% in triplets; and the proportion of perinatal mortality reached 8.0‰ in singletons, 19.0‰ in twins and 62.3‰ in higher order multiples, as illustrated in a study that collected ART records during 2016 from 15 Latin American countries (Zegers-Hochschild et al., 2019).

Studies that compare IVF and twins born from SC have been progressively advancing. Two meta-analyses (Qin et al., 2017; Qin et al., 2016), and several studies from Israel (Barda et al., 2017), the Netherlands (Hack et al., 2018), Portugal (Simões et al., 2015) and China (Lei et al., 2019; Yang et al., 2014; Zhu et al., 2016) have been performed to explore the impact of ART on obstetric and neonatal outcomes of twin pregnancies, but the results remain inconsistent. A possible explanation for the conflicting results is that some studies did not distinguish between monochorionic twinning and dichorionic twinning. It is well documented that the monochorionicity rate among twin pregnancies from ART is lower than that from SC twin pregnancies (about 2% vs. 22%, respectively), and monochorionic pregnancies are associated with worse perinatal outcomes compared with dichorionic pregnancies because of their shared placenta (Carter et al., 2015; Penava & Natale, 2004; Pinborg et al., 2004). Thus, taking chorionicity into account is essential for ascertaining associations of ART with health effects.

Considering that impaired growth during the intrauterine period is associated with catch-up growth and potential long-term risk (Barker, 1998; Eriksson et al., 1999), it is not clear whether ART has an impact on growth in the intrauterine period, and then later on growth in childhood and adolescence. For singletons, a meta-analysis that included 13 eligible studies found that IVF and ICSI were not associated with long-term weight and height outcomes (Bay et al., 2019). The growth of twins conceived by ART has not been extensively studied, but there are three studies that followed subjects from birth to 18 months of age, 3 years of age and 12 years of age. These studies found no evidence for the impact of ART on the length/height and weight of twins (Koivurova et al., 2003; Lee et al., 2010; van Beijsterveldt et al., 2011). However, little attention has been devoted to the comparison of weight and height during school age and adolescence between ART twins and SC twins.

Given these flaws, the present study consists of two aspects: one is to investigate associations between IVF with PTB and low birth weight (LBW) among twins; the other is to examine associations between IVF with length/height and weight in five growth periods: infancy (0 year), toddler period (1–2 years), preschool (3–5 years), primary or elementary school (6–11 years), and adolescence (10–18 years). Further, as mentioned above, chorionicity has an impact on associations of IVF with adverse health-related outcomes, so we studied both all twin pairs and opposite-sex twin pairs. Opposite-sex twins, which are dizygotic, are dichorionic twins, while same-sex twins include both monochorionic and dichorionic twins.

## Materials and Methods

### Data Sources

The data were derived from a questionnaire for twins aged under 18 years in the Chinese National Twin Registry (CNTR), the largest twin registry in Asian countries. The CNTR was established in 2001 and had recruited 61,566 twin pairs in 11 provinces or cities by February 15, 2019, described in detail by Gao et al. (2019). The data were obtained by face-to-face interviews. Cooperation with the Centers for Disease Control and Prevention (CDC) system and the 'Hukou system' improved the coverage rate of the CNTR.

### Study Population

All twins who were conceived by IVF or spontaneously were included. Twin pairs were excluded from analyses if they met any of the following: (1) birth weight <500 g, (2) gestational age >42 weeks, (3) one or two of the co-twins was diagnosed with hypertension, diabetes, genetic diseases or other severe diseases and (4) conceived by intrauterine insemination or ovulation induction. After accurate selection, the study included 26,818 subjects (13,409 twin pairs), of which 25,654 were conceived spontaneously and 1164 from IVF.

### Outcome Variables

LBW was defined as a birth weight <2500 g at delivery, and macrosomia referred to newborns whose birth weight was equal to or greater than 4000 g. PTB was considered as such when delivery occurred before 37 weeks of gestation. We collected possible confounders such as maternal age, delivery mode, feeding pattern in the first 4 months, gender and age.

### Statistical Analysis

The Kolmogorov–Smirnov test was used to examine the normality of continuous variables. Student's $t$ test was used to analyze differences between continuous variables if the normal distribution assumption was met, otherwise the Mann–Whitney U test was used. The chi-squared test or Fisher's exact test was used for analyzing differences between categorical variables. Continuous variables were stated as mean ± standard deviation (*SD*), and categorical variables as number ($n$) and percentage (%).

