Congenital anomalies in offspring of subfertile couples: a registry-based study in the northern Netherlands

Jorien Seggers, M.D.,[a] Hermien E. K. de Walle, Ph.D.,[b] Jorieke E. H. Bergman, M.D., Ph.D.,[b] Henk Groen, M.D., Ph.D.,[b] Mijna Hadders-Algra, M.D., Ph.D.,[a] Marly E. Bos, B.Sc.,[b] Annemieke Hoek, M.D., Ph.D.,[c] and Maaike L. Haadsma, M.D., Ph.D.[b]

[a] Division of Developmental Neurology, Department of Pediatrics, [b] Division of Eurocat Northern Netherlands, Department of Genetics, and [c] Department of Obstetrics and Gynecology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

Objective: To study whether specific congenital anomalies occur more often with a history of subfertility and/or the use of in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI).
Design: Case-only analyses.
Setting: Not applicable.
Patient(s): We included live births, stillbirths, and terminated pregnancies with congenital anomalies without a known cause that had a birth year between 1997 and 2010 (n = 4,525). A total of 4,185 malformed cases were born to fertile couples and 340 to subfertile couples, of whom 139 had conceived after IVF/ICSI and 201 had conceived naturally after >12 months.
Intervention(s): None.
Main Outcome Measure(s): The contribution, expressed in odds ratios (ORs), of a history of subfertility and IVF/ICSI to each specific type of congenital anomaly, imprinting disorder, and syndromal disorder.
Result(s): We found subfertility to be associated with an increase in abdominal wall defects (adjusted OR [aOR] 2.43, 95% CI 1.05–5.62), penoscrotal hypospadia (aOR 9.83, 95% CI 3.58–27.04), right ventricular outflow tract obstruction (aOR 1.77, 95% CI 1.06–2.97), and methylation defects causing imprinting disorders (aOR 13.49, 95% CI 2.93–62.06). In vitro fertilization/ICSI was associated with an increased risk of polydactyly (OR 4.83, 95% CI 1.39–16.77) and more specifically polydactyly of the hands (OR 5.02, 95% CI 1.43–17.65).
Conclusion(s): In our registry-based study, parental subfertility was associated with an increase in abdominal wall defects, penoscrotal hypospadia, right ventricular outflow tract obstruction, and methylation defects causing imprinting disorders. In vitro fertilization/ICSI was associated with an increase in polydactyly, mainly of the hands. (Fertil Steril® 2015;103: 1001–10. ©2015 by American Society for Reproductive Medicine.)
Key Words: In vitro fertilization, assisted reproductive technology, subfertility, congenital anomalies, birth defects

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The increasing use of in vitro fertilization (IVF), with or without intracytoplasmic sperm injection (ICSI), has raised concerns about potential consequences for the resulting offspring, in particular the putative effect on the prevalence of congenital anomalies. A recent meta-analysis showed that infants born after IVF/ICSI (n = 92,671) had a relative risk of 1.32 (95% confidence interval [95% CI] 1.24–1.42) of having any birth defect compared with naturally conceived infants (n = 3,870,760) (1).

The increased number of birth defects in infants conceived via IVF/ICSI has been attributed both to the IVF/ICSI procedure and the parent's underlying subfertility. A role for the IVF/ICSI procedure is conceivable because natural selection of gametes is bypassed, early embryonic development

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Reprint requests: Jorien Seggers, M.D., Developmental Neurology, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands (E-mail: jorienseggers@gmail.com).

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takes place in vitro, and the embryo is transferred into an altered intrauterine environment due to ovarian hyperstimulation. There is also evidence for a role of the underlying subfertility: untreated subfertility and a longer time to pregnancy are associated with an increased rate of birth defects (2–4).

In addition, an increased risk of imprinting disorders like Beckwith-Wiedemann syndrome and Angelman syndrome has been described after IVF/ICSI (5–7). There is evidence to suggest an adverse effect of the IVF/ICSI procedures (8–11), as well as of the underlying subfertility (12), on imprinting status.

