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Early View

Original article

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Fertility treatment among women with asthma
- A case-control study of 3,689 women with live births

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Abstract

Asthma has been linked with prolonged time to pregnancy. Our aim was to explore a possible association between asthma and need for fertility treatment among women with live births.

All women enrolled in the Management of Asthma during Pregnancy (MAP) program at Hvidovre Hospital (HH), Denmark, (cases) were each matched with the three consecutive women giving birth at HH (controls). Information from the Danish National Assisted Reproductive Technology registry was cross-linked with the Danish Medical Birth registry to identify live births. The primary outcome of interest was births following fertility treatment.

Our sample comprised pregnancies from asthmatic (n=932, cases) and non-asthmatic (n=2,757, controls) mothers (n=932), with 12% (n=114) and 8% (n=212), respectively, having had fertility treatment (OR 1.67, 95% CI 1.32-2.13, p<0.001). This association remained statistically significant after adjusting for confounders, incl. BMI (OR 1.31, 95% CI 1.00-1.70, p = 0.047). In women ≥ 35 years, it was 25% (n=63) and 13% (n=82) of cases and controls, respectively, (OR 2.12, 95% CI 1.47-3.07, p< 0.001), which also remained statistically significant after adjusting for confounders (OR 1.65, 95% CI (1.11-2.46), p=0.013).

A higher proportion of the births from asthmatic mothers, compared to non-asthmatic mothers, involved fertility treatment, not least among women aged 35 years and older.

Introduction

In 2015, approximately 8.2 % of all the 58.205 children born in Denmark were conceived via assisted reproductive techniques (ART) or intrauterine insemination (IUI); and in the same year, more than 17,000 ART and 20,000 IUI treatments were performed in Denmark (1). A recent study addressing the long-term outcome of fertility treatments showed that in 58% and 25%, respectively, of women starting IUI and ART treatment were classified as having idiopathic infertility (1). In Denmark fertility treatments are readily accessible and reimbursed by the National Health System in childless couples where the woman is below 40 years of age. Three fresh ART treatments are reimbursed, including adjacent frozen embryo transfers.

Asthma is one of the most common chronic conditions among pregnant women (2). A large number of studies have reported adverse outcomes in pregnancies complicated by asthma (3-5), and recent studies have also reported reproductive changes such as impaired fertility in couples with female asthma (6).

Furthermore, Gade et al. (7) have reported that time to pregnancy (TTP) is prolonged in asthmatic women with unexplained infertility, especially among women with severe asthma and women above 30 years of age. This is further supported by Källen et al. (8), who reported an increased incidence of unwanted childlessness among women prescribed anti-asthma drugs. In contrast, Tata et al. (9) found no difference in the fertility rates (live births per 1000 person-years) of women with allergic disease (asthma, eczema and hay fever) compared to the general population. This study of Tata also found that women with asthma tended to have slightly higher fertility rates when younger (< 35 years), and lower fertility rates when older (≥ 35 years), compared to women without asthma, pointing to age as an important factor.

As it seems difficult to draw valid conclusions with regard to the association between asthma and impaired fertility, large-scale prospective studies are needed to clarify this possible association. The aim of the present study was to investigate the use of ART and IUI treatments and cause of infertility among women with asthma compared to the general population in a large case-control study of women with live births.

Material and methods

Material

The prospective cohort study, the Management of Asthma during Pregnancy (MAP) program, was initiated in 2007, and since then pregnant women have consecutively been recruited through the Department of Gynecology and Obstetrics, Hvidovre Hospital, Denmark. All pregnant women referred to Hvidovre Hospital (HVH) (approximately 7.000 per year, corresponding to 10 % of infants born in Denmark) are informed about the study as part of the welcome letter from the Department of Gynecology and Obstetrics. The letter includes an invitation to participate in the MAP-program together with an e-mail address for response (astmaoggraviditet@regionh.dk). All women who accepted the invitation were given a scheduled appointment (by letter) at the Respiratory out-patient clinic. Women with asthma were included in the MAP cohort provided they fulfilled the following criteria: 1) Diagnosis of asthma (defined according to the GINA-guidelines (10), 2) Current prescribed treatment with at least rescue bronchodilator, and 3) First visit to the Respiratory outpatient clinic within the first 18 weeks of pregnancy. A more detailed description of the MAP-cohort has been published previously (11-13). Only women from the MAP cohort with live birth were included in the present study

Each case was matched to three controls, with the controls being the women of the three consecutive live births given at Hvidovre Hospital on the same day, as described previously (11).

