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Asthma affects time to pregnancy and fertility:

A register-based twin study

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Take home message:

Asthma prolongs time to pregnancy. The negative effect of asthma on fertility increases with age and is growing with disease intensity, indicating that a systemic disease (asthma) characterized by systemic inflammation also can involve reproductive processes.

Summary (Word count: 200):

Background: Coexistence of infertility and asthma has been observed clinically. We therefore investigated the association between asthma and delayed pregnancy in a nationwide population-based cohort of twins.

Methods: A cohort of 15250 twins living in Denmark (aged 12–41 years) participated in a questionnaire study including questions about the presence of asthma and fertility. Differences in time to pregnancy and pregnancy outcome were analyzed in subjects with asthma, allergy and in healthy individuals using multiple regression analysis.

Results: Asthma was associated with increased time to pregnancy 27 % vs. 21.6%, OR=1.31 (1.1-1.6), p=0.009. The association remained significant after adjustment for age, age at menarche, BMI and socioeconomic status (p=0.05 OR=1.25(1-1.6)), and was more pronounced in those above 30 years of age (32.2% vs. 24.9% p=0.04 OR =1.44 (1.1-1.9)). Untreated asthmatics had significant increased risk of prolonged TTP compared to healthy individuals (OR= 1.79 (1.2-2.66) p=0.004), while asthmatics receiving any kind of treatment for asthma trended having a shorter TTP than

untreated asthmatics (OR=1.40, p=0.134).

Conclusion: Asthma prolongs time to pregnancy. The negative effect of asthma on fertility increases with age and is growing with disease intensity, indicating that a systemic disease characterized by systemic inflammation also can involve reproductive processes.

Introduction:

Asthma is one of the most common chronic diseases in women of reproductive age, occurring in up to 8% of pregnancies [1]. Approximately 24% of all couples that attempt to conceive will be infertile for one or more periods lasting for longer than one year [2], and 3-6% of 45-year-old women are involuntarily infertile and have never given birth to a child [3].

Coexistence of asthma and infertility is therefore present in a large group of patients. Several studies show interplay between the severity of asthma and female reproductive health including menstrual cycle, abortions and pregnancy - although the causes for this association is poorly understood [4-6]. Moreover, it has been suggested that estrogen has an impact on the etiology and cause of chronic inflammatory/autoimmune disease [7], but whether estrogen is a friend or foe in patients with chronic inflammatory diseases remains controversial [8]. The effects of asthma on fertility remain poorly investigated, and at present there is only little evidence to suggest a connection between asthma and infertility.

A recent study by Carson et al [9] suggests an association between subfertility, fertility treatment and asthma in children born through in vitro fertilization (IVF). This may be due to the IVF treatment itself but could also be due to a genetic predisposition to asthma. The last assumption suggests that a greater proportion of asthmatic parents seek fertility treatment, indicating a link

between asthma and infertility. This assumption seems credible since studies by Källén B. et al [10] reported that a greater amount of women undergoing IVF treatment are using anti-asthmatic drug.

Furthermore it is well known that patients with other chronic inflammatory and autoimmune diseases (e.g. rheumatoid arthritis and Sjögren's disease) have a prolonged time to pregnancy (TTP) and a reduction in fertility [11,12]. Autoimmune conditions may affect all stages of fertility such as ovarian failures, implantation failure, and pregnancy loss [13].

In contrast to the above, Tata et al [14], found similar fertility rates (live births pr. 1000 person years) in women with allergic disease (asthma, eczema, and hay fever) compared with women from the general population. The study also found that women with hay fever or eczema were more fertile than those without these conditions. Furthermore, asthma was hypothesized to have a different relationship to fertility than eczema and hay fever, as young asthmatic individuals had a higher fertility rate than their older counterparts compared with the healthy group.

Overall, the association between asthma and infertility is not fully resolved. Accordingly, we investigated whether asthmatic patients experience longer waiting times to pregnancy. To examine this, we conducted a twin-based cohort study to estimate population-based TTP and perinatal outcomes in women with asthma compared with women without asthma.