Generalized linear mixed models or linear mixed models (GLMM/LMM) were used to control for the fact that twins share the same mother. The GLMM was used to examine the effects of independent variables on a categorical dependent variable, and the LMM on a continuous dependent variable. For each outcome, we calculated the adjusted odds ratio (a*OR*) and 95% confidence interval (CI), or adjusted beta and 95% CI. A value of $p < .05$ was considered statistically significant for PTB and birth weight level. The threshold of statistical significance was .005 (.05/10) after Bonferroni correction for multiple comparisons of growth in five growth periods. Analyses were performed using RStudio 3.6.2 software.

Due to a relatively high proportion of missing data for PTB and birth weight level, 9.83% and 16.42%, respectively, a sensitivity analysis was conducted by excluding subjects without PTB or birth weight information in the respective association analysis.

## Results

### Study Population

As shown in Table 1, the proportion of opposite-sex twins was 42.44% in the IVF group and 24.71% in the SC group, in line with previous reports. The proportions of cesarean section and PTB in the IVF group were significantly higher than those in the SC group (96.04% vs. 81.72%, $p < .001$, and 45.95% vs. 36.10%, $p < .00$, respectively). And the maternal age in the IVF group was higher than that in the SC group (31.78 ± 3.72 vs. 27.79 ± 4.42 years old, $p < .001$). In contrast, the proportions of artificial feeding and males were similar in both groups (25.17% vs. 23.94%,

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**Table 1.** Maternal, perinatal and feeding characteristics in all twins conceived from IVF and spontaneously

| All twins | | | | | |
|---|---|---|---|---|---|
| | IVF | | SC | | |
| Variables | *n* (1164) | % | *n* (25,654) | % | *p*-Value |
| Twin gender | 1164 | | 25,654 | | <.001 |
| Opposite-sex | 494 | 42.44 | 6338 | 24.71 | |
| Both female | 316 | 27.15 | 9404 | 36.66 | |
| Both male | 354 | 30.41 | 9912 | 38.64 | |
| Maternal age [c] | 31.78 ± 3.72 | | 27.79 ± 4.42 | | <.001[a] |
| Cesarean section | 1162 | | 25,590 | | <.001 |
| No | 46 | 3.96 | 4677 | 18.28 | |
| Yes | 1116 | 96.04 | 20,913 | 81.72 | |
| Artificial feeding | 1160 | | 25,592 | | .356 |
| No | 868 | 74.83 | 19,464 | 76.06 | |
| Yes | 292 | 25.17 | 6128 | 23.94 | |
| Gender | 1164 | | 25,654 | | .690 |
| Female | 563 | 48.37 | 12,573 | 49.01 | |
| Male | 601 | 51.63 | 13081 | 50.99 | |
| PTBs | 1110 | | 23,072 | | <.001 |
| No | 600 | 54.05 | 14,742 | 63.90 | |
| Yes | 510 | 45.95 | 8330 | 36.10 | |
| Birth weight | 1056 | | 21,308 | | .232[b] |
| LBW | 455 | 43.09 | 9442 | 44.20 | |
| Normal birth weight | 601 | 56.91 | 11,866 | 55.56 | |
| Macrosomia | 0 | 0 | 51 | 0.24 | |

Note: [a]tested by Mann–Whitney U test; [b]tested by Fisher's exact test; others were tested by chi-squared test; [c]stated as mean ± standard deviation; IVF, in vitro fertilization; SC, spontaneous conception; PTBs, preterm births; LBW, low birth weight.

**Table 2.** Comparison of preterm birth and birth weight level among all twins conceived from IVF and spontaneously

| All twins | | | | | | | |
|---|---|---|---|---|---|---|---|
| | IVF (*n* = 1164) | | SC (*n* = 25654) | | | | |
| Perinatal outcome | *n* | % | *n* | % | Adjusted *OR* | Adjusted 95% CI | *p*-Value |
| PTBs | 510 | 43.81 | 8330 | 32.47 | 10.57 | 4.27, 26.18 | <.001 |
| LBW | 455 | 39.09 | 9442 | 36.81 | 1.12 | 0.88, 1.41 | .359 |
| Macrosomia | 0 | 0 | 51 | 0.20 | – | – | – |

Note: Adjusting for maternal age, delivery mode and preterm birth (only for LBW and macrosomia). LBW and macrosomia both take normal birth weight (2500 g–3999 g) as reference. IVF, in vitro fertilization; SC, spontaneous conception; PTB, preterm births; LBW, low birth weight.

