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Infertility, infertility treatment, and mixed-handedness in children

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Abstract

Background—Mixed-handedness, which may reflect atypical brain laterality, has been linked to a number of medical conditions as well as prenatal stress.

Aims—The aim of the study was to examine whether infertility or infertility treatment was associated with an increased risk of mixed-handedness in children.

Study design, subjects and outcome measures—We used data from three population-based birth cohorts in Denmark: the Aalborg-Odense Birth Cohort (1984-1987), the Aarhus Birth Cohort (1990-1992) and the Danish National Birth Cohort (1996-2002) (N=7728, 5720 and 29486, respectively). Data on time to pregnancy and infertility treatment was collected during pregnancy. Handedness was reported in a follow-up questionnaire when the children were at least 7 years old. Children were categorized as mixed-handed if the mothers reported that they used both hands equally.

Results—Children born after infertility treatment, particularly intrauterine insemination, had a higher risk of being mixed-handed compared to children of fertile couples with a time to pregnancy ≤ 12 months (odds ratio 1.41, 95% confidence interval 1.09-1.82). Children of couples with unplanned pregnancies, particularly after an oral contraceptives failure, were also more likely to be mixed-handed. There was no association between a long waiting time to pregnancy and mixed-handedness in children.

Conclusions—Children born after infertility treatment, particularly intrauterine insemination, and children exposed to oral contraceptives during early gestation may have a higher risk of being mixed-handed.

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Conflict of interest statement
None declared.

Keywords

Infertility; Infertility treatment; Mixed-handedness; Oral contraceptives; Time to pregnancy

1. Introduction

Infertility, defined as a waiting time to pregnancy (TTP) longer than 12 months, affects about 20% of couples in developed countries. It is estimated that about half of infertile couples seek medical help [1-3]. Currently 1-3% of all children in industrialized countries are born after assisted reproductive technologies (ART) [4,5], and concerns have been raised on the short- and long-term health consequences for children born of infertile couples who conceived either naturally or through infertility treatment [6-9].

Although its etiology is unclear [10,11], handedness is probably determined prenatally, and changes in the hormonal environment in utero have been suggested as one of the possible mechanisms [12-14]. Studies also show that mixed-handedness, which may reflect atypical brain laterality, rather than left-handedness, may be associated with prenatal stress [15-17], language difficulties, and childhood behavior problems [17,18]. Hormonal treatment for infertility, as well as stress associated with infertility and its treatment [19], may thus affect determination of handedness in children conceived through ART. According to one study, however, no significant changes in assessed handedness were seen in children born following ART, although girls born after intracytoplasmic sperm injection (ICSI) were slightly less likely to be left-handed [20].

In this study, we used three Danish birth cohorts to examine whether parental infertility or infertility treatment was associated with mixed-handedness in children.

2. Methods

2.1. Study population

We used data from three population-based birth cohorts in Denmark: the Aalborg-Odense Birth Cohort (1984-1987) [21], the Aarhus Birth Cohort (1990-1992) [9], and the Danish National Birth Cohort (1996-2002) [22]. For all birth cohorts, we had data on socio-demographic, environmental, and lifestyle factors collected through questionnaires during pregnancy. The children in the three cohorts were followed up to the ages of 15-18, 9-11, and 7 years, respectively. The Danish Data Protection Agency, acting as the ethics committee for this type of studies, granted authorization for the implementation of the project (Ref. no. 2005-41-5488).

All pregnant women in Aalborg and Odense were invited to participate in a study launched as a health campaign, "Healthy Habits for Two", between April 1984 and April 1987, which resulted in the Aalborg-Odense Birth Cohort. Midwives handed out a questionnaire to be self-administered at a routine antenatal visit around the 36th gestational week. A total of 11,980 women (87% of the eligible) in the two regions took part in the study. In 2002, a follow-up questionnaire on health and development of the child, including handedness, was mailed to 10,636 mother-child pairs who could be traced by means of the civil registration system (all included children were singletons). A total of 7841 primary caregivers, usually the mothers, responded (74%). We excluded those with no (N=87) or more than one answer (N=26) to the single handedness question, thus leaving 7728 singletons in the Aalborg-Odense Birth Cohort available for analysis.

