Meta-Analyses of Studies Evaluating the Impact of Assisted Reproductive Technology on Malformation in Offspring and Protocol Recommendations for Future Assisted Reproductive Technology Outcome Studies

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OBJECTIVE: To update the estimate of the relationship between assisted reproductive technology (ART) and malformation in the offspring, to make recommendations about procedures for future research, and to estimate how much of the observed outcome might be attributable to ART procedures as opposed to subfertility.

STUDY DESIGN: Meta-analysis of clinical studies that each had more than 500 in vitro fertilization (IVF) or IVF with intracytoplasmic sperm injection (ICSI) patients and which presented adjusted odds ratios (AORs) for the risk of malformation (major or all) in the offspring.

RESULTS: Our meta-analysis found an AOR of 1.28, suggesting that ART increases risk of malformation by 28%. Subgroup analyses showed that studies with longer follow-up found about 30% higher incidence of malformation. ICSI posed a higher malformation risk than did IVF (AOR 1.35 vs. 1.14, respectively).

CONCLUSION: Assuming about 350,000 ART infants are born each year, there is less than a 1% chance, over the background rate of 3%, of having an infant with a malformation. Whether subfertility or ART is the cause of the malformation risk observed remains unsettled and further research is needed. (J Reprod Med 2018;63:325–334)

…the AOR for malformation may in part result from subfertility and the drugs used to treat it, and not entirely from the manipulation of gametes in the laboratory.

Keywords: assisted reproductive techniques, assisted reproductive technology, birth defects, in vitro fertilization, ICSI, IVF, infertility, intracytoplasmic sperm injection, malformation, meta-analysis, pregnancy outcomes, subfertility.

Assisted reproductive technology (ART) (defined here as in vitro fertilization [IVF] and in vitro fertilization combined with intracytoplasmic sperm injection [ICSI]) is coming up on its 40th birthday this year. It is estimated that there have been 5 million ART infants born worldwide during this period,[1] yet there are still considerable research efforts ongoing to improve the success rate and reduce the incidence of adverse pregnancy and offspring outcomes. This study addresses the work related

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to determining a reasonable estimate of the impact of ART on the malformation rate in the offspring, a continuing concern. The reported odds ratios (ORs) in the literature vary from a low of 0.45[2] (a protective effect, i.e., ART has a malformation rate which is only 45% of the rate in non-ART controls) to a high of 6.11[3] (i.e., ART increases the malformation rate more than 6-fold).

A number of published meta-analyses have estimated the odds that ART increases the malformation rate (Table I).[4-13] Our study was designed to determine whether these estimates are somewhat inflated by the technique used in some of these meta-analyses. Some of the meta-analyses in Table I included both adjusted and unadjusted studies. Combining adjusted with unadjusted studies to derive an overall OR estimate could result in an inflated estimate. Generally speaking, the literature on meta-analysis methodology indicates that adjusted and unadjusted studies should not be combined in a meta-analysis.[14] The main reasons for this are that it increases the heterogeneity and, in studies of this type, where there are important confounders, it could inflate the odds ratio. However, combining is not inappropriate when the confounding factors are not related to the outcome. We also sought to determine whether the malformation rate differs in IVF infants as compared with ICSI infants.

We recognize that there is considerable interest in determining whether the poor outcomes of ART are due to the ART procedure or due to subfertility (defined as the inability to conceive after 1 year of regular unprotected intercourse). The difficulty of determining which factors bear what part of the responsibility for the poor outcomes in the infants is reviewed in the discussion.

Materials and Methods

We performed extensive literature searches in the Medline database for meta-analyses published in English (1999–2016) and for clinical studies (1999–2016) on the impact of ART on malformation in the offspring (search terms identified in Table II). We also reviewed the references in each study and numerous review articles as a backup to this search strategy. We did not contact authors. We performed a meta-analysis in accordance with the PRISMA Statement.[15]

Both reviewers reviewed all studies independent-

Table I *Published Meta-Analyses Reporting on Risk of Malformation in ART Offspring*

Author, year	No.[a] of studies in meta-analysis	Did every study used in meta-analysis have adjusted or matched data?	Did meta-analysis analyze adjusted studies separately?	Reported ORs[b] and CIs		
				IVF	ICSI	Overall
Rimm, 2004[4]	19	No	No	1.28 0.93–1.75	1.23 0.80–1.88	1.29 1.01–1.67
Hansen, 2005[5]	25	No	Yes	N/A	N/A	1.29 1.21–1.37
MacDonald, 2005[6]	4	Yes	N/A	N/A	N/A	1.14 0.85–1.52
MacDonald, 2005[7]	14	Yes	N/A	N/A	N/A	1.38 1.03–1.83
Rossi, 2011[8]	4	Yes	N/A	N/A	N/A	1.15 0.80–1.63
Wen, 2012[9]	46	No	Yes	1.30 1.17–1.46	1.58 1.27–1.95	1.37 1.26–1.48
Pandey, 2012[10]	7	No	Yes	N/A	N/A	1.67 1.33–2.09
Jia, 2013[11]	76	No	Yes	1.35 1.09–1.68	1.35 1.16–1.57	1.36 1.25–1.47
Qin, 2015[12]	35	No	Yes	1.15 1.01–1.32	1.13 0.96–1.33	1.11 1.02–1.22
Qin, 2016[13]	28	No	Yes	1.32 1.22–1.42	1.41 1.30–1.52	1.36 1.27–1.46

[a]Number reported here is the number of studies in the publication which reported on the malformation outcome.
[b]Where the meta-analysis used only adjusted studies, the ORs reported in this table are adjusted ORs.