Methods

Information on fertility treatment (2007 to 2013) was obtained from the Danish National Assisted Reproductive Technology (ART) registry and the Medical Birth Registry. The Danish ART registry includes all ART treatment-cycles performed in public and private fertility clinics in Denmark since 1994, and IUI-cycles were added in 2006. Reporting to the ART registry is mandatory for both public and private clinics. A personal identification number enables identification of all treatment cycles received by the same woman, and thereby mapping of the complete fertility treatment history. Women identified in the Danish ART registry were cross-linked with the Danish Medical Birth registry to identify all live births of the same woman. The gestational age at birth was used to link births to treatment

cycles or to identify births after spontaneous conception. All cases and controls were matched based on the personal identification number and all live births of the women from the MAP cohort as well as controls were cross-linked with the information on fertility treatment drawn from the date of the live birth.

Non-Danish residents and couples receiving treatment with donates gametes were excluded from the analyses.

Outcomes of interest

The outcome variables of interest were fertility treatment-related live births and births after spontaneous conception in cases vs. controls. Overall cause of infertility was reported as the combination of female factor infertility, male factor, combined female/male factor and idiopathic infertility, if not stated otherwise.

Asthma-related tests in cases

Spirometry

Spirometry was performed using the Easy One Ultrasonic spirometer (NDD; Zurich, Switzerland), according to the American Thoracic Society (ATS)/European Respiratory Society recommendations (14), and predicted values for forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) were calculated according to reference equations (15). For the FEV_1 % of predicted and the FEV_1/FVC-ratio a value of $\geq$ 80% predicted and > 0.7, respectively, were considered within the reference range.

Fractional exhaled nitric oxide (FeNO)

FeNO was measured using the nitric oxide analyzer (NIOX, Aerocrine, Solna, Sweden), according to the ATS-guidelines (16). Guided with help of a biofeedback monitor, patients exhaled from total lung capacity to residual volume at an expiratory flow rate of 50 ml/s, and against a target resistance of 4-5 cm water. The average of two measurements of the plateau of the FENO curve was recorded as the level of FeNO, and a level of >50 ppb was regarded elevated (17).

Statistical analysis

Data analyses were performed using SPSS Statistics version 22.0. Continuous, primarily descriptive, variables were analyzed using the two-tailed Student t-test. Binary outcomes of interest were analyzed using the chi-square test. Logistic regression analysis was used to estimate odds ratio (OR) with 95% confidence intervals (CI) for the association between asthma status (i.e. cases vs. controls) and fertility treatment. The OR was adjusted for following potential confounding variables: maternal age at time of birth, body mass index (BMI), smoking status, primiparity, being single and in a same sex partnership. A p-value < 0.05 was considered significant.

Ethical approval

This study was performed in accordance with the Helsinki II declaration, and according to Danish legislation. The MAP study is approved by the Research Ethics Committee of the Capital Region of Denmark (H-D-2007-0051) and permission has also been obtained from the Danish Data Protection Agency (2007-41-0770). The study 'The long-term prognosis, risks and trends over time for subfertile couples undergoing fertility treatment in Denmark' is approved by the Danish Data Protection Agency (2012-41-1330). The transmission of data between the two studies required for performing the present analyses was also approved by the Danish Data Protection Agency (2017-231-0223).

Results

Baseline characteristics

Over a 5-year period, a total of 932 pregnancies (i.e. cases) in 872 women with asthma enrolled in the MAP-cohort, were matched with 2,760 consecutive live births (i.e. controls) in 2,617 women also giving birth at Hvidovre Hospital. However, three of the controls had to be excluded due to missing data on fertility treatment, leaving 932 cases and 2,757 controls in the final cohort. Compared to the controls, women with asthma had a higher average age and BMI, were more often non-smokers and nullipara; further details are given in Table 1.

Baseline characteristics, incl. lung function and use of asthma medication, of the 932 cases with asthma are presented in Table 2.

Fertility treatment among women with asthma vs controls

The prevalence of fertility treatment preceding live births was 12.2 % (n=114) among women with asthma compared to 7.7 % (n= 212) in the control group (OR 1.67, 95% CI 1.32-2.13, p<0.0001). And after adjusting for age, BMI, smoking status, primiparity, being single, and in a same sex relationship this association remained significant (OR 1.31, 95% CI 1.00-1.70, p = 0.047). Repeating the analyses with women only contributing with their first pregnancy did not change the overall observations. Furthermore, the prevalence of ever fertility treatment was 16.2% among women with asthma compared to 10.8% among controls (OR 1.59, 95% CI 1.29-1.96, p<0.001).

