Asthma during pregnancy: mechanisms and treatment implications

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ABSTRACT: Asthma is becoming increasingly prevalent worldwide. Numerous historical and prospective cohort studies have investigated the effects of maternal asthma on pregnancy outcome; however, the data has been conflicting and many studies have not used standard classifications for asthma severity. Overall, the literature suggests that asthmatic females are more at risk of low birth weight neonates, pre-term delivery and complications such as pre-eclampsia, especially in the absence of actively managed asthma treated with inhaled corticosteroids. Pregnancy with a female foetus may particularly increase the risk of these outcomes.

In addition, pregnancy has an effect on the course of asthma. The risk of an exacerbation requiring medical intervention may be as high as 50% in females with severe asthma and this may further increase the risk of poor outcomes, particularly low birth weight and pre-term delivery.

The mechanisms responsible for changes in asthma with pregnancy, or alterations in pregnancy outcomes due to asthma have not been thoroughly explored. Maternal inflammatory pathways may contribute to reduced foetal growth through alterations in placental function.

Asthma treatment, by reducing maternal inflammation and preventing exacerbations, is safe for use in pregnant females and contributes to improved outcomes for both mother and foetus.

KEYWORDS: Asthma, corticosteroids, low birth weight, placenta, pregnancy

Asthma is one of the most common chronic medical conditions that causes complications in pregnancy. There is evidence that asthma can adversely impact on pregnancy outcomes, and conversely that pregnancy may result in a change in the clinical status of a female with asthma. Understanding the mechanisms contributing to these events will not only impact on the management of asthma and pregnancy, but may be relevant to antenatal determinants of the rising asthma prevalence. In this Review, the interaction between asthma and pregnancy is examined in terms of clinical outcomes and underlying mechanisms. The implications of these results for the treatment of asthma during pregnancy are then reviewed.

ASTHMA PREVALENCE IN PREGNANT FEMALES

The prevalence of asthma among pregnant females is increasing [1–3]. Recent estimates in the USA suggest that 3.7–8.4% of pregnant females had asthma in 1997–2001, an increase from 3.2% from 1988–1994 [3]. Differences in the definitions of asthma, which range from physician-diagnosed asthma to whether the patient has experienced an episode of asthma or asthma attack in the previous 12 months, contribute to diverse prevalence statistics. KWON et al. [3] found that of the females of child-bearing age who responded as having current asthma, only 61.3% also responded positively to having an episode of asthma in the previous year. In Australia, the rate of asthma is one of the highest in the world [4, 5]. A 1995 study from Western Australia found that 12.4% of pregnant females currently had asthma and 8.8% had an exacerbation or used asthma medication during pregnancy [6]. Asthma is the most common respiratory disorder to complicate pregnancy and represents a significant public health issue.

THE EFFECT OF MATERNAL ASTHMA ON PREGNANCY OUTCOME

In 1961, SCHAEFER and SILVERMAN [7] stated that “The pregnant woman can be reassured that her asthma will have no bearing on her pregnancy or on the outcome of her delivery”. However, between 1950–1962, 19 maternal deaths associated with asthma were reported in England.
and Wales [8] and in the decades that followed, numerous epidemiological studies have demonstrated that asthmatic females are at increased risk of many poor pregnancy outcomes. The following section contains a detailed review of >30 studies, which have examined adverse pregnancy and perinatal outcomes in females with asthma. The methodology used differs widely in the 12 historical cohort studies (table 1), two case-control studies, three cross-sectional surveys, four case series and 13 prospective cohort studies (table 2). These studies have produced conflicting results and many have not used standardised treatment, clinical management or classification systems.

**Historical cohort studies**

Most of the earlier studies of asthma and pregnancy were historical cohort studies, which have the advantage of providing a community-wide perspective on asthma [14, 16]. While many identify an adverse impact of asthma on pregnancy outcomes, they are limited by the lack of information about asthma severity, disease progression and medication use during pregnancy [17]. Studies based upon medical record review can obtain more detailed clinical information and avoid recall bias, but have several disadvantages, including the possibility that mild asthma may not have been documented [14, 16, 17], with such cases possibly included in the control population [29]. This may underestimate any effect of asthma on pregnancy outcomes. Possible confounders, such as maternal smoking or socio-economic status, are not always present in administrative records [16] and coding or data entry errors are possible [14, 16, 34]. Furthermore, since these studies rely on retrospective analysis of data, no possibility exists to study the mechanisms involved [35]. Despite these drawbacks, the large number of subjects used in these studies give them more power to detect associations between maternal asthma and adverse pregnancy outcomes, which may then be followed up with smaller prospective studies.

The first large study of pregnant asthmatic females was published by Gordon et al. [9] in 1970. Patients with actively treated asthma were included in their analysis (n = 277) and 16 of these had severe asthma characterised by regular attacks during pregnancy. When corrected for ethnic background, there was no increase in the incidence of pre-term delivery or low birth weight in asthmatic mothers. However, there was a relatively large number of maternal (n = 5) or perinatal deaths (n = 16), which were more likely to occur in the severe asthmatics [9].

Bahn and Berkedal [10] used the Norwegian medical birth registry (1967–1968) to examine the pregnancies of 381 asthmatics and >112,000 controls who did not suffer from any diseases before or during pregnancy. Pregnancy complications, including hyperemesis gravidarum, haemorrhage and toxaemia, were twice as frequent in asthmatic patients, as were interventions during labour, induced labour and complicated labour. There was a higher rate of neonatal mortality, low birth weight, premature birth and hypoxia at birth in infants from asthmatic mothers. Although information about asthma treatment was not provided, this study was conducted prior to the availability of inhaled corticosteroids (ICS) and at a time when bronchodilators were the main therapy used for asthma [10].

Lao and Huenburg [11] studied 87 asthmatic patients who delivered between 1984–1987 in Hong Kong. Many of these patients did not require medication for asthma and were considered to be in remission during the study period (n = 33). All other patients were treated with bronchodilators and some with oral or ICS. Mothers with asthma were significantly more likely to have a low birth weight baby, epidural analgesia or caesarean section, compared with the control group, matched for age and parity. When asthma treatment was considered, females who did not use any medication had a higher incidence of low birth weight, and those taking medication had a higher incidence of caesarean section [11].

The effects of asthma and asthma medication on pregnancy outcome were examined in a Californian perinatal database study in 1985–1990, comparing asthmatics (n = 81) to 130 controls selected from the reference population [12]. Asthmatics were more at risk of caesarean section, pre-term labour or delivery and pre-term premature rupture of the membranes (PPROM). A significant increase in low birth weight was only observed in the oral-steroid dependent asthmatics (n = 50). However, this was influenced by an unusually high rate of pre-term delivery (54%) in this group. Patients who only used over the counter medications were excluded and thus, this study represented a group of more severe asthmatics [12]. However, the effect of severe asthma could not be separated from that of oral steroid use.

A historical cohort of almost 25,000 pregnant females in Canada found a significant association between pregnancy-induced hypertension (PIH) and asthma, which was treated with ICS during pregnancy [13]. Of the 1,435 females identified with a history of asthma, only 136 were considered to have asthma during pregnancy, as defined by requiring treatment. The association between asthma history and PIH was not significant after adjusting for confounders. Those females treated for asthma may have had more severe disease, but the role of disease severity and ICS treatment in leading to PIH could not be separated.