Table II *Literature Search Strategy*

All combinations of terms in the first column with terms in the second column	
ART	Birth defect
Assisted reproduction	Malformation?
Assisted reproduction technology/ technique/techniques	Anomalies
In vitro fertilization	Congenital malformation?
ICSI	Congenital abnormality
Intracytoplasmic sperm injection	
Infertility treatment?	

"?" retrieves singular and plural terms.

ly and together for inclusion/exclusion and for data extraction.

Studies met eligibility criteria for our meta-analyses if they were (1) published in English, (2) used a matched case-control design, matched or statistically adjusted at least for maternal age, (3) had IVF or ICSI as the exposure of interest, (4) had malformation (major or all) in the offspring as a reported outcome, and (5) reported adjusted odds ratios (AORs) and 95% confidence intervals (CIs). No patient appeared in more than one study. The characteristics of the included studies are presented in Table III.[16-36] Each study has been adjusted at least for maternal age and some for other factors as well. All included studies contained at least 500 patients. We believe that larger studies give a better estimate of the overall OR for the relationship between ART and malformation rate in the offspring. Our review of the literature found that in studies that had <500 ART patients, the OR varied between 0.8 and 6.1, whereas the variation in the larger studies was generally much less.

When analyzing only adjusted studies in a meta-analysis, the numerators and denominators that are given for the number of patients with and without the outcome cannot be used to obtain an overall OR. If they are used, the results will reflect an unadjusted OR because the raw data used does not reflect adjustment. The D/L method of DerSimonian and Laird[37] is appropriate for conducting a meta-analysis of adjusted ORs. This method uses the OR from each study and its 95% confidence interval (CI). The D/L method was used for all of the meta-analyses presented here.

The random effects model was used in all of our meta-analyses. Some of the studies reported IVF and ICSI patients separately; others combined the two procedures. For this reason, the number of studies used here to obtain an OR for each type of clinical procedure was limited.

We divided the 20 included studies into various subgroups and performed 7 different meta-analyses. The subgroups studied were (1) ICSI versus IVF, (2) assessed at birth versus assessed at birth and beyond, and (3) major malformation versus all malformation.

Results

Malformation Rates

The results of our analyses of malformation rates are presented in Table IV, which shows the differences in the percentage of malformation found in studies that evaluated the infants at birth in contrast to those that evaluated defects both at birth and beyond. Among the 20 studies in the analyses, there were only 7 birth and beyond studies. In studies where diagnosis was made only at birth, the percent with a defect was somewhat lower than in the studies where diagnosis was recorded at birth and during a follow-up period. In the ART group, the overall percent with a defect diagnosed at birth was 4.89%; in the non-ART group, it was 3.49%. In the birth and beyond studies, the percent with a defect in the ART group was 6.2%. Comparing the 6.2% with the 4.89% shows that about 27% of the defects were observed after the birth. In the control group, 34% of the malformations were observed in the follow-up period. Taking the average of the 2 estimates indicates that about 30% of the defects were diagnosed after birth. It is recognized that the follow-up period differed among these studies, and this prevents a precise accounting of the percent of defects observed at different periods.

Even though our analyses showed no evidence of ascertainment bias (i.e., differential assessment between cases and controls) in these studies, it is always a concern in studies where the outcome is ascertained during a follow-up period. One method to detect a possible ascertainment bias is to graph the cumulative percentage of subjects diagnosed with a malformation at various points during the follow-up period. Figure 1 shows hypothetical results in 2 panels, where it is assumed that about 70% of the diagnoses are made at birth. Panel A shows that there is no ascertainment bias; in other words, the cumulative percentage curves are similar for the ART and non-ART offspring. This indicates that the distributions of the time to diagnosis of malformation were similar

Table III *ART Outcome Studies (N ≥ 500) Where There Was Adjustment for Confounding Factors*