$p = .356$, and 51.63% vs. 50.99%, $p = .690$). We also show the differences in maternal age, cesarean section, artificial feeding, gender, PTB and birth weight in Supplementary Table S1 for opposite-sex twins, and the results were analogous.

### *Comparison between Twins Conceived by IVF and Twins Conceived Spontaneously*

***PTB and birth weight level.*** After correction for maternal age and delivery mode, PTB in the IVF group was substantially higher compared with the SC group (a*OR* 10.57, 95% CI [4.27, 26.18], $p < .001$); see Table 2. The association between IVF and LBW was not significant, taking normal birth weight (2500 g–3999 g) as a reference after adjusting for maternal age, delivery mode and PTB (a*OR* 1.12, 95% CI [0.88, 1.41], $p = .359$). Considering the small sample size and the rare occurrence of macrosomia, no statistical comparison was made. The results of the sensitivity analysis where subjects without PTB or birth weight record were excluded were similar, with a*OR* 8.21 (95% CI [3.19,21.13], $p < .001$) for PTB and a*OR* 1.04 (95% CI [0.83˜1.29], $p = .741$) for LBW, as shown in Supplementary Table S2.

***Physical development.*** After adjustment for maternal age, delivery mode, gender, PTB, feeding pattern and age, LMM analysis revealed that there were no significant differences between the two groups ($p > .05$) in terms of body length/height and weight at the five stages of growth after Bonferroni correction, with only one exception of body length/height at preschool age (adjusted beta 3.45, 95% CI [1.58, 5.33], $p < .001$), as described in Table 3.

### *Comparison between Dichorionic Twins Conceived by IVF and Twins Conceived Spontaneously*

***PTB and birth weight level.*** IVF-conceived dichorionic twins (only including opposite-sex twins) were at higher risk of PTB than those conceived by SC (a*OR* 13.19, 95% CI [3.24, 53.76], $p < .001$), which was more significant than the results for all twins. The incidence of LBW had no significant difference between the two groups (a*OR* 1.30, 95% CI [0.93, 1.82], $p = .126$); see Table 4. The results of the sensitivity analysis was similar, with a*OR* 10.12 (95% CI [2.32, 44.04], $p = .002$) for PTB and a*OR* 1.13 (95% CI [0.83, 1.52], $p = .441$) for LBW, as shown in Supplementary Table S3.

***Physical development.*** Similar to all twins, there were no significant differences between the two groups ($p > .05$) in terms of body length/height and weight at the five stages of growth for dichorionic twins (only including opposite-sex twins); see Table 5. A summary of body length/height and weight at the five growth stages in all twins and dichorionic twins is presented in Figure 1.

## Discussion

Since the first IVF birth in 1988 in mainland China, ART has been transformed from a miracle to a mature medical technology. As reported previously, the proportion of infants born from ART is up to 4% of births in developed countries and approximately 1% in mainland China. However, with the widespread application of ART, the concerns about the risk of ART are growing.

Our retrospective cohort study, which included 1164 twins resulting from IVF and 25,654 twins conceived spontaneously, indicates two major results. First, and surprisingly, the rate of PTB is 10.57-fold higher in IVF twin pregnancies compared with spontaneous twin pregnancies (a*OR*10.57, 95% CI [4.27, 26.18], $p < .001$); and it increases to 13.16-fold when the comparison only involves opposite-sex twins (a*OR* 13.16, 95% CI [3.23, 53.61], $p < .001$). The results were relatively conservative in the sensitive analysis, in which subjects without variable information of PTB were excluded (a*OR* 8.21, 95% CI [3.19, 21.13], $p < .001$ in all twins, and a*OR* 10.12, 95% CI [2.32, 44.04], $p = .002$ in opposite-sex twins, respectively). This result is surprising because few studies have documented such high a*OR* when focused on the association

