Fertility treatment among women with asthma: a case–control study of 3689 women with live births

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Female asthma is associated with a higher need for fertility treatment, not least among women aged 35 years and older http://ow.ly/flZ530mIAgU

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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) programme at Hvidovre Hospital, Denmark were each matched with the next three consecutive women giving birth at Hvidovre Hospital. Information from the Danish National Assisted Reproductive Technology (ART) 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 mothers (n=932, described as "cases") and non-asthmatic mothers (n=2757, described as "controls"), 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, including body mass index (OR 1.31, 95% CI 1.00–1.70; p=0.047). In women ⩾35 years, 25% of cases (n=63) and 13% of controls (n=82) received fertility treatment (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 involved fertility treatment compared to non-asthmatic mothers, not least among women aged ⩾35 years.

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Introduction

In 2015, approximately 8.2% of all the 58 205 children born in Denmark were conceived *via* use of assisted reproductive technology (ART) or intrauterine insemination (IUI) and, in the same year, more than 17 000 ART and 20 000 IUI treatments were performed [1]. A recent study addressing the long-term outcome of fertility treatments showed that 58% of women starting IUI treatment and 25% starting 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] 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 Källén *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 by Tata *et al.* [9] also found that women with asthma tended to have slightly higher fertility rates when younger (less than 35 years) and lower fertility rates when older (⩾35 years), compared to women without asthma, and 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) programme, 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 (approximately 7000 per year, corresponding to 10% of infants born in Denmark) are informed about the study as part of the welcome letter from the Department. The letter includes an invitation to participate in the MAP programme together with an e-mail address for responses (astmaoggraviditet@regionh.dk). All women who accepted the invitation were given a scheduled appointment (by letter) to attend the respiratory out-patient clinic. Women with asthma were included in the MAP cohort provided they fulfilled the following criteria: 1) they possessed a diagnosis of asthma as defined according to the GINA-guidelines [10]; 2) they were receiving current prescribed treatment with at least a rescue bronchodilator; and 3) they had their 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 a live birth were included in the present study. Each case was matched to three controls, these controls being the women who had the next three consecutive live births at Hvidovre Hospital on the same day, as described previously [11].

Methods

Information on fertility treatment (2007–2013) was obtained from the Danish National ART registry and the Danish Medical Birth registry. The Danish National ART registry includes all ART treatment-cycles performed in public and private fertility clinics in Denmark since 1994, with IUI cycles being added from 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 allows 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 by 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 by the women from the MAP cohort as well as the 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 donated 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 *versus* those in 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 EasyOne Ultrasonic spirometer (NDD, Zurich, Switzerland) according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations [14] and predicted values for forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were calculated according to reference equations [15]. For FEV_1, a predicted value ⩾80% predicted was considered within the reference range, as was a value of >0.7 for the FEV_1/FVC ratio.

Exhaled nitric oxide fraction

Exhaled nitric oxide fraction (F_{ENO}) was measured using a nitric oxide analyser (NIOX, Aerocrine, Solna, Sweden) according to the ATS guidelines [16]. Guided by a biofeedback monitor, patients exhaled from total lung capacity to residual volume at an expiratory flow rate of 50 $mL \cdot s^{-1}$ against a target resistance of 4–5 cmH_2O. The average of two measurements of the plateau of the F_{ENO} curve was recorded as the level of F_{ENO}, with >50 ppb being regarded as elevated [17].

Statistical analysis

Data analyses were performed using SPSS Statistics Version 22.0 software (IBM SPSS, Armonk, NY, USA). Continuous, primarily descriptive variables were analysed using a two-tailed t-test. Binary outcomes of interest were analysed using a Chi-squared test. Logistic regression analysis was used to estimate odds ratios (ORs) with 95% confidence intervals for the association between asthma status (*i.e.* cases *versus* controls) and fertility treatment. The ORs were adjusted for the following potential confounding variables: maternal age at time of birth, body mass index (BMI), smoking status, primiparity, being single and being in a same sex partnership. A p-value of less than 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 2760 consecutive live births (*i.e.* controls) in 2617 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 2757 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 demographic details of the cohort are given in table 1, while baseline characteristics (including lung function and use of asthma medication) for the 932 cases with asthma are presented in table 2.

