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

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Running title: Asthma treatment affects time to pregnancy.

Take Home Message:

Use of short-acting relievers, but not long-term preventers, is associated with reduced fertility in asthmatic women.

Key words asthma, time to pregnancy, fertility

Introduction

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.

Methods

Participants were healthy, nulliparous women recruited to the SCOPE (Screening for Pregnancy Endpoints) 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 preeclampsia, 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 medications use, then classified as having former asthma (doctor diagnosed asthma, no symptoms in previous 12 months and no use of asthma medications), or current asthma (doctor diagnosed asthma, symptoms in 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 beta-agonists

[SABA]), or additional use of reliever medications (i.e. inhaled corticosteroids [ICS] with or without long-acting beta-agonist [LABA]). This resulted in three asthmatic subgroups (former asthma, SABA, or ICS±LABA).

Information was collected on demographics, smoking, family, medical and gynecological history, and anthropometry (height and weight). Maternal ethnicity was self-reported and categorized as Caucasian or Other. The socioeconomic index (SEI) is a measure of socioeconomic position according to income and education, corrected for age [5]. The SEI was calculated for all women in SCOPE (range 10-90), with higher score indicating higher socioeconomic status [6]. Self-reported polycystic ovary syndrome (PCOS) was categorized as yes (confirmed by a scan and/or blood test) or no/unsure. Cigarette use in the three months pre-pregnancy was coded 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 duration of sex (in months) without contraception before the current pregnancy and collected in the first trimester. Subfertility was defined as TTP>12 months.

Fecundability odds ratios (FOR) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models for discrete-time data. FORs estimate the odds of conceiving 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 13th months. The proportional hazard assumptions were checked with Schoenfeld residuals and graphic methods. The association between asthma treatment and TTP was evaluated using logistic regression. Analyses were adjusted for possible confounders (in footnotes to **Table 1)**.

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

Results

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 socioeconomic status.

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

Discussion

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 inhaled corticosteroids 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 of asthma is likely important in optimizing pregnancy outcomes, especially given 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]. Further, asthmatic women with unexplained infertility undergoing fertility treatment experience prolonged TTP (55.6 versus 32.3 months; HR 0.50: 95% CI 0.34-0.74), compared with non-asthmatics [12]. Data on asthma medication use is limited. Compared to non-asthmatics, Gade *et al.* observed increased risks of prolonged TTP among asthmatic women not taking medication (OR 1.79, 95%CI 1.20-2.66), as well as 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) [11]. However, these findings were not adjusted for potential confounders, including socioeconomic status or presence of polycystic ovary syndrome, or paternal factors such as age and BMI that could influence the observed associations. Further, 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, others have hypothesized 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 receiving

fertility treatment, that reported asthmatic women had reduced vascular endothelial growth factor (VEGF; a potent angiogenic factor) compared with non-asthmatic women [13].

Strengths of this study include the large cohort and number of women with asthma, international representativeness, detailed data on reproductive and non-reproductive 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.* identified a sensitivity of 68% and specificity of 94% [14]. 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. Further, 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 inhaled corticosteroid preventer medications to ensure optimal asthma control. Women with asthma planning pregnancy should be encouraged to continue taking their preventer medications.

Authorship

All authors contributed to: (1) either the conception and design of the study, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted, and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

The SCOPE database is provided and maintained by MedSciNet AB (http://medscinet.com). The Australian SCOPE study was funded by the Premier's Science and Research Fund, Government of South Australia (http://www.dfeest.sa.gov.au/science- research/premiers-research-and-industry-fund). The New Zealand SCOPE study was funded by the New Enterprise Research Fund, Foundation for Research Science and Technology; Health Research Council (04/198); Evelyn Bond Trust, Auckland District Health Board Charitable Trust. The Irish SCOPE study was funded by the Health Research Board of Ireland (CSA/2007/2; http://www.hrb.ie). The UK SCOPE study was funded by National Health Service NEAT Grant (Neat Grant FSD025), Biotechnology and Biological Sciences Research council (www. bbsrc.ac.uk/funding; GT084) and University of Manchester Proof of Concept Funding (University of Manchester); Guy's and St. Thomas' Charity (King's College London) and Tommy's charity (http://www. tommys.org/; King's College London and University of Manchester); and Cerebra UK (www.cerebra.org.uk; University of Leeds). L.E. Grzeskowiak is supported by an Australian National Health and Medical Research Council (NHMRC) Early Career Fellowship (APP1070421). V.L.C. is supported by an Australian National Health and Medical Research Council (NHMRC) Senior Research Fellowship (APP1041918). L.C. Kenny is supported by a Science Foundation Ireland Program Grant for INFANT (12/RC/2272). C.T.

Roberts was supported by a National Health and Medical Research Council (NHMRC) Senior Research Fellowship (GNT1020749) and University of Adelaide.

The funding source(s) had no involvement in the conduct of the research and/or preparation of the article.

Conflicts of Interest

The authors report no conflicts of interest

Acknowledgements

The authors wish to thank all of the SCOPE participants and the SCOPE research midwives in each centre, Robyn North for her enormous contributions in establishing the SCOPE study, and Eliza Chan for her role in establishing the database. The SCOPE database is provided and maintained by MedSciNet AB.

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Table 1: Associations between asthma and asthma medication use with fecundability† and prolonged time to pregnancy (>12 months)

	Fecundability Odds Ratio (FOR)†			Prolonged Time To Pregnancy (>12 months) Odds Ratio (OR)		
	Unadjusted FOR (95%CI)	**Adjusted FOR Model 1 (95% CI)**	**Adjusted FOR Model 2 (95% CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR Model 1 (95% CI)**	**Adjusted OR Model 2 (95% CI)**
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)

Abbreviations: FOR, fecundability odds ratio; CI, confidence interval; Odds Ratio, OR; SABA, short-acting beta-agonist: ICS, inhaled corticosteroid: LABA, long-acting beta-agonist

†Fecundability defined as the average per-cycle probability of conception

Model 1: 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: model 1 plus paternal BMI, paternal age