**Table 3.** Association between IVF with body length/height and weight at five growth stages in all twins

| | All twins | | | | |
|---|---|---|---|---|---|
| | IVF ($n = 1164$) | SC ($n = 25{,}654$) | Adjusted beta | Adjusted 95% CI | *p*-Value |
| Body length/height (cm) | | | | | |
| Infancy (0 year) | 64.72 ± 8.88 | 66.39 ± 11.01 | −2.03 | −4.42, 0.36 | .096 |
| Toddler period (1–2 years) | 84.84 ± 8.45 | 85.67 ± 10.17 | −0.21 | −1.73, 1.31 | .785 |
| Preschool age (3–5 years) | 107.14 ± 15.65 | 104.72 ± 11.89 | 3.45 | 1.58, 5.33 | **<.001** |
| School age (6–11 years) | 128.93 ± 12.36 | 131.07 ± 13.95 | 0.71 | −0.84, 2.26 | .368 |
| Adolescence (10–18 years) | 154.04 ± 12.62 | 156.35 ± 14.15 | 1.68 | −0.72, 4.08 | .170 |
| Body weight (kg) | | | | | |
| Infancy (0 year) | 7.89 ± 2.90 | 7.79 ± 2.83 | −0.01 | −0.65, 0.62 | .967 |
| Toddler period (1–2 years) | 12.46 ± 2.54 | 12.93 ± 3.31 | −0.31 | −0.81, 0.19 | .226 |
| Preschool age (3–5 years) | 18.84 ± 6.24 | 18.37 ± 5.13 | 0.99 | 0.19, 1.79 | .015 |
| School age (6–11 years) | 28.91 ± 9.03 | 29.45 ± 9.18 | 1.28 | 0.18, 2.38 | .023 |
| Adolescence (10–18 years) | 41.94 ± 11.21 | 46.26 ± 12.20 | −1.02 | −3.17,1.13 | .353 |

Note: Adjusting for maternal age, delivery mode, gender, preterm birth, feeding pattern and age. IVF, in vitro fertilization; SC, spontaneous conception. The data in bold represents statistical significance after Bonferroni correction.

**Table 4.** Comparison of preterm birth and birth weight level among dichorionic twins (only including opposite-sex twins) conceived from IVF and spontaneously

| | Dichorionic twins | | | | | | |
|---|---|---|---|---|---|---|---|
| | IVF ($n = 494$) | | SC ($n = 6338$) | | | | |
| Perinatal outcome | *n* | % | *n* | % | Adjusted *OR* | Adjusted 95% CI | *p*-Value |
| PTBs | 212 | 42.91 | 1932 | 30.48 | 13.19 | 3.24, 53.76 | <.001 |
| LBW | 187 | 37.85 | 2052 | 32.38 | 1.30 | 0.93, 1.82 | .126 |
| Macrosomia | 0 | 0.00 | 13 | 0.21 | – | – | – |

Note: Adjusting for maternal age, delivery mode and preterm birth (only for LBW and macrosomia). LBW and macrosomia both took normal birth weight (2500 g–3999 g) as reference. IVF, in vitro fertilization; SC, spontaneous conception; PTB, preterm births; LBW, low birth weight.

between IVF with PTB among twin pregnancies. The important finding, however, is that growth at the five stages from infancy to adolescence is similar in the two groups.

A growing body of research has been performed to address whether twin pregnancies from ART have a greater risk of adverse outcomes compared with those conceived spontaneously. However, the results are often contradictory, which may be attributable to differences in the study population, management methods of twin pregnancies, and especially whether or not monochorionicity was considered as a risk factor for adverse outcomes (Qin et al., 2016). Our observation suggests that IVF increases PTB rate, in alignment with that of Barda et al. (2017; 59.0% vs. 47.4%, $p = .002$) and Qin et al. (2016), but in contrast with that of Hack et al. (2018; 36.1% vs. 33.9%, $p = .271$). The latter three studies all took the effect of chorionicity on adverse outcomes into account and only focused on dichorionic twins. The reason why the a*OR* is higher in the present study compared with the three results may be due to the large sample size, which enhances statistical power, and because we excluded any kind of ART except for IVF. After adjusting for PTB, the observation of the comparable LBW rate in two groups, irrespective of chorionicity, confirms the findings of two previous studies that focused on dichorionic twins (Hack et al., 2018) and monochorionic twins (Hack et al., 2018; Simões et al., 2015), and a meta-analysis ignoring chorionicity (Qin et al., 2017).

