Birth defects in children conceived by in vitro fertilization and intracytoplasmic sperm injection: a meta-analysis

Juan Wen, B.S.,[a,b] Jie Jiang, B.S.,[a,b] Chenyue Ding, B.S.,[d] Juncheng Dai, M.D.,[b] Yao Liu, B.S.,[b] Yankai Xia, M.D., Ph.D.,[a,c] Jiayin Liu, M.D., Ph.D.,[a,d] and Zhibin Hu, M.D., Ph.D.[a,b]

[a] State Key Laboratory of Reproductive Medicine, [b] Department of Epidemiology and Biostatistics, [c] Department of Toxicology, Key Laboratory of Modern Toxicology of Ministry of Education, School of Public Health, and [d] Center of Clinical Reproductive Medicine, the First Affiliated Hospital, Nanjing Medical University, Nanjing, People's Republic of China

Objective: To conduct a meta-analysis of studies assessing the effect of IVF and intracytoplasmic sperm injection (ICSI) on birth defects.
Design: Meta-analysis.
Setting: Centers for reproductive care.
Patient(s): Patients treated by IVF and/or ICSI.
Intervention(s): We identified all studies published by September 2011 with data related to birth defects in children conceived by IVF and/or ICSI compared with spontaneously conceived children, or birth defects in the children conceived by IVF compared with those by ICSI. Risk ratios from individual studies were pooled with the fixed and random effect models.
Main Outcome Measure(s): Risk of birth defects in children conceived by IVF and/or ICSI.
Result(s): Of 925 studies reviewed for eligibility, 802 were excluded after screening titles and abstracts, 67 were excluded for duplicated data, data unavailable, or inappropriate control group, 56 were included in the final analysis. Among the 56 studies, 46 studies had data on birth defects in children conceived by IVF and/or ICSI (124,468) compared with spontaneously conceived children. These studies provided a pooled risk estimation of 1.37 (95% confidence interval [CI]: 1.26–1.48), which is also evident in subgroup analysis. In addition, 24 studies had data on birth defects in children conceived by IVF (46,890) compared with those by ICSI (27,754), which provided an overall no risk difference.
Conclusion(s): Children conceived by IVF and/or ICSI are at significantly increased risk for birth defects, and there is no risk difference between children conceived by IVF and/or ICSI. (Fertil Steril® 2012;97:1331–7. ©2012 by American Society for Reproductive Medicine.)
Key Words: Birth defects, IVF, ICSI, meta-analysis

Assisted reproductive technologies (ART), including IVF and intracytoplasmic sperm injection (ICSI), have been widely used in the treatment of human infertility. Since the first child conceived by IVF was born in the United Kingdom in 1978 (1), more than 1 million babies worldwide have been born from IVF and/or ICSI (2). There has always been a concern that the infants conceived by ART are at an increased risk of birth defects. Most publications reported increased risks of birth defects in infants born after ART compared with spontaneously conceived (SC) children (2–24). However, controversial results were also abundant (25–47). Intracytoplasmic sperm injection involves the selection of a single sperm cell and the manual injection of the cell into the egg, thus, it is interesting to compare birth defects risk between IVF and ICSI (2, 19–24, 41–57). Actually, case reports reported severe defects in children conceived by ICSI (58–60). To systematically evaluate published evidence on the association between birth defects and ART and compare the risk difference between IVF and ICSI, we conducted an extensive literature search and meta-analysis.

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Reprint requests: Zhibin Hu, M.D., Ph.D., Hanzhong Road 140, Nanjing, People's Republic of China (E-mail: zhibin_hu@njmu.edu.cn); Jiayin Liu (E-mail: jyliu_nj@126.com); and Yankai Xia (E-mail: yankaixia@njmu.edu.cn).