The Aarhus Birth Cohort, established in 1989, is an ongoing pregnancy cohort that covers all births in the Aarhus University Hospital. The cohort is based on consecutive recruitment in

early pregnancy through the antenatal health care service. The present study was based on children born between January 1990 and June 1992. Prior to the routine antenatal visit at 16 gestational weeks, all Danish-speaking women were asked to complete a self-administered questionnaire. The response rate was 95%. In 2001, parents of 8244 children who were alive and could be traced by means of the civil registration system were asked to fill in a questionnaire concerning child health and development, including handedness. A total of 5974 questionnaires were returned (72%). We excluded twins and triplets (N=128 and 9, respectively), as well as singletons with no answer to the single handedness question (N=117), thus leaving 5720 singletons in the Aarhus Birth Cohort available for analysis.

The Danish National Birth Cohort was established to explore the potential importance of social, environmental, and lifestyle factors during pregnancy and early childhood on health and development of children [22]. Women, recruited early in pregnancy by general practitioners, participated in four computer-assisted telephone interviews (two scheduled at 12 and 30 weeks of gestation and two scheduled when the child was 6 and 18 months, respectively). About 50% of all general practitioners participated in the recruitment, and about 60% of the invited women consented to participate in the cohort. When the child turned 7 years of age, a follow-up questionnaire about child health and development, including handedness, was administered through the internet or conventional mail. Letters were sent to the mothers informing them about how to access the web questionnaire and also that they could request a paper version of the questionnaire. If they did not respond after four weeks, two sequential reminders followed, with the last including a hard copy of the questionnaire. No further letters were sent, but completed forms were returned for months after the last letter. A total of 31508 caregivers, mostly mothers, responded between July 2005 and February 2008 (about 60% of the eligible). We linked the 7-year follow-up data with the first interview data and excluded twins, triplets, and those with no data on the first interview (N=703, 12, and 1140, respectively). We also excluded those with no answer (N=131) or who answered “don’t know” (N=36) to the single handedness question, thus leaving 29486 singletons in the Danish National Birth Cohort available for analysis.

2.2. Infertility and infertility treatment

In the pregnancy questionnaires for all three cohorts, women were asked if their pregnancy was planned, if they had ever been examined or treated for infertility, and for how long they had tried to become pregnant before succeeding [time to pregnancy: three categories for the Aalborg-Odense Birth Cohort (0-6, 7-12, and more than 12 months), exact number of months for the Aarhus Birth Cohort, and four categories for the Danish National Birth Cohort (0-2, 3-5, 6-12, and more than 12 months)]. We classified time to pregnancy for the Aarhus Birth Cohort into the same three categories as for the Aalborg-Odense Birth Cohort (0-6, 7-12, and more than 12 months).

We defined couples as fertile if they planned their pregnancy and conceived within 12 months without being examined or treated for infertility. Couples who planned their pregnancy but took longer than 12 months to conceive without being examined or treated for infertility were labelled as untreated infertile, while couples who reported being examined or treated for infertility were considered as treated infertile. Couples who did not plan their pregnancy and who had not been examined or treated for infertility were classified as couples with an unplanned pregnancy. The latter group also included for all three cohorts a few couples: 1) who planned their pregnancies with no information on time to pregnancy; 2) who reported that they conceived while using contraception; 3) who did not provide information on treatment; and 4) who did not provide information on pregnancy planning. Couples with a “partly planned” pregnancy (an additional answer category, besides planned and unplanned, to the question about pregnancy planning status) were also included for the Danish National Birth

Cohort. We also defined a group of “pure” unplanned pregnancies by restricting to couples who had reported not having planned their pregnancy and who had not received infertility treatment. In the Danish National Birth Cohort, women were also asked whether the unplanned pregnancy was a result of failure of oral contraceptives (regular or mini-pills).

In the Danish National Birth Cohort, if a woman reported that she or her male partner received infertility treatment, she was further asked “what kind of infertility treatment did you or your male partner receive?” She could choose one or more of six specified forms of treatment, or describe treatment in free-text. The six specified treatments were intracytoplasmic sperm injection (ICSI), in vitro fertilization (IVF), intrauterine insemination (IUI), ovulation induction (OI), surgery (e.g., removal of adhesions in fallopian tube or fibroid), and hysterosalpingography (HSG, rinsing of fallopian tubes). If a woman reported more than one procedure, she was classified according to the priority sequence given above. We considered four treatment procedures (ICSI, IVF, IUI and OI) individually, and the others were combined into one group as “other” treatment.

