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A Meta-Analysis of Controlled Studies Comparing Major Malformation Rates in IVF and ICSI Infants with Naturally Conceived Children*

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***Purpose*:** To estimate the risk of major malformations in IVF and ICSI infants.
***Methods*:** Forty-four studies published in English since 1990 where the major malformation rate for IVF or ICSI cases was compared to an appropriate control group were reviewed. Nineteen studies met all selection criteria. In addition, a quality score was developed to assess each study based on sample size, timing of diagnosis, appropriateness of control group and other factors.
***Results*:** In 19 studies, the major malformation rates ranged from 0–9.5% for IVF; 1.1–9.7 for ICSI; and 0–6.9% in the control groups. When ICSI was compared to IVF, and multiple births compared to singleton, there were no statistically significant differences. When data from 16 studies involving 28,524 IVF infants and 2,520,988 spontaneously conceived controls and 7 studies involving 7234 ICSI infants and 978,078 controls were pooled, we found an overall odds ratio for the 19 studies of 1.29 (95% CI 1.01–1.67).
***Conclusions*:** The overall odds ratio of 1.29 was statistically significant at the 5% level. These results may be useful for counseling ART patients and properly designing the consent forms used for ART procedures. It is not clear whether this risk is due to the procedures used in ART. We found that some of these studies have design flaws. All of them lacked an appropriate control group, i.e. infertile patients conceiving spontaneously. These flaws may create biases that would in almost all instances increase the risk of major malformations in the study group. Further research with better designed studies will likely result in a better estimate of the risk of major malformations associated with IVF and ICSI.

KEY WORDS: ART major malformation rate; IVF/ICSI major malformation rate; meta-analysis.

INTRODUCTION

The first IVF birth was in 1978; the first ICSI birth in 1992. There has always been a concern as to whether the infants resulting from these procedures face an increased risk of major malformation (MM) (1,2). A number of studies have addressed this issue but the results vary widely. In the last few years, anecdotal reports of rare conditions, such as Beckwith–Wiedemann Syndrome, following ART have been given sensational media coverage causing fear in patients and concern to practitioners. This study is an effort to obtain an estimate of the risk through a systematic review and a meta-analysis of controlled

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*This meta-analysis of 19 studies suggests that there is approximately a 29% increased risk of major malformation in ART infants.

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observational studies. The analysis is reported using the recommendations of the MOOSE Group (3).

METHODS

Search Strategy and Data Extraction. We conducted, with some assistance from the librarians at our institutions, a systematic search of the literature using the MEDLINE (PubMed), LILACS and EMBASE databases. Search terms included: in vitro fertilization or IVF, intracytoplasmic sperm injection or ICSI, assisted reproductive technology or ART, with major malformation, malformation, congenital defects or adverse effects. MEDLINE is the electronic version of Index Medicus. LILACS (Latin American Literature in Health Sciences) contains papers published in Latin America and the Caribbean some of which are not available in the MEDLINE database. EMBASE is the Excerpta Medica database available on the Dialog search system. Additional studies were identified by engaging in personal communication with published scientists in the field and by tracing recent media reports to scientific publications. We also reviewed the references in each retrieved paper to identify additional studies and searched the internet using our search terms in the on line browser, Internet Explorer. Eligibility and exclusion criteria were determined after a review of all potentially relevant studies. Data extraction was performed jointly by two authors (AAR and ACK) from text, tables and figures in the eligible studies, and consensus was obtained for all data.

Eligible Studies. We included only controlled studies published in English in 1990 or thereafter through September 2003 which presented specific major malformation data and had at least 100 infants (cases plus controls) and ascertainable numerators and denominators for case and control groups. Where studies referenced population-based public health reports for their control group, we sought the cited data sources and identified the numerators and denominators for the rates given in the study. Multiple papers from the same center and/or authors were analyzed to determine whether the most recent publication was an accumulation which included cases reported in earlier publications. If this was evident from our review, then we used only the most recent publication.