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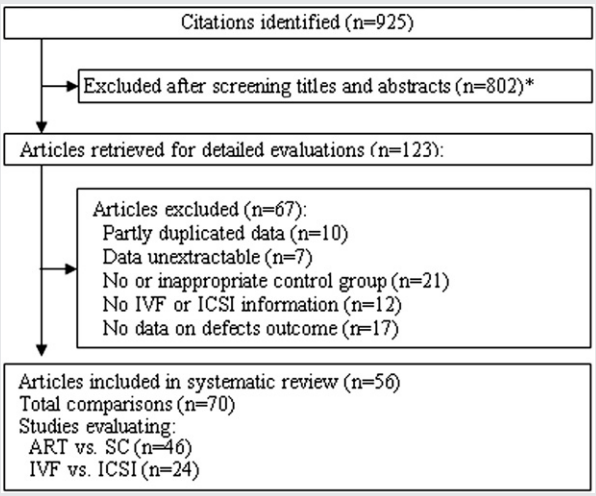
MATERIALS AND METHODS

Search Strategy and Selection Criteria

We retrieved Medline and Embase databases using a broad combination of search terms that included in vitro fertilization/IVF, intracytoplasmic sperm injection/ICSI, assisted reproductive technology/ART, infertility treatment and birth defect, congenital defects or

FIGURE 1



Flow chart of study selection in review of the effect of IVF and ICSI on birth defects. ART = assisted reproductive technologies; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection; SC = spontaneously conceived children. *Including articles not published in English or Chinese.

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congenital abnormality. All publications appearing before September 2011 in these databases were included. Furthermore, we reviewed reference lists in the retrieved articles. Institutional Review Board approval was obtained.

Studies were included if 1) the exposure of interest was IVF and/or ICSI; 2) the outcome of interest was birth defects; 3) comparison of IVF and/or ICSI to SC, or comparison of IVF to ICSI; and 4) risk ratios (RR) with 95% confidence intervals (CI) provided or could be calculated (Fig. 1). Because of language barrier, only studies published in English or Chinese were included for further analysis. We excluded studies that were not published as full reports; studies that were case reports; studies with inappropriate comparison group or without control subjects.

Independent Assessment

Two investigators (J. Wen and J. Jiang) independently reviewed all the articles, and data were checked by other investigators. The two investigators were blinded to identify information from each study, and judged the inclusion and exclusion of the study. Where a study provided birth defect data for IVF and ICSI infants separately compared with a single SC comparison group (24, 47), the data were pooled to form one risk estimate of IVF plus ICSI versus SC. If the sources of study population recruitment overlapped in two or more articles, the one with the more detailed birth defect information was selected (4, 22, 61–64).

Authors, publication year, study location, types of treatment, number of ART infants and control subjects, study design, birth defect subgroup, adjustment for confounders, and other related information were extracted. The concordance rate between the two investigators was 98.4%. Discrepancies were resolved by consensus.

Statistical Analysis

If adjusted RR was not given, crude RR was used. In all the included studies, only an American study was a case-control study (5). Because birth defects are rare, we assumed equivalence of the odds ratio and the relative risk. Therefore, we apply RR for the effect measure of this study. Statistical heterogeneity among studies was evaluated by using the χ^2 test, P values, and I^2 statistics (65). Where the homogeneous test was not significant ($P>.10$), a fixed-effects model was used to obtain summary RR, otherwise, a random-effects model was used. Publication bias was evaluated by using funnel plots and the Begg 's test (66). A P value less than .10 was considered to indicate significant publication bias. All statistical tests were two-sided and calculated using the Stata software (version 9.1; Stata Corp).

RESULTS

Of the 56 included studies, 14 included data on both IVF and/or ICSI children compared with SC children and IVF children compared with ICSI children. A summary of the 56 included studies is given in Supplemental Table 1 (available online). The earliest study was published in 1989 and the latest one in 2011, but more than half of the studies were published within the past 6 years. The sample size of the IVF and/or ICSI patients in each study ranged from 34–16,280. Thirty of 56 studies (54%) had <1,000 IVF and/or ICSI patients, and about half of the studies (54%) were population-based. A few of the studies matched the cases and controls, but the majority of the studies (64%) adjusted confounding factors such as maternal age, parity, sex, year of birth, social class, and/or smoking. Furthermore, 45% of the studies stratified birth defects to various organ systems.