Furthermore, there is no authoritative explanation that IVF induces a higher risk of PTB in twin pregnancies. On the one hand, IVF involves a sequence of laboratory operations, including invasive infertility treatments, exposure of oocytes, sperm and embryos to the external environment, and manipulation of oocytes and embryos. On the other hand, the prevalence of infertility in couples seeking out ART is higher than that in couples undergoing SC. It has been illustrated that infertility influences the obstetrics outcome, and women with endometriosis or anovulation have increased risks of PTB (Kuivasaari-Pirinen et al., 2012).

Too little work has been devoted to the study of the impact of ART on growth in childhood and adolescence. The Taiwan Birth Cohort Study (TBCS) reported there was no significant difference between twins born from ART and SC regarding growth at birth, 6 months old and 18 months old (Lee et al. 2010). The result was supported by earlier research where the growth of children at 1, 2 and 3 years was explored (Koivurova et al., 2003). Another study from the Netherlands Twin Registry investigated growth from birth to 12 years of age and found no significant differences either (van Beijsterveldt et al., 2011). When comparing our findings to these studies, it must be pointed out that there is no evidence for differences in height and weight between IVF twins and SC twins, but no available research could be found that compared with the present results of height or weight at school age and adolescence.

The strengths of our study derive from: (1) it is a large sample study that compares twins conceived by IVF and those from SC in China. (2) To rule out the large confounder of the chorionic effect, we further analyzed only opposite-sex twins to ensure dizygosity, which must be dichorionic. (3) We adjusted for potentially confounding factors such as maternal age and delivery mode.

Nevertheless, our observations should be explained with some caution for the following limitations: (1) we had inadequate control for other confounding factors such as parity, socioeconomic status, maternal lifestyle, including substance abuse, or the management of pregnancy. (2) Parts of the records about length/height and weight were obtained by self-report, which may result in self-reported bias.

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**Table 5.** Association between IVF with body length/height and weight at five growth stages in dichorionic twins

| | Dichorionic twins | | | | |
|---|---|---|---|---|---|
| | IVF (*n* = 494) | SC (*n* = 6338) | Adjusted beta | Adjusted 95% CI | *p*-Value |
| Body length/height (cm) | | | | | |
| Infancy (0 year) | 65.86 ± 9.26 | 66.50 ± 12.19 | 0.32 | −0.76, 1.41 | .563 |
| Toddler period (1–2 years) | 83.94 ± 8.81 | 85.32 ± 8.95 | −0.34 | −1.05, 0.36 | .337 |
| Preschool age (3–5 years) | 105.91 ± 11.47 | 104.03 ± 12.44 | −0.10 | −1.28, 1.08 | .868 |
| School age (6–11 years) | 131.05 ± 11.62 | 131.00 ± 14.04 | 0.90 | −0.77, 2.58 | .290 |
| Adolescence (10–18 years) | 153.05 ± 12.98 | 156.01 ± 14.51 | −1.95 | −4.81, 0.91 | .182 |
| Body weight (kg) | | | | | |
| Infancy (0 year) | 8.03 ± 2.99 | 7.74 ± 2.94 | −0.66 | −5.02, 3.70 | .768 |
| Toddler period (1–2 years) | 12.34 ± 2.44 | 12.87 ± 3.19 | −0.80 | −2.91, 1.32 | .461 |
| Preschool age (3–5 years) | 17.76 ± 5.03 | 18.37 ± 5.10 | 2.69 | −0.33, 5.72 | .081 |
| School age (6–11 years) | 29.58 ± 8.78 | 29.62 ± 9.09 | 1.25 | −1.22, 3.71 | .322 |
| Adolescence (10–18 years) | 40.83 ± 11.43 | 46.43 ± 12.37 | 1.37 | −2.01, 4.75 | .427 |

Note: Adjusting for maternal age, delivery mode, gender, preterm birth, feeding pattern, and age. IVF, in vitro fertilization; SC, spontaneous conception.