	No. of ART patients N > 500			IVF	ICSI	Overall		
Author, year	IVF	ICSI	Total	AOR CI	AOR CI	AOR CI	Malformation assessed	Time to diagnosis
Adler-Levy, 2007[16]			558	1.2 0.83–1.72	—	—	All	Birth
Anthony, 2002[17]			4,224	1.03 0.86–1.23	—	—	All	Birth
Davies, 2012[18,19]	2,301	1,407	3,708	1.06[a] 0.88–1.28	1.56 1.27–1.92	1.24 1.09–1.41	All	5 years
Dhont, 1999[20]	4,196			1.25 0.96–1.64	—	—	All	Birth
Fujii, 2010[21]			1,396	—	—	1.17 0.81–1.69	All	Birth
Halliday, 2010[22]	3,312	3,634	6,946	1.31 1.10–1.56	1.40 1.19–1.65	1.36 1.19–1.55	All	4–15 years
Hansen, 2012[23]			2,911			1.53 1.30–1.79	Major	6 years
Kallen, 2005[24]			16,280	—	—	1.44 1.32–1.57	Major	Birth
Kallen, 2010[25]			15,570	—	—	1.25 1.15–1.37	Major	Birth
Katalinic, 2004[26]		3,372		—	1.24 1.02–1.50	—	Major	Birth
Klemetti, 2005[27]			4,459	—	—	1.31 1.10–1.57	Major	>1 year
Olson, 2005[28]			1,462	—	—	1.30 1.00–1.67	Major	1 year
Ombelet, 2005[29]			2,757	—	1.04 0.68–1.6	—	All	Birth
Pinborg, 2004[30]			1,650			1.24 0.97–1.58	All	1–6 years
Pinborg, 2010[31]			10,329	—	—	1.27 1.09–1.43	Major	1–13 years
Sagot, 2012[32]			903[b]	—	—	2.0 1.3–3.1	Major	Birth
Shevell, 2005[33]			554	—	—	0.90 0.4–2.0	All	Birth
Wang, 2002[34]			1,019	—	—	0.95 0.61–1.49	All	Birth
Wen, 2010[35]			1,044	—	—	1.58 1.10–2.27	Major	Birth
Westergaard, 1999[36]			2,245	—	—	1.04 0.78–1.39	All	Birth

[a]Authors gave separate ORs for singletons and multiples. Combined ORs for IVF, ICSI, and overall are our estimates.
[b]Singletons only.

for the ART and control groups. Panel B shows hypothetical results where the ART group had diagnoses beyond the time that the last diagnosis was made in the non-ART group, suggesting an ascertainment bias, possibly due to weaker follow-up procedures resulting in the "loss" of children with a defect in the non-ART group. Another interpretation could be that the ART procedure somehow "causes" malformation to appear later in the follow-up period than in the non-ART group.

Meta-Analyses

Table V gives the results of our meta-analyses for various subgroups of patients. The total number of ART patients in the 20 studies was 84,500. There were only 5 studies where IVF results were given separately from the ICSI results, and 4 of those studies found no statistically significant difference between outcomes in the ART and non-ART group. There were 13 studies where only an overall AOR for IVF/ICSI was given, and 4 were not statisti-

Table IV *Malformation Rates When Assessment Is Made at Birth or When Assessment Continues Beyond Birth, in the 20 Studies with >500 ART Patients and with Adjusted Odds Ratios*

No. of studies	Malformation	Time of diagnosis	% Malformation	
			ART	Control
8	All[a]	Birth	4.43	3.45
2	All	Birth and beyond	7.30	5.30
5	Major	Birth	5.62	3.56
5	Major	Birth and beyond	5.76	4.44
13	Major+all[b]	Birth	4.89	3.49
7	Major+all	Birth and beyond	6.20	4.68
10	All	Birth+birth and beyond	5.00	3.78
10	Major	Birth+birth and beyond	5.69	4.00

[a]All = reported all malformations together.
[b]Major+all = reported all malformations and major malformations separately.

cally significant. This points up the relevance in a meta-analysis of obtaining separate estimates for IVF and ICSI.

The results of our meta-analyses are presented in Table V. The overall AOR for the 20 studies in the meta-analyses using the D/L procedure was 1.28 (95% CI 1.21–1.36). The highest AOR we found, 1.39, was in a meta-analysis of 9 studies assessing major malformation only: for all malformation, the AOR was 1.22. We found that IVF had a somewhat lower malformation AOR than ICSI.

In those studies where there were diagnostic evaluations at birth and beyond, the AOR of 1.31 was not significantly higher than the AOR of 1.24, when diagnosis was made only at birth. Lastly, the results show that the AOR from the meta-analysis for major malformation was 1.39. These estimates will, of course, be subject to change as more studies are published during the next 20 to 30 years, during which time there will be clinical improvements in ART procedures and selection of patients.

Discussion

This study addresses the risk of malformation rate in ART offspring when only adjusted studies with ≥500 patients are used and when assessments of malformation rate are done at birth as compared to assessments done later.