2.3. Handedness in children and parents

The Aalborg-Odense Birth Cohort and the Aarhus Birth Cohort included a single question “Which hand does your child use the most?” with five response categories (exclusively the right hand, mostly the right hand, both hands equally, mostly the left hand, and exclusively the left hand). Similar questions, with the same five response categories, were asked about each parent’s handedness. The Danish National Birth Cohort used a similar single question for the child “Is your child right- or left-handed?” with three response categories (right-handed, left-handed, and using both hands), but no questions about parental handedness were asked. Additional information was available in the Aalborg-Odense Birth Cohort (Annett Hand Preference Questionnaire [AHPQ]) [23] and the Aarhus Birth Cohort (a AHPQ version, modified for children).

To make the definition of mixed-handedness comparable in the three cohort, we defined mixed-handedness as “using both hands (equally)” to the simple question in all three cohorts. We present results in the paper primarily based on this definition, but we also checked our results with the information from the AHPQ or the modified AHPQ. *A priori*, we decided to use a narrow definition of mixed-handedness, which included Classes 5 and 6 among the 8-class categorization for AHPQ [23]. Classes 5 and 6 were right- and left-handed writers, respectively, who preferred the other hand for at least one of the other five primary actions (throwing, racket, match, hammer and toothbrush). Class 5 also included right-handed writers with left-handed use of scissors. For the modified AHPQ, we applied a similar strategy to define mixed-handedness with the four primary actions (writing, throwing, match, and toothbrush) and use of scissors (questions on racket and hammer were not asked).

2.4. Statistical analysis

We used logistic regression to calculate odds ratios (OR) of mixed-handedness when comparing children of infertile couples, treated or untreated, with children of fertile couples. We also examined the association between categories of time to pregnancy and mixed-handedness in children. Analyses were performed separately for each cohort and for all cohorts combined. Potential confounders included maternal age at the time of childbirth (<25, 25-29, 30-34, 35+ years) and smoking during pregnancy (yes, no). Sex of child (girls, boys) was also included as a covariate. Parental handedness (exclusively the right hand, mostly the right hand, both hands equally, mostly the left hand, and exclusively the left hand) was also included in the analyses for the Aalborg-Odense Birth Cohort and the Aarhus Birth Cohort. Analyses based on pooled data from all three cohorts were also adjusted for the cohort of origin. Since a few women contributed two children to the cohorts, we used a robust variance estimator to calculate

95% confidence intervals (CI) [24]. Because a previous study found that girls born after ICSI were marginally less commonly left-handed [20], we checked possible interactions between infertility status and sex of child by using the Wald test with a level of significance set at 0.05. By including and excluding preterm birth (<37 weeks of gestation) as a covariate in the models, we also checked if a potential association was mediated by preterm birth. We used Stata/SE 9.1 for all analyses.

3. Results

The proportion of mixed-handed children was similar between untreated infertile couples and fertile couples in all three cohorts (Table 1).

Children of treated infertile couples were slightly more frequently mixed-handed than those of fertile couples in all three cohorts (OR 1.41 [95% CI 1.09-1.82] for all cohorts combined) (Table 1). In the Danish National Birth Cohort, where treatment procedures were reported, children conceived after IUI had twice the risk of being mixed-handed (Table 2).

Children of couples with unplanned pregnancies were slightly more often mixed-handed than children born of fertile couples with planned pregnancies in the Aarhus Birth Cohort and the Danish National Birth Cohort (Table 1). Restricting analyses to couples who had not planned their pregnancy and who had not received infertility treatment did not change the results (Table 3). Furthermore, we found that children conceived due to failure of oral contraceptives, which was reported in the Danish National Birth Cohort, had a higher risk of being mixed-handed (Table 3).

Mixed-handedness in children was strongly associated with parental mixed-handedness in the Aalborg-Odense Birth Cohort and the Aarhus Birth Cohort (OR 16.46 [95% CI 10.79-25.12] and 28.54 [15.85-51.37] for maternal mixed-handedness, and OR 7.55 [95% CI 4.90-11.66] and 9.33 [5.17-16.82] for paternal mixed-handedness, respectively).