Two studies from New Jersey, based upon analysis of hospital records in 1989–1992, have examined neonatal [2] and maternal outcomes [14] in asthmatic females. Data from 2,289 asthmatic females were collected and compared to 9,156 control subjects. Maternal asthma was significantly associated with low birth weight, pre-term delivery, small for gestational age (SGA) neonates, congenital anomalies and prolonged infant hospital stay. After adjustment for potential confounders, including age and education, asthmatic mothers also had an increased risk of pre-term labour, placenta previa, caesarean section, prolonged hospital stay and hypertensive disorders of pregnancy, including pre-eclampsia [14].

Demissie et al. [2] found an increase in transient tachypnoea of the newborn in infants of asthmatic mothers after accounting for confounding risk factors, such as caesarean delivery and pre-mature birth. This association was stronger for male infants than female infants, possibly because male sex is a known risk factor for this condition [36], due to differences in foetal lung maturation between the sexes [37]. Schatz et al. [38] earlier described an increased risk of transient tachypnoea, but not respiratory distress syndrome, in a prospective cohort study of

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294 asthmatic females compared with 294 controls, but did not find a link with either asthma severity or medication use. The association is of interest, since transient tachypnoea of the newborn is related to a higher prevalence of asthma and atopic symptoms at 5 yrs of age [39]. It is possible that there are links between the in utero environment in asthmatic pregnancies and the risk of developing childhood asthma in the offspring, independent of genetic factors. This is demonstrated by the fact

## Table 1: Historical cohort studies examining the effect of maternal asthma on pregnancy outcomes

<table>
<thead>
<tr>
<th>Author et al., yr [ref]</th>
<th>Population study yrs</th>
<th>Asthma definition</th>
<th>Sample size</th>
<th>ICS use</th>
<th>Poor outcomes associated with asthma</th>
<th>Poor outcomes not associated with asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>GORDON et al., 1970 [9]</td>
<td>USA</td>
<td>Actively treated asthma</td>
<td>30861 (all) 277 (asthma)</td>
<td>Prior to ICS</td>
<td>Perinatal death (severe asthma)</td>
<td>Low birth weight</td>
</tr>
<tr>
<td>BAHNA and BJERKEDAL, 1972 [10]</td>
<td>Norway</td>
<td>Mother’s health documented by midwife or physician in birth registry</td>
<td>12530 (control) 381 (asthma)</td>
<td>Prior to ICS</td>
<td>Pre-term delivery, low birth weight, hyperemesis, haemorrhage, toxemia, induced/complicated labour, neonatal mortality</td>
<td></td>
</tr>
<tr>
<td>Lao and HUENGSBURG, 1990 [11]</td>
<td>Hong Kong</td>
<td>History of asthma</td>
<td>87 (control) 87 (asthma)</td>
<td>11% used beclomethasone</td>
<td>Low birth weight (mothers not receiving treatment for asthma), C-section (mothers using bronchodilators)</td>
<td></td>
</tr>
<tr>
<td>PELLOW et al., 1992 [12]</td>
<td>USA</td>
<td>Asthma diagnosis reported in perinatal database</td>
<td>130 (control) 81 (asthma)</td>
<td>Unclear</td>
<td>C-section for foetal distress, pre-term labour and delivery, pre-term premature rupture of membranes, gestational diabetes (steroid-dependent asthma), low birth weight (steroid-dependent asthma)</td>
<td>Pre-eclampsia, chronic hypertension, congenital malformations, IUGR</td>
</tr>
<tr>
<td>LEHRER et al., 1993 [13]</td>
<td>USA</td>
<td>Asthma history or asthma requiring treatment</td>
<td>22680 (control) 1435 (asthma history), 136 (asthma with treatment)</td>
<td>136 used ICS</td>
<td>Pregnancy-induced hypertension</td>
<td></td>
</tr>
<tr>
<td>DEMISSIE et al., 1998 [14]</td>
<td>USA</td>
<td>Asthma diagnosis recorded in database</td>
<td>9156 (control) 2289 (asthma)</td>
<td>Unknown</td>
<td>Pregnancy-induced hypertension, pre-eclampsia, low birth weight, pre-term delivery, congenital malformations</td>
<td>Post-partum haemorrhage</td>
</tr>
<tr>
<td>ALEXANDER et al., 1998 [1]</td>
<td>Canada</td>
<td>Completed on prenatal records or maternal admission forms</td>
<td>13709 (control) 817 (asthma)</td>
<td>Unclear</td>
<td>Antepartum and post-partum haemorrhage</td>
<td>C-section, gestational diabetes, pre-term delivery, pregnancy-induced hypertension</td>
</tr>
<tr>
<td>WEN et al., 2001 [16]</td>
<td>Canada</td>
<td>Diagnosis recorded in database</td>
<td>34688 (control) 8672 (asthma)</td>
<td>Unknown</td>
<td>Pre-term labour, pre-eclampsia, pregnancy-induced hypertension, antepartum and post-partum haemorrhage, premature rupture of membranes, C-section</td>
<td>Foetal death</td>
</tr>
<tr>
<td>LIU et al., 2001 [17]</td>
<td>Canada</td>
<td>Diagnosis recorded in database</td>
<td>8772 (control) 2193 (asthma)</td>
<td>Unknown</td>
<td>Small for gestational age, pregnancy-induced hypertension, choioamnionitis, pre-eclampsia, pre-term delivery</td>
<td>Congenital malformations</td>
</tr>
<tr>
<td>OLESEN et al., 2001 [18]</td>
<td>Denmark</td>
<td>Primiparous females with diagnosis of asthma and purchase of prescription drugs for asthma</td>
<td>8717 (control) 303 (asthma)</td>
<td>22.5% used ICS</td>
<td>Small for gestational age (theophylline users), reduced birth weight and length (mothers who reduced intensity of drug treatment during pregnancy)</td>
<td>Congenital malformations</td>
</tr>
<tr>
<td>NORJAVAARA and de VERDIER, 2003 [19]</td>
<td>Sweden</td>
<td>Self-report</td>
<td>29348 (all) 2968 (asthma)</td>
<td>All used budesonide</td>
<td>C-section</td>
<td>Still birth, congenital malformations, reduced birth weight, reduced gestational length</td>
</tr>
</tbody>
</table>

