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SHORT COMMUNICATION

Asthma and asthma medication use among 4-year-old offspring of subfertile couples – association with IVF?



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Abstract This study evaluated the prevalence of asthma and asthma medication use in 213 4-year-old singletons followed from birth onwards, including three groups of children born following: (i) controlled ovarian hyperstimulation IVF/intracytoplasmic sperm injection (ICSI); (ii) modified natural cycle IVF/ICSI; and (iii) natural conception in subfertile couples. The rate of asthma medication was higher in the ovarian hyperstimulation-IVF/ICSI than in the subfertile group (adjusted odds ratios [aOR]: 1.96 [1.00–3.84]). Time to pregnancy, a proxy for the severity of subfertility, was not associated with asthma and asthma medication. In conclusion, controlled ovarian hyperstimulation-IVF/ICSI is associated with the use of asthma medication in 4-year-old offspring of subfertile couples.

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KEYWORDS: assisted reproductive techniques, asthma medication, asthma, in-vitro fertilization, time to pregnancy

Introduction

Asthma is a chronic reversible obstructive lung disease, which is one of the most common diseases amongst children. A recent study suggests an association between assisted reproductive techniques, IVF and intracytoplasmic sperm injection (ICSI), and asthma in the offspring (Carson et al., 2013). It is known that assisted reproductive techniques are associated with an increased risk of preterm birth, low birthweight and Caesarean section, which are risk factors for the development of asthma, making an association between assisted reproductive techniques and asthma plausible (Carson et al., 2013; Helmerhorst et al., 2004). Yet, assisted reproductive technique-related procedures such as ovarian hyperstimulation or the in-vitro procedure may also play a role. In addition, the underlying subfertility is suggested as a causative factor for asthma in the offspring as well (Källén et al., 2013). Therefore, the primary aim of this study was to disentangle the effects of ovarian hyperstimulation from that of the in-vitro procedure on asthma and the use of asthma medication in 4-year-old children. The secondary aim was to study the effect of prolonged time to pregnancy (TTP) – a proxy for the severity of subfertility – on asthma and asthma medication use.

Materials and methods

The children assessed participated in two parallel running prospective studies, the Groningen ART cohort study (Middelburg et al., 2009) and the preimplantation genetic screening (PGS) study (Mastenbroek et al., 2007). Of the Groningen assisted reproductive techniques cohort all children were eligible, of the PGS study only those who were conceived following conventional ovarian hyperstimulation-IVF/ICSI without PGS. The two studies provided us with three groups of 4-year-old singletons born to subfertile parents: (i) 81 singletons born after controlled ovarian hyperstimulation-IVF/ICSI (COH-IVF/ICSI); (ii) 53 singletons born following modified natural cycle IVF/ICSI without ovarian hyperstimulation (MNC-IVF/ICSI); and (iii) 79 singletons conceived naturally by subfertile couples after a TTP >1 year (Sub-NC). Information on socioeconomic status, and the prenatal, perinatal and neonatal periods was obtained 2 weeks after birth. TTP was defined as the time between the start of unprotected intercourse and pregnancy. In case of miscarriage TTP can be <1 year, as TTP has a new onset. At the follow-up assessment parents filled out a dedicated health questionnaire, which included questions on asthma. The medical ethics committee of the UMCG approved the study design of the 4-year follow-up of the Groningen ART cohort study and that of the PGS study, date of approval 09.07.2009 (reference number M09.074824) and parents provided informed consent.

Background data are reported in Table 1. Fisher's exact tests and Mann-Whitney *U*-tests were used to estimate differences between the groups. Multiple logistic regression analyses were performed adjusting for TTP, maternal body mass index (BMI), sex, gestational age, birthweight, Caesarean section, at least one parent with asthma and a currently smoking parent. To study the effect of TTP on asthma and

asthma medication use the groups were pooled, while adjusting for the same set of confounders plus group status and except TTP. Results are expressed as crude and adjusted odds ratios (OR and aOR, respectively) with 95% confidence intervals (95% CI). Probability values of <0.05 are considered significant. Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.0 (IBM Corp., USA).

