Birth Defects in Assisted Reproductive Technology and Spontaneously Conceived Children: A Meta-analysis

Yan JIA, Li-hong GENG, Ying ZHONG
Reproductive Centre, Jinjiang Maternal and Child Health Hospital, Chengdu 610016, China

Objective  To evaluate the risk of birth defects in children born following assisted reproductive technology (ART) and spontaneous conceptions.

Methods  This study carried out an updated systematic review to identify papers published by August 2013 with data relating to birth defects of children conceived using ART (IVF and/or ICSI) compared with those spontaneously conceived and also compared birth defects between subgroups of IVF and ICSI.

Results  Totally 76 studies were identified for review. The individual relative risk (RR) estimated for these studies ranged from 0.44 to 5.51, a significantly increased risk of birth defects was observed (RR=1.36, 95%CI=1.25–1.47) in ART compared with the spontaneously conceived group, which was also evident in the subgroup analysis. Among these studies, 16 studies simultaneously gave data of birth defects comparing IVF and ICSI children, which showed no difference in risk of combined effects (RR=0.90, 95%CI=0.80–1.02), but ICSI had a higher risk in subgroups of clinical research (RR=0.76, 95%CI=0.65–0.89) and crude RR value (RR=0.78, 95%CI=0.67–0.91).

Conclusion  Pooled results from all suitable published studies suggested that children born following ART were at increased risk of birth defects compared with spontaneous conceptions. There is no difference in birth defect risk between children conceived by IVF or ICSI using a summative analysis, however, ICSI had a significant higher risk in birth defect risk comparing with IVF when using subgroup analyses of sample size and RR value.

Key words: birth defects; assisted reproductive technology (ART); IVF; ICSI; Meta-analysis

Corresponding author: Yan JIA; E-mail: greenayan@163.com
The field of assisted reproductive technology (ART) has undergone rapid progress since the birth of Louise Brown[1]. More and more researchers are concerned about the risk of birth defects following ART, from Morin in 1989[2] to more recently Lorraine in 2013[3]. A part of the studies concluded that there was an increased risk of birth defects in ART children compared with spontaneously conceived children, but some other reports described no difference. The previous Meta-analysis from different studies also showed differently results: Rimm[4], Hansen[5], and Wen[6] reported that there was a significantly increased risk of birth defects between ART and naturally conceived children, but McDonald[7] and Rossi[8] gave a contrary conclusion. This may result from different inclusion criteria, literature quantity, or angles of analysis. Our study estimated the risk of birth defects using more stringent selection criteria, there would be an updated number of studies to examine birth defect risk. The intracytoplasmic sperm injection (ICSI) plays a big role in the development of ART, but there are more concerns about whether it would increase the risk of malformation of babies. Actually, some case reports have indicated many severe defects occurred in children conceived by ICSI[9,10], but the most recent Meta-analysis[6] reported there was no significant difference of risk between IVF and ICSI children. Our study also performed a subgroup comparison between IVF and ICSI birth defects, compiling current available data for risk assessment.

Materials & Methods

We performed an extensive literature search of Medline, Embase and Current Contents Databases (1978–2013) using a broad combination of search terms (Table 1). This search strategy was saved and run in each database in August 2013. We also reviewed the reference lists of all identified studies and reviewed articles to search for additional references.

Studies were included if: the exposure of interest was IVF and/or ICSI; the outcome of interest was birth defects; comparison IVF and/or ICSI to naturally conceived children; relative risk (RR) with 95% confidence intervals (95%CI) provided or could be calculated (Figure 1). Because of language barrier, only studies published in English or Chinese were

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<tr>
<td>IVF</td>
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Table 1 Combinations of terms in the first column with all terms in the second column
We excluded studies that were case reports; with inappropriate comparison group or without control subjects; overlapping data; with mixed exposure groups [for example, including children born following ovulation induction (OI) or intrauterine insemination (IUI) within the ‘ART’ group]; and studies focusing on some particular defects.

Three investigators reviewed all the articles independently and the data were checked by other investigators. The three investigators individually identified information from each study, and judged the inclusion and exclusion criteria. Where a study provided definite birth defects data for IVF and ICSI infants compared with spontaneous conception group, the data were pooled to form one risk estimate of IVF versus ICSI as well. If the sources of study population recruitment overlapped in two or more articles, the one with the more details of birth defect information was selected.

Authors, publication year, study location, birth years, sample type, age time assessment,
total number of ART, number and percentage of birth defects, total number of spontaneously conception, key words of compared item, ART treatment, and some adjusted RR and 95%CI were compiled. The concordance rate between the three investigators was 98.1% and discrepancies were resolved by consensus.

