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Inhaled Corticosteroid Use during Pregnancy among Women with Asthma: a Systematic Review and Meta-Analysis

Short running title: **Evaluating inhaled corticosteroid use in pregnancy**

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Conflicts of Interest Statement

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Abstract

Background: Studies demonstrate the prescription rate for inhaled corticosteroids (ICS) decreases in early pregnancy, possibly increasing exacerbation risk. This could be related to non-adherence to prescribed asthma medication, or medication cessation by the patient or doctor. ICS use during pregnancy has not previously been summarised in a systematic review.

Objective: The aim of this systematic review and meta-analysis was to evaluate the use of ICS during pregnancy among asthmatic women, specifically: 1) the prevalence of use, 2) changes of use during pregnancy compared to pre-pregnancy and 3) medication adherence among ICS users.

Methods: We systematically searched literature in Embase, Medline, CINAL and Cochrane, using terms related to asthma, pregnancy and medication use. All English articles reporting ICS among pregnant women with asthma were included. Prevalence, changes in ICS use during pregnancy and ICS adherence were pooled using STATA (version 15.0, StataCorp USA).

Results: 4237 references were retrieved in the initial search. Screening and review led to the inclusion of 52 articles for one or more aims (Aim 1: N=45; Aim 2, N=13; and Aim 3, N=5). The pooled prevalence of ICS use during pregnancy was 41% (95%CI 36-45%); 49% (95%CI 44-55%) in Europe, 39% (95%CI 32-47%) in Australia and 34% (95%CI 27-41%) in North America. In eight prescription databases, ICS prescription rates lowered in the first trimester of pregnancy, compared to pre-pregnancy, increased in the second trimester, and decreased in the third trimester. Five studies reported ICS adherence among pregnant women, using four measures of self-reported non-adherence. In two comparable studies, pooled ICS non-adherence was 40% (95%CI 36-44%).

Conclusions: The prevalence of ICS use among pregnant women with asthma is 41% and varies widely between countries and continents, and prescription rates for ICS change throughout pregnancy. More studies are needed to investigate ICS adherence during pregnancy in women with asthma.

Introduction

Asthma is a common chronic condition during pregnancy, affecting up to 13% of pregnant women worldwide.[1–4] Guidelines recommend the same asthma management for pregnant women as for other adults, which predominately consists of short-acting beta-agonists (SABA) as reliever medication and inhaled corticosteroids (ICS) as controller medication.[5] However, some studies have demonstrated that women tend to cease their asthma medication during pregnancy.[6,7] Cessation of, or non-adherence to, ICS during pregnancy increases the risk of asthma exacerbations, which are associated with poor perinatal and neonatal outcomes, such as pre-term delivery and low birth weight.[8,9]

In an American survey of 501 women of childbearing age with asthma, 39% discontinued or reduced their asthma medication during pregnancy; of this group, one third did not consult with their physician first.[10] Furthermore, an Australian study of 4573 pregnancy-related calls to a national medicines call centre found that 53% of the pregnant women indicated that inadequate information was their motivation to call.[11] Whilst Pijpers et al. did not specifically report on asthma medication, a second Australian study identified a lack of adequate information about asthma medication during qualitative interviews with 23 pregnant women with asthma.[12]

No previous studies have systematically reviewed ICS use among pregnant women with asthma. Therefore, the aim of this systematic review and meta-analysis was to evaluate ICS use during pregnancy among women with asthma, specifically: 1) the prevalence of use, 2) changes in use during pregnancy compared to pre-pregnancy, and 3) medication adherence among ICS users.

Methods

Literature search

We used search terms related to asthma, pregnancy and medication use in Embase, Medline, CINAL and Cochrane (supplement **Table S1**) for articles published up to February 2019. Included articles were published in English, included a population of women with asthma, and had data on one or more of the following outcomes related to asthma medication use during pregnancy: (i) prevalence of ICS use among pregnant women with asthma, (ii) changes in ICS use during pregnancy compared to pre-pregnancy, (iii) adherence to ICS during pregnancy. We did not restrict the study population based on age or nature of asthma diagnosis; the latter was included in the quality assessment. Case reports, review articles, conference abstracts, editorials and letters to the editor were excluded; all other study designs were included. Although clinical trials were included, the purpose of this review was not to examine specific interventions or comparisons. Rather, we extracted the baseline

information of the women with asthma in such studies. In case of multiple publications on the same dataset, the most recent publication or the one reporting the largest population was included. Two reviewers (ALR and KM) independently assessed the articles for inclusion and quality assessment; discrepancies were discussed until consensus was reached. The quality of each article was assessed using an in-house adapted version, of the Newcastle Ottawa Scale[13], to suit extraction of baseline information. (**Supplement**) Quality was determined based on representativeness of the study population, ascertainment of asthma diagnosis, ICS use and ICS adherence measure. Methods were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[14]

Data Extraction

Data was extracted from included studies using a predefined form by one reviewer (ALR), and independently confirmed by a second reviewer (KM). Data extracted included details of the study population, type of data source, continent, and ICS use details including adherence among the pregnant women with asthma. ICS use included self-reported use and ICS dispenses recorded in databases. Changes in use included changes in dispensed prescriptions in different time periods and self-reported changes in use. Adherence to ICS included self-reported measures and calculated adherence based on prescription dispensing.