Material and Methods:

Study population:

The study population comprised all female twins born between 1953 and 1982 who were enrolled in The Danish Twin Registry [15]. Data from the Danish Twin Register were used due to its large size, its detailed questionnaire, and the ability to compare twin sisters in respect to pregnancy outcomes

controlling for unmeasured confounding variables such as genetics and lifestyle factors. Our aim was to generalize the results to the singleton population, which earlier has been shown to be possible [16]. A total of 15250 women participated in a nationwide questionnaire study concerning general health and lifestyle. The study also included questions about asthma and fertility. The age of the participants ranged between 12 and 41 years (mean age 26.8 yrs.) and the participation rate in the general health study was 86%. In total 7979 females did not respond to questions about their fertility. The non-responders were younger than responders (22.3 vs. 32.0 years, which clearly indicates a tendency for younger women not to respond, if they have not been pregnant or had attempted to conceive yet. In contrast non-responding was not related to asthma-status, and hence, responding was only associated with our outcome – not exposure, thereby minimizing bias due to non-responding.

Asthma and Allergy

Asthma cases were identified on the basis of an affirmative response to the question ‘Have you ever had asthma?’. This procedure has been shown reliable for excluding subjects without asthma in population-based studies, which use questionnaire responses as the sole diagnostic criterion. Tóren et al [17] validated the diagnosis of asthma by questionnaires in relation to a clinical diagnosis of asthma; the mean sensitivity for the question about self-reported asthma was 68% in the reviewed studies, while the specificity was 94%.

Allergy cases were identified on the basis of an affirmative response to the question: ’Have you ever had allergy?’.

Medical History

The asthmatic patients were divided into treated and non-treated asthmatics based on two questions in the questionnaire. The questions used were: `I used or have previously used asthma medication (yes/no)? And ‘Do you use, or have you ever used any medication during longer periods on a regular basis or due to attacks? The women, who to the second question responded, that they received medication in the category "medicine to treat obstructive pulmonary disease" were considered as treated asthmatics.

Furthermore the treated asthmatic group was subdivided into a group that received inhaled corticosteroid daily and a group that only received reliever medication. Thereby we were able to assess whether the degree of treatment had an impact on TTP.

Fecundity measures

We evaluated the lifetime prevalence of infertility, which indicates the prevalence of all who are infertile at the time of the survey and/or who had been infertile for a period or periods in their lives. Lifetime prevalence of infertility was identified on the basis of an affirmative response to the question: ‘Have you and your partner ever spent more than one year trying to become pregnant without pregnancy occurring within this year? .

Conception was defined as achievement of a clinical pregnancy.

Abnormal TTP was censored after 12 months because the clinical definition of infertility is defined as one year of unprotected intercourse in the fertile phase of the menstrual cycles without conception [18].

TTP has been proven to be a valuable tool to measure fecundity; it is easy to obtain information about and is well recalled even many years after pregnancy. TTP is influenced by not only biologic factors but also knowledge and behavior. TTP as outcome measure has been extensively used in epidemiological studies aiming to identify the effects of, for example, adverse lifestyle or changes in fertility over time [19].

The mean number of biological children each woman had given birth to calculated the number of children.

We furthermore examined pregnancy outcome in order to assess whether the reason for a possible prolonged TTP could be due to more frequent adverse pregnancy outcomes. Pregnancy outcomes were identified on the basis of the question: Were the outcome of your first pregnancy a live-born child, a stillbirth, miscarriage, abortion or ectopic pregnancy?

Statistical analysis:

Data were analysed with the statistical package SPSS version 20.0 (Chicago, Illinois). Mean and standard deviations (±SD) were calculated for the normally distributed data, whereas median and interquartile ranges (IQR) were used to describe the skewed distributed data. The groups were compared using the two-sample t-test for the normally distributed continuous variables and the non-parametric Mann-Whitney U test for non-normally distributed continuous variables. Fisher's exact test was used for categorical, unpaired data. Values of $P<0.05$ were considered significant.

First, the association between asthma and TTP was analyzed in the whole cohort

(N =15250) with asthma (yes or no) as dependent variable. In multivariate analysis of regression, we explored the potentially confounding effects of age, smoking, body mass index (BMI), age at

menarche and socioeconomic status (years of education).

A 1:1 matched conditional logistic regression analysis (co-twin control analysis) was used to examine the effect of asthma on TTP in twin pairs discordant for asthma. The matching was done with the asthmatic twin in each pair being the case and the non-asthmatic twin being the control. In the co-twin control analysis, a higher risk of long TTP in dizygotic (DZ) co-twins compared with monozygotic (MZ) co-twins in relation to asthma would indicate an underlying genetic relationship between asthma and TTP, whereas a higher risk of long TTP in MZ co-twins compared with DZ co-twins would indicate an underlying non-genetic relationship between asthma and TTP [20].