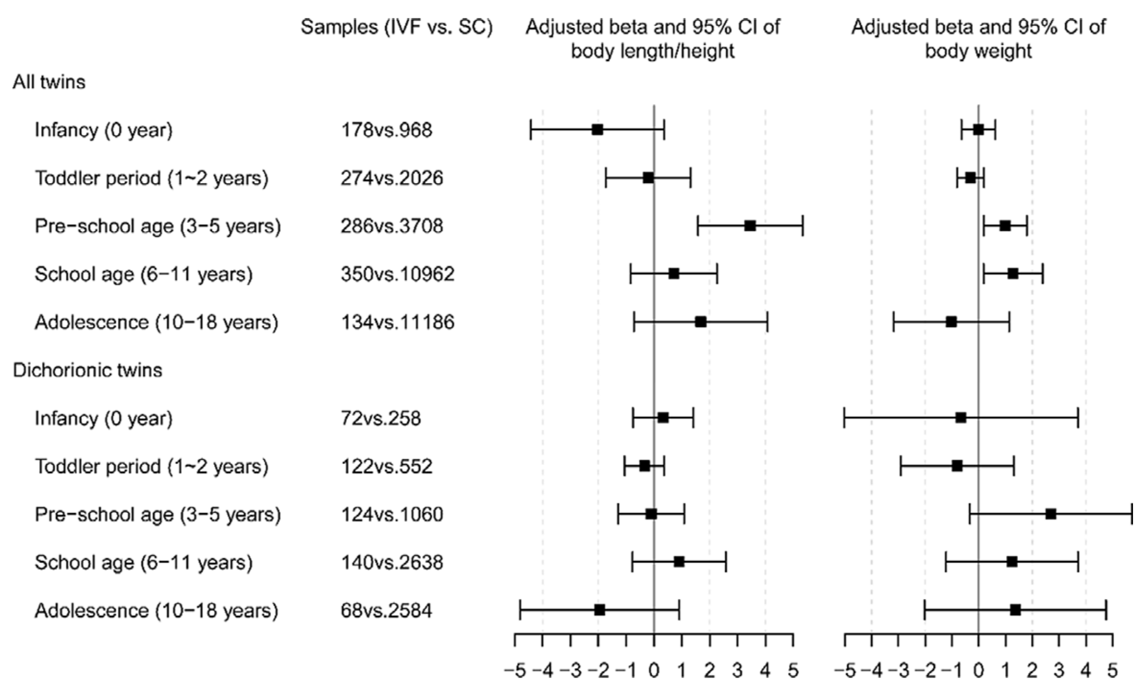


**Fig. 1.** Association between in vitro fertilization with body length/height and weight at five growth stages in all twins and dichorionic twins.

However, pertinent literature has shown that the self-reported height and weight are still correlated with the measured height and weight, and correlation coefficients for height ranged from .62 to .91, and for weight from .84 to .98 (Sherry et al. 2007). (3) The information about whether multifetal pregnancies were reduced for twins could not be known, but this situation is rare, according to the results of a nationwide cohort study (van de Mheen et al., 2014).

In conclusion, it is obvious that the PTB rate is higher in twins conceived via IVF compared with that through SC, but the LBW rate is similar after adjusting for PTB, no matter for all twins or only for dichorionic twins. Growth, including length/height and weight at five stages after adjusting for PTB, is similar for the two groups and for the five stages of infancy (0 year), toddler period (1–2 years), preschool age (3–5 years), school age (6–11 years) and adolescence (10–18 years).

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**Conflict of interest.** None.

**Supplementary material.** To view supplementary material for this article, please visit https://doi.org/10.1017/thg.2021.33.

## References


**Adamson, G. D., de Mouzon, J., Chambers, G. M., Zegers-Hochschild, F., Mansour, R., Ishihara, O., Banker, M., & Dyer, S.** (2018). International committee for monitoring assisted reproductive technology: world report on assisted reproductive technology, 2011. *Fertility and Sterility*, *110*, 1067–1080.

**Bai, F., Wang, D. Y., Fan, Y. J., Qiu, J., Wang, L., Dai, Y., & Song, L.** (2020). Assisted reproductive technology service availability, efficacy and safety in mainland China: 2016. *Human Reproduction*, *35*, 446–452.