Previous studies often faced the limitation of either low numbers of specific congenital anomalies or the absence of information on a history of subfertility without IVF/ICSI treatment. In case of low numbers of specific anomalies, defects were grouped together in larger subgroups for power reasons. Associations have been reported between IVF/ICSI and cardiovascular anomalies, neural tube defects, urogenital anomalies, gastrointestinal anomalies, clefts, musculoskeletal anomalies, and limb anomalies (13–15). A disadvantage of using subgroups is that pathogenetically dissimilar congenital anomalies are pooled. This could explain why the studies provided an incoherent picture. For instance, some found an increased risk of musculoskeletal defects (2, 14, 16–18), whereas others did not (15, 19–22). These contradictions emphasize the necessity for a novel approach evaluating the increased risk for specific types of birth defects like hip dysplasia or a club foot, instead of larger subgroups of defects, such as musculoskeletal defects. In addition, knowledge about which birth defects occur more often after a history of subfertility without IVF/ICSI treatment is scarce.

To address these issues, we analyzed data from Eurocat Northern Netherlands (Eurocat NNL), a voluntary population-based birth defects registry. Unlike previous studies that used non-malformed controls, we performed a case-only study: we studied the effects of subfertility and IVF/ICSI in a dataset of fetuses/children that all have a congenital anomaly. This approach precludes us from investigating the overall risk for a congenital anomaly but allows us to identify which specific congenital anomalies, imprinting disorders, and syndromal disorders with unknown etiology are associated with subfertility or IVF/ICSI.

MATERIALS AND METHODS

Setting and Participants

We used data from Eurocat NNL, which registers fetuses and children with congenital anomalies of mothers who lived in the registration area at the time of birth. An affected child can be registered up to the age of 10 years. Annually, Eurocat NNL monitors approximately 19,000 births in the northern Netherlands. Eurocat NNL uses multiple sources for active case ascertainment, in addition to notification by midwives, general practitioners, well-baby clinic doctors, and medical specialists. Live births, stillbirths, and pregnancies terminated due to congenital anomalies are notified on a voluntary basis. The staff of Eurocat NNL is actively involved in case ascertainment. The participation rate is stable at approximately 80% for years. After consenting to registration, parents receive a questionnaire asking about their health, life style, use of medication, fertility, and pregnancy; another 80% completes the questionnaire. A telephone interview on the use of medication during pregnancy was conducted with all parents who submitted a questionnaire. If inconsistencies in the questionnaire were detected, the interviewer also asked questions about these inconsistencies in the same interview.

Information on congenital anomalies is retrieved from medical files and includes results from genetic tests and pathology reports. Congenital anomalies are classified according to the 9th and 10th revisions of the World Health Organization International Classification of Diseases (ICD). The ICD-9 classification was used up to 2001 and ICD-10 from 2002 onward. Heart defects are further classified into septal defects, conotruncal defects, outflow tract anomalies, and other heart defects (23). Eurocat NNL does not collect information on non-malformed fetuses/children. An overview of the procedures and findings of Eurocat can be found at www.eurocat-network.eu/accessprevalencedata/prevalencetables. Parents consented to the data being registered and used in studies on risk factors for congenital anomalies. Approval from the medical ethics board was not required.

Cases born between 1997 and 2010 were divided into three fertility groups: [1] fertile parents, [2] subfertile parents who eventually conceived naturally (Sub-NC group), and [3] subfertile parents who conceived after IVF or ICSI. Parents were categorized into one of these groups depending on their answers to the questionnaire: they were asked whether they experienced any problem conceiving. If they answered "no," they were considered fertile. If they answered "yes," parents could fill out whether they used any fertility treatment and, if so, which treatment. We searched medical records of fertility clinics of all couples stating they had fertility problems. Couples were defined as subfertile after a time to pregnancy of at least 12 months. Cases were excluded if subfertility could not be confirmed (e.g., no medical records of fertility clinics were available or a time to pregnancy <12 months) or if any treatment other than IVF or ICSI was used.

Methods and Variables

Because we were interested in the possible effect of subfertility on congenital anomalies, we excluded all cases with a known underlying cause for their anomaly, including chromosomal and monogenic disorders and defects resulting from congenital infections or exposure to teratogens. The reason for this is that demonstrating an additional effect of subfertility, when a known cause is already present, requires a larger and different population. For example, Down syndrome is known to be associated with congenital heart defects. To demonstrate an effect of subfertility, the question would be whether children with Down syndrome are even more likely to have a heart defect in case their parents are subfertile. Because we do not expect to be able to demonstrate such associations, and because adding congenital anomalies with a known cause may well mask a possible effect of subfertility on a specific anomaly, we chose to exclude cases with a known underlying cause. We did include all imprinting