Challenges in the successful management of asthma during conception, pregnancy and delivery

Elisabeth J. Gade[1], Casper Tidemandsen[2], Anne V. Hansen[2], Charlotte S. Ulrik[2,3] and Vibeke Backer[3,4]

[1]Dept of Obstetrics and Gynecology, Roskilde Hospital, Copenhagen, Denmark. [2]Dept of Respiratory Medicine, Copenhagen University Hospital-Hvidovre, Copenhagen, Denmark. [3]Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. [4]Dept of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, Copenhagen, Denmark.

Corresponding author: Vibeke Backer (backer@dadlnet.dk)

Check for updates

Shareable abstract (@ERSpublications)
Management of asthma in pregnant women with asthma should follow the general guidelines for good clinical practice. Well-controlled asthma throughout pregnancy is the key to avoiding complications during pregnancy and delivery. https://bit.ly/3OHHxF5

Cite this article as: Gade EJ, Tidemandsen C, Hansen AV, *et al*. Challenges in the successful management of asthma during conception, pregnancy and delivery. *Breathe* 2022; 18: 220013 [DOI: 10.1183/20734735.0013-2022].

Copyright ©ERS 2022

Breathe articles are open access and distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0.

Received: 9 Feb 2022
Accepted: 22 June 2022

Abstract

Asthma and infertility are the most common disorders among women of reproductive age. Time to pregnancy is prolonged in women with asthma, and importantly, age seems to be a more important risk factor regarding fertility in women with asthma compared to women without asthma. Some data have shown a higher frequency of miscarriages in women with asthma, although the data are conflicting on this issue as studies have observed no association between asthma and pregnancy loss. Furthermore, studies have shown no negative effect of asthma on the total number of offspring. Pregnancy may, thus, have a significant impact on women with asthma, as well as on their offspring.

The age of the women has an important impact on ability to conceive, but also for the pregnancy itself, with higher risk of uncontrolled asthma as well as asthma exacerbations with increasing age. Well-controlled asthma decreases the risk of maternal and fetal complications, while poorly controlled and undertreated asthma is associated with a range of risks for both mother and fetus. Asthma treatment should follow the general guidelines for asthma therapy, irrespective of pregnancy status, including treatment with inhaled corticosteroids, β_2-agonists and muscarinic antagonists. Targeted treatment with biologics for severe asthma seems to be without important adverse effects. The use of systemic corticosteroids may be associated with adverse events during the first trimester; however, an exacerbation with the associated risk of hypoxaemia is worse for the fetus. Best possible asthma control may be achieved using repeated measurements of fractional exhaled nitric oxide (F_{ENO}), as the use of F_{ENO} compared with symptoms registration only has been shown to reduce exacerbation rate.

In conclusion, women with asthma should be encouraged to conceive at an early age, might experience miscarriages, but the number of offspring are the same as in women without asthma. Well treated asthma is important for the well-being of both the mother and the unborn fetus.

Introduction

Asthma is one of the most common chronic diseases among women of reproductive age with a prevalence up to 14% depending on geographical region [1–3]. The disease is known to be a potential important risk factor for adverse outcomes for both women and their offspring. Pregnancy may have a significant impact on the manifestations of asthma. Traditionally, it is agreed that one-third of women with asthma, respectively, experience improvement, no change and deterioration of their asthma during pregnancy [4–6]. However, in a recent study by Stevens *et al.* [7] the subgroup with improvement of asthma during pregnancy was not observed. Instead, they found that a larger group of asthmatic women had worsening of their asthma during pregnancy (40%) [7]. A limitation might be that some women with asthma are

followed by their own doctor, and the state of illness might not be reported, and therefore the effect of asthma on pregnancy outcome might be difficult to measure.

There are at least three periods of a woman's reproductive life where asthma may be an important factor: during conception, pregnancy and post-partum. This review will focus on these three periods, and the possible issues facing clinicians working within this area.

Time to pregnancy and impaired fertility in women with asthma

Women with asthma seem to have disadvantages during conception, as they have a prolonged time to pregnancy (TTP) and more often need fertility treatment to achieve a successful pregnancy [8, 9]. It is at present incompletely understood how asthma is associated with infertility, also because asthma does not seem to negatively affect the total number of offspring [10].

