The PRIDE-Asthma cohort:
insight into the short- and long-term effects of asthma and asthma medication during pregnancy

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1. Background

In the last decades, the prevalence of asthma increased substantially and is still increasing in many countries.[1] Approximately 8% of pregnant women have asthma, making it one of the most common chronic conditions during pregnancy.[2] Systematic reviews showed that pregnant women with asthma have an increased risk of pregnancy complications and adverse birth outcomes, including gestational diabetes, preeclampsia, preterm birth, and low birth weight.[3,4] As particularly women with poor levels of asthma control are at increased risk of adverse outcomes, international recommendations emphasize the importance of adequate pharmacological treatment, stating that poor asthma control is associated with higher risks for the unborn child compared with asthma medication use.[5]

Multiple studies using large population-based databases, however, have shown that dispensing rates for asthma medication decline during pregnancy,[6,7] suggestive of non-adherence and/or discontinuation of asthma medication. Indeed, in a small-scale study, almost 30% of Dutch pregnant women discontinued or reduced the use of long-acting bronchodilators and combination preparations of an inhaler corticosteroid and long-acting bronchodilator when becoming pregnant.[8] This may lead to poor levels of asthma control and exacerbations. Although the reasons for non-adherence are generally unknown, lack of information, perception of risks of asthma medication during pregnancy, previous experiences, and fluctuations in severity of asthma are hypothesized to play a role.[9-11] More detailed information on adherence among pregnant women with asthma is scarce, because methodological limitation (e.g., cross-sectional or retrospective designs, no intra-individual comparisons, lack of data on level of asthma control, use of non-validated measurement instruments, and small study populations) hamper the interpretation of previous studies. Furthermore, these studies were unable to take timing of actual medication use in relation to level of asthma control and exacerbations into account, stressing the need for clinical observational studies.[12] More insight into the reasons why pregnant women do not adhere to treatment recommendations may improve counseling by care providers, resulting in better adherence to asthma medication during pregnancy.

It is often assumed that the use of asthma medication during pregnancy is safe, but robust data on the safety of a number of frequently used medications, including salbutamol, salmeterol, fluticasone, and combination preparations, is scarce.[13-16] To further complicate things, multiple biological mechanisms underlying possible associations between maternal asthma and negative birth outcomes have been proposed, such as maternal and fetal hypoxia and changes in placental vascular function,[17,18] a common pathway leading to hyperactivity of smooth muscles in lungs and uterus,[19] and infiltration of mast cells.[20]

Previous studies on the possible detrimental effects of asthma and asthma medication during pregnancy suffered from methodological limitations, including retrospective data collection, small study populations, lack of data on adherence, and the inability to adjust for confounding factors. Systematic reviews and meta-analyses conclude that asthma during pregnancy is associated with a number of pregnancy complications and perinatal outcomes, but also that valid data on medication use are urgently needed to generate more evidence on the safety of asthma treatment during pregnancy.[3,4,16,21] Knowledge on possible associations of asthma or asthma medication with long-term outcomes is also lacking. Furthermore, previous studies were mainly conducted in Anglo-Saxon countries, particularly the United States. Due to differences in prescribing behavior between these countries and The Netherlands, with for example better access to care and easy accessibility to inhalation corticosteroids in our country, it is questionable whether results from previous studies are also applicable to Dutch asthma patients.

2. Objectives

Counseling of pregnant women with asthma is currently hampered by a lack of detailed data on the use of asthma medications and the effects of medication use and the asthma itself on pregnancy outcomes. Additionally, adherence to asthma medication varies among pregnant women and factors that may influence adherence are largely unknown. Therefore, the aims of this project are:

a) To initiate a focus cohort of pregnant women with asthma to support this project and future studies.
b) To design and validate a questionnaire to assess adherence to asthma medication use during pregnancy.
c) To assess reasons for self-initiated discontinuation of asthma medication and changes in asthma medication use during pregnancy:
    i. Do pregnant women discontinue or change their asthma medication at specific moment before conception or during pregnancy? If so, who initiated this? And which factors (e.g., risk perception, beliefs about medication use, level of education) are associated with adherence during pregnancy?
    ii. What are the trajectories of level of asthma control throughout pregnancy and which factors are associated with improvements and deteriorations?