There was no association between categories of time to pregnancy and mixed-handedness in children in any of the three cohorts (data not shown). The Wald tests on the interaction with sex of children revealed no statistical significant results. Preterm birth was modestly associated with mixed-handedness (OR 1.38 [95% CI 1.04-1.82] for the pooled cohorts), but including preterm birth in the models did not change the risk estimates for infertility and infertility treatment (data not shown).

4. Discussion

Infertility treatment, in particular IUI, may be associated with mixed-handedness in children. Also, exposure to oral contraceptives in early pregnancy may increase the risk of being mixed-handed. We found no association between untreated infertility and mixed-handedness in children.

Our finding that infertility treatment may be associated with mixed-handedness in children supports the hormonal hypothesis [12-14]. Infertility treatment usually involves hormonal treatment to induce ovulation, although we found no increased risk of mixed-handedness in children of couples treated with ovulation induction alone. We further found that children conceived due to failure of oral contraceptives had an increased risk of being mixed-handed. These children may have been exposed to high levels of estrogen and progesterone during early pregnancy.

Infertility- and treatment-related stress may be considered an alternative explanation for our finding concerning infertility treatment, although the more invasive treatment procedures (ICSI

and IVF) would on average be more stressful than the less invasive ones (IUI and OI). Stress level may, however, have been reduced in the treated women with successful pregnancy, as some studies indicate [25,26]. Another possibility for the higher risk of mixed-handedness in IUI children is abnormal cilia in the sperm tail. IUI is often indicated for male factor infertility, and ciliary defects of spermatozoa are implicated in organ migration and lateralisation [27].

It is expected that both genetic and environmental factors are important for the determination of handedness [28,29]. We found that mixed-handedness in children was strongly associated with parental mixed-handedness. The association with maternal mixed-handedness was also observed, although on a much smaller magnitude, by Glover and colleagues [16]. In line with previous reports [28,30], preterm birth was associated with mixed-handedness. Maternal age, maternal smoking, and sex of child were also associated with mixed-handedness in children. However, our results on infertility treatment and oral contraceptives failure did not change with adjustment for these variables, which indicates an independent effect.

Our study populations arose from parents enrolled in three Danish birth cohorts during different time periods: the Aalborg-Odense Birth Cohort (1984-1987), the Aarhus Birth Cohort (1990-1992), and the Danish National Birth Cohort (1996-2002). Participation rates at enrolment were 87-95% for the two regional birth cohorts and 30-40% for the national birth cohort, and participation rates at follow-up were 72-74% and 60%, respectively. However, it is unlikely that participation depended on both fertility status in parents and handedness in children. Information on time to pregnancy and infertility treatment was obtained in the pregnancy questionnaires, while information on children's handedness was collected after at least 7 years, which makes it highly unlikely that reporting of handedness was influenced by reporting of time to pregnancy and treatment.

We also examined our results with mixed-handed children as those categorized as classes 5 and 6 by using information from the Annett Hand Preference Questionnaire (AHPQ) or the AHPQ modified to the use among children. In the Aalborg-Odense Birth Cohort, compared to fertile couples, the ORs for untreated infertile couples, treated infertile couples, and couples with unplanned pregnancies were 1.04 (95% CI 0.70-1.55), 0.83 (0.54-1.29), 1.02 (0.78-1.35), respectively. In the Aarhus Birth Cohort, the corresponding estimates were 1.86 (1.04-3.32), 1.70 (0.84-3.44), and 1.17 (0.83-1.65), respectively. While the definition using the AHPQ or the modified AHPQ categorized mixed-handed persons as using different hands for different tasks, the definition using the single question included both using different hands for different actions and using both hands for the same actions. The simple question may then be a more robust indicator of lateralisation than the specific handedness questionnaires. The different results may come from use of different definitions with different questions, as previously pointed out by Basso [31].

Our results suggest that couples undergoing infertility treatment, in particular IUI, may have a higher risk of having children with mixed-handedness, and that women taking contraceptive pills during early pregnancy may have children with an increased risk of mixed-handedness. These findings are novel and need to be replicated in other populations.