When looking at the type of fertility treatment, women with asthma had an increased use of both IUI treatment (OR 1.86, 95% CI 1.28-2.70, p=0.001) and ART treatment (OR 1.51, 95% CI 1.11-2.03, p = 0.007), but this association was no longer statistically significant after adjusting for confounders (Table 3).

Fertility treatment stratified by age among women with asthma vs controls

When re-analyzing fertility treatment after stratifying cases and controls into two age-groups, i.e. of women < 35 years and women ≥ 35 years, no significant association was found between asthma and fertility treatment in the younger age group. On the other hand,

among women ≥ 35 years of age, the prevalence of fertility treatment was 24.8 % (n=63) among women with asthma compared to 13.4 % (n=82) in the control group (OR 2.12, 95% CI 1.47-3.07, p< 0.001). This association remained significant after adjusting for maternal age, BMI, smoking status, primiparity, being single, and in a same sex relationship (OR 1.65, 95% CI 1.11-2.46, p = 0.013) (Table 4). As for the non-age stratified analysis, only including first live birth in the analyses did not change our findings.

Cause of infertility in women who received fertility treatment, asthma vs controls

Cause of infertility, i.e. female factor, male factor, combined or idiopathic, was not significantly different between the asthmatic women and controls, and equally distributed both within the two groups and within each group. Likewise, no difference was found with regard to type of fertility treatment among women with idiopathic infertility.

Lung function and level of therapy in women with asthma and fertility treatment

In the group of asthmatic women, there were no significant differences in lung function (FEV_1< 80% vs. $FEV_1 \geq 80\%$; p=0.33), ($FEV_1/FVC < 0.7$ vs. $FEV_1/FVC \geq 0.7$; p=0.45), neither the F_ENO ($F_ENO \leq 50$ ppb vs. $F_ENO > 50$ ppb; p=0.21) or the use or non-use of treatment with inhaled corticosteroids (ICS) (p=0.26) among women who conceived after fertility treatment and in those who conceived naturally.

Discussion

In the present large-scale case-control study of women with live births we observed that the prevalence of ART conception was higher in women with asthma in pregnancy compared to controls from the background population. In women aged 35 years or older this association was even stronger.

In accordance with previous research, this study shows that there might be an association between asthma and infertility. This supports the findings of Gade et al. (6) that the likelihood of achieving pregnancy is lower among women with asthma. These findings may indicate that years exposed to low-grade systemic inflammation in asthmatic women may have an influence on fertility (18-20). We found a statistical significant association between asthma and fertility treatment after adjusting for basic and lifestyle related factors and found an even stronger association among women aged 35 years or older. Studies have shown that fertility decreases at 32 years of age, with an increase in rate of decline after 37 years of age (21-23). This decrease in fertility with age may explain the stronger association we found after 35 years, because of other competing factors contributing to the infertility in the women with asthma. It could also be argued that the age-related decrease in ovarian reserve is being amplified by asthma. The ageing process has been linked to inflammatory changes in the general population, which could be of importance in the present context (24-26). A synergistic effect of the systemic inflammation characterizing asthma could contribute to an even greater systemic inflammation, possibly worsening the asthmatic disease and impairing the ovarian reserve in fertile women with asthma. When looking at table 4 and the percentage increase in woman who conceived by fertility treatment, comparing the two age groups, the asthmatic women more than tripled the percentage from 7.5 % to 24.8 % compared to the controls 6.1 % to 13.4 %, which make a synergistic effect of asthma to the ovarian ageing processes seems likely.

An important strength is that the study is a large case-control study which was performed at the hospital with the largest number of deliveries in Denmark covering 10 % of all births every year, which enhances the power to detect a difference. Further, the data on fertility treatment are national, hence we have complete coverage of those who received fertility treatment. Due to this national register design the risk of selection bias is very low. Secondly, all the cases were diagnosed with asthma by the same physician and the validity of the diagnoses is therefore very high.