In addition to answering the research questions related to aim C, the focus cohort will be used in multiple future studies on the short- and long-term effects of maternal asthma and the use of asthma medication during pregnancy. This is feasible due to the embedding of this project in the PRegnancy and Infant DEvelopment (PRIDE) Study, an ongoing prospective cohort study among pregnant women and their offspring, with follow-up throughout childhood.[22]

3. Methods

Data collection for the PRIDE Study started with a pilot phase in July 2011, followed by national recruitment since 2016. Pregnant women are invited for participation just before or during the first prenatal care visit (gestational age 8-12 weeks) by participating midwives and gynecologists. Since late 2016, participants are also recruited through the 'Moeders voor Moeders' initiative. Exclusion criterion is <18 years of age. To participate, pregnant women go to the study website (www.pridestudy.nl) and give informed consent for the use of questionnaire data, linkage with registries, and/or obtaining medical records and pharmacy records (median gestational age at enrollment: 10 weeks). Subsequently, participants complete the baseline questionnaire (Q1), followed by questionnaires at gestational weeks 17 (Q2) and 34 (Q3), 2 (Q4) and 6 (Q5) months after the estimate date of delivery, and biannually thereafter. With these Web-based questionnaires, information is obtained on (among others) medical and obstetric history, lifestyle factors, medication use, birth outcomes, and child health, for which multiple validated questionnaires are being used. Currently, over 13,000 pregnancies are included in the PRIDE Study.

3.1. Study population

For this project, a focus cohort of at least 250 pregnant women with asthma, entitled the PRIDE-Asthma cohort, will be established within the PRIDE Study. Using this approach, we will be able to prospectively collect unique, detailed information on the trajectory of severity of asthma throughout pregnancy and its

treatment and link this to future maternal and child health outcomes. These women will be selected when they indicate in Q1 that they ever received a diagnosis of asthma and/or used asthma medication in the previous 4 months (validated approach:[23] sensitivity 86%, specificity 99%). They will be sent the patient information leaflet and informed consent form (Appendix 1) by regular mail. Recruitment is scheduled to start in September 2023. To improve recruitment rates, we aim to advertise the study through the Lung Foundation Netherlands and social media pages targeting pregnant women with asthma.

In addition to the longitudinal cohort, a separate, international, cross-sectional study will be conducted to evaluate a novel adherence scale that will be used for data collection in the focus cohort (see section 3.2.1.1.).

3.2. Data collection

In short, women will be asked to complete four Web-based asthma-specific questionnaires (at enrollment in the focus cohort, at gestational weeks 23 and 35, and 2 months post-partum), the Asthma Control Test (every four weeks throughout pregnancy and two times post-partum), and a medication diary (throughout pregnancy and 2 months post-partum). In addition, consent is asked to obtain data on medical history (general practitioner and pulmonologist) and medication use (pharmacy).

3.2.1. Questionnaires

We will use the electronic data capture system Castor (www.castoredc.com) for administration of the questionnaires. Castor guarantees the highest level of security for the data stored. Data storage is compliant with all relevant regulations, including ICH E6 Good Clinical Practice, GDPR, HIPAA, FDA 21 CRF Part 11, ISO 27001, and ISO 9001.