Analysis

Prevalence data were grouped by source (clinical study or database dataset) and continent. All data is presented as proportions (%) or medium [interquartile range]. Meta-analyses of prevalence of ICS use, changes in prevalence of prescriptions and non-adherence proportions were performed using METAPROP with random effects in STATA (version 15.0, StataCorp USA). Heterogeneity was assessed using I^2. The percentage change in prevalence of prescriptions between two time points was calculated as per **Equation 1**.

Equation 1: Calculation of percent change between two time points

$$\%\ change = \frac{proportion\ time\ point\ 2 - proportion\ time\ point 1}{\text{proportion time point 1}} x\ 100\%$$

Results

In total, 4237 references were retrieved in the initial search. After removal of duplicates, 3468 references were included for title and abstract screening, reducing to 473 for the full text review. One-hundred articles were included for data extraction. At this stage, it was identified that several datasets and clinical studies had >1 paper published utilising the same data. Subsequently, an additional 48 articles were excluded. In total, 52 articles were included for one or more aims (Aim 1: N=45 articles; Aim 2, N=13 articles; and Aim 3, N=5 articles). (**Figure 1**)

Quality assessment of included articles

The median score for quality was 4 [4, 5]. Twenty-one (40%) articles were classified as 'Good', twenty-six articles (50%) as 'Medium' and five articles (10%) as 'Poor' quality.

Prevalence of ICS use during pregnancy: clinical and database studies

Data on the prevalence of ICS use in pregnancy were extracted from 45 publications with a total of 186,307 pregnant women with asthma from 16 different countries. The use of ICS either was self-reported in clinical studies (N=31) or was determined based on prescriptions in database studies (N=14). Prevalence of ICS use among pregnant women with asthma was 41% (95%CI 36-45%, I^2=99.7%), excluding the four studies with 'poor' quality from the prevalence did not materially changes the estimates. The proportion of ICS users was 39% (95%CI 32-46%, I^2=98.8%) in clinical studies and 46% (95%CI 40-53%, I^2=99.9%) dataset studies. (**Table 2, Figure 2**) Prevalence of ICS use was 49% (95%CI 44-55%, I^2=99.6%) in Europe, 34% (95%CI 27-41%, I^2=99.6%) in North America and 39% (95%CI 32-47%, I^2=91.3%) in Australia. Self-reported ICS use in clinical studies was 54% (95%CI 41-66%, I^2=93.0%) in Europe, 39% (95%CI 32-47%, I^2=91.3%) in Australia and 32% (95%CI 21-43%,

I^2=99.1%) in North America. Datasets from Europe and North America had a pooled prevalence of 48% (95%CI 42-54%, I^2=99.8%) and 40% (95%CI 31-50%, I^2=99.8%), respectively. There was significant heterogeneity between continents in the overall analysis (p<0.01) and in the database analysis (p=0.01), and no significant heterogeneity between continents in the clinical analysis (p=0.07) nor between database and clinical analysis (p=0.10).

In 15 studies, prevalence of ICS/LABA combination therapy over ICS use could be determined (pooled 49%, 95%CI 39-59%, I^2=99.9%). The use of combination therapy among ICS users was highest in Australia (73%, 95%CI 62-85%, I^2=61.2%, four studies) compared to North America (45%, 95%CI 2-87%, three studies) and Europe (36%, 95%CI 31-41%, I^2=99.9%, five studies). (**Figure 3**)

Changes in ICS: database studies

The change in dispensed ICS prescriptions before, during and after pregnancy were reported from 12 databases (**Table 3**) in eight publications.[6,7,15–20] Two studies[7,15] collected data on ICS use before, during and after pregnancy using comparable methods and therefore were pooled for analysis/reporting (data from eight European databases). Overall, ICS prescription rate remained stable in the preconception period (12 months preceding last menstrual period (LMP)). The pooled ICS prescription rate dropped in the first trimester (T1) (-8.5% vs. three months prior to LMP; Q4 in **Figure 4**), increased in the second trimester (T2) (+10.0% vs. T1, +0.7% vs. Q4), and decreased in the third trimester (T3) (-11.0% vs. T2). In the 12 months postpartum, the ICS prescription rate lowered further in the first three months (Q5 in **Figure 4**) (-10.7% vs. third trimester), before increasing in each of the following three month intervals, Q6, Q7 and Q8 in **Figure 4**, (+14.6%, +10.8% and +7.4% compared to the previous interval, respectively). (**Figure 4**) **(Table 4)**