Results

Asthma was reported in 24 (11.3%) children, whereas asthma medication was used by 20 (9.4%) children. The prevalence of asthma was similar in the groups (Table 1). Logistic regression confirmed the following: COH-IVF/ICSI versus MNC-IVF/ICSI (reflecting the effect of ovarian hyperstimulation) OR: 1.36 (95% CI: 0.48–3.88), aOR: 1.33 (95% CI: 0.42–4.11); MNC-IVF/ICSI versus Sub-NC (reflecting the effect of the in-vitro procedure) OR: 1.55 (95% CI: 0.47–5.10), aOR: 1.60 (95% CI: 0.43–6.02); COH-IVF/ICSI versus Sub-NC (reflecting the combined effect of ovarian hyperstimulation and the in-vitro procedure) OR: 2.12 (95% CI: 0.58–2.82), aOR: 1.62 (95% CI: 0.92–2.86; *P* = 0.094). However, asthma medication use did differ between the groups (Table 1): COH-IVF/ICSI versus MNC-IVF OR: 1.51 (95% CI: 0.49–4.62; *P* = 0.471), aOR: 1.30 (95% CI: 0.38–4.38); MNC-IVF versus Sub-NC OR: 1.95 (95% CI: 0.50–7.64), aOR: 1.81 (95% CI: 0.37–8.84); COH-IVF/ICSI versus Sub-NC OR: 2.95 (95% CI: 0.90–9.68), aOR: 1.96 (95% CI: 1.00–3.84; *P* = 0.049). Additional adjustment for ICSI or vanishing twin syndrome did not substantially change the outcomes; these confounders were excluded from the final analyses.

Next the groups were pooled to create one subfertile group (TTP of one couple was missing; *n* = 212) to study the effect of TTP (median [range]: 3.4 [0.1–15.9]), on asthma and asthma medication use. TTP of parents of children with asthma was similar to that of parents of children without asthma: 3.0 (0.1–13.2) years versus 3.4 (0.1–15.9) years, respectively (OR: 1.01 [95% CI: 0.85–1.20], aOR: 0.97 [95% CI: 0.80–1.18]). In addition, the TTP of parents of children who used asthma medication: 3.4 (0.1–15.9), did not differ significantly from that of parents of children who did not use asthma medication: 3.0 (0.1–13.2); OR: 1.04 (95% CI: 0.87–1.24), aOR: 1.00 (95% CI: 0.81–1.22).

Discussion

This study indicates that ovarian hyperstimulation in combination with the in-vitro procedure is associated with a higher risk of the use of asthma medication in 4-year-old children born to subfertile couples. The use of asthma medication reflects the presence of moderate to severe asthma. TTP was not associated with asthma and the use of asthma medication. To our knowledge this is the first study assessing separately the effects of ovarian hyperstimulation, the in-vitro procedure and TTP on asthma. This study supports the hypothesis that conventional assisted reproductive techniques (COH-IVF/ICSI) is associated with an increased risk for the use of asthma medication (Carson et al., 2013).

Table 1 Infant, obstetric and parental characteristics of 4-year-old singletons born following COH-IVF/ICSI, MNC-IVF/ICSI and Sub-NC.

