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Is subfertility or fertility treatment associated with long-term growth in the offspring? A cohort study

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Objective: To study whether fertility treatment or subfertility is associated with long-term growth in the offspring.
Design: A prospective follow-up study including 1,773 singletons participating in the Lifestyle During Pregnancy Study at the age of 5.
Setting: Research centers.
Patient(s): A total of 3,478 mother-child pairs were sampled from the Danish National Birth Cohort, and 1,773 completed the outcome measurements. A total of 69 children were born after fertility treatment, whereas 132 were born to subfertile parents conceiving spontaneously but after a time to pregnancy of more than 12 months. The remaining 1,572 children were born to parents conceiving spontaneously within 12 months. At the age of 5, the children participated in a follow-up including anthropometric measurements. Information on important covariates with respect to family background, maternal prenatal exposures, perinatal outcomes, and postnatal parental lifestyle characteristics were obtained from the Danish National Birth Cohort, the 5-year follow-up, and Danish health registers.
Intervention(s): None.
Main Outcome Measure(s): Adjusted mean differences in body weight, height, body mass index (BMI), and head circumference at age 5.
Result(s): Compared with spontaneously conceived children born to fertile parents, no systematic differences were observed for body weight, height, BMI, or head circumference at age 5 in children conceived after fertility treatment or to subfertile parents conceiving spontaneously.
Conclusion(s): There were no differences in child anthropometrics at 5 years between children conceived after fertility treatment or by subfertile parents compared with that of children born to fertile parents. However, children born after fertility treatment may show catch-up growth during childhood. (Fertil Steril® 2014;■: ■–■. ©2014 by American Society for Reproductive Medicine.)
Key Words: Assisted reproduction, subfertility, child development, growth

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During the last decades, the use of fertility treatment has increased dramatically (1, 2). Similarly, there is a continuously growing body of literature evaluating treatment success and safety of the procedures (3–6). It is now generally accepted that fertility treatment increases the risk of obstetrical and neonatal complications, although the risk is partly related to the higher proportions of multiples (7, 8). However, even singletons born after fertility treatment have been shown to have shorter length of gestation, lower birth weight, and increased risk of being small for gestational age (7). The etiology of the impaired fetal growth is largely unknown, but the types of culture media and ovarian stimulation have been suggested to potentially affect birth weight (9, 10). However, other studies suggest that the shorter length of gestation or

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impaired growth is related to the underlying subfertility rather than to the treatment (11–13).

Despite the fact that several studies have advocated long-term follow-up on children born after fertility treatment, only a few long-term assessments have been conducted. Impaired fetal growth and rapid postnatal catch-up may be related to increased risk of cardiovascular disease, obesity, and type 2 diabetes in adult life (14–17). Still, it remains unclear whether smaller anthropometric size at birth in children born after fertility treatment persists later in childhood.

We conducted a follow-up study investigating the growth of children born to subfertile parents or parents conceiving after fertility treatment compared with spontaneously conceived children. We assessed anthropometric measures at birth and at the age of 5 years, hypothesizing that mode and time to conception are associated with both fetal and childhood growth.

MATERIALS AND METHODS

Design and Population

This study is a prospective follow-up, based on the mother-child pairs participating in the Lifestyle During Pregnancy Study (LDPS) (18), which aimed to investigate the influence of different prenatal exposures on child development. The LDPS consists of a sample of participants from the Danish National Birth Cohort (DNBC) (19), a large cohort of pregnant women and their children born in Denmark between 1997 and 2003. A total of 3,478 singletons from the DNBC were invited to the LDPS, and 1,782 (51.2%) participated in the follow-up when the children were 5 years old. Nine children were not measured on any of the outcomes, leaving 1,773 children eligible for analyses. There were no differences between participants and nonparticipants in the LDPS with respect to maternal age, parity, prenatal smoking or alcohol consumption, body mass index (BMI), marital status, child gender, gestational age at birth, or birth weight (20).

Data Collection

Exposure assessment. At a median of 17 weeks of gestation, the first of two prenatal interviews in the DNBC provided information about any treatment for childlessness before the index pregnancy including type of treatment and waiting time to pregnancy (TTP). The information on self-reported fertility treatment in the DNBC has previously been shown to have a high positive predictive value and sensitivity (21). On the basis of this information, we defined two exposure groups and a reference group. The fertility treatment group consisted of children born after in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) and after ovarian stimulation or ovulation induction with or without intrauterine insemination (IUI). The subfertility group was defined as spontaneously conceived children born to parents with a TTP of more than 12 months, whereas the reference group consisted of children born to fertile parents defined as parents conceiving naturally within 12 months.

Follow-up assessment. Child outcome measures were obtained during a 3-hour assessment when the child was between 5.0 and 5.3 years old. To minimize the travel distance for all mothers and children, the assessment took place in the four largest cities in Denmark. Before this, the parents had been mailed a self-explanatory questionnaire regarding the child's general postnatal health and development, as well as maternal and paternal postnatal lifestyle and sociodemographic characteristics. At the follow-up, the children were examined with an eyesight test, audiometric evaluation, and anthropometric measurements. In addition, the children were tested with a comprehensive neuropsychological test battery (22).

Covariates. The following covariates were obtained from the DNBC prenatal interview: parity, prenatal maternal smoking, maternal alcohol consumption during pregnancy, and maternal BMI. At the time of the 5-year follow-up, the following variables were recorded: length of parental education (average total length of education in years for the two parents or length of maternal education if information on the father was unavailable), marital status (single either at the prenatal interview or at the follow-up or married or cohabitating at both), family/home index (defined as normal or suboptimal as determined by the presence of two or more of the following adverse conditions: living with only one biological parent, changes in primary caregivers, day care more than 8 hours/day before age 3, $\geq$14 days of separation from parents, irregular breakfast, maternal depression, and maternal and paternal alcohol intake above the official recommendations from the Danish National Board of Health at the time of the data collection), and child health index (presence or absence of major medical conditions or regular use of prescription medications). Maternal age was obtained directly from the unique Danish personal identification number, as was gender of the child and age of the child at testing. Birth weight and gestational age were obtained from the Danish Medical Birth Register (23).

Data Analyses

The statistical analyses were conducted with Stata version 12 (StataCorp LP) (24). Since the main exposure of interest in the LDPS was maternal alcohol consumption during pregnancy, mothers were originally sampled on the basis of their self-reported average alcohol consumption or binge drinking during and before pregnancy (18). Thus, analyses for the present study were weighted by sampling probabilities computed as the ratio between the number of sampled women and the total number of women available in each strata of alcohol exposure in the DNBC. All statistical tests were two-sided and declared significant at a 5% level. All estimates are accompanied by 95% confidence intervals.

Descriptive analyses and tests of demographical differences among the three groups were conducted using analysis of variance (Gaussian continuous variables), Kruskal-Wallis (non-Gaussian continuous variables), and the χ^2-test (categorical variables). When comparing the fetal growth between groups, we additionally estimated differences in birth weight, gestational age, and length at birth in the two exposure groups separately compared with the reference group (fertile parents, TTP less than 12 months) by conducting linear regression