Both asthma and infertility are common chronic diseases in women of reproductive age and infertility seems to be on the rise worldwide. Infertility has been estimated by the World Health Organization (WHO) to affect 48 million couples and 186 million individuals globally [11–13]. A recent Danish study investigating causes of infertility found that 58% and 25%, respectively, of women initiating intrauterine insemination and assisted reproductive technology had unexplained or idiopathic infertility [14]. Idiopathic or unexplained infertility may be related to unrecognised underlying conditions such as asthma. The true prevalence of impaired fertility among women with asthma is unknown but may be higher than currently assumed.

Several factors have been deemed important concerning the fertility of women with asthma. Asthma is an inflammatory disease, characterised by both airway and systemic inflammation, reversible airflow limitation, with or without atopy, and airway hyperresponsiveness (AHR). The phenotype of asthma and the severity of airway inflammation may be of importance for fertility, as previous studies have shown that age of the woman, non-atopic asthma and no use of inhaled corticosteroid (ICS) have a negative impact on fertility [9, 10, 15–17]. It has been hypothesised that the systemic inflammation may affect the reproductive organs, including the endometrium, and thereby have an impact on various phases of the reproductive cycle, not least the implantation in the uterus. In women with unexplained infertility, Gade *et al*. [18] investigated the uterine lining during implantation in women with asthma and reported lower levels of vascular endothelial growth factor (VEGF) in those being non-atopic, whereas atopic asthmatic females had levels similar to controls. Lower levels of VEGF might have a negative impact on the receptivity of the endometrium and thereby TTP and pregnancy rate. This might indicate that atopic status affects fertility of women with asthma differently.

Age seems to be a more important factor regarding fertility in women with asthma compared with non-asthmatic women. In 2016, Gade *et al*. [15] reported that the negative effect asthma had on TTP increased with age, especially at ⩾35 years, which is supported by the findings of Tata *et al*. [10]. Age has also been linked to a higher need for fertility treatment among asthmatic females. In a case–control study by Hansen *et al*. [9] of women with live births, the need for fertility treatment increased among women with asthma ⩾35 years compared with the controls (OR 2.12, 95% CI 1.47–3.07). These findings are supported by observations by Sheiner *et al*. [16] from a retrospective population-based study. Furthermore, Gade *et al*. [15] showed that in women with unexplained infertility those having asthma were less likely to conceive than non-asthmatic women, especially when older than 35 years.

Miscarriages, age and asthma control during pregnancy

In the general population, about one in four desired pregnancies end in spontaneous abortion [19]. A pregnancy loss is defined as a spontaneous abortion prior to 22 weeks of gestation [20]. The earliest study examining pregnancy outcomes in asthma reported that women with asthma experience an increased number of pregnancy losses [21]. Since then, several studies have reported that women with asthma have a higher incidence of pregnancy losses compared with women without asthma [22–27]. However, the available data are conflicting as other studies have observed no association between asthma and pregnancy loss [28–30]. Studies found an increased risk of one spontaneous abortion in women with asthma compared with women without asthma (OR 1.41, 95% CI 1.33–1.49) [27]. The same study reported that uncontrolled asthma increased the risk of a spontaneous abortions by 26% compared with well-controlled asthma [27]. Furthermore, a meta-analysis including both retrospective and prospective studies found an increased risk of pregnancy loss among those with asthma [26]. In line with this, a nationwide Finnish registry-based cohort study found an association between pregnancy loss and maternal asthma [25]. The inconsistent findings concerning the association between asthma and pregnancy loss may be caused by study heterogeneity, as there are differences with regards to sample size, design, registry-based and clinical

TABLE 1 Adverse outcomes related to asthma during fertility and pregnancy

Mother	Perinatal	Fetus
Subfertility	Preterm birth	Low birthweight
Spontaneous abortion	Increased perinatal mortality	Small for gestational age
Exacerbations		Increased risk of asthma
Pre-eclampsia		Neonatal hospitalisation
Gestational diabetes		
Placental abruption		
Post-partum haemorrhage		
Caesarean section (planned and acute)		

studies, and retrospective and prospective studies. There is also variation in the included cofounders, the most frequent being age, parity and tobacco consumption.

It is well documented that higher age at pregnancy, especially maternal age, is associated with an increased risk of adverse events in pregnant women without asthma [31, 32]. In keeping with this, increasing age among women with asthma is associated with a higher risk [33], as higher maternal age seems to be linked to a higher risk of uncontrolled asthma during pregnancy, which in turn has been linked to poor perinatal outcomes [33]. Thus, the age of the woman has an important impact on her ability to conceive, but also on the pregnancy itself, with a higher risk of uncontrolled asthma and asthma exacerbation.