The baseline questionnaire, which will be sent immediately after we receive the informed consent form for the focus cohort, is the most extensive questionnaire, with an estimated completion time of 15 minutes. The full questionnaire is shown in Appendix 2, covering the following topics:

1) My asthma
   Questions on asthma phenotype, exacerbations, Asthma Control Test (see section 3.2.2), and quality of life (EQ-5D-5L).[24,25]
2) My asthma medication
   Changes in medication use due to pregnancy, the current satisfaction with inhalation medication (based on the Satisfaction with Inhaled Asthma Treatment Questionnaire [SIATQ]),[26] and the novel Adherence to Asthma Medication in Pregnancy Scale (AAMPS, see section 3.2.1.1).
3) Your perception of risk during pregnancy
   Assesses the woman's perception of harmfulness for the (unborn) child of five items: asthma maintenance medication, asthma rescue medication, cranberry, alcohol, and maternal asthma itself. The perception of harmfulness is rated on a 10-point scale according to three different outcomes: child development (e.g., ADHD), miscarriage, and birth defects. The more extended version of this questionnaire has previously been used in a multinational study.[27] Asthma-specific risk questions were also used in a previous (unpublished) study from the UMC Groningen.
4) Your views about medication in pregnancy
   Six pregnancy-specific statements of the Pregnant Women's Belief about Medication Scale, a set of statements specifically designed for medication use during pregnancy.[28]

5) Your needs for information
   Three questions which capture information sources that the woman used during pregnancy and the level of health literacy, as well as four propositions.
6) A comments section to allow women to provide any additional information on asthma medication during pregnancy that they consider important.

The follow-up questionnaires only assess relevant subsections (i.e. those components that may change over the course of pregnancy) that are not covered in the other methods of data collection, including exacerbations, quality of life, satisfaction with inhalation medication, and AAMPS, as well as the 10-item Edinburgh Depression Scale.[29,30] As such, the estimated completion time is less than 10 minutes.

3.2.1.1. Adherence to Asthma Medication in Pregnancy Scale

The Adherence to Asthma Medication in Pregnancy Scale (AAMPS) is a 15-item scale that was conceptualized and drafted by the study team with the aim to measure adherence to asthma medication during pregnancy. The item formulation and response format are intended to capture and assess pregnant women's behavior concerning asthma medication use in an effective manner. The AAMPS is formulated in Dutch (question 39 in the baseline questionnaire [Appendix 3]) and English. Formulation of the AAMPS items is based on the Adherence to Antidepressant in Pregnancy Scale developed by colleagues at the University of Oslo (personal communication) and the Test of Adherence to Inhalers (TAI), which is the recommended patient-reported adherence measure.[31] The AAMPS will be tested for face validity by a representative sample of 5 pregnant women with asthma. These women will not be in the final sample.

The level of adherence is calculated by summarizing points to answers on the AAMPS. A response consistent with the lowest adherence is coded as 0, whereas a response reflecting the highest adherence is coded as 4 (frequency questions) or 2 (yes/no questions). The scale contains both negatively and positively worded items, and reverse scoring is performed for the negatively worded items for the purpose of statistical analysis. Total scores on the preliminary AAMPS range between 0 and 54, with a higher score indicating better adherence to asthma medication.

For field-testing of the AAMPS, we will invite women who are currently pregnant or gave birth in the last 12 months and who are currently using or used asthma medication during pregnancy. Invitations to participate will be distributed through social media, online pregnancy-related websites and forums, and our network of prenatal care providers and pulmonologists. Participants in the PRIDE Study who fulfill the inclusion criteria (but not the inclusion criteria for participation in the PRIDE-Asthma cohort) will be invited as well. Recruitment is scheduled to take place between September 1, 2023 and October 30, 2023, aiming at at least 300 participants. Participants will be asked to complete one questionnaire, which consists of the baseline questionnaire of the PRIDE-Asthma cohort, complemented with additional questions on demographics (i.e., age, level of education, parity, maternal status [gestational age or the age of the infant], concomitant medication use, smoking status, and type of physician for asthma check-ups).