Some of the studies we used included patients who were treated in the mid to late 80s. Some IVF studies included a small number of patients undergoing ICSI without stratifying this in the results. We treated those as IVF studies. Some IVF studies used cryopreserved embryos, some used only fresh embryos and some did not discuss this point or implied that the data was mixed. We included all such studies. This probably did not affect our results as others have shown that the outcome as to MM is the same whether cryopreserved or fresh embryos are used (4–6). The process of selecting the 19 studies that met our inclusion criteria is shown in Fig. 1 (7–25).

Ineligible Studies. There were many reports without control groups that had to be excluded. These included the annual reports from the large national registry maintained by the Society for Assisted Reproductive Technology in cooperation with

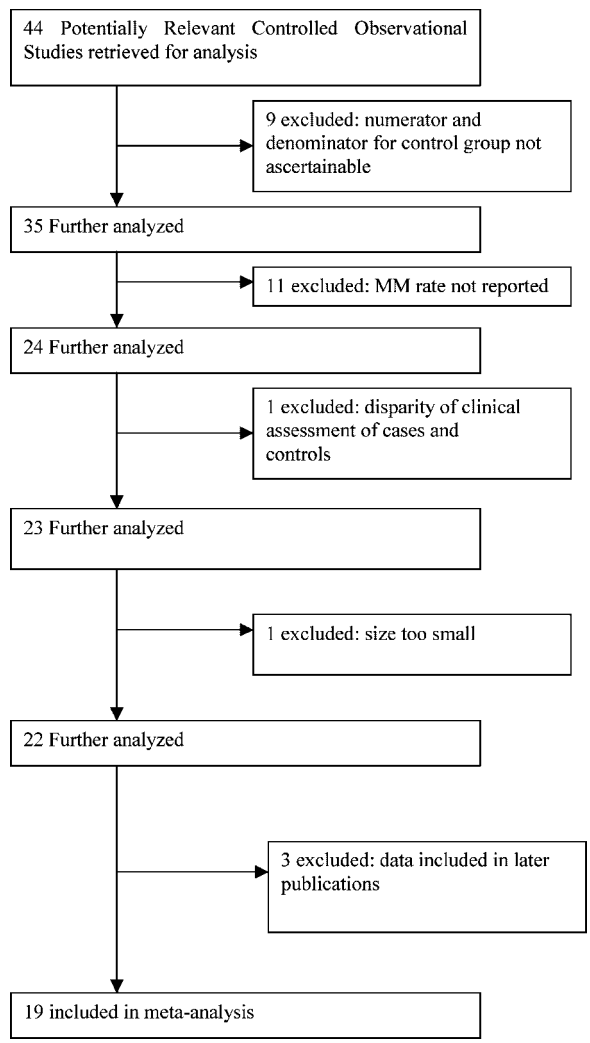

Fig. 1. Flow Diagram. The reasons for exclusion are shown above listed from most important to least important. Many studies were excluded for multiple reasons. Using the hierarchy above, each excluded study is listed once in the highest applicable category.

the Centers for Disease Control in the United States and the Multi-National Cooperative Registry, operated through the European Society for Human Reproduction and Endocrinology. (26,27) From the 44 controlled studies retrieved for close analysis, we excluded studies without ascertainable control groups, studies which did not report malformations as an outcome, and studies which combined MM and minor malformations in a single metric.

Definitions. The included studies defined major malformation as a condition that causes functional impairment or requires surgical correction, or used a slight variation on that definition.

Statistical Methods

In the 19 studies meeting our criteria, sufficient data was available to conduct the following sub-group meta-analyses: 1) IVF singleton births: 8 studies; 2) IVF multiple births: 7 studies; 3) ICSI singleton births: 6 studies; 4) ICSI multiple births: 4 studies; 5) IVF singleton births and multiple births combined: 16 studies; 6) ICSI singleton births and multiple births combined: 7 studies; and 7) overall IVF and ICSI singleton births and multiple births combined: 19 studies. Four of the 19 studies evaluated both an ICSI group and an IVF group. There was no adjustment for multiple comparisons. All subgroups analyzed were not statistically significant ($P < 05$).

