Risk of birth defects increased in pregnancies conceived by assisted human reproduction

Darine El-Chaar, M.D., a, Qiuying Yang, M.D., a,b Jun Gao, M.D., b Jim Bottomley, M.H.A., c
Arthur Leader, M.D., a,d Shi Wu Wen, M.D., a,b and Mark Walker, M.D. a,b,c

a Department of Obstetrics and Gynecology and Neonatal Care, b OMNI Research Group, c Ontario Perinatal Surveillance System, and d The Ottawa Fertility Centre, Ottawa Health Research Institute, The Ottawa Hospital, University of Ottawa, Ottawa, Ontario, Canada

Objective: To assess the risk of birth defects in infants born after assisted human reproduction (AHR).

Design: Retrospective cohort study.

Setting: Niday Perinatal Database for the province of Ontario, 82 sites, both primary and tertiary centers.

Patient(s): In 2005, information about reproductive assistance was reported for 61,569 deliveries.

Intervention(s): The prevalence of birth defects diagnosed in the prenatal period or at birth was estimated for all types of AHR together and then by type of procedure.

Main Outcome Measure(s): The excess risks of birth defects by AHR were calculated by unconditional logistic regressions using spontaneously conceived pregnancies as the reference and were expressed by odds ratio and 95% confidence intervals and adjusted for maternal age, smoking, infant gender, gestation, and parity.

Result(s): The prevalence of birth defects with AHR procedures was 2.91%, which was a 1.55-fold higher (95% confidence interval [CI], 1.03–2.38) than in the non-AHR population (1.86%). Specific anomalies that increased with AHR were gastrointestinal (odds ratio [OR], 9.85; 95% CI, 3.44–28.44), cardiovascular (OR, 2.30; 95% CI, 1.11–4.77), and musculoskeletal defects (OR, 1.54; 95% CI, 0.48–4.94). The risks of birth defects by types of AHR were 2.35% for ovulation induction, 2.89% for IUI, and 3.45% for IVF.

Conclusion(s): There is a significant increased risk of birth defects associated with AHR, and the risk is higher in IVF and IUI. The potential risk of anomalies associated with AHR may be considered in the counseling that is offered to infertile couples. (Fertil Steril® 2009;92:1557–61. ©2009 by American Society for Reproductive Medicine.)

Key Words: Birth defects, intrauterine insemination, in vitro fertilization, ovulation induction, assisted human reproduction, assisted reproductive technology

An increasing number of couples seek fertility enhancement with assisted human reproduction (AHR) procedures such as ovulation induction (OI), IUI, IVF, and intracytoplasmic sperm injection (ICSI). Data collected from 25 European countries showed that 324,238 IVF cycles were performed in 2002, representing about 2%–3% of all births (1). The Society for Assisted Reproductive Technology’s annual report for the year 2001 showed that 108,130 IVF cycles were performed with 29,585 deliveries, resulting in the birth of 41,168 neonates, which accounted for about 1% of births in the United States (2).

The concerns about health issues of infants born after AHR have been attributed to the occurrence of multiple births and preterm deliveries and the sequelae associated with these conditions such as low birth weight or small for gestational age (3–7). The introduction of ICSI in 1992 raised additional concerns. The first concerns were raised by Lancaster (8), who studied the increased risk of birth defects and the long-term outcomes in children conceived by assisted reproduction. Although ICSI requires more manipulation of sperm and eggs, as it involves injecting a single sperm into an oocyte, its risk of birth defects is comparable to IVF (9–15).

In recent years, several studies have investigated the prevalence of birth defects associated with AHR in addition to maternal complications and birth outcomes. These studies have, for the most part, looked at the effect of IVF, and the results have been conflicting. The limitations in these studies include suboptimal sample sizes, lack of appropriate...
A few studies have found an increase, of up to 50% in some cases (9), in the risk of birth defects in children conceived through IVF or IVF with ICSI (9, 16–20). In 2005, Hansen et al. published a systematic review and looked at pooled epidemiological data on the risk of birth defects after assisted reproduction technologies (21). Of the 25 papers identified, only seven were appropriate for inclusion in a meta-analysis. Their review and meta-analysis suggested that infants born after IVF are at increased risk of birth defects. There has been no study yet that has demonstrated the risk of birth defects comparing different AHR techniques.

The objective of the present study was to assess the association of AHR and its three variants, OI, IUI, and IVF, with the risk of birth defects in the newborn in a large Canadian population.

**MATERIALS AND METHODS**

This study was based on the 2005 Niday Perinatal Database of Ontario, Canada, which is part of the Ontario Perinatal Surveillance System, and included more that 95% of births in Ontario. There were 82 participating sites at the time, including both hospitals and midwifery groups. Sites can either enter data directly into the database (64 sites) or can upload data from their own databases (18 hospitals). The database includes information on the number of women giving birth and babies born in the province, maternal and prenatal factors, health services factors, intrapartum interventions, birth outcomes, and infant health.