**Statistical analysis**

Data from studies were summarized in two-by-two tables. Because birth defects are rare, we assumed equivalence of the odds ratio (OR) and RR. Therefore, we applied RR for the effect measure of this study. If adjusted RR was not given, crude RR was used. RR and their 95%CI were calculated for individual study based on the data. The Meta-analysis procedures were performed using the Metaform-package (version 1.6) in R (version 2.14). Some advanced analysis also ran in the R statistical platform, such as Egger’s regression test, cumulative meta-analysis, sensitivity analysis, and meta-regression. We applied the $Q$ statistic and $I^2$ metric to test heterogeneity among the studies, then according to the relevant recommendations, random-effects models were used to estimate the pooled RR. To evaluate publication biases in the Meta-analysis, we conducted Begg’s and Egger’s test. And cumulative meta-analysis, subgroup analysis, sensitivity analysis, and Meta-regression were performed to estimate the sources of heterogeneity.

**Results**

**ART vs Spontaneously conceived children**

**Heterogeneity analysis**

There were 76 studies\(^{2,3,11-84}\) included. After combining all of the data, the heterogeneity analysis was made: $F=85.93$, $P<0.0001$.

For IVF and/or ICSI children compared with spontaneously conceived children, a significantly increased risk of birth defects was observed ($RR=1.36$, 95%CI=1.25–1.47, Figure 2). The individual risk estimated for these studies ranged from 0.44 to 5.51. There was a huge heterogeneity among the studies. Then a subgroup analysis was performed to see if any parameter significantly influenced the heterogeneity.

**Subgroup analysis**

We grouped these studies accordingly: 1) publication years: with the progress of ART, especially since the arrival of ICSI technology, the rate of malformations may have changed over the years. We set the cutoff of publication year to 2005, more than half of the studies were published after that year (2005–2013), and 36 papers published before that year (1989–2004); 2) study location: because of the technological level, racial predisposition, traditional habits and customs, different areas might have different results about the comparison, so we classified them into 4 subgroups according to the location. All studies came from 28 countries on 5 main continents, 8 studies derived from Oceania, 13 studies from Asia, 41
Figure 2 Individual risk ratio estimates and pooled risk ratio estimates comparing birth defects in children conceived by ART to spontaneous conception.
studies from Europe and 11 from North America, the other 3 studies were not classified into any group because 2 of them were multicentric research, and only one study came from Africa-Egypt; 3) sample type: the sample size ranged from 76 to 16,280, most of the large samples were based on the population studies, and the smaller samples were based on clinical research, so we grouped them into 2 subgroups: the population group which had 48 studies with sample size ranging from 221 to 16,280, and the clinical studies which had 28 studies with sample sizes ranging from 76 to 3,199; 4) time of assessment: 48 studies assessed birth defects when the baby was born, other 28 studies observed the defects after 6 months to 13 years; 5) \( RR \) value: we previously cited the adjusted \( RR \) because they had corrected some influencing factors such as maternal age, parity, sex, year of birth, social class, and/or smoking, 42 studies used adjusted \( RR \), and 34 studies used crude \( RR \) because we could not get the adjusted \( RR \) from the studies; 6) fertilization technology: 24 studies applied IVF (the studies clearly defined), 14 studies used ICSI, and 38 studies applied IVF and ICSI.

Most of the \( P \) values showed that these classified parameters had no influence on the combined effect (Table 2). Only the studies from Oceania showed ART did not have a significantly increased risk of birth defects when compared with spontaneously conceived pregnancies \( (P=0.312, 1, RR=1.15, 95\% CI=0.88-1.50) \), other 3 continents demonstrated a significant difference.

**Sensitivity analysis**

The study of El-chaar et al. 2002\(^{[62]} \) had the maximum influence on the combined effect. After removing it, \( RR=1.32, 95\% CI=1.24-1.41, Z=8.58, P<0.0001, Q=192.6, P=0.036, I^2=74.25 \), therefore indicating that it had no significant effect on the pooled estimate.

**Cumulative Meta-analysis**

This analysis was an observation of cumulative results of studies performed at different years, which also could assess the influence of each study on the comprehensive effect. In this analysis, the comparison began to demonstrate a trend indicating a difference between the two groups, that ART children had a higher birth defect risk than spontaneously conceived (SC) children (Figure 3), from 2001 onward until 2013.

**IVF vs ICSI**

The following analysis obtained information from the 76 studies about any difference of birth defect rate between IVF and ICSI. We extracted 16 studies and compared them according to the same analysis path mentioned above\(^{[11,12,15,19,20,24,29,36,39,41,46,52,57,70,76,77]} \).