Results:

Of 15250 respondents, 955 (6.3 %) reported a history of asthma. The distribution of women with asthma according to age, smoking, BMI, age at menarche, and educational level is shown in Table 1. The distribution of covariates among asthmatic individuals and non-asthmatic individuals was similar, with the exception of BMI, which was significantly higher in the asthmatic group (22.24 vs. 21.66, $p<0.001$), and age at menarche, which was significantly younger among asthmatics (13.07 yrs. vs. 13.18 yrs., $p= 0.029$).

The proportion of women whose time to pregnancy was prolonged was significantly higher in the asthmatic group compared with the non-asthmatic group (27 % versus 21.6%, respectively, OR=1.31 (1.07-1.61), p=0.009) (Table 2). The association remained significant after adjustment for age, BMI, and smoking, OR=1.27 (1.01-1.59), p=0.04. Additional adjustment for age at menarche and socioeconomic status led to a further small decrease in risk, OR=1.25 (1.0-1.58), p=0.05. Restricting the analysis to women above 30 years of age showed an even stronger tendency towards

long waiting time to pregnancy among asthmatic individuals (32.2 vs. 24.9%, OR =1.44 (1.10-1.88), p=0.04 after adjustment for confounders).

We investigated whether suffering from allergies only or suffering from both asthma and allergy, had an influence on fertility (Table 4). Individuals with allergy had the same TTP as the general population (21.2% vs. 21.6% OR: 0.91 (0.76 to 0.1)). Women with both allergy and asthma had an indicated but not significantly prolonged TTP compared with the general population (26.5% vs. 21.6% OR: 1.28 (0.96 to 1.72). The increased risk of prolonged TTP among women with asthma and allergy was comparable to being asthmatic alone with a decreased odds ratio (26.5% vs. 27%) (Table 3). Allergy is therefore not significantly associated with changes in TTP.

Women with asthma were found to conceive earlier in life than those without (23.74 vs. 24.53 years, p<0.001) and were consequently younger when giving birth for the first time (25.49 vs. 26.19 years, respectively, p=0.001) (Table 1). The mean number of offspring in the two groups was similar (1.86 vs. 1.83 child, p=0.509) and the proportion of childless women was identical in the two groups (6.5% vs. 6.2% p=0.355)(Table 2).

The sub-fertile group (TTP >1 year) (asthmatics and healthy cohort) differed from the fertile groups (TTP <1 year) with respect to several descriptive variables (Table 4). They had a higher prevalence of obesity (higher BMI), were older, had a shorter education and a greater proportion were smokers. There were no differences in these variables between the subjects with asthma and the healthy group.

Untreated asthmatics had a significantly increased risk of prolonged TTP compared to healthy individuals (30.5 vs. 21.6%, OR=1.79, p=0.004), while asthmatics receiving any kind of treatment for asthma trended to have a shorter TTP than untreated asthmatics (23.8 vs. 30.5%, OR=1.40, p=0.134). Asthmatics receiving daily-inhaled corticosteroid treatment also showed increased risk of

prolonged TTP compared to healthy subjects (33.0 vs. 21.6%, OR= 2.34, p=0.003), (Table 5).

There were no significant differences between those with asthma and those without regarding stillbirths, extra uterine pregnancies and spontaneous abortions. However, there was a tendency towards increased risk (12.3 vs. 9.8 %, OR=1.27(0.93-1.80)) of miscarriage in the asthmatic group. This effect was not statistically significant (p=0.169) (Table 6).

Co-twin control analysis in twin pairs discordant for asthma showed no significant difference in the risk of TTP in the asthmatic compared with the non-asthmatic twin (OR=0.29, p=0.12 in MZ twins and OR=0.77, p=0.53 in DZ twins, respectively). However, only 80 twin pairs were included in this analysis: 26 MZ twin pairs and 54 DZ twin pairs. The risk of long TTP was not significantly different in DZ co-twins compared with MZ co-twins, indicating a direct adverse effect of asthma on TTP not mediated through genetic or non-genetic confounding factors.

Discussion

This study showed that TTP is significantly prolonged in asthmatic individuals even after adjusting basic variables such as BMI, age and smoking. The impact of asthma on TTP is consistent in older and younger individuals, with an increasing tendency with age. This finding supports the findings of Tata LJ et al. [14], who showed that women with asthma tend to have lower fertility rates when older compared with healthy women of similar age.