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Table 1

Mixed-handedness in children according to parents' pregnancy planning status and infertility treatment, the Aalborg-Odense Birth Cohort, the Aarhus Birth Cohort, and the Danish National Birth Cohort

Pregnancy planning status and infertility treatment	No. of children	No. of mixed-handed	%	Crude OR	Adjusted OR (95% CI)
Aalborg-Odense Birth Cohort^a					
Fertile couples	4866	106	2.2	1.00	reference
Untreated infertile couples	619	14	2.3	1.04	0.95 (0.52-1.76)
Treated infertile couples	643	21	3.3	1.52	1.44 (0.83-2.51)
Unplanned pregnancies	1600	28	1.8	0.80	0.79 (0.48-1.29)
Aarhus Birth Cohort^a					
Fertile couples	2863	40	1.4	1.00	reference
Untreated infertile couples	351	1	0.3	0.20	0.19 (0.03-1.45)
Treated infertile couples	225	4	1.8	1.28	1.23 (0.47-3.19)
Unplanned pregnancies	2281	51	2.2	1.61	1.71 (1.06-2.75)
Danish National Birth Cohort^b					
Fertile couples	18737	392	2.1	1.00	reference
Untreated infertile couples	1952	42	2.2	1.03	0.97 (0.70-1.34)
Treated infertile couples	1615	45	2.8	1.34	1.33 (0.97-1.82)
Unplanned pregnancies	7182	200	2.8	1.34	1.26 (1.06-1.51)
All cohorts, combined^c					
Fertile couples	26466	538	2.0	1.00	reference
Untreated infertile couples	2922	57	2.0	0.96	0.93 (0.70-1.23)
Treated infertile couples	2483	70	2.8	1.40	1.41 (1.09-1.82)
Unplanned pregnancies	11063	279	2.5	1.25	1.21 (1.04-1.40)

Logistic regression; OR: odds ratio; CI: confidence interval.

^a Adjusted for maternal age, smoking during pregnancy, sex of child, and parental handedness.

^b Adjusted for maternal age, smoking during pregnancy, and sex of child.

^c Adjusted for maternal age, smoking during pregnancy, sex of child, and cohort of origin.

Table 2

Mixed-handedness in children according to infertility treatment procedures, the Danish National Birth Cohort

Treatment procedure	No. of children	No. of mixed-handed	%	CrudeAdjusted OR ^a OR(95% CI)
ICSI	126	2	1.6	0.750.75 (0.18-3.03)
IVF	492	15	3.0	1.471.35 (0.79-2.31)
IUI	457	19	4.2	2.031.98 (1.24-3.18)
OI	418	9	2.2	1.031.00 (0.51-1.95)
Other	122	0	0.0	--

Logistic regression; OR: odds ratio; CI: confidence interval; Reference group: children born of fertile couples with time to pregnancy of less than 12 months. ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilization; IUI: intrauterine insemination; OI: ovulation induction.

^a Adjusted for maternal age, smoking during pregnancy, and sex of child.

Mixed-handedness in children of couples who had not planned their pregnancy and who had not received infertility treatment (defined as couples with pure unplanned pregnancies), the Aalborg-Odense Birth Cohort, the Aarhus Birth Cohort, and the Danish National Birth Cohort

	No. of children	No. of mixed-handed	%	Crude OR	Adjusted OR (95% CI)
Aalborg-Odense Birth Cohort^a					
Unplanned pregnancies	1240	21	1.7	0.77	0.70 (0.41-1.22)
Aarhus Birth Cohort^a					
Unplanned pregnancies	1949	41	2.1	1.52	1.60 (0.97-2.62)
Danish National Birth Cohort^b					
Unplanned pregnancies	3196	103	3.2	1.56	1.39 (1.11-1.74)
Pregnancies after failure of oral contraceptives ^c	256	17	6.6	2.38	2.11 (1.21-3.68)

Logistic regression; OR: odds ratio; CI: confidence interval; Reference group: children of fertile couples in the corresponding cohort.

^a Adjusted for maternal age, smoking during pregnancy, sex of child, and parental handedness.

^b Adjusted for maternal age, smoking during pregnancy, and sex of child.

^c Within the group of pure unplanned pregnancies, children conceived without use of oral contraceptives served as reference group.