Of the six database studies[6,16–20] that could not be included in the pooled analysis due to differences in data collection, two used the same Korean dataset but examined different outcomes.[16,17] The first, by Koo et al reporting on 115,169 pregnant women with asthma, assigned ranks to controller medication for asthma, with low ranks ('1' and '2') for ICS only inhalers and low ICS dose

combination inhalers, rank '3' for medium-to-high ICS dose combination inhalers, and the highest rank '4' to OCS.[17] Authors reported a drop in daily rank-sum values in early pregnancy compared to the year before pregnancy, indicating cessation of medication and/or change from higher ranked to lower ranked medications.[17] The second publication, by Lee et al., restricted analyses to women with asthma (N=5589) needing healthcare utilisation (hospital visit and a physician's diagnosis and care) during pregnancy. In this group of women, a 7.9% increase in ICS treatment was observed in the second trimester compared to the first, and a 5.6% decrease in the third trimester compared to the second.[16]

Enriquez et al. reported a 23% drop in ICS use in the first trimester of pregnancy among women (N=8149) enrolled in a pregnancy database in Tennessee (United States).[6] A 2009 study by of 11,258 pregnancies complicated by asthma in Canada reported that 41% of women were using ICS during pregnancy, and 44% during the year before conception .[19] A subset of pregnancies (n=4920) included in this study were examined further in a 2012 study by Blais et al., comparing ICS use during pregnancy and pre-pregnancy.[18] The changes were based on ICS daily dose in the nine months before pregnancy and in the nine months during pregnancy. Compared to pregnancy, approximately 30% of women discontinued their ICS medication (defined as >75% reduction in daily dose), 19% reduced their ICS dose (26-75% reduction in daily dose), and 29% increased their ICS dose (>25% increase in daily dose) during pregnancy.[18] Data from a Swedish database[21] included midwife-reported start and discontinuation of asthma medication during pregnancy, the study reported that less than 5% of women using ICS some time during pregnancy discontinued their medication in the first or second trimester. About 40% of the women using ICS during pregnancy had this medication at the start of their pregnancy and around 46% started ICS treatment during the first trimester. A vast majority of the women (around 80%) who were using ICS during pregnancy did not cease their medication during pregnancy.[21]

In Italian[7], French[15] and Dutch[7] databases, a change in type of medication was observed during pregnancy. There was an increase in ICS-mono prescriptions but a decrease in ICS/LABA combination prescription. In the study by Charlton et al.[7], Norway was the only country with a higher prevalence of combination therapy compared to ICS-mono therapy, while in other countries ICS-monotherapy was more prevalent than combination therapy.

Self-reported changes to ICS treatment

Self-reported changes to asthma treatment were documented in five studies of pregnant women with asthma, using (online) questionnaires or interviews.[3,10,22–24] In a survey of 102 pregnant women with asthma in Australian, 37% reported controller use prior to pregnancy, yet only 18% reported use during pregnancy.[3] Furthermore, 39% of pregnant women with asthma stated that they 'often' or 'always' make changes to their recommended ICS treatment to suit their lifestyle, with an additional 31% selecting 'sometimes'. Another study, based on a questionnaire (N=501)[10], reported that 39% of the pregnant women with asthma ceased of reduced their medication. An additional study reported 33% had ceased or reduced asthma medication, based on face-to-face interviews (N=58)[22] In a questionnaire-based study of 171 women with asthma[23], 47% reported to have ceased, or wanted to cease, their asthma medication during pregnancy. Moreover, a study of 123 pregnant women with asthma presenting to an emergency department reported that 16% had ceased ICS medication prior to the event.[24]

Adherence to ICS during pregnancy

Five studies reported asthma medication adherence among pregnant women.[22,25–28] All studies collected self-reported non-adherence; of which, only one also reported medication possession rates (MPR).[25] Two studies[26,27], both from the same research group but reporting on different study populations, collected self-reported adherence using the question: "It can be difficult to remember all of your medicines when things get busy. How many times in the last week have you missed a dose of your controller?", with non-adherence defined as ≥20% of prescribed dosages missed in the past

week.[26,27] Pooled non-adherence from these two studies was 40% (95%CI 36-44%; ICS users 447/1107). In a study of 32 women with asthma, 56% reported irregular use of their controller medication during pregnancy, compared to 68% pre-pregnancy, both reported retrospectively within 24 hours after delivery.[28] Lim et al. used the non-adherence subscale of the Beliefs and Behaviour Questionnaire to assess non-adherence in 58 women.[22] Median scores in the two study groups were 8 (6-11) and 7.5 (6-11); scores could theoretically range from 4-20 with higher scores indicating non-adherence. However, no cut-off values were provided to indicate when a participant was considered non-adherent to prescribed therapy, thus prevalence data on ICS non-adherence was unavailable. Baarnes et al. used two methods to determine adherence and compared both.[25] The first method was self-reported adherence rated as 'good', 'moderate' or 'low'; the second calculated MPR over pregnancy using dispensed prescriptions to categorise adherence as 'good' (MPR>80%), 'moderate' (41-79%), 'poor' (1-40%) and 'non-adherent' (0%). The proportion of women with 'good' adherence based on MPR (14%) was lower than self-reported 'good' adherence during pregnancy (73%). Based on MPR, 18% of the women did not fill an ICS prescription during pregnancy.