It strengthens our findings that those with asthma in general tend to conceive at an earlier age compared to those without, which in theory should make them more fertile than the healthy group. There seems to be no obvious explanation for this observation.

Untreated asthmatics have a significantly increased risk of prolonged time to pregnancy compared to healthy. Furthermore TTP seems to be reduced in asthmatics receiving treatment for their asthma

compared to non-treated asthmatics, but being treated for asthma does not negate the shown effect completely compared to healthy subjects. However, when dividing the treatment groups into subgroups, our data show that asthmatics, which received inhaled corticosteroid, also have an excess risk compared with healthy individuals. This could indicate that the negative effect of asthma on fertility increases with the severity of the disease, as asthmatics in need of corticosteroids, are suffering from a moderate to severe degree of asthma. Another explanation, which should not be excluded, is that treatment with inhaled corticosteroids could be the cause of the prolonged time of pregnancy. This does not seem obvious since the increased risk of prolonged TTP for the corticosteroid-treated asthmatics did not differ from the untreated asthmatics compared to the healthy group.

Based on our results, one could assume that the prolonged TTP among asthmatics could be explained by the increased tendency for spontaneous abortion in this group. Although we must be cautious to conclude on a trend that is not significant, it is worth noting that the risk of spontaneous abortions in asthmatics seems increased by 27%. Furthermore this trend is consistent with recent results from Blais et al [21], who showed an increased risk of spontaneous abortions (OR 1.41, CI95%: 1.33-1.49) among asthmatics, which were independent of the severity of the asthmatic disease.

Our results are in line with the knowledge available about asthma's effect on pregnancy. Studies have shown that asthma influences the fetus during pregnancy by increasing the risk of abortions, preterm birth, low birth weight and perinatal mortality. Conversely, well-medicated asthma during pregnancy improves intrauterine growth of the fetus and lowers adverse perinatal outcomes [22]. This tendency also seems to be the case when attempting to become pregnant exemplified by our observation.

Our data show that the number of offspring is identical between asthmatics and healthy subjects, consistent with the findings of Tata et al. [14]. However, Karmause et al. [23] showed that atopic individuals tend to have fewer children. Interestingly, while the waiting time to pregnancy in those with asthma is longer, they ultimately have the same number of children as those without. This may be partly explained by the fact that they try to become pregnant at an earlier age, but other unknown factors may also play a role.

The above suggests that asthma has a major impact on fertility and pregnancy and that this effect may be reduced by treatment. With this in mind, it seems natural to assume that the systemic inflammation that characterizes asthma may account for some of the effect of asthma on infertility. In both animal and human studies, systemic inflammation in asthma has been shown to affect organs other than the respiratory system, particularly the brain, the cardiovascular system (altered vascular reactivity), and the blood (altered cytokine profile in plasma)[24]. An explanation for our findings, which would be in accordance with this, could be a change in the blood supply of the uterus, or an increased infiltration of inflammatory cells in the mucosal layer in the uterus. In terms of fertility, an altered blood supply or an increased infiltration of inflammatory cells into the endometrial lining could lead to impaired implantation or even rejection of the fertilized egg. This assumption is supported by the findings of Ponnoth et al. [25], who showed that systemic inflammation caused by asthma in mice could alter the vascular reactivity in the body (impaired vasorelaxation to adenosine). In line with this, others have shown an increased risk of cardiovascular disorders in asthmatic patients [26]. The role of systemic inflammation in those with asthma, regarding both fertility and other organs in the body, is still unclear and further research is needed to understand the mechanisms that link asthma with its co-morbidities [27].

The apparently increased negative impact of asthma on fertility with age may be explained by prolonged exposure to the systemic inflammation with age. If the systemic inflammation that

characterizes asthma is the cause of the observed impact on the fertility, a treatment option for fertile asthmatic patients could be of a more systemic nature such as leucotriene receptor antagonists or other targeted therapies.

In regards to inflammation and asthma, it has been indicated, that there might be a common inflammatory pathway between endometriosis and asthma as well as the metabolic syndrome and asthma. In terms of endometriosis, studies of women that suffer from this disease have a higher prevalence of asthma and allergy than among the general population [28]. Furthermore leucotriene antagonists intended for asthma treatment have been found useful in the treatment of endometriosis [29]. There is also growing evidence that the metabolic syndrome (abdominal obesity, insulin resistance, hypertension and dyslipidaemia) is a strong risk factor for asthma - even stronger then obesity [30]. A Study by Huisstede A et al [31], showed a correlation between eosinophilia, lung function and metabolic syndrome, while BMI had no correlation to this.