Overall, 46 studies accessed birth defects of IVF and/or ICSI children compared with SC children, involving 124,468 IVF and/or ICSI infants. As shown in Table 1, for IVF and/or ICSI children compared with SC children, a significantly increased risk of birth defects was observed (RR = 1.37, 95% CI 1.26–1.48). The individual risk estimate for these studies ranged from 0.56–5.53 (Fig. 2).

In our analysis, a small Australia study had a very low RR of 0.56 (95% CI 0.37–0.84) (39), significantly different from other studies. In that study, birth defects were assessed at 2 years of age, and neonatal deaths were excluded. Thus, we removed that study in all subsequent analysis. After removal of this study, the adjusted/crude RR of ART versus SC was 1.39 (95% CI 1.29–1.50).

The pooled adjusted RR or crude RR was 1.36 (95% CI 1.25–1.47) and 1.45 (95% CI 1.33–1.59), respectively, indicating an adjustment of the potential confounding factors that may help clarify the true risk estimates, although the heterogeneity test was not significant between the two subgroups ($P=.298$) (Table 1). We also stratified our analyses to IVF or ICSI compared with SC, population or clinic-based studies, study sample size, and defect-affected systems. In our results, the RR of ICSI compared with SC (1.58) was larger than that of IVF compared with SC (1.30), but statistical significance was not reached (heterogeneity test: $P=.113$). The RR of clinic-based studies (1.67) was significantly larger than that of

TABLE 1

Results of birth defects in children conceived by IVF and/or ICSI.

	No. of comparisons	Pooled RR[a] (95% CI)	Pooled RR[b] (95% CI)	*P* value[c]	I^2 (%)[c]
ART vs. SC					
All defects (adjusted/crude data[d])	46		1.37 (1.26–1.48)	.000	74.6
All defects (adjusted/crude data[e])	45		1.39 (1.29–1.50)	.000	72.6
Adjusted data	33		1.36 (1.25–1.47)	.000	65.3
Crude data	27		1.45 (1.33–1.59)	.000	80.7
Subgroup analyses					
Population or Clinic-based data					
Population-based data	26		1.34 (1.24–1.45)	.000	78.9
Clinic-based data	19		1.67 (1.32–2.11)	.031	41.4
No. conceived by ART					
>1,000	23		1.31 (1.21–1.41)	.000	78.6
<1,000	22		1.77 (1.43–2.18)	.008	47.4
IVF or ICSI vs. SC					
IVF vs. SC	16		1.30 (1.17–1.46)	.055	39.1
ICSI vs. SC	15		1.58 (1.27–1.95)	.001	61.6
Systems					
Nervous system	15		2.01 (1.27–3.20)	.000	89.3
Genitourinary system	17		1.69 (1.33–2.15)	.000	86.4
Digestive system	19		1.66 (1.28–2.16)	.000	72.5
Circulatory system	21		1.64 (1.30–2.07)	.000	91.0
Musculoskeletal system	18		1.48 (1.09–2.02)	.000	90.8
Eye, ear, face, and neck	15		1.43 (1.01–2.05)	.000	84.5
IVF vs. ICSI					
All defects (adjusted/crude data[d])	24		1.05 (0.91–1.20)	.003	50.6
Subgroup of IVF vs. ICSI					
System					
Nervous system	4	0.80 (0.51–1.27)		.534	0.0
Digestive system	8	1.28 (0.90–1.82)		.327	13.2
Genitourinary system	8		1.00 (0.71–1.41)	.073	46.0
Circulatory system	8	0.95 (0.79–1.13)		.170	32.3
Musculoskeletal system	8	0.83 (0.69–1.00)		.495	4.6
Eye, ear, face, and neck	7	1.14 (0.82–1.57)		.755	0.0

Note: ART = assisted reproductive technologies; ICSI = intracytoplasmic sperm injection; SC = spontaneously conceived children.
[a] With fixed-effect model.
[b] With random-effect model.
[c] For heterogeneity test.
[d] Included adjusted or crude RR, if adjusted RR was not given, crude RR was used.
[e] After excluding Sauder et al., 1996.