Discussion

To our knowledge, this is the first systematic review and meta-analysis to evaluate ICS use in pregnant women with asthma. We report a pooled ICS use prevalence of 41% (95%CI 36-45%) among pregnant women with asthma, based on 45 studies of mostly 'good' quality, and varied between countries and continents. The prevalence of ICS use was lower in clinical studies, in which women self-reported medication use, compared to clinical databases, where prevalence is based on dispensed prescriptions. This suggests that women fill their prescription, but do not necessarily use the medication or use it as prescribed during pregnancy. ICS prescription rates changed during pregnancy, with a decrease in the first trimester compared to pre-pregnancy, and an increase the second trimester compared to the first. However, few studies reported on ICS adherence during

pregnancy, all reporting self-reported (non-)adherence and only one additionally reported an objective measure. Self-reported non-adherence ranged from 39%-56%.

Although few studies reported on the pre-pregnancy period, the drop in ICS prescriptions suggest that ICS use during pregnancy is low. A study reporting on 10,302 adults with asthma showed ICS use ranged from 45-62% worldwide, with the lower proportion in the United States and higher proportions in Europe/Canada and the Asia-Pacific region[29], a similar pattern found in our study. In addition, it is unknown whether women in childbearing age who are planning to conceive are more diligent in controlling their asthma to be in best health for conception and pregnancy. Data from previous studies suggest that women with asthma may be under-treated during pregnancy. In the study of Ali et al.[30], 41% of pregnant women with asthma were using controller medication pre-enrolment, and after asthma assessment (including symptoms and lung inflammation measurement) at enrolment, the proportion of women with prescribed controller medication increased to 63%. In agreement, another study using found similar increases in ICS prescription rates, with asthma review and management during pregnancy (41% at enrolment, and 69% at end of study).[31] Another study found that even among pregnant women with moderate or severe asthma, based on National Heart, Lung and Blood Institute guidelines 1997, 13-21% was not using ICS. Furthermore, an observational study by Ibrahim et al. found 69% of pregnant women for whom ICS was indicated, based on the Global Initiative for Asthma (GINA) guidelines, did not receive ICS.[32] Therefore, we hypothesise that women with asthma are undertreated with controller medication during pregnancy.

The difference in ICS use prevalence between the continents may be related to health care accessibility or differences in asthma or perinatal guidelines that are followed. Asthma is more common in the lower socio-economic status segment of the population.[33] However, SES was not reported by all studies and therefore we cannot estimate the effect of SES on ICS use during pregnancy. Health care accessibility in the United States of America for this lower SES segment might be lower compared to European and Australian health care accessibility.[34] Therefore, ICS use among

American women during pregnancy might be lower than in other countries, due to their inability to purchase these medications. However, this issue is not limited to the lower income segment. Adults with above-average income reported financial barriers for access to care more often in the United States as adults in other developed countries.[34,35] The drop of ICS prescriptions was larger in the American database (-23%) compared to the drop in the European databases (pooled -8.5%), which may reflect a difference in clinical practice/ guidelines and/or the attitudes surrounding ICS use in pregnancy. This might also explain the lower prevalence of ICS reported based on American observational studies.

Our results show a drop in ICS prescription rate in the first trimester, despite prescription rates across the year before pregnancy remaining stable, in European and American databases.[6,7] The reason for this drop may be pregnancy. The number of dispensed ICS prescriptions in the first trimester of pregnancy lowered in the majority of included databases, with a pooled dispense rate decrease of 8.5%. This change in dispensed prescriptions is not in accordance with American and European asthma guidelines, which recommend pregnant women continue with their pre-pregnancy asthma treatment. The increase in ICS prescriptions from trimester one to trimester two, might reflect a loss/change in asthma control, with asthma exacerbations known to cluster around the end of the second trimester.[8,36,37] This hypothesis is supported by the observed increase in SABA prescriptions in the second trimester[6,7]; however, the rate of dispensed OCS prescriptions did not change within pregnancy. Most databases in the European study[7] did not capture hospital pharmacy prescriptions; with only the United Kingdom databases (CPRD and GDP) capturing some hospital inpatient prescriptions, and therefore the increase in OCS prescriptions may not be captured in these databases. In the American database[6] and the aforementioned UK based databases[7], an increase in OCS prescriptions was also observed in the second trimester. Therefore, the increase of ICS prescription rates during pregnancy may likely be because of asthma exacerbations or increased symptoms.