Pregnancy complications and perinatal outcomes among asthmatic women

Well-controlled asthma decreases the risk of maternal and fetal complications (table 1), while poorly controlled and undertreated asthma is associated with a range of risks for both mother and fetus [34].

Approximately a quarter of pregnant women with asthma have an emergency visit or hospitalisation during their pregnancy, with a higher risk during the second and third trimesters [35]. The higher risk of asthma exacerbations is related to the pre-pregnancy severity of asthma, inappropriate/non-compliance with asthma medication use, smoking, obesity, gestational weight gain [36], and inadequate prenatal care (table 2).

There are both short- and long-term risks to the mother and fetus caused by poorly controlled maternal asthma.

In addition, women with asthma have increased risks related to the unborn infant, including perinatal asphyxia, small for gestational age (SGA), preterm birth and fetal mortality in unobserved pregnancies. Furthermore, the risk of fetal growth restriction and preterm birth is significantly increased if maternal asthma is combined with cigarette smoking or second-hand smoke exposure [37, 38]. In women with asthma a higher risk of obstetric complications, such as gestational diabetes (RR 1.39, 95% CI 1.17–1.66), pre-eclampsia (OR 1.14, 95% CI 1.06–1.22) and caesarean section rate (RR 1.31, 95% CI 1.22–1.39), is found [34, 39, 40].

Asthma and allergy management during pregnancy and birth

The increased risks to the mother and the fetus can be reduced by optimised management of asthma and allergic rhinitis during pregnancy. The challenge is that women with asthma often discontinue their treatment due to anxiety about the risk of adverse events due to drug exposure for the developing fetus [41].

TABLE 2 Benefits of good asthma control during pregnancy

Better oxygenation of the fetus (or less risk of perinatal asphyxia)
Reduced risk of pregnancy complications for both mother and child
Reduced risk of gestational diabetes
Reduced risk of intrauterine growth retardation and small for gestational age
Reduced risk of preterm labour and preterm delivery
Reduced risk of asthma exacerbation
Reduced need of oral corticosteroids
Decreased risk of pre-eclampsia, placental abruption and placenta praevia
Reduced risk of caesarean section delivery
Reduced risk of prolonged post-partum hospital stay

Preconception health counselling by all healthcare providers is therefore of importance to increase adherence with asthma therapy and to assess and manage comorbidities, such as rhinitis, tobacco exposure and obesity, as suboptimal management contributes to subfertility, increased symptom burden, exacerbations, and poor quality of life during pregnancy [17, 42, 43]. Tobacco exposure is an important risk factor for increased asthma symptoms and exacerbations during pregnancy. Pregnant women with asthma should be advised to avoid tobacco smoke and if possible, to reduce exposures to pollutants, irritants and perfumes [44].

Pregnant women with moderate-to-severe asthma should have an obstetric review in the first trimester to increase adherence to anti-asthma medication by clarifying medical concerns, asthma education, and if needed, referral to an asthma specialist. If a woman with asthma experiences inadequate asthma control or acute worsening of asthma during pregnancy, she should be referred for further evaluation. If acceptable asthma control is not obtained or requires high-dose anti-asthma treatment and/or treatment with systemic corticosteroids, the patient should be offered growth scans in both the second and third trimester with the aim of reducing the risk of fetal complications such as intrauterine growth restriction and fetal mortality [45, 46].

Pharmacological management of asthma before and during pregnancy

Pharmacological treatment, primarily inhaled medication, is the cornerstone of asthma management in pregnancy. All available guidelines are consistent in stating that treatment should be similar for pregnant and non-pregnant patients. The safety of the drugs for the pregnant women and the unborn fetus, including the importance and effectiveness of the drug selected, should be addressed whenever possible. When changing treatment or adding new pharmacological treatment molecules with well-established safety profiles should be seen as the first choice.

Asthma treatment and fertility

Reported observations show that monotherapy with short-acting β_2-agonist (SABA) is associated with impaired fertility, whereas asthma therapy with ICS with or without add-on long-acting β_2-agonist (LABA) is not [17]. This suggests that controller medications may play a role not only in improving asthma control, but also may lead to a reduction in the associated systemic inflammation that may be the driver of impaired fertility. This is supported by a smaller observational study showing that women treated for severe asthma with add-on biologic therapy, presumably targeting both the local and systemic inflammation, experienced an improvement in fertility [47]. However, there is not full consensus as a recent study from 2020, by Crowe *et al.* [48], found only a limited association between a history of asthma or use of asthma medication and fecundability. Their findings, however, indicated a reduction in fecundability in women with adult-onset asthma [48].