An extensive set of data quality checks were included in the data entry module of the database, and a final set of checks was done by the analyst to ensure data quality. A user guide has been prepared to ensure consistency of definitions for each variable among the participants. In addition, each organization has received training to manage the system’s data entry and reporting capabilities.

All deliveries for which information about reproductive assistance was reported were identified as the study population from the 2005 Niday Perinatal Database. Subjects were then subdivided into different subgroups according to the use of AHR (Fig. 1). The exposed group was the group that used AHR, which included OI, IUI, and IVF/ICSI. The comparison group was the rest of the population, who did not require reproductive assistance for their pregnancy.

Overall prevalence of birth defects was compared among the whole AHR group as well as among the different types of AHR, OI, IUI, or IVF, with the nonexposed group as the control. We also compared the different subtypes of birth defects, including cardiovascular, gastrointestinal, musculoskeletal, neural tube defects, or facial defects.

Analysis of variance or the $\chi^2$-test was used to compare the maternal characteristics among each AHR subtype compared with the natural conception group.

The excess risks of birth defects by AHR were calculated by unconditional logistic regressions using spontaneously conceived pregnancies as the reference and were expressed by odds ratio (OR) and 95% confidence intervals (CIs). The excess risks of subtypes of birth defects, including cardiovascular, gastrointestinal, musculoskeletal, neural tube defects, or facial defects and all other unknown birth defects, were also estimated. Independent variables were entered in to the regression models as dummy variables as follows: maternal age ($\leq 19$, 20–24, 25–29, 30–34, 35–39, $\geq 40$), parity (nulliparous and multiparous), smoking (yes or no), and sex of baby (male or female). All data were analyzed using the Statistical Analysis System, version 9.1 (SAS Institute Inc., Cary, NC).

Ethics approval for the study was obtained from the Ottawa Hospital Research Ethics Board.

**RESULTS**

In 2005, information about reproductive assistance was reported for 61,569 deliveries, with 1399 cases that conceived by AHR. Therefore, there were 1399 patients who underwent AHR and 60,170 controls. The patients were divided into subgroups of 298 OI, 173 IUI, and 319 IVF (Fig. 1). Some of the subjects in the subgroups were lost when analyzing for the presence of birth defects owing to missing data, however, the demographics and characteristics of the groups remained similar (data not shown).

Mothers in the AHR group had a tendency to be older and were less likely to have had a child previously (Table 1). The women undergoing AHR were also less likely to smoke than women in the natural conception group.

In a total of 790 infants, 2.91% conceived by AHR were diagnosed with a major birth defect in the prenatal period or shortly after birth. In comparison, a prevalence of major birth defects of 1.86% was found in the control group of 43,462 spontaneously conceived singletons (adjusted OR, 1.55; 95% CI, [1.01, 2.38]; Table 2).
Compared with infants conceived naturally, a significantly greater proportion of those conceived with AHR had gastrointestinal, cardiovascular, and musculoskeletal defects (Table 2). There was no increase in neural tube defects or facial defects.

When we explored each different AHR technique, we found that the prevalence of birth defects in 298 infants conceived by OI is 2.35% (Table 3). In the 173 infants conceived by IUI, the prevalence of birth defects is 2.89%. Finally, in the 319 infants conceived by IVF, the prevalence of birth defects is the highest, at 3.45%.

**DISCUSSION**

Our study, based on the entire 2005 Ontario population in the Niday database that reported information on reproductive assistance, found that infants conceived with AHR techniques were more likely than naturally conceived infants to have a birth defect diagnosed in the prenatal period or at birth. The risk appeared to be higher in infants conceived through IUI or IVF compared with OI. There was an observed trend in our study that with increased reproductive intervention the risk of birth defect increases; however, this was not statistically significant in a Pearson $\chi^2$-test (5.65; $P=.13$). Our study also found that the AHR-related risks of birth defects were particularly high for gastrointestinal, cardiovascular, and musculoskeletal birth defects.

One strength of our study is the inclusion of infants conceived by infertile patients treated by procedures other than just IVF, which had been the focus of most studies thus far. The Niday database is unique in that it captures non-IVF pregnancies. In our study, we did not separate IVF from IVF/ICSI, because of limitations of the database; however, most studies looking at the risk of birth defects in ICSI versus IVF have found no difference (9–15). Our investigations were designed to address the methodological problems of previous research; our approach was population based, we had a large sample size, and we used the same source of data for the three groups of AHR infants as well as for the control group. The definition of birth defects detected was also the same for all groups in the study.

In 2002, Hansen et al. found that infants conceived by IVF and ICSI have twice the risk of a major birth defect as naturally conceived children (9). Their study had the strength of a 1-year follow-up of their cases, but it is interesting to...
note that two-thirds of major defects were diagnosed during the first week of life, and more than 90% were diagnosed by 6 months of age. This means that, although in our study we present the birth defects diagnosed intrapartum or shortly after birth, we have identified the majority of the cases with birth defects. Our risk of birth defects was not as elevated as in the Hansen et al. study, but this likely attributed to the shorter follow-up of our infants.