Fertility treatment among women with asthma versus *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). After adjusting for age, BMI, smoking status, primiparity, being single, and being 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 (OR 1.86, 95% CI 1.28–2.70; p=0.001) and ART-based treatment (OR 1.51, 95% CI 1.11–2.03; p=0.007); however, this association was no longer statistically significant after adjusting for confounders (table 3).

TABLE 1 Demographic characteristics of the study population

Characteristics	Cohort	Cases	Controls	p-value
Subjects	3689	932	2757	
Demographics				
Age years	31.0±4.8	31.4±4.7	30.8±4.8	**<0.001**
BMI[#] kg·m^{-2}	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[¶]

Data are presented as n, n (%), or mean±SD. Values in bold type are significant (p<0.05). BMI: body mass index. [#]: information was missing for 26 control subjects; [¶]: p-value determined from analysis with Fisher's exact test.

Fertility treatment stratified by age among women with asthma versus *controls*

When reanalyzing fertility treatment after stratifying cases and controls into two age-groups (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 being 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 births in the analyses did not change our findings.

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

Cause of infertility (*i.e.* female factor, male factor, combined or idiopathic factors) was not significantly different between the asthmatic women and the controls, and was equally distributed both between the two groups and within each group. Likewise, no difference was found with regard to the 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 either lung function (FEV_1 <80% predicted *versus* FEV_1 ⩾80% predicted (p=0.33) and FEV_1/FVC <0.7 *versus* FEV_1/FVC ⩾0.7 (p=0.45)), F_{ENO} (⩽50 ppb *versus* >50 ppb (p=0.21)), or the use/non-use of inhaled corticosteroid (ICS) treatments (p=0.26) between women who conceived after fertility treatment and those who conceived naturally.

TABLE 2 Characteristics with regard to lung function and asthma therapy in women with asthma (cases) on first visit to the Management of Asthma during Pregnancy (MAP) programme

Characteristics	Cases
Subjects	932
Lung function	
FEV_1 <80% predicted	150 (16.1)
FEV_1/FVC <0.7	46 (4.9)
F_{ENO} >50 ppb	43 (4.6)
Asthma therapy	
ICS	598 (64.2)
As a monotherapy	394 (42.3)
In combination with LABAs	204 (21.9)
Oral corticosteroids	1 (0.1)
Leukotriene receptor antagonist	8 (0.9)

Data are presented as n or n (%). FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; F_{ENO}: exhaled nitric oxide fraction; ICS: inhaled corticosteroids; LABA: long-acting β_2-agonist.

TABLE 3 Mode of conception and specified fertility treatment in women with asthma (cases) having a live birth

Characteristics	Cases	Controls	OR (95% CI)	p-value
Subjects	932	2757		
Mode of conception				
Fertility treatment[#]	114 (12.2)	212 (7.7)	1.67 (1.32–2.13)	**<0.001**
Spontaneous conception	818 (87.8)	2545 (92.3)	0.60 (0.47–0.76)	**<0.001**
Specified fertility treatment				
IUI	46 (4.9)	75 (2.7)	1.86 (1.28–2.70)	**0.001**
ART[¶]	68 (7.3)	137 (5.0)	1.51 (1.11–2.03)	**0.007**

Data are presented as n or n (%) unless otherwise stated. The p-values in bold type are significant (p<0.05). IUI: intrauterine insemination; ART: assisted reproductive technology. [#]: when adjusted for maternal age, body mass index, smoking status, primiparity, being single and being in a same sex relationship, data was as follows: OR 1.31 (95% CI 1.00–1.70), p=0.047; [¶]: ART was *in vitro* fertilisation, intracytoplasmic sperm injection, frozen embryo transfer, aspiration of sperm, or unspecified.

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 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 the years of exposure to low-grade systemic inflammation experienced by asthmatic women may have an influence on fertility [18–20].