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population-based studies (1.34) (heterogeneity test: $P = .081$); and the RR of the groups with sample size less than 1,000 (1.77) was significantly larger than that of the groups with sample size more than 1,000 (1.31) (heterogeneity test: $P = .009$). In addition, subgroup analyses by defect-affected system were all significant, especially the nervous system (RR = 2.01, 95% CI 1.27–3.20) (Table 1).

Twenty-four studies were for birth defects in children conceived by IVF compared with those by ICSI, involving 46,890 IVF infants and 27,754 ICSI infants. Overall, there is no risk difference for birth defects between IVF and ICSI groups (RR = 1.05, 95% CI 0.91–1.20), which is consistent with the risk estimates when compared with SC children. The individual point estimates for these studies ranged from 0.33–3.05 (Fig. 3). In subgroup analysis, the difference in risk for musculoskeletal system malformations was approaching significance, but considering multiple comparisons, we believe that it is not reliable evidence.

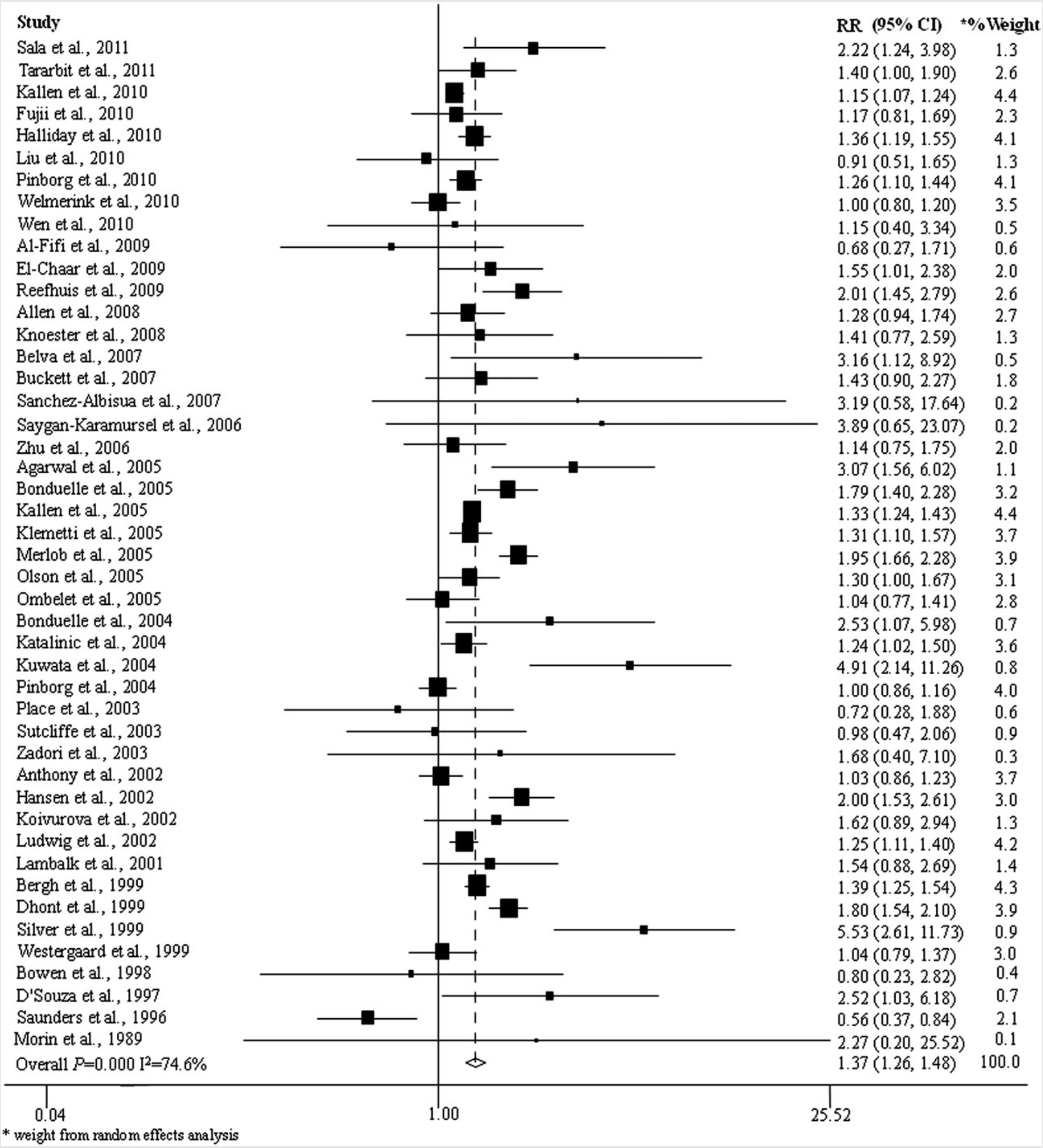
Then we evaluated publication bias by using funnel plots (Supplemental Figs. 1 and 2, available online) and the Begg's test. The *P* value of the Begg's test for the adjusted/crude data of IVF and/or ICSI versus SC and IVF versus ICSI were 0.293 and 0.552, respectively, indicating that there was no obvious publication bias in our analysis.