The possible causal connections between respectively endometriosis and asthma and the metabolic syndrome and asthma, could be some of the explanatory factors behind asthma patients impaired fertility as both diseases are known to reduce fertility [32,33].

There are some limitations to this study.

One is possible recall bias as our data were obtained from self-administered questionnaires. Validation studies have shown that self-reported TTP in questionnaires gives an accurate representation of the TTP distribution [34, 35], even with longer recalls up to 20 years [36].

Another possible bias is lack of generalisability to the singleton population as a whole. It is well known that twin pregnancies are at increased risk for preeclampsia, preterm birth and SGA (small for gestational age) [37, 38]. Further, it has been suggested that children born with low birth weight and of a mother with preeclampsia are at greater risk of asthma [39], although evidence is

circumstantial [40, 41]. A possible higher proportion of asthmatics in our dataset than in the general population would, however, not affect the relationship with TTP. Moreover, the proportion of asthmatics in our cohort was 6.3%, which corresponds well with estimates from the general population (6.6%) [42]. Unfortunately, we had no data on birth weight, and therefore we were not able to take this into account in our analyses.

Despite these issues, twins can be assumed to be representative of the population because they are born into all social groups, and their morbidity/mortality after infancy is equivalent to the mortality of the general population [43]. They can therefore epidemiologically be analyzed as individuals. Furthermore studies of twins have shown that twins represent the fecundity of the general population [44].

Another limitation to this study is incomplete information about fertility related disease and the severity of asthma.

Further, it would have been interesting to have information on whether the participants had sought fertility treatment or if their partner had reduced fertility. It was therefore not possible, based on the present data, to determine whether asthmatics seek fertility treatment more frequently than healthy, which we, based on our findings, might expect.

Lastly, a large number of participants did not respond to questions about their fertility. This group was significantly younger than the other respondents. We therefore assume, that they had not used their fertility potential at the time of the questionnaire. This could be considered as a selection bias, but analysis of regression shows that the dropouts are representative of the whole cohort in terms of asthma status, smoking and BMI. Accordingly, the large number of dropouts does not seem to be critical to our results. Furthermore, when we restricted the analysis to women above 30 years of age, in whom the response rate to the fertility questions was high, the negative effect of asthma on TTP was even more pronounced, indicating that, at worst, the lack of response diluted our estimate.

In conclusion, asthmatics experience a longer TTP, but achieve ultimately the same average number of children. These findings seem contradictory, but those with asthma were also found to have an earlier start to their reproductive life, leading to a similar number of offspring. These findings could be related to systemic inflammation as our data indicate that receiving asthma medication reduces time to pregnancy, but further evidence is needed for confirmation.

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Conflict of Interest Statement:

E.J.G., S.F.T, S.L., K.O.K, S.L and VB do not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Table 1. Characteristics of the study population

	Total cohort n = 15.250	Healthy n =14.011	Asthmatic n =955	Prevalence of asthma	OR (95% CI)	*P* value
Age groups					(-0.68-0.36)	0.557
12-17 yrs.	2.425	2.276 (16.2)	149 (15.6)	6.1		
18-25 yrs.	3.937	3.671 (26.2)	266 (27.9)	6.8		
26-30 yrs.	3.187	2.989 (21.3)	198 (20.7)	6.2		
31-35 yrs.	2.935	2.751 (19.6)	184 (19.3)	6.3		
36-42 yrs.	2.482	2.324 (16.6)	158 (16.5)	6.4		
Current smoking	4.608 (30.9)	4.309 (30.9)	299 (31.4)	6.5	1.02(0.89-1.18)	0.773
BMI (SD)*	21.69 (3.7)	21.66(3.7)	22.24 (4.7)		(0.27-0.89)	**<0.001**
Yrs. of Education					(-0.23-0.12)	0.556
0 yrs.	374	345 (2.5)	29 (3.0)	7.8		
1-9 yrs.	2.703	2.515 (18.0)	188 (19.7)	7.0		
10-13 yrs.	8.597	8.060 (57.5)	537 (56.2)	6.2		
13-15 yrs.	3.048	2.869 (20.5)	179 (18.7)	5.9		
16-25 yrs.	242	2.20 (1.6)	22 (2.3)	9.1		
Age at menarche (SD)*	13.17(1.4)	13.18 (1.4)	13.07(1.5)	6.4		**0.029**
Age at conception (SD)*	24.49(5.3)	24.54 (5.3)	23.74(5.7)	6.3	(0.4- 0.90)	**<0.001**
Age at first birth **(**SD)*	26.14(4.2)	26.19 (4.2)	25.49(4.2)	6.7	(0.30-1.12)	**0.001**

Note. All figures are numbers(%), *SD= Standard deviatition

Table 2. The relationship between asthma and prolonged TTP (TTP> 1 yr.)