**Barda, G., Gluck, O., Mizrachi, Y., & Bar, J.** (2017). A comparison of maternal and perinatal outcome between in vitro fertilization and spontaneous dichorionic-diamniotic twin pregnancies. *Journal of Maternal-Fetal & Neonatal Medicine*, *30*, 2974–2977.

**Barker, D. J. P.** (1998). In utero programming of chronic disease. *Clinical Science*, *95*, 115–128.

**Bay, B., Lyngsø, J., Hohwü, L., & Kesmodel, U. S.** (2019). Childhood growth of singletons conceived following in vitro fertilisation or intracytoplasmic sperm injection: A systematic review and meta-analysis. *BJOG*, *126*, 158–166.

**Calhaz-Jorge, C., de Geyter, C., Kupka, M. S., de Mouzon, J., Erb, K., Mocanu, E., Motrenko, T., Scaravelli, G., Wyns, C., & Goossens, V.** (2016). Assisted reproductive technology in Europe, 2012: results generated from European registers by ESHRE. *Human Reproduction*, *31*, 1638–1652.

**Carter, E. B., Bishop, K. C., Goetzinger, K. R., Tuuli, M. G., & Cahill, A. G.** (2015). The impact of chorionicity on maternal pregnancy outcomes. *American Journal of Obstetrics and Gynecology, 213*, 390.e1–7.

**Eriksson, J. G., Forsen, T., Tuomilehto, J., Winter, P. D., Osmond, C., & Barker, D. J.** (1999). Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *BMJ*, *318*, 427–431.

**Farhi, A., Reichman, B, Boyko, V., Hourvitz, A., Ron-El, R., & Lerner-Geva, L.** (2013). Maternal and neonatal health outcomes following assisted reproduction. *Reproductive Biomedicine Online*, *26*, 454–461.

**Fujii, M., Matsuoka, R., Bergel, E., van der Poel, S., & Okai, T.** (2010). Perinatal risk in singleton pregnancies after in vitro fertilization. *Fertility and Sterility*, *94*, 2113–2117.

**Gao, W., Cao, W., Lv, J., Yu, C., Wu, T., Wang, S., Meng, L., Wang, D., Wang, Z., Pang, Z., Yu, M., Wang, H., Wu, X., Dong, Z., Wu, F., Jiang, G., Wang, X., Liu, Y., Deng, J., Lu, L., & Li, L.** (2019). The Chinese National Twin Registry: A 'gold mine' for scientific research. *Journal of Internal Medicine*, *286*, 299–308.

**Hack, K. E. A., Vereycken, M. E. M. S., Torrance, H. L., Koopman-Esseboom, C., & Derks J. B.** (2018). Perinatal outcome of monochorionic and dichorionic twins after spontaneous and assisted conception: A retrospective cohort study. *Acta Obstetricia et Gynecologica Scandinavica*, *97*, 717–726.

**Hansen, M., Kurinczuk, J. J., de Klerk, N., Burton, P., & Bower, C.** (2012). Assisted Reproductive Technology and Major Birth Defects in Western Australia. *Obstetrics and Gynecology*, *120*, 852–863.

**Koivurova, S., Hartikainen, A. L., Sovio, U., Gissler, M., Hemminki, E., & Järvelin, M. R.** (2003). Growth, psychomotor development and morbidity up to 3 years of age in children born after IVF. *Human Reproduction*, *18*, 2328–2336.

**Kuivasaari-Pirinen, P., Raatikainen, K., Hippeläinen, M., & Heinonen, S.** (2012). Adverse outcomes of IVF/ICSI pregnancies vary depending on aetiology of infertility. *ISRN Obstetrics and Gynecology*, *2012*, 451915.

**Lee, S. H., Lee, M. Y., Chiang, T. L., Lee, M. S., & Lee, M. C.** (2010). Child growth from birth to 18 months old born after assisted reproductive technology ¾ Results of a national birth cohort study. *International Journal of Nursing Studies*, *47*, 1159–1166.

**Lei, L. L., Lan, Y. L., Wang, S. Y., Feng, W., & Zhai, Z. J.** (2019). Perinatal complications and live-birth outcomes following assisted reproductive technology: a retrospective cohort study. *Chinese Medical Journal*, *132*, 2408–2416.