Despite conflicting data, it seems very likely that best possible asthma control may, at least to some extent, reverse the negative effect of asthma on fertility [17]. However, further research is needed concerning the association between asthma control and fertility.

Asthma management during pregnancy

Monotherapy with SABA is not recommended for asthma in adults (Global Initiative for Asthma) [41]. Recent trials in mild asthma have shown that as needed use of a fixed combination of LABA with fast onset of action and low-dose ICS, *e.g.* formoterol and budesonide, can be recommended as step one asthma therapy [49]. If required to achieve asthma control, it can be used as both maintenance and reliever therapy (MART), which has been shown to be effective in asthma management resulting in lower overall use of ICS and fewer exacerbations [49, 50]. SABA can be used as reliever therapy, but always together with maintenance ICS in fixed combination with LABA if required.

Fetal malformation due to exposure to inhaled SABA is unlikely. Systemic administration is only used for tocolysis, including to suppress premature labour, but has well recognised cardiovascular and metabolic adverse effects. Systemic SABA during delivery might have a tocolytic effect. LABA should never be prescribed as reliever therapy or as maintenance therapy without ICS, so if needed to achieve asthma control if should be used in fixed combination with ICS. There are limited human data on LABA and their possible effects on the fetus, but the available data are reassuring.

Low and medium doses of ICS have not been associated with increased risk of malformations, preterm delivery, low birthweight or SGA. However, higher doses might be associated with adverse events, but it will be difficult to disentangle this from adverse events caused by the severity of the underlying disease and/or higher frequency of exacerbations. By contrast, conflicting data exist concerning systemic steroid

use in pregnant women, where some have shown increased risk of cleft lip, cleft palate, preterm delivery, low birthweight and pre-eclampsia, if treated during the first trimester, but this should be held against the high risks associated with exacerbations potentially causing fetal hypoxaemia.

Salmeterol, which has the longest safety record, can be used in fixed combination with ICS (ICS/LABA) as maintenance therapy together with SABA as needed. Other LABAs in fixed combination with ICS can be considered, not least in case of adherence issues. The new monoclonal antibody treatments for severe asthma are likely to be safe as well as these drugs do not pass the placenta, or at least not in a sufficient quantity to cause fetal harm, and if indicated prior to pregnancy, should be continued during pregnancy [51, 52].

Lastly, the use of montelukast might have a limited effect on asthma control, and there is a lack of data concerning the effect on the fetus, but continued use may be considered for women achieving pre-pregnancy asthma control on add-on montelukast. Although differences between the congenital adverse effect of antihistamines exist, in general H_1-antihistamines have not been linked to increased risk of anomalies. Loratadine or cetirizine should be preferred as they have the longest safety records, but a recent study based on nationwide data from Denmark has shown that fexofenadine treatment during pregnancy and breastfeeding is not associated with increased risks for the fetus/baby [51, 53].

Asthma monitoring

Awareness of symptom control, adequate medication and close management during pregnancy is recommended in order to reduce the risk of complications during pregnancy. Best possible asthma control may be achieved using repeated measurements of fractional exhaled nitric oxide (F_{ENO}), based on a study performed in pregnant women randomly allocated to either usual care (*i.e.* symptom control), level of lung function, or the use of F_{ENO} [54]. Using F_{ENO}-guided asthma management resulted in lower daily doses of ICS and fewer exacerbations. A follow-up study of the same cohort showed that children born to asthmatic mothers managed with F_{ENO} during pregnancy had less asthma-like symptoms, doctor-diagnosed asthma and use of SABA than the group monitored with symptoms only during pregnancy [55]. F_{ENO} as a monitoring tool has also been demonstrated to lead to faster asthma control with decrease in AHR in non-pregnant asthma patients, than use of symptom-based tools alone [56]. Furthermore, another study of pregnant women with asthma showed that using F_{ENO} in the management of asthma also ensured a lower level of exacerbations together with a lower level of controller treatment [54]. Exacerbations, and poor asthma control, have been shown to be the main driver of complications during pregnancy and delivery in several studies [57, 58]. However, findings from both case–control [59] and randomised controlled [60] studies suggest that close monitoring during pregnancy, and by that improved asthma control, is associated with a risk for adverse outcomes very close to that in non-asthmatic women. No previous history of asthma exacerbations and stable asthma early in pregnancy are associated with a low risk of asthma exacerbation during pregnancy [61, 62], whereas being prescribed moderate- to high-dose ICS is associated with a higher risk [61].