Regarding limitations of the study, only asthmatic women with live births were included. Thus, asthmatic women who received fertility treatment without conceiving was not included, which is a potential bias, but unfortunately, we do not have access to these data. However, the proportion of

ever having had fertility treatment was significantly higher among women with asthma compared to the controls, and taken together with the observation that less women with asthma than controls ever had a fertility treatment related live births, these observations suggest that the success rate is similar or lower among women with asthma. This assumption is supported by the study by Gade et al demonstrating that among women with unexplained infertility, women with asthma were less likely to conceive compared to non-asthmatic women (6). Secondly, the selection of controls was a random sample of the background population corresponding to the women with the three consecutive live births and potentially these women may have had asthma. Optimally we would have included controls that for sure did not have asthma. However, the two above mentioned limitations have probably just weakened the association between asthma and need for fertility treatment. Finally, on the basis of the prevalence of asthma in Denmark (27) approximately two-third of women with asthma giving birth each year at Hvidovre Hospital are enrolled in the MAP program. The women enrolled in the MAP cohort are comparable to the background population of pregnant women with regard to age and marital status (11). However, as in other population studies, there is a risk of several types of bias including factors associated with lifestyle that are not easily measured. Compared to the women in the control group, the asthmatic women enrolled in the MAP program seemed more resourceful overall than the control group, because they, amongst other things, more often were non-smokers, had more stable relationships, and more often attended for prenatal screening. In line with this, the participation in the study was voluntary. It has been shown that people who voluntarily participate in studies are generally more resourceful and socio-economically strong women (28-34). This group in general also has a higher rate of fertility treatment (35).

Other studies suggest that the complex interaction between asthma and female sex hormones might provide the explanation for the infertility (6). Later onset of menarche among non-conceiving asthmatic women may impair their fertility, as it has been associated with low levels of anti-Müllerian hormone (low ovarian reserve) (36). However, data are conflicting in this area and other studies show opposite conclusion (37). It was not possible to analyze this in the present study. However, it would be interesting to follow a cohort of asthmatic women looking at the antral follicle count as well as their levels of anti-Müllerian hormones comparing them to age-matched controls.

The central issue regarding asthma and infertility seem to be that the change in the inflammatory level of the body can affect fertility. Particularly cytokines and growth factors play an important role in the process of implantation (18, 19, 38-41) and are also deeply involved in the inflammatory response of asthma (42, 43). Both the balance between Th1 and Th2 responses in the adaptive

immune system has been considered important, as well as focus has been on IL6, a key mediator of immune and acute phase responses, and several studies indicate that an imbalance or dysregulation may disturb implantation and be harmful to pregnancy (38-40) Following these hypotheses, it seems likely that asthma can affect fertility, but better understanding of the actions, interactions and immunological functions in asthma are needed. This may be a possible target for infertility in asthmatic women in the future.

On the other hand, our results found no association between asthma severity markers such as FEV_1, FEV_1/FVC-ratio and FeNO and the need for fertility treatment. This is, however, inconsistent with a register-based twin study done by Gade et al. (7) in which asthmatics had a longer TTP, though the asthmatics in that study were untreated which is not the case in our cohort of the present study.

In conclusion, the proportion of women conceiving by fertility treatment was higher amongst women diagnosed with asthma compared to the general population and after adjusting for basic and lifestyle related factors the association remained statistically significant. Among women aged 35 years and older the association was observed even stronger.
Based on the findings in this study asthmatic patients may be counseled not to wait too long before having children. However, more knowledge about the effect of the immune system and asthma on fertility is needed.

Conflict of interest

The authors (AVH, ZA, SSM, JB, AP & CSU) declare that they have no conflict of interests in relation to this manuscript.

Author contribution

The MAP program was initiated and developed by CSU, and CSU takes responsibility for the integrity of all data on cases as well as responsibility for the content of the manuscript. ZA has composed the control group and collected the background data from the obstetric medical records. SM has collected and is responsible for all the data on fertility treatments. AVH had full access to all of the data in the study, and together with ZA takes responsibility for the accuracy of the data analysis. AVH drafted and revised the manuscript. ZA, SSM, JB, AP and CSU contributed substantially to the interpretation, and the writing of the manuscript.

