Asthma treatment impacts time to pregnancy: evidence from the international SCOPE study

To the Editor:

Asthma is a common chronic disease affecting the lives of reproductive age women and is associated with 8–13% of pregnancies [1]. While maternal asthma has been consistently associated with significant perinatal morbidities and mortality [2, 3], impacts on fertility are conflicting. In light of limited and conflicting evidence, the aim of this study was to examine the impact of asthma and asthma medication use on fecundability and time to pregnancy.

Participants were healthy, nulliparous women recruited to the Screening for Pregnancy Endpoints (SCOPE) study between November 2004 and February 2011 in Auckland (New Zealand), Adelaide (Australia), Cork (Ireland), and Manchester and London (United Kingdom). The SCOPE study is a multicenter prospective cohort study with the primary aim of developing screening tests for prediction of pre-eclampsia, spontaneous preterm birth and small-for-gestational-age neonates. Ethical approval was obtained from local ethics committees (New Zealand AKX/02/00/364, Australia REC 1712/5/2008, London, Leeds and Manchester 06/MRE01/98 and Cork ECM5 (10) 05/02/08). All women provided written informed consent. Detailed methods have been described previously [4].

Asthma was self-reported and identified according to the question "Have you been diagnosed with asthma by a doctor?". Asthmatic women were further divided by asthma symptoms and asthma medication use and then classified as having former asthma (doctor diagnosed asthma, no symptoms in the previous 12 months and no use of asthma medications) or current asthma (doctor diagnosed asthma, symptoms in the previous 12 months or use of asthma reliever or preventer medications). Women with current asthma were further divided according to use of intermittent reliever medications only (*i.e.* short-acting β-agonists (SABA)) or additional use of reliever medications (*i.e.* inhaled corticosteroids (ICS) with or without long-acting β-agonists (LABA)). This resulted in three asthmatic subgroups: former asthma, SABA and ICS±LABA.

Information was collected on demographics, smoking, family, medical and gynaecological history, and anthropometry (height and weight). Maternal ethnicity was self-reported and categorised as Caucasian or other. The socio-economic index is a measure of socio-economic position according to income and education, corrected for age [5]. This index was calculated for all women in the SCOPE study (range 10–90), with a higher score indicating higher socio-economic status [6]. Self-reported polycystic ovary syndrome was categorised as yes (confirmed by a scan and/or a blood test) or no/unsure. Cigarette use in the 3 months pre-pregnancy was coded as any *versus* not smoking. Age at menarche was reported as a continuous variable. Information collected from the biological father included age and BMI.

Self-reported time to pregnancy (TTP) was defined as the duration of sex (in months) without contraception before the current pregnancy and was collected in the first trimester. Subfertility was defined as TTP >12 months. Fecundability odds ratios (FORs) and 95% confidence intervals were estimated using Cox proportional hazards models for discrete-time data. FORs estimate the odds of conceiving in each cycle, given exposure to asthma, conditional on not being pregnant in the previous cycle. FORs <1 denote reduction in fecundability or longer TTP, and FORs >1 denote shorter TTP (TTP was censored at the 13th month). The proportional hazard assumptions were checked with Schoenfeld residuals and graphic methods and the association between asthma treatment and TTP was evaluated using logistic regression. Analyses were adjusted for possible confounders (see the footnotes to table 1) and statistical significance

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was defined as a two-sided p-value <0.05. Analyses were undertaken using STATA-IC 14 (Stata, College Station, TX, USA).

Of 5617 women in the study, 1106 (19.7%) reported doctor-diagnosed asthma. Among women with asthma, 656 (11.7%) were identified as current asthmatics and 450 (8.0%) were former asthmatics. Compared with non-asthmatics, women with either current or former asthma were younger, had higher BMIs, were more likely to smoke and be of Caucasian ethnicity, and had lower socio-economic status.

Table 1 shows that, compared to non-asthmatics, current asthmatics managed with SABAs had adjusted FORs (model 2) that were 15% lower (0.85 (95% CI 0.75–0.96)) whereas no difference was observed for former asthmatics (1.00 (95% CI 0.89–1.13)) or current asthmatics using ICS±LABAs (0.98 (95% CI 0.84–1.15)). Compared to non-asthmatics, point estimates for subfertility were increased among women using SABAs (adjusted odds ratio (OR) 1.30 (95% CI 0.93–1.81)) but not for women with former asthma (0.89 (95% CI 0.62–1.28)) or current asthma patients using ICS±LABAs (1.08 (95% CI 0.69–1.71)). Additional sensitivity analyses were undertaken including women who conceived following the use of assisted reproductive technologies; however, this did not appreciably change any of the risk estimates (results not shown).