Adherence with controller therapy and exacerbations

Adherence with controller therapy is the major challenge in asthma management, not least during pregnancy [63], as studies have shown that the rate of filled prescriptions for asthma controller medication fall by up to 30% during early pregnancy [64, 65]. Asthma is associated with a slight increase in the risk for fetal [28] and maternal complications both during pregnancy and delivery, but this association is primarily driven by the impact of poor asthma control [58, 59, 66]. Previous studies of women with asthma have shown that an adherence with controller medication >80% prevents 24% of asthma exacerbations and 60% of asthma-related hospitalisations [67]. The reasons for the decline in adherence to controller medication during pregnancy are likely to be highly complex, but probably include concerns about the safety of the medication, the general assumption that medication should be avoided as much as possible during pregnancy and lack of information about the importance of best possible asthma control during pregnancy to reduce the risk of adverse outcomes. Therefore, healthcare providers, including midwives and general practitioners, need to be able to answer questions related to the safety of asthma medication throughout pregnancy, delivery and breastfeeding in order to address the concerns the pregnant women may have and by that, hopefully, facilitate better adherence and reduce the risk of adverse outcomes.

The overall aim of best possible adherence with asthma medication during pregnancy should, therefore, be to achieve and maintain the best possible asthma control. Individualised surveillance of asthma during pregnancy may be guided by information on history of exacerbations and current level of treatment and disease control.

Delivery, labour and offspring

Induction of labour is rarely indicated due to asthma only. This could be due to a higher planned caesarean section rate among moderate to severe asthmatic patients compared with mild asthma patients (RR 1.19, 95% CI 1.09–1.31) [34]. Another reason that induction of labour among asthmatic women is rare could be that serious obstetric complications during labour are increasingly prevented due to a well-functioning and close collaboration between obstetricians and respiratory physicians regarding pregnant asthmatic women. This is supported by Friedman *et al*. [68] who showed that severe respiratory complications from 2000 to 2018 decreased from 72 per 10 000 deliveries with asthma to 14 per 10 000 deliveries with asthma (average annual percentage change −9.4%, 95% CI −13.3% to −5.3%).

However, women with asthma who attempt to deliver vaginally have a higher risk of emergency caesarean section deliveries (OR 1.29), which could be due to increased maternal respiratory symptoms during labour, but more likely reflects perinatal complication due to maternal asthma decreasing the unborn baby's recourses during birth, *i.e.* SGA, preterm delivery and pre-eclampsia.

Children borne by women with asthma who had exacerbation during pregnancy have an elevated risk of asthma (OR 1.23, 95% CI 1.13–1.33) and pneumonia (OR 1.12, 95% CI 1.03–1.22) during the first 5 years of life [58].

Conclusion

Asthma seems to affect all parts of a woman's reproductive life from menarche to menopause, although it especially seems to challenge fertility and pregnancy. Asthma is associated with subfertility with an increasing tendency in women above the age of 35 years, compared with both young women with asthma and non-asthmatic women. The influence of asthma medication on fertility is controversial; however, the tendency in the recent studies seems to be that treatment for asthma and adherence to asthma medication is as important for fertility as it is for a successful pregnancy in asthmatic women.

The association between pregnancy loss and maternal asthma is not fully established and needs further investigation.

During pregnancy, asthma can have an impact on both the mother's health and her unborn child's health. Well-controlled asthma throughout is associated with little to no risk of asthma-related pregnancy complications.

Treatment of asthma during pregnancy follows the same guidelines as for non-pregnant asthmatic women. As for non-pregnant patients with asthma, a stepwise approach to treatment according to symptom control and asthma severity is recommended. Fixed combination low-dose ICS plus formoterol can be used as both maintenance and, if necessary, reliever therapy. Maintenance therapy with ICS plus SABA as reliever is an option, and if necessary, with add-on LABA (in fixed combination). For patients with mild symptoms of allergic rhinitis, the drug of first choice is an oral first- or second-generation H_1-antihistamine [53]. Intra-nasal corticosteroids, the most effective type of drugs for allergic rhinitis, are used for those with moderate-to-severe rhinitis.

Studies have shown that avoiding asthma triggers and tobacco exposure during pregnancy, and good adherence with asthma controller medication are key factors for a safe pregnancy for women with asthma. To ensure this, preconception health counselling by a general practitioner/healthcare provider of all women with asthma and close monitoring during pregnancy of women with moderate to severe asthma are crucial.