We found a statistically 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. Studies have shown that fertility decreases at 32 years of age, with an increase in the 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, due to other competing factors contributing to infertility in the women with asthma. It could also be argued that the age-related decrease in ovarian reserve is being amplified by asthma. In the general population the ageing process has been linked to inflammatory changes, which could be of importance in the present context [24–26]. A synergistic effect of the systemic inflammation that characterises asthma could be to 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, and comparing the two age groups, it is notable that the asthmatic women more than tripled the percentage (which increased

TABLE 4 Mode of conception and type of fertility treatment in women with asthma (cases) compared to controls, as stratified by age

Characteristics	Age <35 years				Age ⩾35 years			
	Cases	Controls	OR (95% CI)	p-value	Cases	Controls	OR (95% CI)	p-value
Subjects	678	2147			254	610		
Mode of conception								
Spontaneous conception	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**
Specified fertility treatment								
IUI	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**
ART[¶]	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 presented as n or n (%) unless otherwise stated. The p-values in bold type are significant (p<0.05). IUI: intrauterine insemination; ART: assisted reproductive technology. [#]: when adjusted for maternal age, body mass index, smoking status, primiparity, being single and being in a same sex relationship, data was as follows: OR 1.09 (95% CI 0.76–1.56), p=0.64 (age <35 years) and OR 1.65 (95% CI 1.11–2.46), p=0.013 (age ⩾35 years); [¶]: ART was *in vitro* fertilisation, intracytoplasmic sperm injection, frozen embryo transfer, aspiration of sperm, or unspecified.

from 7.5% to 24.8%) as compared to the control group (which increased from 6.1% to 13.4%), which makes a synergistic effect of asthma on the ovarian ageing processes seem likely.

An important strength of the study is that it is a large case-control study 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. Furthermore, the data on fertility treatment is national and hence complete coverage of those who received fertility treatment is available. 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 excluding asthmatic women who received fertility treatment without conceiving, which is a potential bias. Unfortunately, we do not have access to these data; however, the proportion of those ever having had fertility treatment was significantly higher among women with asthma compared to the controls. Taken together with the observation that fewer women with asthma ever had a fertility treatment related live birth compared to controls, these observations suggest that the success rate is similar or lower among women with asthma. This assumption is supported by Gade *et al.* [6], who demonstrated that among women with unexplained infertility those with asthma were less likely to conceive compared to non-asthmatic women. Secondly, the selection of controls was a random sample of the background population (corresponding to the women with the next three consecutive live births) and these women may potentially have had asthma. Optimally, we would have included controls that we were sure did not have asthma. However, the two above mentioned limitations have probably just weakened the association between asthma and the need for fertility treatment. Finally, on the basis of the prevalence of asthma in Denmark [27], approximately two-thirds of women with asthma giving birth each year at Hvidovre Hospital are enrolled in the MAP programme. 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 which are not easily measured (including factors associated with lifestyle). Compared to the women in the control group, the asthmatic women enrolled in the MAP programme seemed more resourceful overall. Amongst other things they were more often non-smokers, had more stable relationships and more often attended for prenatal screening. Additionally, participation in the study was voluntary and it has been shown that people who voluntarily participate in studies are generally more resourceful and socio-economically strong [28–34]. This group also has a higher rate of fertility treatment in general [35].

Other studies suggest that the complex interaction between asthma and female sex hormones might provide the explanation for 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 the opposite conclusion [37]. Unfortunately, it was not possible to analyse this in the present study and 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) while comparing them to age-matched controls.

The central issue regarding asthma and infertility seems to be that the change in the inflammatory level of the body can affect fertility. In particular, 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]. The balance between Type-1 T-helper cell (Th1) and Type-2 T-helper cell (Th2) responses in the adaptive immune system has been considered important, and there has also been a focus on interleukin-6 (IL-6; a key mediator of immune and acute phase responses), where 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 a better understanding of the actions, interactions and immunological functions in asthma are needed. This may be a possible target for research into 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 F_{eNO}, and the need for fertility treatment. This is inconsistent with a register-based twin study performed by Gade *et al.* [7] in which asthmatics had a longer TTP; however, the asthmatics in that study were untreated which is not the case in the cohort of our present study.

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

Author contributions: The MAP programme was initiated and developed by C.S. Ulrik and she takes responsibility for the integrity of all data on cases, as well as responsibility for the content of the manuscript. Z. Ali composed the control group and collected the background data from the obstetric medical records. S.S. Malchau collected and is responsible for all data on fertility treatments. A. Vejen Hansen had full access to all of the data in the study and, together with Z. Ali, takes responsibility for the accuracy of the data analysis. A. Vejen Hansen drafted and revised the manuscript. Z. Ali, S.S. Malchau, J. Blafoss, A. Pinborg and C.S. Ulrik contributed substantially to the interpretation and the writing of the manuscript.

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