DISCUSSION

This report reviewed and pooled epidemiological data assessing the risk of birth defects after ART and compared the risk difference of birth defects after ICSI and IVF. Our results suggest that there is a significantly increased risk of birth defects in infants conceived by ART, but ICSI did not increase the risk compared with IVF.

According to the source of control, we divided studies into population-based studies and clinic-based studies. The RR of clinic-based group was significantly larger than that of population-based ones. This may be because hospitals do not actively seek birth defect information beyond that obtained at birth and therefore clinic-based control data are likely to underestimate the rate of birth defects. In addition, the RR of the group with a sample size less than 1,000 was significantly larger than that of the group with sample size of

FIGURE 2



Individual risk ratio estimates and pooled ratio estimates from the studies relating IVF and ICSI children compared with spontaneously conceived children. Abbreviations as in Fig. 1. *Weight from random effects analysis.

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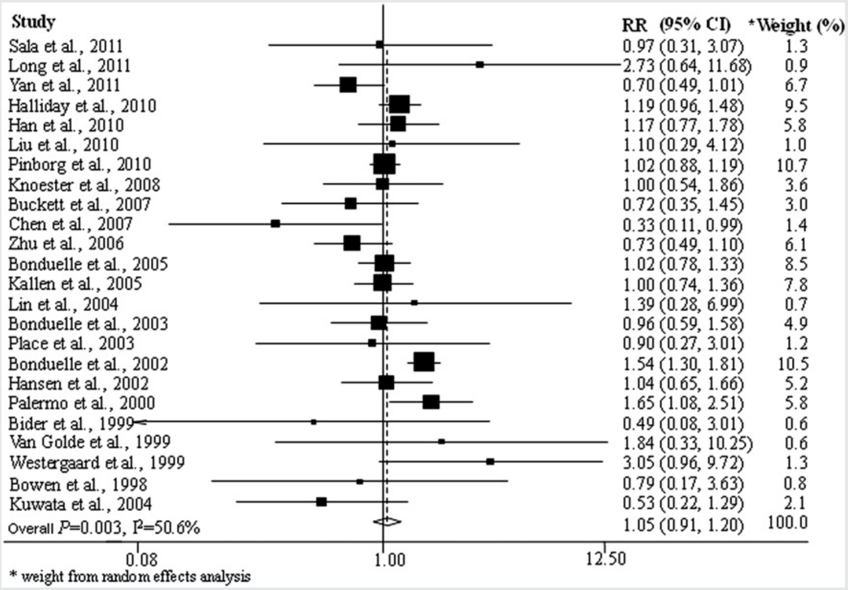
more than 1,000. Because larger sample studies are more representative and have less bias, the results of studies with larger sample size tended to be more reliable, and were similar to the adjusted RR. Although the difference in the prevalence of defects among the various systems was not significant, the effect of ART on the nervous system is relatively obvious, compared with the effects on eyes, ears, face, and neck, which may suggest that the earlier developed systems were more sensitive to birth defects by ART.

There is considerable heterogeneity among the 56 included studies. The differences included methodologies for assessing the case and control infants and the extent of

FIGURE 3



Individual risk ratio estimates and pooled risk ratio estimates from studies relating birth defects in children conceived by IVF compared with ICSI. Abbreviations as in Fig. 1. *Weight form random effects analysis.