Key points

- Asthma is common among patients with impaired fertility.
- Patients with asthma have a longer time to pregnancy and may have an increased risk of pregnancy loss, but no differences in number of offspring compared with non-asthmatic women.
- Management of asthma in pregnant asthmatic women is similar to non-pregnant asthmatic women, and good asthma control throughout pregnancy is the key to avoiding complications during pregnancy and delivery.

Conflict of interest: The authors have nothing to disclose.

References

1 Clark JM, Hulme E, Devendrakumar V, *et al.* Effect of maternal asthma on birthweight and neonatal outcome in a British inner-city population. *Paediatr Perinat Epidemiol* 2007; 21: 154–162.
2 Kwon HL, Belanger K, Bracken MB. Asthma prevalence among pregnant and childbearing-aged women in the United States: estimates from national health surveys. *Ann Epidemiol* 2003; 13: 317–324.
3 Flores KF, Bandoli G, Chambers CD, *et al.* Asthma prevalence among women aged 18 to 44 in the United States: National health and nutrition examination survey 2001–2016. *J Asthma* 2020; 57: 693–702.
4 Hansen C, Joski P, Freiman H, *et al.* Medication exposure in pregnancy risk evaluation program: the prevalence of asthma medication use during pregnancy. *Matern Child Health J* 2013; 17: 1611–1621.
5 Janssens T, Ritz T. Perceived triggers of asthma: key to symptom perception and management. *Clin Exp Allergy* 2013; 43: 1000–1008.
6 Schatz M, Harden K, Forsythe A, *et al.* The course of asthma during pregnancy, post partum, and with successive pregnancies: a prospective analysis. *J Allergy Clin Immunol* 1988; 81: 509–517.
7 Stevens DR, Perkins N, Chen Z, *et al.* Determining the clinical course of asthma in pregnancy. *J Allergy Clin Immunol Pract* 2022; 10: 793–802.e10.
8 Gade EJ, Thomsen SF, Lindenberg S, *et al.* Asthma affects time to pregnancy and fertility: a register-based twin study. *Eur Respir J* 2014; 43: 1077–1085.
9 Vejen Hansen A, Ali Z, Malchau SS, *et al.* Fertility treatment among women with asthma: a case–control study of 3689 women with live births. *Eur Respir J* 2019; 53: 1800597.
10 Tata LJ, Hubbard RB, McKeever TM, *et al.* Fertility rates in women with asthma, eczema, and hay fever: a general population-based cohort study. *Am J Epidemiol* 2007; 165: 1023–1030.
11 Mascarenhas MN, Flaxman SR, Boerma T, *et al.* National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. *PLoS Med* 2012; 9: e1001356.
12 Boivin J, Bunting L, Collins JA, *et al.* International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Hum Reprod* 2007; 22: 1506–1512.
13 Rutstein SO, Shah IH. Infecundity, Infertility, and Childlessness in Developing Countries. DHS Comparative Reports No. 9. Calverton, ORC Macro and the World Health Organization, 2004. www.who.int/publications/m/item/infecundity-infertility-and-childlessness-in-developing-countries---dhs-comparative-reports-no.-9
14 Malchau SS, Henningsen AA, Loft A, *et al.* The long-term prognosis for live birth in couples initiating fertility treatments. *Hum Reprod* 2017; 32: 1439–1449.
15 Gade EJ, Thomsen SF, Lindenberg S, *et al.* Fertility outcomes in asthma: a clinical study of 245 women with unexplained infertility. *Eur Respir J* 2016; 47: 1144–1151.
16 Sheiner E, Mazor M, Levy A, *et al.* Pregnancy outcome of asthmatic patients: a population-based study. *J Matern Fetal Neonatal Med* 2005; 18: 237–240.
17 Grzeskowiak LE, Smithers LG, Grieger JA, *et al.* Asthma treatment impacts time to pregnancy: evidence from the international SCOPE study. *Eur Respir J* 2018; 51: 1702035.
18 Gade EJ, Thomsen SF, Lindenberg S, *et al.* Lower values of VEGF in endometrial secretion are a possible cause of subfertility in non-atopic asthmatic patients. *J Asthma* 2015; 52: 336–342.
19 Macklon NS, Geraedts JPM, Fauser BCJM. Conception to ongoing pregnancy: the “black box” of early pregnancy loss. *Hum Reprod Update* 2002; 8: 333–343.
20 Kolte AM, Bernardi LA, Christiansen OB, *et al.* Terminology for pregnancy loss prior to viability: A consensus statement from the ESHRE early pregnancy special interest group. *Hum Reprod* 2015; 30: 495–498.
21 Bahna SL, Bjerkedal T. The course and outcome of pregnancy in women with bronchial asthma. *Allergy* 1972; 27: 397–406.
22 Syed RZ, Zubairi ABS, Zafar MA, *et al.* Perinatal outcomes in pregnancy with asthma. *J Pak Med Assoc* 2008; 58: 525–527.
23 Sobande AA, Archibong EI, Akinola SE. Pregnancy outcome in asthmatic patients from high altitudes. *Int J Gynecol Obstet* 2002; 77: 117–121.
24 Tata LJ, Lewis SA, McKeever TM, *et al.* A comprehensive analysis of adverse obstetric and pediatric complications in women with asthma. *Am J Respir Crit Care Med* 2007; 175: 991–997.
25 Kemppainen M, Lahesmaa-Korpinen AM, Kauppi P, *et al.* Maternal asthma is associated with increased risk of perinatal mortality. *PLoS One* 2018; 13: e0197593.
26 Murphy VE, Wang G, Namazy JA, *et al.* The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis. *BJOG* 2013; 120: 812–822.
27 Blais L, Kettani FZ, Forget A. Relationship between maternal asthma, its severity and control and abortion. *Hum Reprod* 2013; 28: 908–915.
28 Shaked E, Wainstock T, Sheiner E, *et al.* Maternal asthma: pregnancy course and outcome. *J Matern Neonatal Med* 2019; 32: 103–108.
29 Baghlaf H, Spence AR, Czuzoj-Shulman N, *et al.* Pregnancy outcomes among women with asthma. *J Matern Neonatal Med* 2019; 32: 1325–1331.