In order to contribute to increased applicability/generalizability and a more comprehensive understanding of adherence to asthma medication, data will also be collected at an international level to include different perspectives and to be able to make cross-cultural comparisons. Next to The Netherlands, envisioned participating countries are Norway, Belgium, Switzerland, Ireland, Italy, France, and Serbia. Collaborators from participating countries will translate the AAMPS and questionnaire for this cross-sectional study into

the respective countries' official languages and perform back-translation to ensure the highest alignment across translations. We aim to include at least 250 women per participating country. The collaborators will be responsible for IRB approval in their own countries.

3.2.2. Asthma Control Test

The Asthma Control Test (ACT) is a brief, easy to administer, patient-based index of asthma control.[32] It assesses the level of asthma control in the previous four weeks. It consists of five items:

1) During the last 4 weeks, how much of the time has your asthma kept you from getting as much done at work, school, or home?
   All of the time | Most of the time | Some of the time | A little of the time | None of the time
2) During the last 4 weeks, how often have you had shortness of breath?
   More than once a day | Once a day | 3 to 6 times a week | Once or twice a week | Not at all
3) During the last 4 weeks, how often have your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) woken you up at night or earlier than usual in the morning?
   4 or more nights a week | 2 to 3 nights a week | Once a week | Once or twice | Not at all
4) During the last 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as salbutamol)?
   3 or more times per day | Once or twice per day | 2 or 3 times per week | Once a week or less | Not at all
5) How would you rate your asthma control during the last 4 weeks?
   Not controlled at all | Poorly controlled | Somewhat controlled | Well controlled | Completely controlled

In this project, the official Dutch translation of the ACT will be administered online every four weeks during pregnancy and in the first 8 weeks after delivery. The ACT yields a score between 5 and 25, with a higher score indicating better levels of asthma control.

3.2.3. Medication diaries

To obtain data on medication use with sufficient granularity to answer the research questions, paper-based medication diaries will be administered. These will replace the questions on medication use in the regular PRIDE Study questionnaires to decrease participant burden. Individual diaries cover a time period of six weeks, collecting information on the exact name of the medication, daily dose, and time period of use. On the first page, respondents can write down the name of any medication used on a daily basis, with deviations on the separate days. They will be sent a new diary every six weeks until 8 weeks after delivery to increase completion rates, with a reminder if the dairy is not returned within two weeks. These diaries have been used in previous studies embedded in the PRIDE Study.[33,34]

3.3. Statistical analyses

3.3.1. Descriptive analyses

Sociodemographic and health characteristics of the study population will be described and summarized as counts and proportions, mean and standard deviation, or median and interquartile range as appropriate. Missing data will be explored.

3.3.2. Evaluation of the AAMPS

Initial evaluation of the AAMPS will take place in the cross-sectional study sample of women not included in the PRIDE-Asthma cohort. The analyses will be performed for the complete study population from all participating countries, as well as stratified by pregnancy status (currently pregnant versus post-partum) and by country.

3.3.2.1. Validity analysis – Principal Component Analysis

Principal component analysis (PCA) will be conducted to extract the important information (underlying factors) from the questions in the AAMPS and to express this information as a set of new variables called principal components. Principal components represent attitudes and beliefs that captured the most variance across the 15 different scale items. The data will be tested to ensure they meet the requirements for PCA using the Kaiser-Meyer-Olkin measure of Sampling Adequacy (intended value >0.5) and Bartlett's test of sphericity (intended value ≤0.05 of the significance level).[35] We will only keep factors with eigenvalues >1.[36] After the factors have been determined, rotation of the retained factors will be performed (varimax rotation) to help clarify the relationship among factors, simplifying the loadings of items and identifying the factor upon which the data loads.[37] Factors will be deployed into subscales according to where their loadings are. The association between individual factors as well as between factors and the whole scale will be evaluated with the Pearson's or Spearman correlation coefficient.