ICS: inhaled corticosteroid; C-section: caesarean section; IUGR: intrauterine growth restriction.
<table>
<thead>
<tr>
<th>Author yr [ref]</th>
<th>Population study yrs</th>
<th>Asthma definition</th>
<th>Sample size</th>
<th>ICS use</th>
<th>Active patient management</th>
<th>Poor outcomes associated with asthma</th>
<th>Poor outcomes not associated with asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOMBROWSKI et al., 1986 [20]</td>
<td>1982–1985</td>
<td>Not specified</td>
<td>116 (control); 153 (asthma; 85 theophylline)</td>
<td>Unknown</td>
<td>No</td>
<td>Pre-eclampsia (reduced incidence in theophylline users within asthma group)</td>
<td></td>
</tr>
<tr>
<td>STENIUS-AARNIALA et al., 1988 [21]</td>
<td>1978–1982</td>
<td>ATS criteria [22]</td>
<td>198 (control); 181 (asthma)</td>
<td>Some females used beclomethasone &lt;400 μg day⁻¹</td>
<td>Yes</td>
<td>Pre-eclampsia, C-section</td>
<td></td>
</tr>
<tr>
<td>STENIUS-AARNIALA et al., 1996 [23]</td>
<td>1982–1992</td>
<td>ATS criteria [22]</td>
<td>237 (control); 504 (asthma)</td>
<td>Budesonide or beclomethasone used by 70% of subjects</td>
<td>Yes</td>
<td>Elective C-section, pre-eclampsia (mothers with no acute attack versus control)</td>
<td></td>
</tr>
<tr>
<td>DOUCETTE and BRACKEN, 1993 [24]</td>
<td>1980–1982</td>
<td>Self-reported history or diagnosis recorded in medical records</td>
<td>3859 (control); 32 (asthma)</td>
<td>Unknown</td>
<td>No</td>
<td>Pre-term labour (history of asthma in previous 12 months), pre-term delivery (respiratory problem during pregnancy)</td>
<td></td>
</tr>
<tr>
<td>SCHATZ et al., 1995 [25]</td>
<td>1978–1990</td>
<td>Clinical diagnosis during pregnancy, including pulmonary function tests</td>
<td>486 (control); 486 (asthma)</td>
<td>8% used ICS</td>
<td>Yes</td>
<td>Pre-term labour, pre-eclampsia, gestational diabetes, low birth weight, congenital malformations</td>
<td></td>
</tr>
<tr>
<td>JANA et al., 1995 [26]</td>
<td>1983–1992</td>
<td>ATS criteria [22]</td>
<td>364 (control); 182 (asthma)</td>
<td>Beclomethasone used by some subjects</td>
<td>Yes</td>
<td>Low birth weight (asthma requiring hospitalisation)</td>
<td></td>
</tr>
<tr>
<td>MINERBI-CODISH et al., 1998 [27]</td>
<td>1993–1994</td>
<td>Symptom history</td>
<td>77 (control); 101 (asthma)</td>
<td>23% used ICS</td>
<td>No</td>
<td>Pre-term delivery, preterm delivery, low Apgar score</td>
<td></td>
</tr>
<tr>
<td>SOBANDE et al., 2002 [28]</td>
<td>1997–2000</td>
<td>Acute asthma in emergency room</td>
<td>106 (control); 88 (asthma)</td>
<td>Unknown</td>
<td>Not prior to ER presentation</td>
<td>Pre-eclampsia, C-section</td>
<td></td>
</tr>
<tr>
<td>MIRHSASHI et al., 2003 [29]</td>
<td>1997–1999</td>
<td>Self-reported doctor or hospital diagnosis</td>
<td>271 (control); 340 (asthma)</td>
<td>31% used ICS</td>
<td>No</td>
<td>Infant mortality, induction of labour, congenital malformations</td>
<td></td>
</tr>
<tr>
<td>MURPHY et al., 2003 [30]</td>
<td>1998–2002</td>
<td>Doctor diagnosis</td>
<td>44 (control); 138 (asthma)</td>
<td>67% used ICS</td>
<td>Yes</td>
<td>Reduced birth weight (female neonates from mothers not using ICS)</td>
<td></td>
</tr>
<tr>
<td>BRACKEN et al., 2003 [31]</td>
<td>1997–2001</td>
<td>Doctor diagnosis and/or symptoms during pregnancy</td>
<td>1333 (control); 872 (asthma)</td>
<td>Some subjects used ICS</td>
<td>No</td>
<td>Pre-term delivery (oral steroids and theophylline), IUGR (mothers classified as mild or moderate persistent severity)</td>
<td></td>
</tr>
<tr>
<td>TRICHE et al., 2004 [32]</td>
<td>1997–2001</td>
<td>Doctor diagnosis and/or symptoms during pregnancy</td>
<td>1052 (control); 606 (asthma)</td>
<td>Some subjects used ICS</td>
<td>No</td>
<td>Pre-eclampsia (mothers classified as moderate or severe persistent symptoms)</td>
<td></td>
</tr>
<tr>
<td>DOMBROWSKI et al., 2004 [33]</td>
<td>1994–1999</td>
<td>Doctor diagnosis</td>
<td>881 (control); 873 (mild asthma); 814 (moderate asthma), 52 (severe asthma)</td>
<td>ICS used by 21% of moderate/severe groups</td>
<td>Yes</td>
<td>Neonatal sepsis (mild asthma), C-section (mild/severe asthma), pre-term delivery &lt;37 weeks (oral steroid users)</td>
<td></td>
</tr>
</tbody>
</table>

ICS: inhaled corticosteroid; ATS: American Thoracic Society; C-section: caesarean section; ER: emergency room; IUGR: intrauterine growth restriction.
that the development of atopy in children is more closely
associated with maternal asthma or immunoglobulin (IgE)
levels, rather than paternal asthma or IgE [40–42]. Therefore,
as well as the immediate implications of poor pregnancy out-
comes on the offspring of asthmatic mothers, there may be
long-term implications for these children. Appropriately
grown neonates of asthmatic mothers had increased nucleated
red blood cell counts, haematocrit, leukocytes and lympho-
cytes within the first day of life, compared with those of
nonasthmatic pregnancies [43]. Studies investigating the long-term
effects of asthmatic pregnancies on offspring have found an
increase in the prevalence of left-handedness [44], wheezing at
15 months of age [38] and childhood respiratory diseases in
general [45], while others found no long-term developmental
effects [46].

A Canadian historical cohort study of 817 asthmatic females
and 13,709 nonasthmatic females in 1991–1993 examined
medical records to assess medication use during pregnancy
[1]. Over 45% of asthmatic females did not use any medication
to treat asthma, while 37.1% used β2-agonists. The use of ICS
was unclear, with 17% using “steroids”. Regardless of
medication use, asthmatic females were found to be at
increased risk of antepartum or post-partum haemorrhage,
possibly due to alterations in platelet function in asthmatics
[47, 48]. In addition, neonates from asthmatic mothers who
used steroids were found to be at increased risk of hyperbili-
rubinemia [1]. In a previous prospective cohort study, no
alteration in neonatal risk for hyperbilirubinemia in mild or
severe asthmatics was found [21].

Kallen et al. [15] examined the effect of asthma on pregnancy
outcomes using the medical birth registry and the hospital
had an increased risk of pre-term delivery, low birth weight, or
prolonged pregnancy (>41 weeks gestation) [15]. This study
used two approaches to identify females with asthma and
would have identified those with very mild asthma (asthma
recorded by midwives) as well as those with severe asthma
requiring hospitalisation (asthma documented in hospital
discharge registers). Despite this, the study did not separate
subjects based on disease severity, which may have been a
confounder.

Using Canadian administrative data (1989–1996), maternal
asthma was associated with all adverse outcomes examined by
Wen et al. [16]: namely, pre-term labour, PIH, pre-eclampsia,
antepartum haemorrhage, membrane disorders (including
PPROM), post-partum haemorrhage and caesarean delivery.
Many of these associations were stronger in teenage mothers
than adult mothers [16], possibly due to the increased risk of
complications in adolescent pregnancies.

A study of 2,193 asthmatic and 8,772 nonasthmatic singleton
pregnancies in Quebec was carried out in 1991–1996 [17]. After
adjusting for confounders, such as maternal age and pre-
existing diabetes or hypertension, maternal asthma was
associated with an increased incidence of pre-term labour
and delivery, small and large for gestational age neonates, PIH,
chorioamnionitis, abruptio placenta and caesarean delivery.
Interestingly, this group analysed data separately based upon
foetal sex and found that the risks of pre-term birth and
pre-eclampsia were higher in asthmatic females pregnant with
a female foetus, compared to those pregnant with a male
foetus. The prevalence of asthma in this population was very
low and similar among those pregnant with a male or female
foetus [17]. The cause of the increased risk to the female foetus
was not examined in this study, but may be related to foetal
sex-specific effects on maternal asthma [30, 49].