Our results revealed that some women had a change from ICS/LABA combination therapy to ICS mono therapy and that the proportion of women on ICS/LABA is smaller in most countries compared to ICS mono therapy. Although this is not in line with guideline recommendations, which recommend continuing with pre-pregnancy medication, this change, may be related to the safety categorisation of ICS medications during pregnancy. Budesonide (monotherapy) is categorised as A by the Therapeutic Goods Administration (TGA) in Australia (taken by limited number of pregnant women without increase in malformations of other harmful effects on the fetus), whilst combination therapies are categorised as B3 (taken by limited number of pregnant women without increase in malformations of other harmful effects on the fetus, animal studies have shown evidence of fetal damage but the significance is considered uncertain in humans).[38] More data on the safety of combination therapy during pregnancy is needed to re-evaluate the pregnancy-safety categorisations, and inform both the medical and general community regarding asthma medication use during pregnancy. [10]

Non-adherence may also be related to the drop in ICS prescription rates in pregnancy, i.e. women themselves may discontinue or reduce their medication because of their pregnancy. However, our results highlight the lack of studies examining asthma medication adherence during pregnancy, with only five studies reporting a measure of adherence. Non-adherence proportions ranged from 39% to 56%, which is higher than the 31% respiratory medication non-adherence reported in a review of 41 studies of pulmonary diseases.[39] All studies used self-reported adherence, which is likely subject to social desirability bias. The one study which also objectively measures adherence using MPR found a difference of 59% with self-reported adherence[25] indicating the decreased accuracy of self-reported adherence. Thus, there is a need for more objective measurement of medication adherence in studies, and/ or a validated tool to assess self-reported adherence, including cut-off values to determine non-adherence. From the limited data available, non-adherence to ICS medication during pregnancy appears high and may have adverse consequences for the health of both mother and child; therefore, non-adherence needs more attention in asthma research. It is important to

adequately educate pregnant women with asthma about their medications. This education has also been demonstrated to decrease ICS non-adherence.[26]

One of the strengths of this study is the systematic approach to reviewing the literature and the inclusion of a meta-analysis. Furthermore, this study addressed important questions that have not been previously examined, even in a general population. Another strength is the large number of studies including a large number of pregnant women with asthma (N=186,307) from 16 countries. We did not restrict the study population based on asthma severity; by including all asthma severities our pooled prevalence represents the average pregnant women with asthma population. Most of the included articles were of 'good' or 'moderate' quality. Only five (10%) of the included articles were assessed as 'Poor'. The main contributing reason was the population, with all but one study reporting on a selected population of pregnant women with asthma only or failing to report the study population source[40]. This study has several limitations. Due to the limited number of studies from, Asia[16,41], the Middle East[23,28,32] and South America[42], we were not able to provide a stable pooled prevalence for these continents. No studies from Africa were included in this systematic review. Furthermore, there were no database studies from Australia. Heterogeneity was high in the meta-analyses; however, this was expected since we included all studies reporting on ICS use during pregnancy even if this was only reported in the demographics of a study, regardless of time period. Another reason for the high heterogeneity is that the prevalence of ICS use was at any time during pregnancy and not restricted to a trimester. Other contributing factors may be a large variation in sample sizes, variation in asthma prevalence in countries and the use of different asthma and/or perinatal guidelines. We acknowledge that the prevalence of ICS use during pregnancy is confounded by time, and prevalence has increased after studies indicated the safety of ICS use during pregnancy. The few studies reporting on adherence all used different self-reporting methods (except for two studies from the same research group) to assess self-reported adherence and therefore the meta-analysis for non-adherence was limited to two studies.

In conclusion, the prevalence of ICS use among pregnant women with asthma worldwide is 41% and varies widely between countries and continents. However, prescription rates for ICS appear to change across pregnancy. More studies are needed to investigate ICS adherence during pregnancy in women with asthma.

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Table 1. Characteristics of included studies

Study	Country	Study Design	Study Population	Asthma Definition	ICS prevalence (n/N)	Changes in ICS use	Adherence to ICS	QA score
Ács et al. 2005[43]	Hungary	Observational population-based dataset	Pregnant women with and without bronchial asthma (BA)	Dx BA in medical records or self-reported	106 / 757	NA	NA	5
Al Ghobain et al. 2018[23]	Saudi-Arabia	Cross-sectional survey	Women in childbearing age with Hx asthma	Physician dx in any medical record	63 / 131	46.8% wanted to stop/ stopped ICS	NA	4
Ali et al. 2018[30]	Denmark	Single-arm intervention cohort study	Pregnant women with asthma attending outpatient respiratory clinic <18 weeks gestation	Dx according to GINA, current asthma Rx	521 / 1283	NA	NA	4
Amaral et al. 2017[44]	Portugal	Longitudinal study	Pregnant women with asthma and allergic rhinitis	Medical records Dx	27 / 42	NA	NA	5
Baarnes et al. 2016[25]	Denmark	Single-arm intervention cohort study	Pregnant women with asthma attending outpatient respiratory clinic <18 weeks gestation with current ICS prescription	Dx according to GINA, current asthma Rx	NA	NA	Self-reported and MPR	6
Bakhireva et al. 2005[45]	United States of America	Multicentre controlled cohort study	Pregnant women with asthma, <20 weeks gestation	Current Dx of asthma	438 / 654	NA	NA	4
Beau et al. 2017[15]	France	Observational Study	Pregnant women with asthma	At least two dispensed asthma Rx in year before	1331 / 2977	Switch from ICS/LABA to ICS mono therapy in early pregnancy	NA	5