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matching for maternal age. There are also many competing risks that could increase the rate: age of mother, factors causing the infertility in the mother or father, prior treatment for infertility, duration of infertility, environmental exposures, risk behaviors such as alcohol and smoking, and the ART procedures themselves. As we can see, the overall effect decreased after adjustment for some variables.

Factors associated with ART that may increase the risk of birth defects include the underlying infertility in the couples seeking treatment, and factors associated with the ART procedures themselves. Some researchers have argued that the excess risk of birth defects found in infants born after ART treatment may be due to the underlying infertility of the couples seeking treatment, rather than the treatments themselves (63, 67). Ericson and Kallen (63) proposed that the excess risk for some specific defects after ICSI may be related to paternal subfertility with a genetic background. A careful analysis of the outcome of singleton pregnancies resulting from IVF versus artificial insemination obtained with or without the use of ovarian stimulatory agents and obtained with or without the use of a semen donor, suggests that female infertility is an important risk factor (67). Thus, the major limitation of the study is that the comparison group for IVF and/or ICSI is SC rather than babies born to infertile couples who conceived without these procedures. The reason why we did not do a meta-analysis with this comparison group is because there are very few such studies in the literature. It has recently been suggested that, to address this question, an appropriate comparison group would include children born to infertile couples who do eventually conceive spontaneously without ART treatment (68).

Taken together, large-scale research on the prevalence of ART-associated birth defects and long-term follow-up of the infants are still essential for the estimation of birth defects risk after ART. In addition, studies of special defects are also needed.

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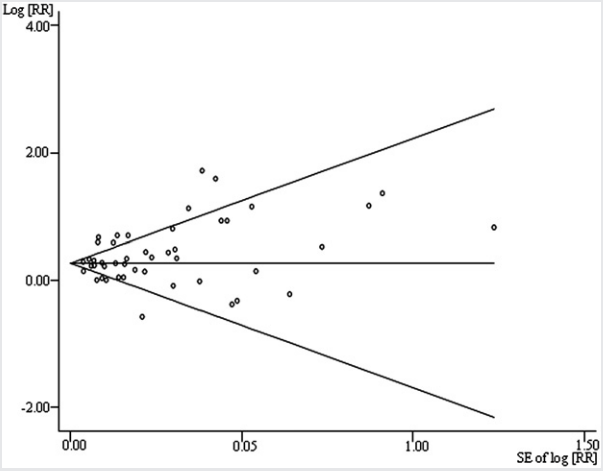
SUPPLEMENTAL FIGURE 1



Funnel plot of log (RR) against SE of log (RR) for studies relating birth defects in IVF and/or ICSI children compared with spontaneously conceived children.

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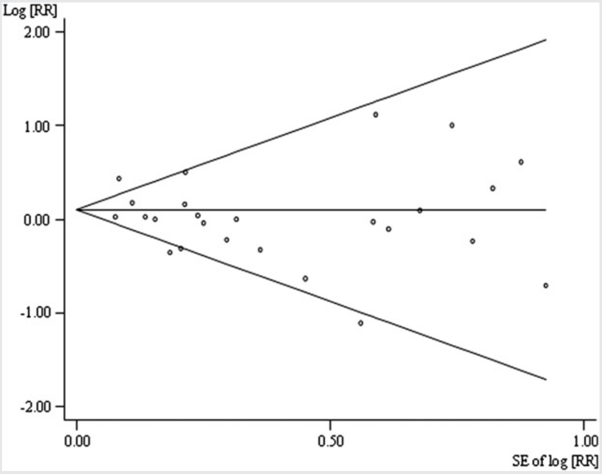
SUPPLEMENTAL FIGURE 2



Funnel plot of log (RR) against SE of log (RR) for studies relating birth defects in children conceived by IVF compared with by ICSI.

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SUPPLEMENTAL TABLE 1

Details of studies included in the meta-analysis of effects of IVF and/or ICSI on birth defects.