A Danish population-based study collected data from a birth
registry and prescriptions database (1991–1996) to study the
use of asthma medications by pregnant females and relate this
to perinatal outcome [18]. Less than 2% of all Danish females
were prescribed asthma medications during pregnancy.
Asthma treatment was defined as one of five levels: 1) inhaled
β2-agonist; 2) inhaled steroid; 3) systemic β2-agonist; 4)
systemic steroid; and 5) theophylline. Data was analysed
based on whether asthmatic females were prescribed treatment
of a higher or lower level than prior to pregnancy. The results
showed that asthmatic females who decreased their medic-
ation level during pregnancy (78 of 342 asthmatics) had babies
with reduced birth weight and length, with a lower mean
gestational age compared with nonasthmatic females, or
asthmatic females who increased their medication level during
pregnancy. This was particularly evident among 22 females
who decreased their medication use from inhaled steroid to
inhaled β2-agonist. This study was limited by a lack of
information regarding compliance and the reasons for alter-
ations in asthma management [18]. These may have included a
clinical improvement in lung function and asthma symptoms,
or may have been due to a reduction in prescribing as a result
of fears of drug use during pregnancy. Furthermore, prescrip-
tion rates may not necessarily correlate with actual medication
used during the pregnancy.

A recent historical cohort study from Sweden found that
budesonide use in pregnancy does not affect gestational age,
birth weight, birth length or the rate of still-births or multiple
births [19]. This data came from 2,968 females who used
inhaled budesonide during pregnancy and was compared to
7,719 females who used asthma medications other than
steroids, and a control population of >293,000 females. The
authors acknowledged that a comparison of asthmatic mothers
with similar severity would be of benefit, since inadequate
asthma control may be a confounder. Another Swedish
medical birth registry study previously reported no increase
in congenital malformations in females who used budesonide
during early pregnancy [50].

**Case-control studies**

There are only two case-control studies that examine the
contribution of maternal asthma to pre-term labour or
delivery. In a study of females participating in a pre-natal
screening programme in 1994–1995 in the USA, the prevalence
of asthma, defined as a lifetime history of asthma diagnosis,
was compared in 312 females who delivered pre-term and 424
control subjects who delivered at term [51]. Significantly more
pre-term cases had a positive asthma history (6.4%) compared
with control cases (3.3%), after adjustment for multiple
confounders [51]. A similar case-control study was previously
reported by Kramer et al., [52] with histories of asthma
diagnosis or symptoms more commonly associated with
idiopathic pre-term labour. However, the risk of pre-term
lack of medication compliance. However, they found no
which were associated with respiratory tract infections and
hospitalisations and emergency room visits in these patients,
severe asthma and found a high rate of exacerbations,
APTER
threatened abortion [6].

In Western Australia, there was no significant relationship between doctor-diagnosed asthma, asthma ever or current asthma during the pregnancy.

Cross-sectional surveys and case series
There are numerous cross-sectional surveys and case series examining the relationship between maternal asthma during pregnancy and perinatal outcomes. In many of these studies the lack of a control group is a disadvantage, with most comparing outcomes among females with asthma to a population estimate or institutional rate. In addition, a survey of exposure and outcome at one point in time may be influenced by recall bias and does not address the temporal association between the exposure and outcome that could be better investigated using a longitudinal study design.

A self-report questionnaire administered in Italy in 1987 found that maternal asthma was a risk factor for low birth weight [53]. When other variables were considered, this relationship was only found to hold in male infants, mothers who smoked and those who lived in an industrial town, suggesting that other risk factors contribute to the effect of asthma on pregnancy outcome. However, there were only four male infants of low birth weight and three female infants of low birth weight among the 55 mothers with asthma [53]. Therefore, these results should be interpreted with caution, as the sample sizes of the subanalyses were very small.

In 1993, >1,000 parents of children aged 5–11 yrs were surveyed in the UK, with regard to the child’s history of respiratory disease and pregnancy-related factors, including birth weight and pre-term delivery [45]. Pre-term birth was significantly more likely to be reported when the mother was asthmatic, but not when the father was asthmatic, compared with children of nonasthmatic parents. There were several disadvantages to this study, including the self-report of maternal asthma and the potential for recall bias on the part of the parent, given the amount of time that had passed since the pregnancy. In addition, pre-term birth was assessed by asking the question “Was your baby born prematurely?”, which could lead to errors as a result of the participant’s misunderstanding of the clinical definition of pre-term birth. Maternal smoking was an additional risk factor for pre-term delivery and no association was found between parental asthma and low birth weight [45].

In a cross-sectional survey of recently post-partum females in Western Australia, there was no significant relationship between doctor-diagnosed asthma, asthma ever or current asthma (defined by attacks of wheezing in the past 12 months) and PIH, low birth weight, pre-term delivery, PROM and threatened abortion [6].

After et al. [54] examined a case series of 28 adolescents with severe asthma and found a high rate of exacerbations, hospitalisations and emergency room visits in these patients, which were associated with respiratory tract infections and lack of medication compliance. However, they found no evidence of an increased rate of PIH, pre-term delivery or intrauterine growth restriction (IUGR) in asthmatic adolescents compared with general estimates for adolescent pregnancies [54].

Marie et al. [55] examined asthma in 200 pregnancies in Tennessee in 1986–1989 by medical record review. There was no increased rate of pre-term delivery or low birth weight among asthmatic females compared with the general population, which were very high (17.7 and 6.3%, respectively). However, IUGR was significantly more likely in females with moderate or severe asthma, who required hospitalisation during pregnancy, compared with subjects with mild asthma, who were not hospitalised for asthma during pregnancy. The caesarean section rate and incidence of post-partum exacerbations were also significantly increased in moderate and severe asthmatics compared with mild asthmatics. Asthmatic subjects who had a caesarean delivery were 18 times more likely to have exacerbations of asthma post-partum compared with asthmatics who had a vaginal delivery. The mechanism for this effect is unknown [55]. None of the subjects in this study used ICS and additional medical problems, such as hypertension, diabetes and obesity were present in 21% of patients.

A retrospective analysis of medical records by Beckmann [35] for 1992–1997 in the USA assessed outcomes in 782 asthmatic females. Over 90% of these subjects were mild asthmatics (according to hospital records) and almost half did not use any asthma medication during pregnancy. Only 6% of the asthmatics used a β2-agonist and inhaled steroid for treatment. There was an increased incidence of meconium staining, pre-term labour and oligohydramnios among asthmatic females compared with the general population. This study lacked power to demonstrate a relationship between steroid use and outcomes associated with altered placental function, such as IUGR, PIH and oligohydramnios [35].

Greenberger and Patterson [56] studied 80 pregnancies in females with severe asthma and found that those who had been hospitalised with status asthmaticus delivered neonates of reduced birth weight compared with those who were not hospitalised for asthma, suggesting that an acute attack of asthma may put the foetus at additional risk, particularly of IUGR.