Appropriate Control Group

One of the unresolved issues in ART outcome studies and the meta-analyses of them is the source of control patients. Control groups used are mainly hospital-based controls or population-based controls of normal women conceiving spontaneously. Such groups do not take into account that ART couples may have genetic or other underlying conditions which make them subfertile, which could contribute to the increase in malformation rate. More appropriate controls may be either subfertile couples who have a spontaneous conception or

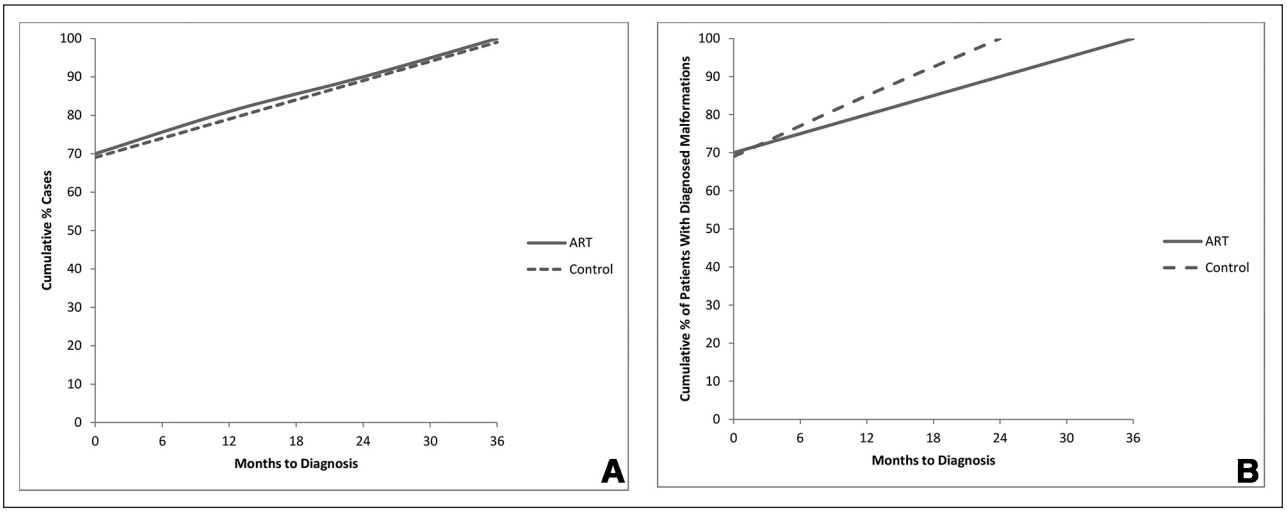

Figure 1 Comparison of two theoretical outcome studies where time to diagnosis is reported. When that data is presented graphically, it is easy to determine whether ascertainment bias is absent (Panel A) or present (Panel B).

Table V *Results of the Meta-Analyses of Subgroups in the 20 ART Studies That Had AORs and >500 ART Patients*

Group	No. of studies	No. of ART patients	AOR (95% CI)
All	20	84,581	1.28 (1.21–1.36)
IVF	5	14,591	1.14 (1.05–1.27)
ICSI	4	15,681	1.35 (1.19–1.53)
Assessed at birth	13	57,995	1.24 (1.13–1.36)
Assessed at birth and beyond	7	24,469	1.31 (1.22–1.40)
All malformations	11	44,191	1.22 (1.16–1.29)
Major malformations	9	47,760	1.39 (1.29–1.49)

ART couples who, before or after an ART pregnancy, have a naturally conceived offspring. This concept is supported by a study which found, after adjusting for the effect of subfertility, that the AOR for major malformation in the ART group was 1.01 and not statistically significant.[38]

There is a great deal of evidence in the literature to support the view that subfertile patients have underlying conditions that may predispose them to adverse pregnancy outcomes. Past investigators found subfertile patients to have elevated risks for preterm birth, low birth weight, perinatal mortality, small for gestational age, and other issues. Some of the important studies are presented in Table VI,[39-51] and a few are discussed here. A sibling cohort study by Romundstad et al[46] compared ART offspring to their spontaneously conceived siblings. The study revealed little difference in birth weight, perinatal mortality, and gestational age. ART made no difference or, if anything, was protective as to those risks.

Davies et al[18] reported that spontaneous conceptions in non-ART pregnancies of women who had previously had an ART pregnancy exhibited an increased risk of any birth defect when compared to spontaneous conceptions from fertile women (OR 1.25; 95% CI 1.01–1.56), and subfertile women conceiving without ART also had an increased risk of birth defects (OR 1.29; 95% CI 0.99–1.68).

The idea of using subfertile couples conceiving spontaneously as controls has been criticized on the basis that some of those apparently untreated subfertile couples may in fact have been treated with drugs (such as clomiphene citrate) and that the drugs, rather than their underlying subfertility, may have contributed, at least in part, to the malformation rate outcome. Kallen et al[52] studied over 4,000 Swedish women who delivered after ovarian stimulation alone and compared them to all women giving birth in Sweden during the same 5-year period without ovarian stimulation or IVF. The treated group was found to have an excess risk for preterm birth, low birth weight, perinatal mortality, and malformation. All these risks were reduced when adjustment for subfertility was made; and the excess risk for malformation disappeared.