**Heterogeneity analysis**

For ICSI compared with IVF children, there was no significant difference observed in the risk of birth defects \( (RR=0.90, 95\% CI=0.80-1.02, P=0.271, F=21.54; Figure 4) \). The individual risk estimated for these studies ranged from 0.53 to 3.05. There was no heteroge-
neity in our studies.

**Subgroup analysis**

We found that in the subgroup of clinical research (Table 3), ICSI had a higher risk of birth defects compared with IVF ($RR=0.76$, 95%CI=0.65–0.89; $P=0.000 5$). In the crude $RR$ subgroup, ICSI had the same trend when compared with IVF ($RR=0.78$, 95%CI=0.67–0.91; $P=0.002 2$). Other groups had not shown any significant difference.

**Sensitivity analysis**

The study of Ericson et al.[70] had the maximal influence on the combined effect. After removing it, $RR=0.96$, 95%CI=0.87–1.06, $Z=−0.75$, $P=0.452$, $Q=12.41$, $P=0.574$, $I^2=0$, which had no significant effect on the pooled estimate.

**Cumulative Meta-analysis**

In this analysis, the comparison did not show any difference of birth defect rate between IVF and ICSI from 1999 to 2013 (Figure 5). Latest cumulative $RR=0.90$, 95%CI=0.80–1.02.

**Publication bias**

We evaluated publication bias by using funnel plots (Figures 6, 7) and the Egg’s test.
Figure 3 Cumulative Meta-analysis of ART vs SC
The *P* values of the Egg’s test for the adjusted/crude data of ART versus SC, and IVF versus ICSI were 0.904 and 0.685, respectively, indicating that there was no obvious publication bias in our analysis.

**Discussion**

This analysis reviewed and pooled epidemiological data assessing the risk of birth defects
using ART versus spontaneous conception, and IVF versus ICSI. Our results suggest that there was a significantly increased risk of birth defects in children conceived by ART compared with spontaneous conception, but ICSI did not increase the risk when compared with IVF.
According to the publication years, both the latest (2005–2013), and previous ones (1989–2004) indicated a significantly higher risk using ART. Also, the cumulative Meta-analysis showed that the trend was retained between 2001 and 2013. The reason that the previous studies underestimated the risk may be due to the hospitals want to push the ART and underrating some adverse factors at the initial stage, or they may not have sufficient samples to properly assess the risk at that period. It is possible to produce different results based on sample analysis from different races and areas: the RR in Oceania, Europe, Asian and North America were: 1.15, 1.29, 1.51, 1.57, respectively. Studies from Oceania showed no significant difference in birth defect risk between ART and spontaneously conceived children, maybe it was related to a limited number of studies. And we may need larger sample sizes for further analysis. We divided the studies into population and clinic groups. Both the large sample size such as population group and small sample size such as clinic groups displayed a higher risk of birth defects in the ART group, which was different from the conclusion of Wen et al. The difference may be due to distinguishing criteria of Wen’s study using groups-dividing according to sample size, smaller or larger than 1 000 people. Forty-eight studies assessed birth defects as soon as infants were born, and 28 studies assessed birth defects of the babies/children aged 6 months to 13 years. Both groups of studies revealed that there was a higher risk of birth defects from ART children, which matched the reported conclusion. The risk of birth defects was unrelated to the assessment time.

There are so many complicating risks that could increase the rate of birth defects: age of mother, environmental exposures, risk behaviors such as alcohol consumption and smoking, other factors causing infertility, and the ART procedures themselves. As we can see, the overall risk ratio decreased after adjustment for some variables (RR=1.33 for adjustment and 1.37 for crude) but no statistical significance was demonstrated. Some researchers have argued that the causes of infertility themselves or the process of seeking treatment itself rather than the treatment alone, may lead to an increased level of birth defects risk. A Meta-analysis suggested ART do not increase the risk of malformations as much as reported after adjusting for the effect of subfertility (RR=1.01, 95%CI=0.82–1.23). We need more studies to assess children born from infertile couples who have not accepted any treatment at all, which, of course, is difficult to arrange.

Silver et al. said that the male offspring birthed from male-factor infertility couples had more risk of malformations of hypospadias (RR=5.53, 95%CI=2.61–11.73), so it is interesting to compare birth defects in children conceived by IVF and ICSI. Ericson et al. proposed that the excess risk for some specific defects after ICSI may be related to paternal subfertility associated with genetic abnormalities. Our analysis and the result of Wen et al. both...
displayed that there were no significant differences between IVF and ICSI. In further studies maybe we could compare some special malformations between children conceived by IVF and ICSI.

In conclusion, to assess the technology, a stricter method of comparison about the prevalence of birth defects associated with ART is needed. For IVF and ICSI, we need more refined birth defects analysis to demonstrate the differences.

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(Received on October 10, 2013)