Characteristics	COH-IVF/ICSI (n = 81)	MNC-IVF/ICSI (n = 53)	Sub-NC (n = 79)
Infant characteristics			
Male gender, n (%)	44 (54)	26 (49)	41 (52)
First born, n (%)	49 (60)	37 (70)	49 (62)
Breastfeeding (>6 weeks), n (%) ^a	28 (47)	24 (45)	39 (50)
Obstetric characteristics			
ICSI, n (%)	50 (62)	26 (49)	NA
Vanishing twin syndrome ^a , n (%)	8 (13)*/#	1 (2)*	0 (0)#
Maternal smoking during pregnancy ^a , n (%)	7 (9)	7 (13)	9 (11)
Caesarean section, n (%)	22 (27)	8 (15)	21 (27)
Preterm birth (<37 weeks), n (%)	8 (10)	6 (11)	5 (6)
Gestational age (weeks), median (range)	39.4 (30.7–42.3)*	40.2 (34.6–42.6)	40.0 (30.1–42.7)*
Birthweight (g), mean (σ)	3403 (600)	3384 (586)*	3578 (519)*
Parental characteristics			
TTP in years, median (range) ^a	4.1 (0.1–15.9)*	3.8 (0.1–13.2)#	2.1 (0.1–11.3)*/#
Maternal BMI conception, median (range)	23.6 (15.5–42.5)	23.4 (16.8–30.2)	24.1 (15.5–42.5)
Maternal age at conception, median (range)	34.2 (26.3–41.0)*/#	32.5 (25.3–37.5)*	33.0 (22.2–40.3)#
Paternal age at conception ^a , median (range)	36.4 (27.5–56.1)*	34.0 (28.3–47.8)*	35.0 (25.5–48.7)
High level of maternal education ^b , n (%)	31 (38)	20 (38)	37 (47)
High level of paternal education ^{a/b} , n (%)	37 (47)	17 (33)	29 (37)
≥1 parent with asthma, n (%)	4 (5)	3 (6)	6 (8)
≥1 currently smoking parent ^a , n (%)	16 (20)	19 (36)	24 (30)
Outcome at age 4			
Asthma, n (%)	12 (15)	6 (11)	6 (8)
Use of asthma medication, n (%) ^c	11 (14)	5 (9)	4 (5)

BMI = body mass index; COH-IVF/ICSI = infants born following controlled ovarian hyperstimulation IVF/ICSI; ICSI = intracytoplasmic sperm injection; MNC-IVF/ICSI = infants born following modified natural cycle IVF/ICSI; NA = not applicable; Sub-NC = naturally conceived infants born to subfertile parents; TTP = time to pregnancy.

Statistically significant numbers are displayed in bold; the symbols denote which groups differ significantly from each other. COH-IVF/ICSI vs. MNC-IVF/ICSI: maternal age at conception $P = 0.001$, paternal age at conception $P = 0.021$ and vanishing twin syndrome $P = 0.038$. MNC-IVF/ICSI vs. Sub-NC: birthweight $P = 0.048$ and TTP $P = 0.001$. COH-IVF/ICSI vs. Sub-NC: gestational age $P = 0.009$, maternal age at conception $P = 0.041$, TTP $P < 0.001$ and vanishing twin syndrome $P = 0.001$.

^aMissing values: breastfeeding (>6 weeks) COH-IVF/ICSI $n = 21$, Sub-NC $n = 1$; ≥1 currently smoking parent COH-IVF/ICSI $n = 1$; maternal smoking during pregnancy COH-IVF/ICSI $n = 2$; paternal age at conception COH-IVF/ICSI $n = 13$, MNC-IVF/ICSI $n = 1$; paternal education COH-IVF/ICSI $n = 3$, MNC-IVF/ICSI $n = 1$; TTP Sub-NC $n = 1$, vanishing twin syndrome COH-IVF/ICSI $n = 18$.

^bHigher vocational education or university education.

^cContinuous or intermittent use of medication; drugs used: corticosteroids and beta-2-adrenoceptor agonists as single drug or in combination.

A strength of the study is its unique design. The subfertile control group prevents overestimation of the effect of IVF/ICSI. Other strengths are the prospective and assessor-blinded study design, the minimal attrition (<10%) and the ability to adjust for the presence of parental asthma.

A limitation of this study is the lack of a fertile control group. This precludes a conclusion on the effect of the presence or absence of subfertility. In addition, the size of the MNC-group is relatively small, preventing firm conclusions on the effect of MNC-IVF/ICSI.

In conclusion, ovarian hyperstimulation in combination with the in-vitro procedure is associated with the use of asthma medication in 4-year-old children born to subfertile couples. Knowing that the use of assisted reproductive techniques are steadily increasing, it is of utmost importance that future studies further investigate the effect of parental subfertility and the assisted reproductive techniques procedures on child health, including asthma.

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