	Non- Asthma	Asthma	OR (CI 95%)	*P* value
TTP > 1 yr.	1.415 (21.6)	120 (27.0)	1.31(1.07-1.61)	**0.009**
Adjusted, 1 step*			1.27 (1.01-1.59)	**0.04**
Adjusted, 2 step**			1.25 (1.0-1.58)	0.05
Temp. infertile***	1.003 (15.4)	88 (20.2)	0.81(0.53-1.21)	0.355
Childless****	403 (6.2)	28 (6.4)	1.02(0.99-1.05)	0.552

***** Adjusted for age, BMI & smoking, All figures are numbers(%)

** Adjusted for age, BMI, smoking, age at menarche and education status. All figures are numbers(%)

***Temporarily infertile: Proportion of women that have conceived, despite infertile period in their live.

****Childless: Proportion of women from the total cohort, who never despite attempts conceived.

Table **3.** The Association between prolonged TTP, allergy and asthma.

	TTP> 1 year	OR (CI95%)	*P value*	Adjusted OR* CI95%)	Adjusted *P* value*
Healthy	1438 (21.6)	1.00			
Allergy	194 (21.2)	0.95 (0.82-1.10)	0.522	0.91(0.76-1.10)	0.30
Asthma & allergy	59 (26.5)	1.28 (0.96-1.72)	0.100	1.14(0.82-1.58)	0.43

***** Adjusted for age, BMI, smoking, age at menarche and education status. All figures are numbers(%)

Table 4. The Association between TTP and the descriptive variables.

	TTP<1 year n = 5.468	TTP> 1 year n = 1.561	OR (CI95 %)	*P* value
Age*	31.7 (5.6)	33.3(4.7)	(1.30-1.90)	**<0.001**
BMI *	22.4 (3.7)	22.7 (4.1)	(0.1-0.5)	**0.01**
Yrs. of Education**	11.0 (2.4)	10.6 (2.3)	(-0.5--0.2)	**<0.001**
Current smoking *	2.052 (0.5)	753 (0.5)	0.7 (0.61-0.76)	**<0.001**
Age at menarche *	13.25(1.4)	13.26(1.5)	(-0.09-0.08)	0.899

Note:
*SD = Standard deviation
**SEM = Standard error of mean

Table 5. The effect of asthma medication on TTP

Medication definition	Prolonged TTP (%)	OR (95% CI)	P-value
Self-reported medication*			0.000
Non-asthma	1410 (21.6)	1.00	
Untreated	60 (30.5)	1.79 (1.20-2.66)	0.004
Any treatment	65 (23.8)	1.13 (0.85-1.51)	0.389
Corticosteroids	37 (33.0)	2.34 (1.33-4.13)	0.003
Other treatments	28 (17.4)	0.76 (0.51-1.15)	0.199
Medication question**			
Treated	71 (26.0)	1.00	
Untreated	20 (34.5)	1.13 (0.93-1.28)	0.198

Note.
*Calculated on basis of question: 'Do you , or have you ever used any medication during longer periods on a regular basis or due to attacks?'
**Calculated on the basis of questions: I'm using or have previously used asthma medication.

Table 6. Pregnancy outcome in a cohort of asthmatics and non-asthmatics.

Pregnancy outcome (PO)	Healthy(%)	Asthmatics(%)	OR (CI 95 %)	*P-value*
Nb. of PO in total	5224 (91.9)	349 (6.2)	1(0.25-2.6)	0.548.
Live births	4313 (82.5)	281 (80.3)		0.685
Stillbirths	57 (1.1)	3 (0.9)		0.445
Spontaneus abortions	512 (9.8)	43 (12.3)	1.27(0.93-1.8)	0.169
Ex- uterine pregnancy	70 (1.3)	1 (0.3)		0.247

List of acronyms:

TTP: Time to pregnancy

PO: pregnancy outcome

BMI: Body Mass Index

IVF: In vitro fertilization

DZ: Dizygotic twins

MZ: Monozygotic twins

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