				delivery				
Beckmann 2003[46]	United States of America	Retrospective chart audit	Pregnant women with asthma in tertiary care facility	Asthma recorded on delivery record	31 / 567	NA	NA	5
Bikov et al. 2012[47]	Hungary	Cross-sectional case-control	Pregnant and non-pregnant women with and without asthma	Dx according GINA guidelines	16 / 31	NA	NA	2
Blais et al. 2012[18]	Canada	Cross-sectional	Pregnant women with asthma, singleton deliveries, >=1 ICS prescription in 9 months before pregnancy.	Asthma Dx in RAMQ, ≥1 asthma Rx in two years prior to pregnancy	NA	29.5% discontinued ICS and an additional 19% reduced ICS dose during pregnancy compared to nine months pre-pregnancy	NA	5
Bracken et al. 2003[48]	United States of America	Prospective cohort	Pregnant women with and without asthma	Hx of physician Dx for asthma	144 / 872	NA	NA	4
Chambers 2003[10]	United States of America	Descriptive survey	Women with asthma in childbearing age	No description	NA	39% reduced or ceased asthma medication during pregnancy	NA	2
Charlton et al. 2015[49]	United Kingdom	Observational cohort	Pregnant women with asthma, singleton deliveries	Asthma Dx in medical record and ≥2 asthma Rx, or≥6 asthma Rx, in study period	10770 / 18120	NA	NA	5
Charlton et al. 2016[7]	United Kingdom, Norway, Netherlands, Denmark	Descriptive drug utilisation study	Pregnant women from seven European regions	Use of asthma Rx	NA	20% drop in asthma prescriptions during pregnancy compared to the year before	NA	5

	and Italy					pregnancy.		
Cossette et al. 2013[50]	Canada	Observational cohort	Pregnant women with asthma, singleton deliveries (live and still) (2 pregnancies/woman, most recent deliveries)	Asthma Dx in RAMQ, ≥1 asthma Rx in one years prior to pregnancy	4198 / 7376	NA	NA	5
De Araujo et al. 2016[42]	Brazil	Cross-sectional	Pregnant women with asthma (singletons)	Dx of asthma and referral to asthma clinic	73 / 103	NA	NA	3
Dombrowski et al. 2004[51]	United States of America	Prospective observational cohort	Pregnant women with and without asthma	Hx of physician-Dx (self-reported)	194 / 1739	NA	NA	4
Enriquez et al. 2006[6]	United States of America	Observational cohort	Pregnant women with asthma	ICD code on record	2445 / 8149	23% drop in ICS in first trimester	NA	5
Firoozi et al. 2009[19]	United States of America	Observational cohort	Pregnant women with asthma, singleton deliveries	ICD Dx and≥1 asthma Rx in two years prior or during pregnancy	4649 / 11258	44% using ICS preconception	NA	5
Fitzsimons et al. 1986[52]	United States of America	Observational cohort	Pregnant women with severe asthma	Chronic asthma of such severity that despite long term administration of theophylline ephedrine continuous administration of corticosteroids	21 / 51	NA	NA	2

				was needed to prevent hospitalisation				
Forinash et al. 2016[53]	United States of America	Prospective, quasi-experimental	Pregnant women with asthma ≥18yrs Excluding currently not prescribed any inhaler	Not defined	9 / 30	NA	NA	3
Garne et al. 2016[54]	Denmark	Cohort linkage study	Pregnant women in congenital anomaly registers in Norway, Wales and Denmark	Use of asthma Rx	12,240 / 19,510	NA	NA	5
Grzeskowiak et al. 2016[55]	Australia	Prospective cohort study	Pregnant women with asthma	Doctor Dx	61 / 189	NA	NA	4
Hansen et al. 2013[56]	United States of America	Observational cohort	Pregnant women with asthma	Asthma Dx during 180 prior to conception till delivery date	12973 / 38495	NA	NA	5
Hasegwa et al. 2015[57]	United States of America	Observational cohort	Pregnant women with asthma attending emergency department for asthma	History of physician Dx	25 / 89, 9 / 36	NA	NA	4
Ibrahim et al. 2019[32]	Qatar	Cross-sectional prospective	Pregnant women with asthma	Hx of physician Dx	41 / 79	NA	NA	4
Ivancsó et al. 2016[58]	Hungary	Cross-sectional	Pregnant women with asthma, excluding current smokers or >5 PY, any other chronic disease, acute infection, fetal infection, multi-fetal gestation	Dx according GINA guidelines	8 / 14	NA	NA	3