The standard DerSimonian and Laird method (28) was used for the meta-analysis using the Number Cruncher Statistical Software (2004) software package. The first step was to compute the odds ratio for each study and its 95% confidence interval. We tested for the heterogeneity of odds ratios across the studies. If studies are homogeneous, it is assumed that the same underlying unknown effect of ART on MM rates is plausible across all studies. In that situation, a "fixed effect" meta-analysis model should be used and this usually results in smaller 95% confidence intervals and is less conservative. If the heterogeneity test is statistically significant, then it must be assumed that the odds ratio for each study comes from a hypothetical random distribution of odds ratios, each with a hypothetical fixed mean and variance. In this case, the random effects model is used and will result in a more conservative estimate with wider 95% confidence intervals, and fewer statistical significances. This model assumes further that the various studies are actually estimating different odds ratios and takes into account the increase in variation under this assumption. The random effects model was used in our meta-analysis because the test for heterogeneity was statistically significant ($P < 0.0001$). This heterogeneity undoubtedly results from the actual variation among the 19 studies with regard to study design, age of assessment of infants, assessment method and country of origin, among other factors. Though studies varied in these ways, there was within-study consistency in all 19 studies, as this was part of the inclusion criteria.

Quality Assessment

We devised a quality scale for evaluating the included studies using the five factors that are most relevant to controlling for the types of biases that can effect these types of controlled studies. The factors were: 1) sample size, 2) similarity of the timing of the evaluation of case infant versus control infant, 3) matching of cases and controls for age and other relevant factors, such as socioeconomic status (SES), 4) similarity of the medical evaluation of the infant in case and control groups, and 5) appropriateness of control group as compared to the most appropriate control group, namely infertile patients who conceived spontaneously. We used a five-point scale for each factor (with 1 for poor and 5 for excellent) and gave equal weight to each factor. We summed the scores so that five was the lowest possible quality score and 25 was the highest attainable score. Two authors (AAR, ACK) graded the studies together and compared the scores three times. During each review, the five factors in each study were thoroughly discussed. The differences in scores between reviews decreased with each review and were negligible by the last review. The scores from the third review were used. Though this type of scoring system is rather arbitrary, we made an effort to apply the criteria uniformly.

RESULTS

The studies had wide variation in MM rates. (Table I) For example, the MM rates varied between 0% and 9.5% for IVF and between 1.1% and 9.7% for ICSI. The control groups MM rates varied between 0% and 6.9%. This wide variation is likely attributable to differences in study design between the studies.

The odds ratios for the meta-analysis of singleton vs. multiple births and IVF vs. ICSI are shown in Table II. None of these odds ratios were significantly different between the groups. The data were pooled across IVF/ICSI and singleton/multiple to obtain an overall odds ratio of 1.29, (95% CI, 1.01–1.67). The