Author(s), publication year	Location	No. conceived by IVF and/or ICSI	No. conceived by IVF	No. conceived by ICSI	Study evaluated	Adjusted[a] or crude data	ART vs. SC RR[b] (95% CI)	IVF vs. ICSI RR[b] (95% CI)
Bonduelle et al., 2005	Europe	977	437	540	Both	Adjusted	1.79 (1.40–2.28)	1.02 (0.78–1.33)
Tararbit et al., 2011	France	5,493			ART vs. SC	Adjusted	1.40 (1.00–1.90)	
Kallen et al., 2010	Sweden	15,570			ART vs. SC	Adjusted	1.15 (1.07–1.24)	
Reefhuis et al., 2009	USA	9,584			ART vs. SC	Adjusted	2.01 (1.45–2.79)	
El-Chaar et al., 2009	Canada	790			IVF vs. SC	Adjusted	1.55 (1.01–2.38)	
Belva et al., 2007	Belgium	150			ICSI vs. SC	Crude	3.16 (1.12–8.92)	
Olson et al., 2005	USA	1,462			ART vs. SC	Adjusted	1.30 (1.00–1.67)	
Merlob et al., 2005	Israel	1,910			ART vs. SC	Crude	1.95 (1.66–2.28)	
Klemetti et al., 2005	Finland	4,559			IVF vs. SC	Adjusted	1.31 (1.10–1.57)	
Agarwal et al., 2005	Multiple locations	76			ICSI vs. SC	Adjusted	3.07 (1.56–6.02)	
Katalinic et al., 2004	Germany	3,372			ICSI vs. SC	Adjusted	1.24 (1.02–1.50)	
Bonduelle et al., 2004	Multiple locations	300			ICSI vs. SC	Adjusted	2.53 (1.07–5.98)	
Ludwig et al., 2002	Germany	3,372			ICSI vs. SC	Crude	1.25 (1.11–1.40)	
Silver et al., 1999	USA	481			IVF vs. SC	Crude	5.53 (2.61–11.73)	
Dhont et al., 1999	Belgium	5,539			ART vs. SC	Adjusted	1.80 (1.54–2.10)	
Bergh et al., 1999	Sweden	5,856			IVF vs. SC	Adjusted	1.39 (1.25–1.54)	
D'Souza et al., 1997	UK	278			IVF vs. SC	Adjusted	2.52 (1.03–6.18)	
Sala et al., 2011	Italy	225	88	137	Both	Crude	2.22 (1.24–3.98)	0.97 (0.31–3.07)
Pinborg et al., 2010	Denmark	11,233	7,564	3,669	Both	Adjusted	1.26 (1.10–1.44)	1.02 (0.88–1.19)
Halliday et al., 2010	Australia	6,946	3,312	3,634	Both	Adjusted	1.36 (1.19–1.55)	1.19 (0.96–1.48)
Kallen et al., 2005	Sweden	16,280	11,283	4,949	Both	Adjusted	1.33 (1.24–1.43)	1.00 (0.74–1.36)
Kuwata et al., 2004	Japan	232	148	84	Both	Adjusted	4.91 (2.14–11.26)	0.53 (0.22–1.29)
Hansen et al., 2002	Australia	1,138	837	301	Both	Adjusted	2.00 (1.53–2.61)	1.04 (0.65–1.66)
Wen et al., 2010	Canada	1,044			ART vs. SC	Adjusted	1.15 (0.40–3.34)	
Welmerink et al., 2010	USA	2,182			IVF vs. SC	Adjusted	1.00 (0.80–1.20)	
Fujii et al., 2010	Japan	1,408			ART vs. SC	Adjusted	1.17 (0.81–1.69)	
Al-Fifi et al., 2009	Saudi Arabia	253			ICSI vs. SC	Crude	0.68 (0.27–1.71)	
Allen et al., 2008	UK	1,524			IVF vs. SC	Crude	1.28 (0.94–1.74)	
Sanchez-Albisua et al., 2007	Germany	34			ICSI vs. SC	Crude	3.19 (0.58–17.64)	
Saygan-Karamursel et al., 2006	Turkey	274			ICSI vs. SC	Adjusted	3.89 (0.65–23.07)	
Ombelet et al., 2005	Belgium	2,757			ICSI vs. SC	Adjusted	1.04 (0.77–1.41)	
Pinborg et al., 2004	Denmark	3,393			ART vs. SC	Crude	1.00 (0.86–1.16)	
Zadori et al., 2003	Hungary	262			IVF vs. SC	Adjusted	1.68 (0.40–7.10)	
Sutcliffe et al., 2003	Multiple locations	264			ICSI vs. SC	Adjusted	0.98 (0.47–2.06)	
Koivurova et al., 2002	Finland	304			IVF vs. SC	Adjusted	1.62 (0.89–2.94)	
Anthony et al., 2002	Netherlands	4,224			IVF vs. SC	Adjusted	1.03 (0.86–1.23)	
Lambalk et al., 2001	Netherlands	480			IVF vs. SC	Adjusted	1.54 (0.88–2.69)	
Saunders et al., 1996	Australia	314			IVF vs. SC	Adjusted	0.56 (0.37–0.84)	
Morin et al., 1989	USA	83			IVF vs. SC	Adjusted	2.27 (0.20–25.52)	
Liu et al., 2010	China	567	415	152	Both	Crude	0.91 (0.51–1.65)	1.10 (0.29–4.12)
Knoester et al., 2008	Netherlands	87	81	81	Both	Adjusted	1.41 (0.77–2.59)	1.00 (0.54–1.86)
Buckett et al., 2007	Canada	377	217	160	Both	Adjusted	1.43 (0.90–2.27)	0.72 (0.35–1.45)
Zhu et al., 2006	Denmark	6,278	1,483	398	Both	Adjusted	1.14 (0.75–1.75)	0.73 (0.49–1.10)
Place et al., 2003	Belgium	118	52	66	Both	Adjusted	0.72 (0.28–1.88)	0.90 (0.27–3.01)
Westergaard et al., 1999	Denmark	2,245	1,913	180	Both	Adjusted	1.04 (0.79–1.37)	3.05 (0.96–9.72)
Bowen et al., 1998	Australia	173	84	89	Both	Adjusted	0.80 (0.23–2.82)	0.79 (0.17–3.63)