30 Vaezi A, Haghighi L, Beigmohammadi F, *et al.* Maternal asthma, pregnancy, delivery and birth outcomes: a retrospective cohort study. *Iran J Allergy Asthma Immunol* 2017; 16: 92–98.
31 Magnus MC, Wilcox AJ, Morken NH, *et al.* Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. *BMJ* 2019; 364: l869.
32 De La Rochebrochard E, Thonneau P. Paternal age and maternal age are risk factors for miscarriage; results of a multicentre European study. *Hum Reprod* 2002; 17: 1649–1656.
33 Grzeskowiak LE, Smith B, Roy A, *et al.* Patterns, predictors and outcomes of asthma control and exacerbations during pregnancy: a prospective cohort study. *ERJ Open Res* 2016; 2: 00054-2015.
34 Tinker SC, Broussard CS, Frey MT, *et al.* Prevalence of prescription medication use among non-pregnant women of childbearing age and pregnant women in the United States: NHANES, 1999–2006. *Matern Child Health J* 2015; 19: 1097–1106.
35 Hasegawa K, Craig SS, Teach SJ, *et al.* Management of asthma exacerbations in the emergency department. *J Allergy Clin Immunol Pract* 2021; 9: 2599–2610.
36 Ali Z, Nilas L, Ulrik CS. Determinants of low risk of asthma exacerbation during pregnancy. *Clin Exp Allergy* 2018; 48: 23–28.
37 Hodyl NA, Stark MJ, Scheil W, *et al.* Perinatal outcomes following maternal asthma and cigarette smoking during pregnancy. *Eur Respir J* 2014; 43: 704–716.
38 Grarup PA, Janner JH, Ulrik CS. Passive smoking is associated with poor asthma control during pregnancy: a prospective study of 500 pregnancies. *PLoS One* 2014; 9: e112435.
39 Wang G, Murphy VE, Namazy J, *et al.* The risk of maternal and placental complications in pregnant women with asthma: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2014; 27: 934–942.
40 Murphy VE, Namazy JA, Powell H, *et al.* A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG* 2011; 118: 1314–1323.
41 Reddel HK, FitzGerald JM, Bateman ED, *et al.* GINA 2019: a fundamental change in asthma management: Treatment of asthma with shortacting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J* 2019; 53: 1901046.
42 Wang H, Li N, Huang H. Asthma in pregnancy: pathophysiology, diagnosis, whole-course management, and medication safety. *Can Respir J* 2020; 2020: 9046842.
43 Kwah JH, Stevens WW. Asthma and allergies in pregnancy. *Allergy Asthma Proc* 2019; 40: 414–417.
44 Powell H, Murphy VE, Hensley MJ, *et al.* Rhinitis in pregnant women with asthma is associated with poorer asthma control and quality of life. *J Asthma* 2015; 52: 1023–1030.
45 Danish Society for Obstetrics and Gynecology. Danish guideline: Lung Diseases and Pregnancy. 2018. www.dsog.dk/in-english
46 Das J, Andrews C, Flenady V, *et al.* Maternal asthma during pregnancy and extremes of body mass index increase the risk of perinatal mortality: a retrospective cohort study. *J Asthma* 2021; in press [https://doi.org/10.1080/02770903.2021.1993249].
47 Ozden G, Pınar Deniz P. May mepolizumab used in asthma correct subfertility? *Ann Med* 2021; 53: 456–458.
48 Crowe HM, Wise LA, Wesselink AK, *et al.* Association of asthma diagnosis and medication use with fecundability: a prospective cohort study. *Clin Epidemiol* 2020; 12: 579–587.
49 Beasley R, Holliday M, Reddel HK, *et al.* Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med* 2019; 380: 2020–2030.
50 Couillard S, Connolly C, Borg C, *et al.* Asthma in pregnancy: an update. *Obstet Med* 2021; 14: 135–144.
51 Middleton PG, Gade EJ, Aguilera C, *et al.* ERS/TSANZ Task Force Statement on the management of reproduction and pregnancy in women with airways diseases. *Eur Respir J* 2020; 55: 1901208.
52 Palmeira P, Quinello C, Silveira-Lessa AL, *et al.* IgG placental transfer in healthy and pathological pregnancies. *Clin Dev Immunol* 2012; 2012: 985646.
53 Andersson NW, Torp-Pedersen C, Andersen JT. Association between fexofenadine use during pregnancy and fetal outcomes. *JAMA Pediatr* 2020; 174: e201316.
54 Powell H, Murphy VE, Taylor DR, *et al.* Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet* 2011; 378: 983–990.
55 Morten M, Collison A, Murphy VE, *et al.* Managing asthma in pregnancy (MAP) trial: FeNO levels and childhood asthma. *J Allergy Clin Immunol* 2018; 142: 1765–1772.e4.
56 Bernholm KF, Homøe A-S, Meteran H, *et al.* F_{eNO}-based asthma management results in faster improvement of airway hyperresponsiveness. *ERJ Open Res* 2018; 4: 00147-2017.
57 Ali Z, Hansen AV, Ulrik CS. Exacerbations of asthma during pregnancy: Impact on pregnancy complications and outcome. *J Obstet Gynaecol (Lahore)* 2016; 36: 455–461.
58 Abdullah K, Zhu J, Gershon A, *et al.* Effect of asthma exacerbation during pregnancy in women with asthma: a population-based cohort study. *Eur Respir J* 2020; 55: 1901335.
59 Ali Z, Nilas L, Ulrik CS. Low risk of adverse obstetrical and perinatal outcome in pregnancies complicated by asthma: a case control study. *Respir Med* 2016; 120: 124–130.