Table I. Studies Used in Meta Analysis of Major Malformations in ART Infants

Study	IVF or ICSI	Study		Control		Stratification[a]	Quality Score[b] (component scores)
		N	Mal # (%)	N	Mal # (%)		
Bowen (7)	IVF	84	3 (3.5)	80	4 (5.0)	Combined	17 (1, 5, 5, 5, 1)
Bowen	ICSI	89	4 (4.5)	80	4 (5.0)	Combined	
Sutcliff (8)	ICSI	208	10 (4.8)	221	10 (4.5)	Singleton	18 (3, 5, 4, 5, 1)
Palermo (9)	ICSI	808	10 (1.2)	297,468	7,322 (2.5)[c]	Singleton	16 (5, 5, 1, 4, 1)
Palermo	ICSI	1,251	12 (1.0)	297,468	7,322 (2.5)	Multiple	
Palermo	IVF	1,796	30 (1.7)	297,468	7,322 (2.5)	Combined	
Palermo	ICSI	2,059	22 (1.1)	297,468	7,322 (2.5)	Combined	
Wennerholm (10)	ICSI	736	27 (3.7)	645,310	13,422 (2.1)	Singleton	18 (5, 4, 5, 3, 1)
Wennerholm	ICSI	1,139	47 (4.1)	645,310	13,422 (2.1)	Combined	
Wennerholm	ICSI	403	20 (5.0)	645,310	13,422 (2.1)	Multiple	
Ericson (11)	IVF	9,175	250 (2.7)	1,690,577	38,883 (2.3)	Combined	21 (5, 5, 5, 5, 1)
Anthony (12)	IVF	4,224	28 (0.7)	314,605	1,700 (0.5)	Combined	19 (5, 4, 5, 4, 1)
Hansen (13)	IVF	527	50 (9.5)	3,906	164 (5.3)	Singleton	19 (4, 5, 4, 5, 1)
Hansen	ICSI	186	18 (9.7)	3,906	164 (5.3)	Singleton	
Hansen	IVF	310	25 (8.1)	94	4 (4.3)	Multiple	
Hansen	ICSI	115	8 (7.0)	94	4 (4.3)	Multiple	
Hansen	IVF	837	75 (9.0)	4,000	168 (4.2)	Combined	
Hansen	ICSI	301	26 (8.6)	4,000	168 (4.2)	Combined	
Isaksson (14)	IVF	1,901	83 (4.4)	345	12 (3.5)	Singleton	21 (5, 5, 5, 5, 1)
Isaksson	IVF	952	39 (4.1)	200	7 (3.5)	Multiple	
Isaksson	IVF	2,853	122 (4.3)	545	19 (3.5)	Combined	
Ludwig (15)	ICSI	3,372	291 (8.6)	30,940	2,140 (6.9)	Combined	18 (5, 3, 4, 5, 1)
Ludwig	ICSI	1,944	166 (8.5)	30,940	2,140 (6.9)	Singleton	
Ludwig	ICSI	1,428	125 (8.8)	30,940	2,140 (6.9)	Multiple	
Merlob (16)	IVF	964	92 (9.5)	3,775	70 (1.9)	Combined	13 (4, 5, 1, 2, 1)
MRC (17)	IVF	1,581	35 (2.2)	196,380	5,378 (2.7)	Combined	19 (5, 4, 4, 5, 1)
MRC	IVF	939	19 (2.0)	196,380	5,378 (2.7)	Singleton	
MRC	IVF	642	16 (2.5)	196,380	5,378 (2.7)	Multiple	
Westergaard (18)	IVF	2,245	107 (4.8)	2,245	103 (4.6)	Combined	16 (5, 2, 5, 3, 1)
D'Souza (19)	IVF	278	7 (2.5)	278	0 (0.0)	Combined	19 (3, 5, 5, 5, 1)
D'Souza	IVF	150	5 (3.3)	278	0 (0.0)	Singleton	
D'Souza	IVF	128	2 (1.6)	278	0 (0.0)	Multiple	
Verlaenen (20)	IVF	140	0 (0.0)	140	0 (0.0)	Singleton	15 (2, 5, 5, 2, 1)
Sutcliffe (21)	IVF	91	3 (3.3)	83	2 (2.4)	Combined	17 (1, 5, 5, 5, 1)
Sutcliffe	IVF	68	2 (2.9)	83	2 (2.4)	Singleton	
Sutcliffe	IVF	23	1 (4.3)	83	2 (2.4)	Multiple	
Zadori (22)	IVF	188	4 (2.1)	188	1 (0.5)	Singleton	18 (2, 5, 5, 5, 1)
Zadori	IVF	301	5 (1.7)	262	3 (1.1)	Combined	
Zadori	IVF	113	1 (1.4)	74	2 (2.7)	Multiple	
Pinborg (23)	IVF	3393	139 (4.1)	10239	488 (4.8)	Multiple	19 (5,5,3,5,1)
Place (24)	IVF	52	3 (5.8)	59	3 (5.1)	Singleton	17 (1,5,5,5,1)
Place	ICSI	66	5 (7.6)	59	3 (5.1)	Singleton	
Wennerholm (25)	IVF	510	15 (2.9)	252	8 (3.2)	Combined	20 (4,5,5,5,1)