We show that asthma is associated with reduced fertility but the greatest impact is among women with current asthma receiving intermittent reliever treatment with SABAs. The lack of associations with ICS ±LABAs use suggests that preventer medications may play a protective role in improving asthma control and reducing associated systemic inflammation which may drive impaired fertility. This is important as women and healthcare professionals express concerns regarding the safety of preventer medications such as ICS during pregnancy. These concerns lead to poor adherence and discontinuation of asthma medications during pregnancy, with negative impacts on asthma control and pregnancy outcomes [7]. Preconception management in asthma is likely important in optimising pregnancy outcomes, especially given that 50% of asthma exacerbations occur in the first half of pregnancy [8].

Literature on the relationship between asthma and fertility is sparse and conflicting. Population-based pregnancy cohort studies of women with asthma report associations with subfertility [9], use of fertility medications [10] and prolonged TTP [11]. Furthermore, asthmatic women with unexplained infertility undergoing fertility treatment experience prolonged TTP compared with non-asthmatics (55.6 *versus* 32.3 months; hazard ratio (HR) 0.50 (95% CI 0.34–0.74)) [12]. Data on asthma medication use is limited. Compared to non-asthmatics, Gade *et al.* [11] observed increased risks of prolonged TTP among asthmatic women not taking medication (OR 1.79 (95% CI 1.20–2.66)) and among women using ICS (OR 2.34 (95% CI 1.33–4.13)) but not among women using any other asthma medications (OR 0.76 (95% CI 0.51–1.15)). However, these findings were not adjusted for potential confounders including socio-economic status and the presence of polycystic ovary syndrome, or paternal factors such as age and body mass index (BMI) that could influence the observed associations. Furthermore, fertility and asthma medication data were collected retrospectively, with a mean age at data collection of 32 years, whereas mean age at conception was 25 years [11].

While the exact mechanisms underpinning our observations remain unclear, it has been hypothesised that asthma reduces uterine blood supply or increases infiltration of inflammatory cells into the decidua (the uterine mucosal layer), which impairs implantation [11]. This is supported by a recent study of women with unexplained infertility who were receiving fertility treatment, which reported that asthmatic women had reduced vascular endothelial growth factor (VEGF; a potent angiogenic factor) compared with non-asthmatic women [13].

TABLE 1 Associations of asthma and asthma medication use with fecundability and prolonged time to pregnancy (>12 months)

	Fecundability[#] odds ratio			Prolonged TTP odds ratio		
	Unadjusted	Adjusted (model 1[¶])	Adjusted (model 2[+])	Unadjusted	Adjusted (model 1[¶])	Adjusted (model 2[+])
Non-asthmatic (n=4511)	1	1	1	1	1	1
Asthmatic (n=1106)						
Former (n=450)	1.12 (1.01–1.24)	1.02 (0.92–1.14)	1.00 (0.89–1.13)	0.84 (0.61–1.15)	0.97 (0.70–1.34)	0.89 (0.62–1.28)
Current (n=656)						
SABA only (n=421)	0.95 (0.85–1.06)	0.85 (0.76–0.95)	0.85 (0.75–0.96)	1.10 (0.82–1.47)	1.26 (0.92–1.73)	1.30 (0.93–1.81)
ICS±LABA (n=235)	1.01 (0.87–1.16)	0.93 (0.81–1.08)	0.98 (0.84–1.15)	1.07 (0.72–1.57)	1.20 (0.80–1.79)	1.08 (0.69–1.71)

Data are presented as odds ratio (95% CI) unless otherwise stated. TTP: time to pregnancy; SABA: short-acting β-agonist; ICS: inhaled corticosteroids; LABA: long-acting β-agonist; BMI: body mass index. [#]: fecundability was defined as the average per-cycle probability of conception; [¶]: model 1 factors were maternal BMI, maternal age, recruitment site, socioeconomic status, ethnicity (Caucasian/other), polycystic ovary syndrome (yes/no), smoking status (yes/no) and age at menarche; [+]: model 2 factors were the same as model 1 plus paternal BMI and paternal age.

Strengths of this study include the large cohort and number of women with asthma, representative international scope, detailed data on reproductive and nonreproductive characteristics and inclusion of many possible confounders. Limitations include that asthma was self-reported and medication use was reported at 15 weeks' gestation and assumed to reflect the whole periconceptual period. When comparing self-reported asthma in questionnaires to a clinical diagnosis of asthma, Toren *et al.* [14] identified a sensitivity of 68% and a specificity of 94%. We further strengthened the identification of asthmatics by including data on asthma medication use. Absence of data on asthma control and lung function during pregnancy means that we could not examine associations according to asthma severity. Furthermore, the cohort recruited nulliparous women who were at low risk of pregnancy complications. Therefore, generalizability of the findings to multiparous women is uncertain.

In conclusion, the management of asthma with SABAs was associated with reduced fertility, whereas the management of asthma with ICS with or without LABAs was not. These findings support appropriate management of asthma with ICS preventer medications to ensure optimal asthma control. Women with asthma planning a pregnancy should be encouraged to continue taking their preventer medications.

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