Prospective cohort studies
Recently, a number of large prospective cohort studies of asthma in pregnancy have been published. Studies that prospectively examine pregnant females with asthma alongside a control group of females without asthma have the advantage of being able to assess lung function, treatment or asthma symptoms during pregnancy in relation to pregnancy outcomes, while close follow-up ensures that asthma is well-characterised and effectively managed throughout pregnancy [25]. However, significant associations between maternal asthma and adverse outcomes are frequently not observed. This may be due to small sample sizes [30], a high prevalence of ICS use among participants [30], active management of asthmatic subjects [25, 30, 33] or a bias towards mild asthma in some studies [33]. While participation in a closely monitored study itself may reduce the risk of an adverse outcome, this remains the most ethical approach to asthma management.
One problem when comparing prospective studies is that each population of asthmatics examined varies with regard to steroid use, general treatment and asthma severity, with some studies focussed on mild asthmatics and others on females with severe asthma, making comparison between studies difficult. In addition, standard classification systems are sometimes not employed and the criteria used to assess disease severity differ between studies.

DOMEBOWSKI et al. [20] prospectively followed 153 pregnant females with asthma and 116 healthy control females and found a reduced incidence of pre-eclampsia among theophylline users, but only compared with females with asthma who did not use theophylline. They suggested that the ability of theophylline to reduce vascular reactivity and platelet aggregation via increasing cAMP may be responsible for this trend [20]. However, another study found that pregnant females using theophylline were more likely to have an asthma exacerbation or develop pre-eclampsia than patients not using theophylline [57]. Although asthma severity was not specifically described in these subjects, the authors explain these findings as being possibly due to the higher prevalence of severe asthmatics among the theophylline users and, therefore, the effect on pre-eclampsia may have been independent of theophylline use [57]. A recent randomised controlled trial comparing theophylline use with inhaled beclomethasone found no differences between the two medications in maternal or perinatal outcomes, including pre-eclampsia [58].

A study of asthmatic mothers was conducted in Finland in 1978–1982 [21]. The study prospectively followed 181 asthmatic females during pregnancy, with 17 having two pregnancies in the study. Data on the control population was obtained retrospectively from labour records of subjects matched for age, parity and delivery date. A disadvantage was that only 20% of study subjects were recruited during the first trimester, with 26% of subjects recruited in the third trimester, making it difficult to follow changes in asthma during pregnancy. However, this study did classify females based on asthma severity as very mild, mild, moderately severe or severe. Skin-prick tests and serum IgE were used to assess atopy in these subjects, and although 62% were classified as atopic, this was unrelated to poor pregnancy outcome. There was a significantly higher incidence of pre-eclampsia in asthmatics (15%) compared with control subjects (5%). Mild pre-eclampsia occurred more often in females with severe asthma (29%) compared with females with very mild asthma (9%). The use of systemic steroids may also have contributed to the high frequency of pre-eclampsia, which was 25% compared with 10% in asthmatic females who did not use systemic steroids. Asthmatic subjects had a higher rate of caesarean section, but no differences in perinatal outcome, including birth weight, were found [21].

The same group performed another study of 504 pregnant females with asthma and found that females who had an acute attack during the pregnancy were less likely to have been using ICS prior to the attack [23]. However, there was no difference in pregnancy outcomes, including length of gestation and birth weight in females who had an acute attack, compared with both the control group and those who did not have an acute attack during pregnancy. The authors suggest that prompt treatment of these patients with ICS contributed to the positive outcome [23]. A disadvantage of these studies was their “mixed cohort” nature, with the asthmatic group being prospectively recruited and followed, and the control group data being retrospectively collected from medical records. This study design may have contributed to an over-estimate of poor outcomes with maternal asthma due to closer monitoring of the asthmatic females compared with control subjects who were not prospectively studied.

DOUCETTE and BRACKEN [24] performed a prospective cohort study of 32 females with asthma and 3,859 controls. The history of asthma was obtained by self-report during an interview or documentation in medical records and ICS use was not described. There was a two-fold increased risk for pre-term labour and delivery in association with maternal respiratory “problems” during pregnancy, while no effect of asthma on low birth weight was observed [24].

Over many years, SCHATZ and colleagues [25, 59] have performed the most comprehensive prospective cohort studies of the effects of asthma on pregnancy outcome, as well as the effects of pregnancy on asthma progression. This group actively managed asthmatic females during their pregnancies, measured lung function by spirometry at several time points and related these measurements to pregnancy outcome. In initial studies where 352 asthmatic females had at least three lung function measurements during pregnancy, there was a correlation between mean per cent predicted forced expiratory volume at one second (FEV1) and birth weight [59]. Subjects with an FEV1 in the lowest quartile (<83% predicted) were significantly more likely to have an infant with a birth weight in the lowest quartile (<3150 g) or a ponderal index <2.2, indicative of asymmetric IUGR [60, 61]. There was no relationship between low FEV1 and pre-term delivery, PIH or pre-eclampsia. A later study by this group on 486 females with actively managed asthma and 486 controls, found no significant differences in the incidences of pre-eclampsia, perinatal mortality, low birth weight, IUGR, pre-term delivery or congenital malformations [25]. This study was conducted over a period of 12 yrs and asthmatic subjects were well-characterised and actively managed. Although only 8% of subjects used ICS, the close management of asthmatic females may have contributed to the negative findings. Control subjects were also well-characterised as they also underwent pulmonary function testing, and were matched for maternal age, parity, smoking and delivery date [25].

JANA et al. [26] examined 182 asthmatic pregnancies in India in 1983–1992 and compared outcomes to 364 nonasthmatic pregnancies. Most females had well controlled asthma (91%) and were using medications including oral or inhaled β₂ agonists, theophylline, oral steroids or inhaled beclomethasone. In addition, there was close cooperation between the obstetrician and chest physician in the patient’s management. No significant increase in the rate of pre-term labour, low birth weight, caesarean section, perinatal mortality, haemorrhage or foetal distress was found in the asthmatic group compared with the control group. However, 15% of the asthmatics had a severe asthma attack during pregnancy, which required hospitalisation, and in these females there was a significant reduction in birth weight [26], suggesting that
poorly controlled asthma may contribute to reduced foetal growth.

A prospective study in Israel comparing asthmatic mothers (n=101) and control mothers (n=77), matched for age and ethnicity, collected data by interview at 1 day post-partum and from medical records [27]. Altogether, 23% of asthmatics used ICS and asthma was defined as having a history of recurrent episodes of wheeze, chest tightness, shortness of breath and cough. Asthmatic females were classified as mild (no inhaled steroid use), moderate (inhaled steroid use, no hospitalisations for asthma) or severe (inhaled and oral steroid use and possibly hospitalisations for asthma). Significantly more asthmatic females suffered from urinary tract or upper respiratory tract infections (31% of females with mild or moderate asthma and 69% of females with severe asthma) compared with nonasthmatic females (5%). The marked effect of severity on infections may be related to suppression of the immune system following prolonged corticosteroid use. There was no significant effect of asthma on pre-term delivery, gestational age, birth weight and PIH [27].

Sorande et al. [28] studied the pregnancy outcomes of asthmatic patients residing at high altitude in Saudi Arabia, hypothesising that the low oxygen environment may further contribute to pregnancy complications through a worsening of asthma. They studied 88 asthmatic females and 106 nonasthmatic females in 1997–2000. Asthmatic patients were managed by a medical specialist and treated with β2-agonist alone (n=57), in combination with oral theophylline (n=20) or with oral prednisolone (n=11). Asthmatic pregnancies were more likely to be complicated by pre-eclampsia, congenital malformations, low Apgar score or perinatal mortality and mean birth and placental weights were significantly reduced in asthmatics compared with nonasthmatics. Gestational age at delivery was not different between the groups. It is possible that the hypoxic environment contributed to an amplification of poor outcomes in these asthmatic subjects. However, females were selected for the study because they had visited the emergency room with asthma while they were pregnant, and the outcomes may simply have been observed due to the severity of their asthma. No comparison with a similar group of asthmatic females at low altitude was made [28] and thus the effect of high altitude residence on pregnancy outcomes with maternal asthma could not be properly examined.