Infertility is a broad term covering a multitude of problems, and in about 20% of infertile couples no specific problem is identified. Infertility can be hormonal; related to age, exercise, obesity, or infectious disease; immunological; or associated with defined gametic abnormalities. Most—perhaps all—of these factors likely have a genetic component.[53,54]

The perennial problem is determining whether adverse clinical outcomes in ART infants are due to the ART procedures or due to subfertility. Since it is not possible to study the effect of ART without subfertility, a definitive assignment of cause may never be possible. However, the preponderance of the existing evidence, including an Evidence Report/Technology Assessment prepared for the Agency for Healthcare Research and Quality of the U.S. Department of Health and Human Services,[55] concludes that much of the increased risk for congenital anomalies observed after ART may be related to maternal and/or paternal characteristics, including a history of subfertility.

Cost Versus Benefit

A review of the literature of meta-analyses on this topic suggests that the malformation rate is around 1.3 or that there is an increase of 30% over the malformation rate in non-ART controls, which is about 3%. In other words, the excess risk of malformation appears to be about 1% over the background risk of 3%. If we assume that ART increases the malformation rate by 30% and there are about 350,000 ART births per year,[56] we can estimate the number of malformed infants born each year as a result of ART. If the ART group did not have an increased risk of malformation rate, we would expect about 10,500 ($0.03 \times 350{,}000$) infants born with a malformation requiring clinical attention. In the ART group, assuming the rate is 30% higher or 3.9%, there would be 13,650 infants with a malformation. The difference, 3,150 infants per year with a malformation, can be viewed as a significant annual "cost" of ART. This cost estimate as-

Table VI *Summary of Important Literature on Adverse Pregnancy Outcomes in Subfertile Patients*

Author, year	Country	Nature of study	Outcome reported	OR[a]	95% CI
Henriksen, 1997[39]	Denmark	Compared untreated subfertile women (TTP >12 mo) to fertile women (TTP ≤6 mo)	PTB	1.6	1.0–2.7
Draper, 1999[40]	England	Compared to women with untreated infertility normal controls	Perinatal death	3.3	1.6–6.8
Basso, 2003[41]	Denmark	Compared offspring of primiparous women (TTP ≥12 mo) to offspring of primiparous women (TTP <12 mo)	PTB LBW	1.36 1.27	1.08–1.71 0.76–2.10
Basso, 2005[42]	Denmark	Compared singletons of untreated subfertile women (TTP >12 mo) to singletons of fertile women (TTP <3 mo)	Neonatal death	3.32	1.47–7.53
Zhu, 2006[43]	Denmark	Compared offspring of untreated subfertile (TTP >12 mo) to offspring of normal couples (TTP ≤12 mo)	Major malformation	1.20	1.07–1.35
Zhu, 2007[44]	Denmark	Compared SC singletons (TTP >12 mo) to singletons of subfertile couples undergoing various infertility treatments	Perinatal death SGA	0.27 1.25	0.91-1.77 1.10-1.42
Sun, 2007[45]	Denmark	Compared singletons of untreated subfertile couples (TTP >12 mo) to singletons of fertile couples (TTP ≤12 mo)	Epilepsy	1.38	1.00–1.89
Romundstad, 2008[46]	Norway	Compared ART children to their SC siblings	SGA Perinatal mortality	0.99 0.36	0.62–1.57 0.20–0.67
Raatikainen, 2010[47]	Finland	Compared SC pregnancy outcomes of untreated subfertile (TTP 13–24 mo) to normal fertile couples (TTP 0–6 mo)	PTB C-section SGA	1.32 1.24 1.16	1.01–1.73 1.04–1.49 0.92–1.46
		Compared SC pregnancy outcomes of untreated subfertile (>37 mo) to normal fertile (TTP 0–6 mo)	PTB C-section SGA	1.44 1.83 1.41	0.96–2.16 1.41–2.37 0.99–1.99
Raatikainen, 2012[48]	Finland	Compared ART pregnancies to SC pregnancies with TTP ≥2 years	LBW PTB C-section SGA	1.31 1.28 1.21 0.95	0.84–2.18 0.81–2.03 0.89–1.64 0.65–1.39
Hayashi, 2012[49]	Japan	Compared IUI pregnancy outcomes (w/o medication) to matched controls from general population	LBW v LBW SGA Infant death	1.17 1.23 1.27 1.22	1.04–1.32 0.99–1.52 1.04–1.55 0.83–1.80
		Compared OS pregnancy outcomes to matched controls from general population	LBW v LBW SGA Infant death	1.35 1.36 1.45 1.23	1.21–1.50 1.13–1.61 1.21–1.73 0.87–1.75
Malchau, 2014[50]	Denmark	Compared singletons born after IUI-H to SC singletons	PTB LBW SGA	1.3 1.4 1.4	1.1–1.5 1.2–1.7 1.2–1.6
Stern, 2015[51]	United States	Compared offspring of non-ART subfertile patients diagnosed with endometriosis to general population	PTB LBW SGA	1.66 1.46 1.08	1.26–2.18 1.07–1.99 0.81–1.43
		Compared offspring of non-ART subfertile patients diagnosed with ovulation disorders to general population	PTB LBW SGA	1.38 1.38 1.16	1.10–1.74 1.09–1.76 0.93–1.46

[a]The ORs shown here are as presented in the papers cited. They are adjusted or unadjusted depending on which the authors published.
IUI = intrauterine insemination, LBW = low birth weight, OS = ovulation stimulation treatment, PTB = pre-term birth, SC = spontaneous conception without ART, SGA = small for gestational age, TTP = time to pregnancy, TTP >12 mo = subfertile.

sumes that the ART procedures, rather than underlying subfertility or other factors, are the cause of the increased number of infants with a malformation.

