

Long-awaited pregnancy: intelligence and academic performance in offspring of infertile parents—a cohort study

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Objective: To study whether fertility treatment, subfertility, or pregnancy planning are related to long-term intellectual development.

Design: Cohort study.

Setting: Not applicable.

Patient(s): A total of 5,032 singletons born from 1990 to 1992 in the Aarhus Birth Cohort were followed up to a mean age of 19 years. These children were born as a result of fertility treatment ($n = 210$), had subfertile parents who took more than 12 months before conceiving naturally ($n = 334$), had fertile parents who conceived naturally within 12 months ($n = 2,661$), or had parents who reported the pregnancy as unplanned ($n = 1,827$).

Intervention(s): The children were followed up using questionnaires and information from Danish national registers.

Main Outcome Measure(s): Parent reported school difficulties at ages 9–11 years, register-based school grades at ages 16, 17, and 19 years, and conscription intelligence test scores at age 19 years.

Result(s): We found no evidence of school difficulties in childhood, impaired school performance in adolescence, or lower intelligence in young adulthood in multivariate analyses adjusted for parental age, educational level, maternal parity, before pregnancy body mass index (BMI), smoking and alcohol intake in pregnancy, cohabitation status, child gender, and age.

Conclusion(s): In the longest follow-up of cognitive development of children conceived after fertility treatment or by subfertile parents conducted so far, this study did not show any association between pregnancy planning, subfertility, or fertility treatment and cognitive ability or academic performance. (Fertil Steril® 2016; ■:■-■. ©2016 by American Society for Reproductive Medicine.)

Key Words: Fertility treatment, subfertility, child development, intelligence, school performance

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Despite the planning of a pregnancy, conception cannot be taken for granted. Although the pregnancy rate per month for a

fertile couple is around 25% and age-dependent (1, 2), an estimated 10%–15% take more than 12 months to conceive (3, 4). An increasing number

of couples seek fertility treatment with hormonal stimulation, IUI, or in vitro manipulation of gametes (5). Fortunately, fertility treatment only rarely leads to complications for the woman (6). However, several studies have linked subfertility and fertility treatment to adverse pregnancy outcomes (7), although it remains unclear whether these result from the treatment procedures, the family background, or the subfertility per se.

Long-term investigations of the mental health and development of children born after assisted reproduction

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are still very few (8). Few studies have yielded reassuring results, although no studies have yet reached into adulthood. Adverse effects may be subtle, and thus the monitoring of child development should be considered an ethical obligation to assess and ensure the safety of fertility treatment. As more than three decades have now passed since the introduction of IVF, the number of children reaching adulthood is increasing, making long-term follow-up possible.

In this cohort study, we investigated whether parental subfertility, fertility treatment, or pregnancy planning was associated with the child's subsequent intellectual development as assessed by school difficulties at age 9–11 years, school grades at ages 16, 17, and 19 years, and intelligence test scores at age 19 years making this study the longest follow-up so far on cognitive development of children conceived by subfertile parents and by parents who conceived after fertility treatment.

MATERIALS AND METHODS

Design and Population

This cohort study was based on participants from the Aarhus Birth Cohort, a large on-going Danish birth cohort initiated in 1989 (9). Data were collected through the consecutively recruitment of unselected women in early pregnancy who intended to give birth at Aarhus University Hospital, Aarhus, Denmark. Being the only maternity ward in the second-largest Danish city, it covered a population of approximately 250,000 during the study period and participants were recruited at their routine antenatal care visit, which >97% of Danish women attend (10). At approximately 16 weeks gestation the enrolled women completed two questionnaires to obtain information on medical and obstetric history, waiting time to pregnancy (TTP), fertility treatment, lifestyle during pregnancy, and socioeconomic factors. At the time of birth, the attending midwife registered information about the newborn along with any medical or obstetric complications.

To examine long-term follow-up into adolescence and young adulthood, we studied a population of children born during the first years of the cohort (January 1, 1990 to June 30, 1992), who participated in a follow-up in 2001 when the children were 9–11 years old (11). In 2001, the mothers of 7,953 live singletons born in the Aarhus Birth Cohort, living in Denmark, and traceable were invited to a follow-up. Of these, 5,841 (73%) completed comprehensive questionnaires covering the development of the child, parent reported school difficulties, and socioeconomic information on the family. For the present study, we excluded children with unavailable information on the planning of pregnancy, waiting TTP, or fertility treatment, and children with missing data on all outcome measures leaving 5,032 singletons born by 4,962 mothers eligible for follow-up (Supplemental Fig. 1, available online).

Subfertility, Fertility Treatment, and Pregnancy Planning

Based on information from the early pregnancy questionnaires, we categorized the children into four groups depending on the TTP, mode of conception, and planning of the

pregnancy. The fertility treated parent group consisted of all children conceived after any type of fertility treatment (e.g., IVF, ovarian stimulation, induction of ovulation with or without IUI). The subfertile parent group consisted of children conceived spontaneously but to parents with a TTP of >12 months. The spontaneously conceived comprised children conceived within 12 months of trying. If parents reported the pregnancy as unplanned and spontaneously conceived the child was categorized into the unplanned parenthood group regardless of TTP.

School Performance and Intelligence

According to law, all Danish children must attend compulsory education from the age of 6 years (12). The Danish primary and lower secondary school comprise 10 school years including one preschool year (grade 0) followed by grades 1–9, and an optional 10th grade. All children are assessed with grades whether attending public (81%), private (16%), or boarding school, home teaching, or institutions (3%) (13). After completing primary and lower secondary school, pupils may attend upper secondary school, which takes an additional 2–3 years and grants access to higher education (e.g., university) depending on the grades achieved. Danish grades comprise a seven-point grading scale ranging from –3 to 12, where –3 and 00 is a fail, 02 is a pass, 4 is considered a fair performance, 7 a good performance, 10 a very good performance, and 12 an excellent performance. Before 2006, grades were given on an 11-point scale, but have all been transformed to the 7-point scale and updated in the national educational registers using a standard algorithm. Attendance in Danish schools is free at all levels from preschool to university. Information on school performance, academic achievement, and cognitive ability was obtained at four time points. First, we obtained information on reading, spelling, and arithmetic difficulties as reported by the parents in the follow-up in 2001 when the children were 9–11 years old (none; minor; some; severe). Second, we obtained individual-level information from Statistics Denmark on school grades at the completion of the Danish primary and lower secondary school (Folkeskolen) when the children were aged 14–16 years (14). Third, we obtained individual-level information from Statistics Denmark on school grades for the children continuing to the completion of Danish upper secondary school (Gymnasiet) when the children were 18–20 years (14). The individual school grades were categorized according to related subjects areas determined a priori to minimize the number of outcome variables. Whereas grades are given by the teacher for each completed subject, examination marks are only available for pupils randomly selected for examination in a particular subject. Thus, final marks for each subject were calculated as averages of continuous assessment and examination marks.

Intelligence was assessed by the BPP (in Danish: Børge Priens Prøve) using data from the Danish Conscription Register (15). The BPP is a test of intelligence administered to all men at the time of conscription for military service (16). All Danish men are required to appear before the draft board at the time of their 18-year birthday. This is mandatory unless

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