As part of the childhood asthma prevention study in Sydney, Australia, pregnant females with physician-diagnosed asthma, and nonasthmatic pregnant females whose partners or other children had asthma, were prospectively studied [29]. Because females were recruited at 36 weeks, there was no evaluation of the effect of asthma on pre-term delivery. However, recruitment this late in pregnancy may also have led to an under-estimation of the effect of asthma on other outcomes, such as low birth weight and pre-eclampsia, since subjects with these outcomes may also be more likely to deliver early. Of 340 asthmatic females, 31% did not use any medication for asthma during pregnancy, while 35% of females used short acting β2-agonists alone and 31% used ICS. This study was complicated by the fact that several (21 of 271) nonasthmatics were using β2-agonists for wheezing during pregnancy, despite no previous doctor diagnosis of asthma. These females may have had mild asthma, but were not assessed during the study or excluded from analysis. Hypertension was significantly increased in the asthmatic group compared with the nonasthmatic group. There was no significant effect of asthma on other outcomes including pre-eclampsia, gestational diabetes, induced labour, caesarean delivery or any neonatal outcomes, including birth weight [29].

Since 1998, the current authors’ group in Newcastle, Australia, has prospectively followed asthmatic and nonasthmatic subjects throughout their pregnancies, conducting a detailed examination of the relationships between mother, placenta and foetus [30, 49, 62, 63]. Asthmatic females were classified based on both severity and inhaled steroid intake independently, according to the Australian asthma management guidelines [64], which are comparable to the guidelines of the National Heart Lung and Blood Institute [65]. Females were assigned an asthma severity rating of mild, moderate or severe according to symptoms, asthma history and other features, including FEV1 and peak expiratory flow (PEF). Females were assigned to the most severe category that applied for any one of these criteria. These classifications are similar to those used in the multi-centre studies reported recently [33, 66]. In addition, females were classified based on their inhaled steroid intake (budesonide, beclomethasone dipropionate or fluticasone propionate), calculated for each trimester and expressed as the mean daily dose of beclomethasone dipropionate (BDP) or equivalent, where 1 μg BDP was considered equivalent to 1 μg budesonide or 0.5 μg fluticasone propionate [67]. Classifications were no glucocorticoid (no ICS during pregnancy), low (<400 μg daily), moderate (400–1500 μg daily) or high (>1500 μg ICS daily). Oral steroid medication was used periodically by a small number of subjects. All asthmatic females used the short acting β2-agonist, salbutamol, for symptom relief when required. Birth weight was examined in asthmatic females (n=138) and compared with the nonasthmatic control group (n=44). The current authors demonstrated that growth of the female foetus was significantly reduced when asthmatic females did not use any ICS for treatment [30]. This occurred regardless of asthma severity, with most of these females having mild asthma, which was not considered severe enough by their physician to warrant the use of ICS. The use of ICS by asthmatic mothers was associated with female birth weights which were comparable to the nonasthmatic control group, while male birth weights of all asthmatic females were unaffected by asthma or its treatment. The results suggested that a mild inflammatory disease can have significant effects on foetal growth. The current authors propose that this occurs primarily through alterations in placental function [30].

Two large multicentre prospective cohort studies have recently been conducted in different parts of the USA, examining the effects of maternal asthma on pre-term delivery, pre-eclampsia and low birth weight. Bracken et al. [31] studied females in Massachusetts and Connecticut, recruited through obstetric practices and hospital clinics, while Dombrowski et al. [33] conducted a study in 16 university hospital centres across the USA.

The study of Bracken et al. [31] included 832 asthmatic females and 1,266 nonasthmatic controls. Asthma was defined as a
lifet ime history of doctor-diagnosed asthma, and symptoms and medication use during pregnancy were recorded and each rated as intermittent, mild persistent, moderate persistent or severe persistent, according to the 2002 Global Initiative for Asthma (GINA) guidelines [68]. Asthmatic females using theophylline or oral steroids had an increased risk of pre-term delivery. There was no relationship between symptom scores and pre-term delivery risk. However, there was an increased risk of IUGR in females with daily asthma symptoms but no association with treatment. This relationship was strongest in females who had not been diagnosed as asthmatic by a doctor, but who were experiencing symptoms and was not significant when this subgroup was removed from the analysis [31]. Assessment by a physician would have been useful to investigate potential cases of asthma in these 449 females [31, 69]. Although the assumption was made that most of these females had undiagnosed asthma and would benefit from closer monitoring during pregnancy [69], it seems surprising that one-third of females in a control population of relatively good socio-economic status were under-diagnosed asthmatics. It is possible that the symptoms reported by many of these females (cough or wheeze or chest tightness at least once during pregnancy) may have been general symptoms of dyspnoea due to the pregnancy itself, which are experienced by up to 75% of pregnant females without asthma [70]. However, it was alarming that for nearly 100 females, symptoms were mild persistent and for a smaller group of ~20 females, symptoms occurred daily.

As part of the same prospective cohort study, Triche et al. [32] found that females classified by GINA guidelines as having moderate-to-severe asthma symptoms during pregnancy were at increased risk of pre-eclampsia, suggesting that active asthma symptoms may affect maternal physiology, possibly as a result of increased inflammation.

DomBrowski et al. [33] tested the hypothesis that there would be an increased incidence of pre-term delivery among females with moderate or severe asthma. The classification of mild, moderate and severe asthma was modified from the National Asthma Education Program to include medication use [66]. Pregnancy outcomes were examined in 881 nonasthmatic controls, 873 females with mild asthma (FEV1 >80% predicted, not taking daily asthma medications, similar to intermittent asthma by GINA guidelines), 814 females with moderate asthma (FEV1 60–79%, using one or more daily asthma medications, similar to mild and moderate persistent) and 52 females with severe asthma (FEV1<60%, may be using oral corticosteroids, more severe than persistent by GINA guidelines as all females used oral steroids). There was an overall increase in the caesarean delivery rate in the moderate/ severe group, and neonatal sepsis in the mild asthmatic group, compared with the nonasthmatic control group, but no significant difference in the rates of pre-term delivery (either <32 or <37 weeks gestation) among all asthmatics compared with the control group [33]. However, pre-term delivery (<37 weeks gestation) was associated with severe asthma, which may have been due to oral steroid use. Bracken et al. [31] also observed an increased risk for pre-term birth of similar magnitude, in females using oral steroids. These studies from Bracken et al. [31] and DomBrowski et al. [33] were comparable in terms of gestational age at recruitment (<24 and <26 weeks, respectively), criteria for asthma (doctor diagnosis), the schedule of study visits or telephone interviews, and the data collected. In addition to collecting information about symptoms, medication use and exacerbation history, most patients in the DomBrowski et al. [33] study were actively managed and had spirometry performed as part of their study visits. By contrast, Bracken et al. [31] did not actively manage asthma in their cohort and data was collected by home and telephone interviews. Bracken et al. [31] used a classification system that examined symptoms and treatment as separate characteristics, and performed analyses on mixed groups of females with and without doctor-diagnosed asthma, subdivided based on the reporting of symptoms associated with asthma. DomBrowski et al. [33] gave an overall severity rating that considered symptoms, lung function and medication use. Although the study numbers were larger in the study by DomBrowski et al. [33], their results related to pre-term delivery were similar to those found by Bracken et al. [31].