[a] Combined means results were presented for singleton and multiple births combined. Singleton means results given for singleton births only. Multiple means results given for twin and higher order multiple births only.
[b] As described in methods.
[c] Note that the 2.5% major malformation rate in the controls is not the rate presented in this paper, but rather is the rate reported in the New York State Department of Health Congenital Malformations Registry (which the paper cites) for major malformations diagnosed in the first three days of life. This is the figure comparable to that reported for the cases, which were evaluated at birth.

odds ratios along with their 95% CI for each study are shown in Fig. 2. Note that there was one study where there was a statistically significant ($P < 0.05$) protective effect of ART and four studies where there was a statistically significant ($P < 0.05$) risk associated with ART. The overall odds ratio obtained suggests that there is, at this time, based on the 19 studies currently available, a statistically significant increased risk of MM associated with IFV or ICSI.

DISCUSSION

Though ART has benefited the quality of life of hundreds of thousands of couples, it is not clear what the cost is for this benefit. There has been substantial research to derive an estimate of the cost by studying the adverse effects of the procedure. The parameters used to estimate cost include birth weight, prematurity, minor and major malformations,

Table II. Odds Ratio From a Meta-Analysis in Subgroups and Overall

	OR	95% CI Lower	95% CI Upper	Number of studies
IVF Single	1.51	0.85	2.7	8
IVF Multiple	0.92	0.75	1.12	7
ICSI Single	1.33	0.90	1.95	6
ICSI Multiple	1.18	0.60	2.37	4
IVF All	1.28	0.93	1.75	16
ICSI All	1.23	0.80	1.88	7
IVF/ICSI[a]	1.29	1.01	1.67	19

[a] Using a single OR for each publication all statistical significance tests for heterogeneity were $P < .0001$ and random effects model was used.

developmental outcome, chromosomal abnormalities, multiple births, perinatal mortality and MM. Concern regarding MM among ART practitioners is borne out by the fact that studies of the MM rate begin to appear soon after the use of ART procedures.

In spite of the many studies of MM following ART procedures, there is at the present time no generally accepted quantification of this risk. Some studies find no increase in risk while others find a two-fold increase in risk associated with ART. All of the studies

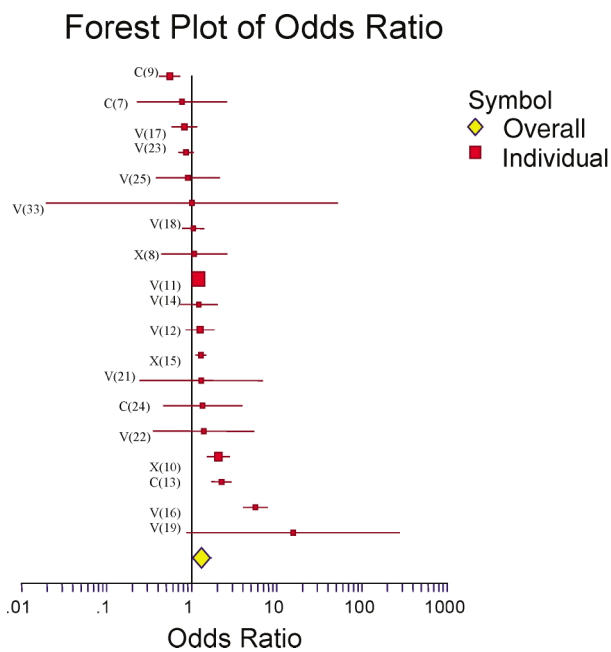

Fig. 2. Odds ratios and 95% confidence intervals for the 19 studies. V: IVF study; X: ICSI study; C: combined results of ICSI and IVF; ↓: Overall odds ratio. The reference number for each study is given in parentheses.

can be criticized on one or more grounds, mainly because there are many different factors that have to be considered and it is extremely challenging to design and carry out a perfect study.

There were wide differences in design among the 19 studies. These differences included the time of examination of the infants in the ART and control groups, the extent of matching for maternal age and other factors, methodologies for assessing the case and control infants, and the type of control group, although all of the included studies used a control group from the general population. Among the foregoing design issues, the most significant was the failure to use the most appropriate control group, namely: infertile couples who eventually conceive spontaneously without treatment for infertility.