Källen et al. 2007[59]	Sweden	Cohort linkage study	Pregnant women with and without asthma	Use of asthma Rx	12,188 / 24,369	NA	NA	4
Kemppainen et al. 2018[60]	Finland	Observational cohort	Pregnant women with and without asthma	The right for justification of reimbursement for asthma medication based on strict criteria	13777 / 26674	NA	NA	5
Koo et al. 2017[17]	Republic of Korea	Observational cohort	Pregnant women with asthma	ICD Dx and asthma Rx or diagnostic testing for asthma in two years before deliery	NA	Drop in daily rank-sum values in early pregnancy compared to pre-pregnancy.	NA	4
Lee et al. 2016[16]	Republic of Korea	Observational cohort	Pregnant women with asthma Restricted to 1 pregnancy/woman	Definition 1: ICD-10 code J45 or J46 that was repeated with at least a 1 month interval; and (2) definition 2: definition 1 plus use of any asthma Rx at least once.	2967 / 5589	7.9% increase in ICS in second trimester compared to first trimester and 5.6% decrease in ICS in third trimester compared to second trimester.	NA	5
Lim et al. 2012[12]	Australia	Interviews	Pregnant women with asthma (Exclusion no asthma symptoms in past 10y)	not defined	15 / 23	NA	NA	4

Lim et al. 2014[22]	Australia	Single-blind randomised controlled trial	Pregnant women with asthma (Exclusion no asthma symptoms in past 10y)	not defined	32 / 58	32% reported cessation/reduction of medication since becoming pregnant.	Subscale of Beliefs and Behaviour Questionnaire – median scores of 8 and 7.5	4
Louik et al. 2010[61]	United States of America	Observational cohort	Pregnant women with asthma	Physician Dx	292 / 502	NA	NA	3
McCallister et al. 2011[24]	United States of America	Retrospective chart review	Women attending ED with acute asthma	Determined by treating clinician	30 / 123	NA	NA	5
Mihrshahi et al. 2003[62]	Australia	Randomised Controlled Trial	Pregnant women with family history of asthma	Patient reported	106 / 340	NA	NA	3
Murphy et al. 2005[27]	Australia	Prospective cohort study	Pregnant women with asthma	Doctors Dx	NA	NA	Self-reported non-adherent (missed≥20% last week dosages): 40%	4
Osei-Kumah et al. 2010[40]	Australia	Observational cohort	Pregnant women	not specified	198 / 359	NA	NA	2
Otsuka et al. 2005[41]	Japan	Retrospective chart review	Pregnant women with asthma	Not specified	8 / 193, 117 / 399	NA	NA	5
Palmsten et al. 2018[63]	United States of America	Observational cohort	Pregnant women with asthma	Self-reported Dx	88 / 172	NA	NA	4
Rejno et al. 2014[20]	Sweden	Observational cohort	Pregnant women with singleton gestation	Patient-reported, specialist Dx in database, two	NA	46% started ICS in first trimester.	NA	5

				asthma Rx in year before pregnancy				
Robijn et al. 2018[26]	Australia	Combination of 2 prospective cohorts and 2 RCTs	Pregnant women with asthma (1 cohort severe asthma excluded)	Patient reported physician Dx	35 / 85, 87 / 299, 195 / 511	NA	Self-reported non-adherent (missed≥20% last week dosages): 40%, 42% and 39%	4
Sawicki et al. 2012[3]	Australia	Survey	Pregnant women	Self-reported asthma	19 / 102	Before pregnancy 38 women used ICS, 50% drop in pregnancy. 39% always/often make changes to ICS treatment	NA	4
Schatz et al. 1988[64]	United States of America	Prospective cohort	Pregnant women with documented reversible obstructive airways disease	Clinical diagnosis from allergy clinic	37 / 366	NA	NA	5
Smy et al. 2016[65]	Canada	Retrospective observational cohort	Pregnant women with asthma	Not specified	56 / 87	NA	NA	4
Stenius-Aarniala et al. 1996[37]	Finland	Prospective cohort	Pregnant women with asthma treated at in pulmonary divisions	ATS and American College of Chest Physicians asthma criteria 1975	297 / 504	NA	NA	2
Tegethoff et al. 2012[66]	Denmark	National cohort	Pregnant women with singletons with asthma	Women's self-report	1231 / 4083	NA	NA	4

Vasilakis et al. 2013[67]	United Kingdom	Matched cohort	Singleton offspring of mothers with asthma	Dx of asthma any time before or during pregnancy and at least 1 Rx around conception	4735 / 7911	NA	NA	5
Wright et al. 2010[68]	United States of America	Prospective birth cohort	Expectant families with mother or father with AR, eczema, and/or asthma in poverty area	Not defined	54 / 307	NA	NA	4
Yilmaz et al. 2013[28]	Turkey	Observational cohort	Pregnant women with asthma admitted for delivery.	Hx of physician Dx, use of asthma Rx in past year	13 / 32	NA	Self-reported irregular use: 56%	4
Zairina et al. 2016[69]	Australia	Prospective cohort	Pregnant women with and without asthma, singleton pregnancy	Self-reported and used asthma Rx in 12 months before or during current pregnancy	8 / 20	NA	NA	3
Zetstra et al. 2013[70]	Netherlands	Observational cohort	Pregnant women with asthma	At least 1 asthma Rx between 1 year prior to conception to 6 months after birth	184 / 647	NA	NA	5