Similarly, the total number of "normal" ART infants (350,000 – [0.039 × 350,000]), or 336,350 infants, can be viewed as the clear "benefit" from the ART procedure. The benefit has many dimensions, including positive impacts on the relationship of the parents to each other and to the child and other family members. Does the benefit outweigh the cost? The high volume of ART procedures each year suggests that subfertile couples have concluded that the benefits to be derived from having an offspring greatly outweigh the <1% chance above the background rate that their offspring will have a malformation.

Recommendations for Future ART Outcome Studies

During the past 12 years there have been 10 meta-analyses studying the relationship between ART and malformation in the offspring. During the next 12 years there are likely to be many clinical outcome studies and meta-analyses. Therefore, it seems reasonable to propose some guidelines that may improve future research in this area. Table VII lists some ideas for study designs that may help future research in this area. One of the main issues is the reporting of unadjusted studies. As mentioned earlier, these studies may give an inflated OR and could tend to obscure the true defect rate attributable to ART or some other cause. It is hoped that in the future all reported clinical studies in this area will provide AORs.

It appears to continue to be an open question whether ICSI poses a greater risk of malformation than IVF alone. In this study we found a strong suggestion that there is excess risk associated with ICSI. Davies et al[18] made a similar finding. However, many investigators have reported essentially no difference in outcomes between IVF and ICSI. Since the use of ICSI has increased dramatically,[57,58] we recommend that results for IVF and ICSI be collected and reported separately.

It is recognized that there are 2 important weaknesses in the meta-analyses presented here. First, the method of adjustment is not similar in all studies; that is, the confounding variables used in the adjustment are not the same in all studies. Also, some studies used a statistical adjustment procedure, while others used matching of ART patients with controls for adjustment. Second, the clinical factors describing malformation differ among the studies. Though these differences exist, they are thought to have only a small effect on the AOR differences among the 20 studies.

Table VII *Recommendations for Future ART Outcome Studies*

Suggestions regarding future meta-analyses
1. Do not combine adjusted and unadjusted studies.
2. Use the DerSimonian and Laird method in the calculations of the OR of adjusted studies.
3. When adjusting, maternal age is the most important variable, and at least this adjustment must be made.
4. AORs for IVF and ICSI should be reported separately.

Recommendations for the conduct of future outcome studies
1. If possible, follow-up should be at least two years for cases and controls.
2. To identify ascertainment bias, if follow-up is beyond birth, the cumulative percentage of time to diagnosis should be reported for patients in the treatment and control groups.
3. IVF and ICSI data should be gathered, analyzed, and reported separately.

Conclusion

Using large studies of the relationship of ART and malformation in the offspring, the meta-analysis shows that at this time, ART increased the risk of malformation about 28%. Subfertile couples who conceived spontaneously without ART experienced excess risk for various adverse pregnancy outcomes. This suggests that the AOR for malformation may in part result from subfertility and the drugs used to treat it, and not entirely from the manipulation of gametes in the laboratory.

References

1. Simpson JL: Birth defects and assisted reproductive technologies. Semin Fetal Neonatal Med 2014;19:177-182
2. Ho CH, Peng FS, Chen HF, et al: Twin pregnancies conceived by assisted reproductive technology: maternal and perinatal outcomes. Taiwanese J Obstet Gynecol 2005;44:332-337
3. Verlaenen H, Cammu H, Derde MP, et al: Singleton pregnancy after in vitro fertilization: Expectations and outcome. Obstet Gynecol 1995; 86:906-910
4. Rimm AA, Katayama AC, Diaz M, et al: A meta-analysis of controlled studies comparing major malformation rates in IVF and ICSI infants with naturally conceived children. J Assist Reprod Genet 2004;21:437-443
5. Hansen M, Bower C, Milne E, et al: Assisted reproductive technologies and the risk of birth defects–a systematic review. Hum Reprod 2005;20:328-338
6. McDonald S, Murphy K, Beyene J, et al: Perinatal outcomes of in vitro fertilization twins: A systematic review and meta-analyses. Am J Obstet Gynecol 2005;193:141-152
7. McDonald SD, Murphy K, Beyene J, et al: Perinatal outcomes of

singleton pregnancies achieved by in vitro fertilization: A systematic review and meta-analysis. J Obstet Gynaecol Can 2005;27:449-459