**Ombelet, W., Cooke, I., Dyer, S., Serour, G., & Devroey, P.** (2008). Infertility and the provision of infertility medical services in developing countries. *Human Reproduction Update*, *14*, 605–621.

**Penava, D., & Natale, R.** (2004). An association of chorionicity with preterm twin birth. *Journal of Obstetrics and Gynaecology Canada*, *26*, 571–574.

**Pinborg, A., Loft, A., Rasmussen, S., Schmidt, L., Langhoff-Roos, J., Greisen, G., & Andersen, A. N.** (2004). Neonatal outcome in a Danish national cohort of 3438 IVF/ICSI and 10,362 non-IVF/ICSI twins born between 1995 and 2000. *Human Reproduction*, *19*, 435–441.

**Qin, J. B., Sheng, X. Q., Wang, H., Chen, G. C., Yang, J., Yu, H., & Yang, T. B.** (2017). Worldwide prevalence of adverse pregnancy outcomes associated with in vitro fertilization/intracytoplasmic sperm injection among multiple births: A systematic review and meta-analysis based on cohort studies. *Archives of Gynecology and Obstetrics*, *295*, 577–597.

**Qin, J. B., Wang, H., Sheng, X., Xie, Q., & Gao, S.** (2016). Assisted reproductive technology and risk of adverse obstetric outcomes in dichorionic twin pregnancies: A systematic review and meta-analysis. *Fertility and Sterility*, *105*, 1180–1192.

**Sherry, B., Jefferds, M. E., & Grummer-Strawn, L. M.** (2007). Accuracy of adolescent self-report of height and weight in assessing overweight status: A literature review. *Archives of Pediatrics & Adolescent Medicine*, *161*, 1154–1161.

**Simões, T., Queirós, A., Marujo, A. T., Valdoleiros, S., Silva, P., & Blickstein, I.** (2015). Outcome of monochorionic twins conceived by assisted reproduction. *Fertility and Sterility*, *104*, 629–632.

**Steptoe, P. C., & Edwards, R. G.** (1978). Birth after the reimplantation of a human embryo. *Lancet*, *2*, 366.

**Sunderam, S., Kissin, D. M., Zhang, Y., Folger, S. G., Boulet, S. L., Warner, L., Callaghan, W. M., & Barfield, W. D.** (2019). Assisted reproductive technology surveillance ¾ United States, 2016. *Morbidity and Mortality Weekly Report (MMWR) Surveillance Summaries*, *68*, 1–23.

**van Beijsterveldt, C. E., Bartels, M., & Boomsma, D. I.** (2011). Comparison of naturally conceived and IVF-DZ twins in the Netherlands Twin Registry: A developmental study. *Journal of Pregnancy*, *2011*, 517614.

**van de Mheen, L., Everwijn, S. M., Knapen, M. F., Oepkes, D., Engels, M., Manten, G. T., Zondervan, H., Wirjosoekarto, S. A., van Vugt, J. M., Erwich, J. J., Nij Bijvank, S. W., Ravelli, A., Heemelaar, S., van Pampus, M. G., de Groot, C. J., Mol, B. W., & Pajkrt, E.** (2014). The effectiveness of multifetal pregnancy reduction in trichorionic triplet gestation. *American Journal of Obstetrics and Gynecology*, *211*, 536.e1-6.

**Yang, X., Li, Y., Li, C., & Zhang, W.** (2014). Current overview of pregnancy complications and live-birth outcome of assisted reproductive technology in mainland China. *Fertility and Sterility*, *101*, 385–391.

**Zegers-Hochschild, F., Schwarze, J. E., Crosby, J. A., Musri, C., & Urbina, M. T.** (2019). Assisted reproductive techniques in Latin America: The Latin American Registry 2016. *Reproductive Biomedicine Online*, *39*, 452–460.

**Zhu, L., Zhang, Y., Liu, Y., Zhang, R., Wu, Y., Huang, Y., Liu, F., Li, M., Sun, S., Xing, L., Zhu, Y., Chen, Y., Xu, L., Zhou, L., Huang, H., & Zhang, D.** (2016). Maternal and live-birth outcomes of pregnancies following assisted reproductive technology: A retrospective cohort study. *Scientific Reports*, *6*, 35141.