Summary: effect of asthma on pregnancy

The results of prospective cohort studies into the effects of asthma on pregnancy outcome have not always supported the findings from previous historical cohort studies and case-control studies. However, the prospective cohort study design is superior for examining temporal relationships between maternal asthma during pregnancy and subsequent perinatal outcomes. Associations between asthma and pre-eclampsia, asthma and low birth weight have most commonly been demonstrated by both historical or prospective cohort and case-control studies. Foetal sex may be a confounder, and studies reporting no adverse perinatal outcomes may have done so due to a lack of separate data analysis for females pregnant with male and female foetuses. In addition, maternal atopy has rarely been examined as a possible risk factor. There are deficiencies in classification approaches in some prospective studies. Classification at enrolment [33], rather than constant monitoring of females [31], and classification that considers asthma throughout pregnancy is one difference between studies. In some studies, control patients were not assessed for the absence of asthma [29, 31], while in other studies, spirometry and close assessment of control subjects confirmed that they did not have asthma [30, 33]. The use of standard classification systems and close monitoring of all patients has improved the quality of data obtained from prospective cohort studies of asthma and pregnancy.

A meta-analysis of the association between asthma in pregnancy and low birth weight (<2,500 g) was conducted, with studies grouped by ICS use. In four studies involving 1,453 females with asthma and >156,000 nonasthmatic females, where ICS were not used during pregnancy, there was a significantly increased risk of low birth weight in the asthmatic pregnancies (fig. 1, relative risk (RR) 1.55; 95% confidence interval (CI) 1.28–1.87; p<0.00001). In contrast, there was no significant increase in the risk of low birth weight with asthma when ICS were used by some (range 8–30%) of the females with asthma (fig. 1, RR 1.19, 95% CI 0.97–1.45, p=0.10). Females with asthma not using ICS were at significantly increased risk of delivering a low birth weight infant, whereas the use of inhaled corticosteroid medication seemed to protect against this effect, although the difference
Mechanisms for the effect of maternal asthma on pregnancy outcomes

Despite the lack of studies directly addressing possible mechanisms, several authors have proposed that maternal hypoxia, inflammation, medication, smoking [14–17, 25, 51] and altered placental function [30, 62, 63] may contribute to poor pregnancy outcomes in females with asthma (fig. 2).

Hypoxia may contribute to low birth weight, pre-eclampsia, congenital malformations, spontaneous abortions and placenta previa in asthmatic females [28]. Reduced partial pressure of oxygen (PO2) is a feature of acute severe asthma or status asthmaticus [72–74] and a small decrease in maternal PO2 can have serious effects on the foetus [75], since the slope of the foetal oxygen dissociation curve is steep in the 50% oxygen saturation range [76]. Administration of oxygen to mothers in labour resulted in increased umbilical cord O2 values at delivery, suggesting that there is a relationship between maternal and foetal oxygen [76]. However, maternal hypoxia during asthmatic pregnancies has never been directly investigated in relation to foetal outcome and while it is unlikely to explain the finding of reduced female foetal growth in females with mild asthma [49], it may contribute to reduced growth in subjects who have been hospitalised with an exacerbation of asthma during pregnancy [26, 56].

Various aspects of placental physiology may affect foetal growth in pregnancies complicated by asthma, including placental blood flow, which is important for supply of nutrients to the foetus, and enzyme activity of 11[b]-hydroxysteroid dehydrogenase type 2 (11[b]-HSD2), which protects the foetus from excess maternal glucocorticoids. Using a perfusion method, placental vascular responses to both dilator and constrictor agonists were significantly reduced in placentae from females with moderate and severe asthma, by reducing the supply of nutrients to the foetus. In the placenta of asthmatic females who did not use ICS and were pregnant with a female foetus, a significant reduction in 11[b]-HSD2 enzyme activity was also observed [63], which was related to the decreased growth observed in female foetuses of mothers with asthma. In addition, there was a significant reduction in cord blood concentrations of oestriol in females, indicating suppression of adrenal function as a result of excess maternal cortisol reaching the foetus [30].

The release of bioactive mediators, such as inflammatory products, from the mother, could also be involved in these mechanisms. Poor pregnancy outcomes, including low birth weight and pre-term delivery, are also features of other inflammatory diseases, including rheumatoid arthritis [77–79], malaria [80–82], systemic lupus erythematosus [83], inflammatory bowel disease [84–86] and periodontal disease
contribute to low birth weight. Similarly JANA et al. [26] found
reduced birth weight only when subjects had experienced an
acute episode of asthma during pregnancy and GREENBERGER
and PATTERSON [56] found that females with severe asthma
who had experienced at least one episode of status asthmaticus
had babies of reduced birth weight compared with those who
did not.

In the study by MURPHY et al. [30], maternal asthma severity,
inflammation, lung function and treatment with ICS were
examined in relation to foetal growth. It was proposed that
maternal inflammation may be related to reduced female birth
weight, since the use of ICS was protective [30]. Cytokine
expression in the placenta was also examined and an increased
ratio of T-helper cell (Th)2:Th1 cytokines in placenta from
asthmatic females who did not use ICS and were pregnant
with a female foetus was found. Inflammatory pathways in the
placenta may be altered as a result of decreased 11β-HSD2
activity and the associated increase in local cortisol concentra-
tions [49]. In addition, maternal white blood cell counts were
examined and a significant increase in the number of
circulating monocytes with advancing gestation was found
only in asthmatic females who did not use ICS and were pregnant
with a female foetus [30]. Changes in circulating inflammatory
cells may contribute to altered maternal asthma during
pregnancy, which possibly leads to changes in
placental function and ultimately, altered foetal development.
Asthma treatment has been widely investigated as a possible
mediator of the adverse pregnancy outcomes. However,
studies from the current authors’ group [30, 63] and others
[93] have not found any significant adverse effect of inhaled
steroid use on foetal growth in females with asthma. In fact,
asthma treatment appeared to protect against this adverse
foetal outcome [30]. Studies in which asthma was actively
managed [25, 30, 33] and where the majority of subjects used
ICS, were more likely not to report adverse outcomes in
association with maternal asthma, than studies conducted
prior to the introduction of ICS, or historical cohort studies
where inhaled steroid use was unknown and could not be
taken into account into the analysis.

Smoking, a contributor to low birth weight, has consistently
been reported to be more common among asthmatics than
nonasthmatics [1, 2, 6, 15, 27, 29, 35]. However, most studies
have found that maternal smoking does not fully explain the
association between asthma and adverse pregnancy outcomes
[6]. Further research into the effect of smoking during
asthmatic pregnancies in relation to both adverse pregnancy
outcomes and the efficacy of inhaled or oral steroid treatment
is warranted.

A common pathway leading to hyperactivity of the smooth
muscle in both the bronchioles and the myometrium has been
proposed to explain the increased incidence of pre-term labour
in asthmatics [24, 52, 94]. BERTRAND et al. [94] initially
suggested this mechanism after finding evidence of airway
hyperreactivity in the mothers of premature infants, but this
was not confirmed by another group examining airway
responsiveness in mothers of premature or low birth weight
children [95]. At least one study has suggested an additional
risk of prolonged pregnancy in asthmatic females, which could
not be explained by this same mechanism [15]. In addition,
data from recent prospective cohort studies suggests that the
risk of pre-term delivery may be largely explained by oral
steroid use [31, 33].