Hx History, Dx Diagnosis, Rx Medication; NA Not Applicable. MPR Medication Possession Rates

Table 2. Prevalence of inhaled corticosteroid use in pregnant women with asthma

Continent	N studies	N participants	Estimate (95% CI)	I^2
Australia				
Clinical Studies	8[3,12,22,26,40,55,62,69]	1986	39 (32-47)	91.3
Database Studies	0	NA	NA	
Overall	***8***	***1986***	***39 (32-47)***	***91.3***
Europe				
Clinical Studies	5[30,37,44,47,58]	1874	54 (41-66)	93.0
Database Studies	9[7,15,43,54,59,60,66,67,70]	105,048	48 (42-54)	99.7
Overall	***12***	***106,922***	***49 (44-55)***	***99.6***
North America				
Clinical Studies	13[24,45,46,51–53,57,61,63–65,68]	5595	32 (21-43)	99.1
Database Studies	4[6,19,50,56]	65,413	40 (31-50)	99.8
Overall	***17***	***70,873***	***34 (27-41)***	***99.6***
Other				
Clinical Studies	5	937		
Brazil	1[42]	103	71*	NA
Japan	1[41]	592	11 (9-14)[#]	NA
Qatar	1[32]	79	52*	NA
Saudi Arabia	1[23]	171	78*	NA
Turkey	1[28]	32	41*	NA
Database Studies				
Republic of Korea	1[16]	5589	53*	NA
Overall	***6***	***6526***		
Worldwide				
Clinical Studies	31	10,392	39 (32-46)	98.8
Database Studies	14	175,915	46 (40-53)	99.9
Overall	***45***	***186,307***	***41 (36-45)***	***99.7***

[*]One study only, no confidence interval; [#] Two datasets in one study; NA not applicable

Table 3. Databases used for medication prescriptions for changes in prescriptions around pregnancy			
Country/Region	Database for Prescriptions		Source of Prescriptions
UK[7]	Clinical Practice Research Datalink	CPRD	GP prescriptions
Wales[7]	The General Practice Dataset	GPD	GP prescriptions
Denmark[7]	Danish Prescription Registry	DPR	Pharmacy dispensing
Norway[7]	Norwegian Prescription Registry	NPR	Pharmacy dispensing
Italy/Tuscany[7]	Tuscany Prescription Database	TPD	Pharmacy dispensing
Italy/Emilia Romagna[7]	Emilia-Romagna Prescription Database	ERPD	Pharmacy dispensing
Netherlands[7]	IADB.nl database	IADB	Pharmacy dispensing
France[15]	EFEMERIS	EFEMERIS	Pharmacy dispensing
Sweden[20]	Swedish Prescribed Drug Register	SPDR	Pharmacy dispensing
Korea[16,17]	Health Insurance Review and Assessment	HIRA	Pharmacy dispensing
US/Tennessee[6]	Tennessee Medicaid	TM	Pharmacy dispensing
Canada/Quebec [18,19]	Régie de l'Assurance-Maladie du Québec (RAMQ)	RAMQ	Community Pharmacy dispensing

Table 4. Prevalence of dispensed inhaled corticosteroid prescriptions among women before, during and after pregnancy in three months intervals.	
Time period	Prevalence (95%CI)
Q1 (12-9 months pre-pregnancy)	2.29 (1.67-2.91)
Q2 (9-6 months pre-pregnancy)	2.35 (1.74-2.97)
Q3 (6-3 months pre-pregnancy)	2.33 (1.70-2.95)
Q4 (3-0 months pre-pregnancy)	2.29 (1.72-2.86)
T1 (Trimester 1)	2.10 (1.56-2.63)
T2 (Trimester 2)	2.30 (1.63-2.98)
T3 (Trimester 3)	2.05 (1.45-2.65)
Q5 (0-3 months post-pregnancy)	1.83 (1.24-2.42)
Q6 (3-6 months post-pregnancy)	2.10 (1.42-2.77)
Q7 (6-9 months post-pregnancy)	2.32 (1.59-3.06)
Q8 (9-12 months post-pregnancy)	2.50 (1.69-3.30)

Figure legends

Figure 1. Flow diagram of included studies

Figure 2. Prevalence of inhaled corticosteroid use among pregnant women with asthma in Australia, Europe, North America and worldwide, based on clinical studies (triangle), database datasets (square) and both types combined (circle). * Worldwide includes all studies regardless of continent.

Figure 3. Proportion of ICS/LABA combination therapy among pregnant women using ICS containing controller medication. (dotted line indicates pooled proportion for Australia, Europe and North America)

Figure 4. Changes in dispensed inhaled corticosteroid prescriptions before, during and after pregnancy in three-month intervals.

Supplement

Table S1. Search terms

Quality Assessment

Figure S1. Forest plot of ICS use among pregnant women with asthma grouped by continent.

Figure S2. Forest plot of ICS use among pregnant women with asthma in datasets, grouped by continent.

Figure S3. Forest plot of ICS use among pregnant women with asthma in clinical studies, grouped by continent.