3.3.2.2. Reliability analysis – internal consistency

Cronbach's alpha coefficient will be calculated and used as a measure of internal consistency of the AAMPS indicating how closely related a set of items in the scale are as a group. In general, a Cronbach's alpha coefficient of 0.70 or higher is considered as "acceptable". Very high reliability (0.90 or higher), however, is not necessarily desirable, as this indicates that the items may be redundant.[38] Cronbach's alpha coefficient will also be determined for each factor of the scale separately.

3.3.2.3. Construct validity

We will determine associations between scores on the AAMPS and existing validated instruments to establish the scale's construct validity. We will calculate the Pearson's or Spearman correlation coefficient to estimate the association between the level of asthma medication adherence according to the AAMPS and scores on the ACT and modified SIATQ.

3.3.2.4. Association analysis – factors related to adherence to asthma medication

To identify factors related to low adherence, the AAMPS score will be analyzed both as a continuous and as a binary outcome (cut-off value to be established in this project). Factors that will be considered include:

- Socio-demographic factors
- Maternal health and medication-related factors
- Concomitant medication use
- Beliefs about medication
- Risk perception of different substances and maternal asthma during pregnancy.

We will apply univariable and multivariable linear (continuous AAMPS score) and logistic (binary AAMPS score) regression analyses to estimate the associations. Depending on the patterns of missingness, we will conduct a complete case analysis or impute missing values.

3.3.3. Asthma medication use patterns and adherence

Discontinuation of and switches in asthma medication use before and during pregnancy will be described and summarized using basic statistics. Depending on the outcomes, this may be visualized using treatment pathways or Sankey plots. Univariable and multivariable regression analyses will be used to estimate associations between adherence and the factors assessed in the questionnaires.

3.3.4. Trajectories of level of asthma control

Unsupervised clustering methods will be used to identify subgroups of women with similar trajectories of levels of asthma control throughout pregnancy and the post-partum period. These trajectories, as well as potential changes in the trajectories (improvement or deteriorations), will be linked to granular asthma medication use data from the diaries and other time-varying circumstances, depending on the gestational age, using univariable and multivariable regression analysis.

4. Ethical considerations

Participation in the PRIDE-Asthma cohort and the cross-sectional study for evaluation of the AAMPS is completely voluntary and participants may withdraw at any moment. Paper-based (PRIDE-Asthma cohort) and digital (cross-sectional study) informed consent will be obtained. For the cross-sectional study, participants may opt-in for a price draw (5 Bol.com vouchers of €20). No other incentives for participation will be available.

Although this study is not subject to the Medical Research Involving Human Subjects Act (WMO), this study will be submitted for review to the CMO Radboudumc. Data protection will receive maximal attention. The Castor platform is fully equipped to collect the data according to the current guidelines and regulations. The analytical files will not contain data that may identify the research participant. All statistical analyses will be conducted in the Digital Research Environment (DRE, www.mydre.org).

5. Privacy

Data protection will receive maximal attention. The Castor platform is fully equipped to collect the data according to the current guidelines and regulations. The analytical files will not contain data that may identify the research participant. All statistical analyses will be conducted in the Digital Research Environment (DRE, www.mydre.org).

Data collection in the cross-sectional study will be anonymous, unless the participant provides the email address for participation in the price draw. The e-mail address will be used for that purpose only and will not be included in the analytical filesFor the PRIDE-Asthma cohort, collection of personal identifiable data is necessary for data collection, but will not be stored in Castor or any analytical files.

6. Publication

We aim to publish at least 3 Open Access publications with the data collected in this project, focusing on:

- Design and validation of the AAMPS.
- Adherence to asthma medication and patterns of asthma medication use throughout pregnancy and the post-partum period.

- Trajectories of level of asthma control throughout pregnancy and the post-partum period.

The AAMPS will be made freely available for research purposes. In addition, the PRIDE-Asthma cohort will be used in dozens of future projects linking maternal asthma and asthma medication use during pregnancy to adverse maternal and child health outcomes through embedding in the PRIDE Study.

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