8. Rossi AC, D'Addario V: Neonatal outcomes of assisted and naturally conceived twins: Systematic review and meta-analysis. J Perinat Med 2011;39:489-493
9. Wen J, Jiang J, Ding C, et al: Birth defects in children conceived by in vitro fertilization and intracytoplasmic sperm injection: A meta-analysis. Fertil Steril 2012;97:1331-1337
10. Pandey S, Shetty A, Hamilton M, et al: Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: A systematic review and meta-analysis. Hum Reprod Update 2012;18:485-503
11. Jia Y, Geng L, Zhong Y: Birth defects in assisted reproductive technology and spontaneously conceived children: A meta-analysis. Reprod Contracept 2013;24:237-252
12. Qin J, Wang H, Sheng X, et al: Pregnancy-related complications and adverse pregnancy outcomes in multiple pregnancies resulting from assisted reproductive technology: A meta-analysis of cohort studies. Fertil Steril 2015;103:1492-1508
13. Qin J, Liu X, Sheng X, et al: Assisted reproductive technology and the risk of pregnancy-related complications and adverse pregnancy outcomes in singleton pregnancies: A meta-analysis of cohort studies. Fertil Steril 2016;105:73-85
14. Voils CI, Crandell JL, Chang Y, et al: Combining adjusted and unadjusted findings in mixed research synthesis. J Eval Clin Pract 2011;17:429-434
15. Moher D, Liberati A, Tetzlaff J, et al; PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. PLoS Med 2009;6:e1000097
16. Adler-Levy Y, Lunenfeld E, Levy A: Obstetric outcome of twin pregnancies conceived by in vitro fertilization and ovulation induction compared with those conceived spontaneously. Eur J Obstet Gynecol Reprod Biol 2007;133:173-178
17. Anthony S, Buitendijk SE, Dorrepaal CA, et al: Congenital malformations in 4224 children conceived after IVF. Hum Reprod 2002;17:2089-2095
18. Davies MJ, Moore VM, Wilson KJ, et al: Reproductive technologies and the risk of birth defects. N Engl J Med 2012;366:1803-1813
19. Davies MJ, Moore VM, Haan EA: Reproductive technologies and the risk of birth defects: The authors reply. N Engl J Med 2012;367:875-z876
20. Dhont M, De Sutter P, Ruyssinck G, et al: Perinatal outcome of pregnancies after assisted reproduction: A case-control study. Am J Obstet Gynecol 1999;181:688-695
21. Fujii M, Matsuoka R, Bergel E, et al: Perinatal risk in singleton pregnancies after in vitro fertilization. Fertil Steril 2010;94:2113-2117
22. Halliday JL, Ukoumunne OC, Baker HW, et al: Increased risk of blastogenesis birth defects, arising in the first 4 weeks of pregnancy, after assisted reproductive technologies. Hum Reprod 2010;25:59-65
23. Hansen M, Kurinczuk JJ, de Klerk N, et al: Assisted reproductive technology and major birth defects in Western Australia. Obstet Gynecol 2012;120:852-863
24. Kallen B, Finnstrom O, Nygren KG, et al: In vitro fertilization (IVF) in Sweden: Risk for congenital malformations after different IVF methods. Birth Defects Res A Clin Mol Teratol 2005;73:162-169
25. Kallen B, Finnstrom O, Lindam A, et al: Congenital malformations in infants born after in vitro fertilization in Sweden. Birth Defects Res A Clin Mol Teratol 2010;88:137-143
26. Katalinic A, Rosch C, Ludwig M: Pregnancy course and outcome after intracytoplasmic sperm injection: A controlled, prospective cohort study. Fertil Steril 2004;81:1604-1616
27. Klemetti R, Gissler M, Sevon T, et al: Children born after assisted fertilization have an increased rate of major congenital anomalies. Fertil Steril 2005;84:1300-1307
28. Olson CK, Keppler-Noreuil KM, Rornitti PA, et al: In vitro fertilization is associated with an increase in major birth defects. Fertil Steril 2005;84:1308-1315
29. Ombelet W, Peeraer K, De Sutter P, et al: Perinatal outcome of ICSI pregnancies compared with a matched group of natural conception pregnancies in Flanders (Belgium): A cohort study. Reprod Biomed Online 2005;11:244-253
30. Pinborg A, Loft A, Rasmussen S, et al: Neonatal outcome in a Danish national cohort of 3438 IVF/ICSI and 10,362 non-IVF/ICSI twins born between 1995 and 2000. Hum Reprod 2004;19:435-441
31. Pinborg A, Loft A, Aaris Henningsen AK, et al: Infant outcome of 957 singletons born after frozen embryo replacement: The Danish National Cohort Study 1995-2006. Fertil Steril 2010;94:1320-1327
32. Sagot P, Bechoua S, Ferdynus C, et al: Similarly increased congenital anomaly rates after intrauterine insemination and IVF technologies: A retrospective cohort study. Hum Reprod 2012;27:902-909
33. Shevell T, Malone FD, Vidaver J, et al: Assisted reproductive technology and pregnancy outcome. Obstet Gynecol 2005;106:1039-1045
34. Wang JX, Norman RJ, Kristiansson P: The effect of various infertility treatments on the risk of preterm birth. Hum Reprod 2002;17:945-949
35. Wen SW, Leader A, White RR, et al: A comprehensive assessment of outcomes in pregnancies conceived by in vitro fertilization/intracytoplasmic sperm injection. Eur J Obstet Gynecol Reprod Biol 2010;150:160-165
36. Westergaard HB, Johansen AM, Erb K, et al: Danish National In-Vitro Fertilization Registry 1994 and 1995: A controlled study of births, malformations and cytogenetic findings. Hum Reprod 1999;14:1896-1902
37. DerSimonian R, Laird N: Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7:177-188
38. Rimm AA, Katayama AC, Katayama KP: A meta-analysis of the impact of IVF and ICSI on major malformations after adjusting for the effect of subfertility. J Assist Reprod Genet 2011;28:699-705
39. Henriksen TB, Baird DD, Olsen J, et al: Time to pregnancy and preterm delivery. Obstet Gynecol 1997;89:594-599
40. Draper ES, Kurinczuk JJ, Abrams KR, et al: Assessment of separate contributions to perinatal mortality of infertility history and treatment: A case-control analysis. Lancet 1999;353:1746-1749
41. Basso O, Baird DD: Infertility and preterm delivery, birthweight, and caesarean section: A study within the Danish National Birth Cohort. Hum Reprod 2003;18:2478-84
42. Basso O, Olsen J: Subfecundity and neonatal mortality: Longitudinal study within the Danish national birth cohort. BMJ 2005;330:393
43. Zhu JL, Basso O, Obel C, et al: Infertility, infertility treatment, and congenital malformations: Danish national birth cohort. BMJ 2006;333:679-683
44. Zhu JL, Obel C, Bech BH, et al: Infertility, infertility treatment and fetal growth restriction. Obstet Gynecol 2007;110:1326-1334
45. Sun Y, Vestergaard M, Christensen J, et al: Epilepsy and febrile seizures in children of treated and untreated subfertile couples. Hum Reprod 2007;22:215-220
46. Romundstad LB, Romundstad PR, Sunde A, et al: Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: A population-based cohort study. Lancet 2008;372:737-743
47. Raatikainen K, Harju M, Hippelainen M, et al: Prolonged time to pregnancy is associated with a greater risk of adverse outcomes. Fertil Steril 2010;94:1148-1151
48. Raatikainen K, Kuivasaari-Pirinen P, Hippelainen M, et al: Comparison of the pregnancy outcomes of subfertile women after infertility treatment and in naturally conceived pregnancies. Hum Reprod 2012;27:1162-1169
49. Hayashi M, Nakai A, Satoh S, et al: Adverse obstetric and perinatal