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Table 1

Demographic characteristics of the study population comprising 3,689 cases and controls (i.e. 932 cases with asthma and 2,757 controls)

Characteristics	Cohort	Cases	Controls	p-value
Subjects n	*3,689*	*932*	*2,757*	
Demographics				
Age (years)	31.0 (±4.8)	31.4 (±4.7)	30.8 (±4.8)	< **0.001**
BMI (kg/cm^2)[1]	23.6 (±4.3)	24.1 (±4.6)	23.4 (±4.1)	< **0.001**
Current smokers	238 (6.5)	39 (4.2)	199 (7.2)	= **0.001**
Primiparity	2125 (57.6)	626 (67.2)	1499 (54.4)	< **0.001**
Single parent	127 (3.4)	40 (4.3)	87 (3.2)	= 0.100
Same sex partner	18 (0.5)	7 (0.8)	11 (0.4)	= 0.182[2]

Data are given as mean with SD in brackets or numbers with percentages in brackets. Bold values indicate significant p-values < 0.05.

[1] Information missing in 26 controls, [2] Fisher's Exact Test

Table 2

Characteristics with regard to lung function and asthma therapy in 932 women with asthma (cases) at first visit in the Management of Asthma during Pregnancy program.

Characteristics	**Cases**
Subjects n	*932*
Lung function	
FEV_1 < 80 %pred	150 (16.1)
FEV_1/FVC < 0.7	46 (4.9)
FeNO > 50 ppb	43 (4.6)
Asthma therapy	
Inhaled corticosteroids (ICS)	598 (64.2)
- as monotherapy	394 (42.3)
- in combination with long-acting beta-2 agonist	204 (21.9)
Oral corticosteroids	1 (0.1)
Leukotriene receptor antagonist	8 (0.9)

Data are given as numbers with percentages in brackets.

Table 3

Mode of conception and specified fertility treatment in women with asthma (cases, n=932) and controls (n=2,757) with live birth.

Characteristics	Cases	Controls	OR (95% CI)	p-value
Subjects n	*932*	*2,757*		
Mode of conception				
Fertility treatment	114 (12.2)	212 (7.7)	1.67 (1.32-2.13)	<**0.001**
Adjusted[1]			1.31 (1.00-1.70)	=**0.047**
Spontaneous conception	818 (87.8)	2545 (92.3)	0.60 (0.47-0.76)	<**0.001**
Specified fertility treatment				
Intrauterine insemination	46 (4.9)	75 (2.7)	1.86 (1.28-2.70)	=**0.001**
Assisted reproductive technology[2]	68 (7.3)	137 (5.0)	1.51 (1.11-2.03)	=**0.007**

Data are given as numbers with percentages in brackets, unless otherwise stated in table. Bold values indicate significant p-values < 0.05.

[1] Adjusted for: maternal age, body mass index (BMI), smoking status, primiparity, being single, and being in a same sex relationship. [2] Assisted reproductive technology: in vitro fertilization, Intracytoplasmic sperm injection, Frozen embryo transfer, Aspiration of sperm, Unspecified.

Table 4

Mode of conception and type of fertility treatment in women with asthma (cases) compared to controls, stratified by age, i.e. women < 35 years and women ≥ 35 years, respectively.

Age groups:	Age < 35 years				Age ≥ 35 years			
Characteristics	**Cases**	**Controls**	**OR (95% CI)**	**p-value**	**Cases**	**Controls**	**OR (95% CI)**	**p-value**
Subjects n	*678*	*2,147*			*254*	*610*		
Mode of conception								
Spontaneous ception	627 (92.5)	2017 (93.9)	-	= 0.17	191 (75.2)	528 (86.6)	-	<0.001
Fertility treatment	51 **(7.5)**	130 **(6.1)**	1.26 (0,90 – 1,76)	= 0.17	63 **(24.8)**	82 **(13.4)**	2.12 (1.47 - 3.07)	<0.001
Adjusted[1]			1.09 (0,76 - 1.56)	= 0,64			1.65 (1.11 - 2.46)	=0.013
Intrauterine insemination	18 (2.7)	44 (2.0)	1.30 (0,75 - 2.27)	= 0.35	28 (11.0)	31 (5.1)	2.31 (1.36 - 3.95)	=0.002
Assisted reproductive technology	33 (4.9)	86 (4.0)	1.23 (0.81- 1.85)	= 0.330	35 (13.8)	51 (8.4)	1.75 (1.11 - 2.77)	=0.015

Data are given as numbers with percentages in brackets, unless otherwise stated in table. Bold values indicate significant p-values < 0.005.

[1] Adjusted for: maternal age, body mass index (BMI), smoking status, primiparity, being single, and being in a same sex relationship. [2]Fisher's Exact Test.