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SUPPLEMENTAL TABLE 1

Continued.

Author(s), publication year	Location	No. conceived by IVF and/or ICSI	No. conceived by IVF	No. conceived by ICSI	Study evaluated	Adjusted[a] or crude data	ART vs. SC RR[b] (95% CI)	IVF vs. ICSI RR[b] (95% CI)
Yan et al., 2011	China		7,096	3,103	IVF vs. ICSI	Crude		0.70 (0.49–1.01)
Long et al., 2011	China		1,575	388	IVF vs. ICSI	Crude		2.73 (0.64–11.68)
Han et al., 2010	China		4,670	3,837	IVF vs. ICSI	Crude		1.17 (0.77–1.78)
Chen et al., 2007	China		991	283	IVF vs. ICSI	Crude		0.33 (0.11–0.99)
Lin et al., 2004	China		134	185	IVF vs. ICSI	Crude		1.39 (0.28–6.99)
Bonduelle et al., 2003	Belgium		207	439	IVF vs. ICSI	Crude		0.96 (0.59–1.58)
Bonduelle et al., 2002	Belgium		2,295	2,840	IVF vs. ICSI	Crude		1.54 (1.30–1.81)
Palermo et al., 2000	USA		1,796	2,059	IVF vs. ICSI	Crude		1.65 (1.08–2.51)
Van Golde et al., 1999	Spain		132	120	IVF vs. ICSI	Crude		1.84 (0.33–10.25)
Bider et al., 1999	Israel		80	60	IVF vs. ICSI	Crude		0.49 (0.08–3.01)

Note: ART = assisted reproductive technologies; ICSI = intracytoplasmic sperm injection; SC = spontaneously conceived children; Both = studies evaluating both IVF and/or ICSI vs. SC and IVF vs. ICSI; Adjusted [a]: included adjusted and matched data; RR [b]: pooled from adjusted RR or crude RR, if adjusted RR was not given, crude RR substituted for it.

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