outcomes of singleton pregnancies may be related to maternal factors associated with infertility rather than the type of assisted reproductive technology procedure used. Fertil Steril 2012;98:922-928

50. Malchau SS, Loft A, Henningsen AK, et al: Perinatal outcomes in 6,338 singletons born after intrauterine insemination in Denmark, 2007 to 2012: The influence of ovarian stimulation. Fertil Steril 2014; 102:1110-1116
51. Stern JE, Luke B, Tobias MS, et al: Adverse pregnancy and birth outcomes associated with and without assisted reproductive technology treatment. Fertil Steril 2015;103:1438-1445
52. Kallen B, Olausson PO, Nygren KG: Neonatal outcome in pregnancies from ovarian stimulation. Obstet Gynecol 2002;100:414
53. Shah K, Sivapalan G, Gibbons N, et al: The genetic basis of infertility. Reproduction 2003;126:13-25
54. Reddy UM, Wapner RJ, Rebar RW, et al: Infertility, assisted reproductive technology, and adverse pregnancy outcomes. Obstet Gynecol 2007;109:967-977
55. Myers ER, McCrory DC, Mills AA, et al: Effectiveness of assisted reproductive technology (ART). Evid Rep Technol Assess (Full Rep) 2008;(167):1-195
56. European Society for Human Reproduction and Embryology (ESHRE) website; ART Factsheet (July 2014). Available at http://www.eshre.eu/ESHRE/English/Guidelines-Legal/ART-fact-sheet/page.aspx/1061. Accessed November 13, 2015
57. Boulet SL, Mehta A, Kissin DM, et al: Trends in use of and reproduction outcomes associated with intracytoplasmic sperm injection. JAMA 2015;313:255-263
58. Kupka MS, Ferraretti AP, de Mouzon J, et al; European IVF Monitoring Consortium, for the European Society of Human Reproduction and Embryology: Assisted reproduction technology in Europe, 2010: Results generated from European registers by ESHRE. Hum Reprod 2014;29:2099-2113