Swedish studies in this field have found an increased risk in congenital malformations after IVF procedures compared with the general population, but the increase in their studies has been attributed to parental characteristics (16, 17). In another European study in Finland, IVF infants were found to have more cardiac anomalies than control infants, which is consistent with the findings of increased cardiovascular defects in our study; however, the investigators did not find an increase in birth defects overall in the IVF group compared with naturally conceived infants (22). Our study is one of the few conducted in North America; the only other major American study is that of Olson et al., who found a small but significant increased risk of birth defects in children conceived by IVF (18). Their adjusted OR of a major birth defect in IVF conceived children was 1.30 (95% CI, [1.00, 1.67]), and for IUI-conceived children it was 1.11 (95% CI, [0.67, 1.84]). Our study results were more significant and included the risks for children conceived by OE as well, which was not looked at in any previous studies.

Some of the studies mentioned previously have also observed similar findings to ours with an increased risk of gastrointestinal, cardiovascular, and musculoskeletal defects (9, 22, 23). These are interesting observations and can help to generate hypotheses; however, these data should be interpreted cautiously as they were based on small subgroups of our study subjects. With the splitting of AHR techniques into the three groups, our sample size is decreased, and hence the likelihood of a type II error is increased. When looking at the three groups of AHR, our primary outcome identified is the rate of birth defects; we did attempt to correlate the increasing birth defects with increasing interventions, but this was not significant.

A potential weakness in our study is the fact that we did not adjust for multiples in our multivariate analysis. However, we found there would be no difference in doing so because in AHR most twins are dizygotic and because it is primarily in monozygotic twins that an increase in malformations is detected (24). We also did not adjust for the use of toxins, such as drugs and alcohol, since most woman undergoing AHR treatment are less likely to be exposed to toxins and tend to be of higher socioeconomic status (25–27). A lack of adjustment for these factors is therefore likely to lead to an underestimation rather than overestimation of the risk of birth defects. The sample size in our study was adequate; however, there were smaller numbers in each different subgroup of AHR or anomaly type. Therefore, our findings regarding each specific type of AHR and different type of birth defects should be interpreted with caution, since they were based on small numbers of infants in each group.

As with any study using an administrative database to generate epidemiological data, there may be administrative errors such as incomplete data, underreporting, and coding errors. We had 1399 patients who underwent some type of AHR; of those, 790 specified the type of AHR. Therefore, all the subjects could not be included in our study because of this missing information. As there was no difference in demographics between these groups, we do not feel there is any selection bias, and the effect of this is to reduce the overall size effect, giving a more conservative estimate. Another potential drawback in the database is the potential for nondisclosure of information from the patients. The rate of multiples in the natural conception group is quite high in our study (2.84%, data not shown), therefore one could speculate in this case about the nondisclosure of information in this group of use of AHR. Therefore, the risk of birth defects in the natural conception group may be lower than what we reported and we may therefore be seeing an underestimation of the actual increase of risk of birth defects when compared with the AHR group.

An ascertainment bias may also exist if AHR-conceived infants are followed more carefully and are more closely examined compared with infants conceived naturally. They

<table>
<thead>
<tr>
<th>TABLE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth defects in infants conceived with OI, IUI, IVF, or naturally.</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ovulation induction</th>
<th>IUI,</th>
<th>IVF,</th>
<th>Natural conception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>1.73</td>
<td>1.57</td>
<td>0.38</td>
</tr>
<tr>
<td>Neural tube defects</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Gastrointestinal&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>1.73</td>
<td>0.63</td>
<td>0.06</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>0</td>
<td>0</td>
<td>0.94</td>
<td>0.27</td>
</tr>
<tr>
<td>Facial</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.09</td>
</tr>
<tr>
<td>Other</td>
<td>2.35</td>
<td>0.58</td>
<td>2.19</td>
<td>1.18</td>
</tr>
<tr>
<td>All anomaly</td>
<td>2.35</td>
<td>2.89</td>
<td>3.45</td>
<td>1.86</td>
</tr>
</tbody>
</table>

<sup>a</sup><sup>P_0.01</sup>.

will then be more likely to be diagnosed with a birth defect than non-AHR infants.

There is scientific plausibility to the finding of an increased risk of birth defects in AHR, given the interventions required in these treatments. Elements that may contribute to increasing birth defects include the advanced age of one or both partners of the infertile couple, the essential cause of infertility, or the medications used to induce ovulation or to maintain the luteal phase. Recently, attention has been directed toward epigenetic errors that might be intrinsic in the infertile couple or stimulated as a consequence of the infertility treatment itself. In some studies it was found that the embryo culture media used in IVF may predispose the embryo to imprinting disorders (28–30).

Further research in these interventions is needed to clarify each individual contribution. A possible way to address this question appropriately is to set up a large prospective population-based study using birth registries of AHR with naturally conceived infants as controls. The follow-up of infants in these studies should also include long-term effects on psychological and mental development, in addition to the short-term health consequences of mortality, morbidity, and clinically recognizable congenital anomalies.

REFERENCES