We recommend that future studies strive to use more appropriate control groups. Use of such a control group is possible, as Saunders *et al* demonstrated in their study comparing IVF births to births among infertile patients on the IVF waiting list at the same hospital (1). Unfortunately MM was not an outcome reported in that study, but it is interesting to note that the risk of the waiting list group for preterm delivery and low birth weight, while lower then that of the IVF group, exceeded that of the general population. It may not be ethically or practically possible to do prospective trials randomizing infertile patients into a "no treatment" group and IVF waiting lists may be a thing of the past. Nonetheless, there may be patients who had difficulty conceiving, but did conceive, while under the care of their family doctor or general obstetrician/gynecologist. Collaboration with family doctors and general Ob-Gyns may lead to more appropriate control groups.

Another problem with the control group in many of these 19 studies is that the controls were not matched for maternal age. In some cases, statistical adjustments were carried out, but these may have been inadequate. Another issue relates to the timing of assessment of infant. Ideally case and control infant should be assessed no earlier than at the age of 6 months, as it has been reported that 90% of MM are diagnosed by the age of 6 months and only 66% at birth (28).

To what else could the increased MM rate shown in this meta-analysis be attributed? There are many competing risks that could elevate the MM rate. These include: age of mother, factors causing the infertility in the mother or father, a balanced translocation or other chromosomal abnormalities in one of the parents, prior treatment for infertility, prior pregnancy loss, SES, duration of infertility, education, environmental

exposures, risk behaviors such as alcohol and smoking and the ART procedures themselves. For example, in a carefully designed case control study, Draper and colleagues showed that a history of infertility contributes significantly to perinatal mortality, absent the use of ART (30). Recurrent pregnancy loss is an indicator for increased risk for birth defects, again without regard to the use of ART (31). In two large registry studies (32,33) infertility itself, independent of treatment, appears to be associated with preterm birth and other adverse birth outcomes. The female partners of couples undergoing ART have been found to exhibit an increased frequency of chromosomal abnormalities (34). Infertile males have also been shown to have an increased frequency of chromosomal abnormalities, including mircrodeletions and balanced translocations (35,36). Suffice it to say that it is not altogether unexpected that when infertile couples bear infants, following the use of ART, those infants are at some risk for major malformations and other adverse outcomes.

Our analysis showed a lower increased risk of MM for IVF and ICSI multiples (OR 0.92 and 1.18 respectively) than for IVF and ICSI singleton births. (Table II) This unexpected finding may be due to the fact that after ART, the majority of multiples are dizygotic. In naturally occurring multiple births, a substantial proportion of twins are monozygotic and the malformation rate is increased among such twins. A similar observation was made by Wennerholm (13) regarding the lower odds ratio for any malformation in the ICSI twins in his study as compared to the ICSI singletons.

What are the prospects of finding a higher or lower odds ratio during the next ten years using meta-analysis? We examined this question by evaluating the most recent studies as compared to those published in the early nineties. We hoped to find that the more recent studies were better designed and that there was some indication that special efforts were made to eliminate problems such as surveillance bias (i.e. a more thorough evaluation of ART infants than of the infants in the control group) and unmatched controls. We did not find any trend to suggest that the more recent studies were better designed.

The potential biases discussed in this paper tend to increase the risk associated with ART. Eliminating these biases in future studies may reduce the overall odds ratio of 1.29 that we found. In the meantime, however, the results presented here can be used to augment the discussion of potential risk in the consent forms used for ART procedures. Disclosure is important from both a patient care and medical-legal standpoint. Ideally the disclosures in consent forms should avoid creating unwarranted alarm based on anecdotal reports of rare conditions, and instead provide a scientific summary of the literature and indicate what is known about the magnitude of the risk of MM.

CONCLUSIONS

This meta-analysis of 19 studies suggests that there is approximately a 29% increased risk of MM in ART infants. We discussed methods to improve controlled studies of the risk of MM attributable to ART. Future controlled studies following our recommendations may explain what portion of the observed increased risk is actually attributable to ART.

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