60 Lim AS, Stewart K, Abramson MJ, *et al.* Multidisciplinary approach to management of maternal asthma (MAMMA): a randomized controlled trial. *Chest* 2014; 145: 1046–1054.

61 Bokern MP, Robijn AL, Jensen ME, *et al.* Factors associated with asthma exacerbations during pregnancy. *J Allergy Clin Immunol Pract* 2021; 9: 4343–4352.e4.

62 Ali Z, Thomsen SF, Ulrik CS. Predictors of atopic disease in children of women with asthma. *Pediatr Allergy Immunol* 2021; 32: 1369–1373.

63 Baarnes CB, Hansen AV, Ulrik CS. Enrolment in an asthma management program during pregnancy and adherence with inhaled corticosteroids: the "management of asthma during pregnancy" program. *Respiration* 2016; 92: 9–15.

64 Zetstra-Van Der Woude PA, Vroegop JS, Bos HJ, *et al.* A population analysis of prescriptions for asthma medications during pregnancy. *J Allergy Clin Immunol* 2013; 131: 711–717.

65 Enriquez R, Wu P, Griffin MR, *et al.* Cessation of asthma medication in early pregnancy. *Am J Obstet Gynecol* 2006; 195: 149–153.

66 Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax* 2006; 61: 169–176.

67 Bårnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. *Respir Care* 2015; 60: 455–468.

68 Friedman AM, DiMango EA, Guglielminotti JR, *et al.* Trends in and maternal outcomes of delivery hospitalizations of patients with an asthma diagnosis. *Obstet Gynecol* 2022; 139: 52–62.