The large number of adverse outcomes associated with asthma
suggests there is a complex interaction of factors associated
with the disease and possibly its treatment, which may alter
normal maternal physiology during pregnancy. The current
authors have identified maternal inflammation leading to
altered placental function as a relevant mechanism that
importantly can be modified by ICS therapy. In addition, the
prevention of severe exacerbations of asthma during preg-
nancy is likely to lead to improved perinatal outcomes.

THE EFFECT OF PREGNANCY ON ASTHMA

The consensus has remained for many years that one-third of
females experience a worsening of asthma during pregnancy,
one-third improve and one-third remain unchanged [96, 97].
However, it is unclear whether this is due to changes in asthma
severity, asthma control or exacerbations during pregnancy. A
variety of methods have been used to obtain this data (table 3).
Current studies are limited by their subjective nature. Most
have used subjective questionnaires to ascertain the global
change in asthma experienced during pregnancy, while a few
studies have obtained data from daily symptom recording or
changes in treatment requirements. Relatively few studies
have examined objective measures, such as lung function by
peak flow meter or spirometry, or airway hyperresponsive-
ness. In addition, few studies have employed more than one
type of analysis to examine maternal asthma alterations during
pregnancy.

Despite the variation in results reported by individual studies,
it is clear that pregnancy itself can have a major impact on
asthma in some subjects. Cases of severe life threatening
asthma requiring first trimester termination have been
reported and an improvement in maternal asthma within
24 h of termination has been observed [108, 109]. However,
the course of an individual subject’s asthma during pregnancy
remains unpredictable. An understanding of the mechanisms
that contribute to worsening or improved asthma during
pregnancy is important for ensuring the best outcome for both
mother and baby.

Changes in asthma symptoms during pregnancy

Studies examining changes in asthma symptoms during pregnancy
date back to 1967 when WILLIAMS [8] examined
hospital records of 210 asthmatic females and found that
overall, 24% worsened and 42% improved during pregnancy.
Subjects with severe asthma were more likely to worsen, a
finding supported by more recent studies [66, 96].

SCHATZ et al. [97] examined the progression of asthma in 330
females during pregnancy and up to 12 weeks post-partum.
TABLE 3  
Studies examining the effects of pregnancy on asthma

<table>
<thead>
<tr>
<th>Study type and author yr [ref]</th>
<th>Population</th>
<th>Sample Size</th>
<th>Method for assessing asthma changes</th>
<th>Asthma worse</th>
<th>Asthma unchanged</th>
<th>Asthma improved</th>
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<tr>
<td><strong>Changes in asthma symptoms during pregnancy</strong></td>
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<tr>
<td>WILLIAMS, 1967 [8]</td>
<td>UK</td>
<td>210 (asthma)</td>
<td>Examination of hospital records</td>
<td>24%</td>
<td>34%</td>
<td>42%</td>
</tr>
<tr>
<td>GLUCK AND GLUCK, 1976 [96]</td>
<td>USA</td>
<td>47 (asthma)</td>
<td>Symptoms (wheeze) and/or medication requirements</td>
<td>43%</td>
<td>43%</td>
<td>14%</td>
</tr>
<tr>
<td>GLUE et al., 1984 [98]</td>
<td>England</td>
<td>67 (asthma)</td>
<td>Self-report of overall changes</td>
<td>14%</td>
<td>30%</td>
<td>33%</td>
</tr>
<tr>
<td>SCHATZ et al., 1988 [97]</td>
<td>USA 1978–1984</td>
<td>336 (asthma)</td>
<td>Daily symptom diaries and subjective classification of overall changes</td>
<td>35%</td>
<td>33%</td>
<td>28%</td>
</tr>
<tr>
<td>LAO and HUENSUGBURG, 1990 [11]</td>
<td>Hong Kong</td>
<td>87 (asthma)</td>
<td>Frequency and severity of symptoms/attacks and third trimester PEF</td>
<td>30%</td>
<td>39%</td>
<td>31%</td>
</tr>
<tr>
<td>BECKETT et al., 1998 [99]</td>
<td>England</td>
<td>34 (asthma)</td>
<td>Questionnaire on symptoms and treatment</td>
<td>41%</td>
<td>32%</td>
<td>27%</td>
</tr>
<tr>
<td>KURZCZER et al., 1999 [6]</td>
<td>Australia</td>
<td>79 (asthma)</td>
<td>Self-report of overall changes in breathing</td>
<td>35%</td>
<td>35%</td>
<td>16%</td>
</tr>
<tr>
<td>KIRCHER et al., 2002 [100]</td>
<td>USA 1978–1984</td>
<td>671 (asthma)</td>
<td>Daily symptom diaries and subjective classification of overall changes</td>
<td>36%</td>
<td>26%</td>
<td>34%</td>
</tr>
<tr>
<td>BECKMAN, 2002 [101]</td>
<td>Internet survey</td>
<td>166 (asthma)</td>
<td>Self-report of overall changes</td>
<td>41%</td>
<td>14%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Changes in asthma treatment during pregnancy</strong></td>
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<tr>
<td>FEIN and KAMIN, 1964 [102]</td>
<td>USA</td>
<td>50 (atopy)</td>
<td>Overall change in treatment</td>
<td>21%</td>
<td>67%</td>
<td>12%</td>
</tr>
<tr>
<td>MURPHY et al., 2003 [30]</td>
<td>Australia</td>
<td>71 (asthma)</td>
<td>Change in ICS use from first to third trimester</td>
<td>ICS increased with female foetus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DODDS et al., 1999 [103]</td>
<td>Canada</td>
<td>817 (asthma)</td>
<td>Use of β2-agonists and steroids</td>
<td>Steroid use greater with female foetus</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Changes in lung function or airway hyperresponsiveness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIMS et al., 1976 [104]</td>
<td>England</td>
<td>12 (control)</td>
<td>Serial spirometry (FEV1 and FVC)</td>
<td>No changes with pregnancy</td>
<td>Overall no alteration</td>
<td>Overall PC20 improved in second trimester</td>
</tr>
<tr>
<td>JUNPER et al., 1989 [105]</td>
<td>Canada</td>
<td>27 (asthma)</td>
<td>Airway hyperresponsiveness to methacholine and spirometry and medications use</td>
<td>Overall no alteration</td>
<td>Overall PC20 improved in second trimester</td>
<td>71% (subjective) 34% (peak flow)</td>
</tr>
<tr>
<td>WHITE et al., 1989 [106]</td>
<td>England</td>
<td>16 (asthma)</td>
<td>Questionnaire (perception of symptoms), daily bronchodilator use and peak flow</td>
<td>6% (subjective)</td>
<td>23% (subjective)</td>
<td></td>
</tr>
<tr>
<td><strong>Asthma exacerbations during pregnancy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STENIUS-ARRILA et al., 1996 [23]</td>
<td>Finland</td>
<td>504 (asthma)</td>
<td>Acute attack of asthma not controlled by normal rescue medications</td>
<td>9.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HENDERSON et al., 2000 [107]</td>
<td>USA</td>
<td>1564 (asthma)</td>
<td>Exacerbation and hospitalisation or acute asthma without hospitalisation</td>
<td>2% hospitalised 15% acute asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCHATZ et al., 2003 [66]</td>
<td>USA 1994–2000</td>
<td>1739 (sub-divided into mild, moderate and severe asthma)</td>
<td>Exacerbations (emergency department visits, unscheduled doctor visits, oral steroids or hospitalisation)</td>
<td>12% (mild), 26% (moderate), 52% (severe)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICS: inhaled corticosteroid; PEF: peak expiratory flow; FEV1: forced expiratory volume at one second; FVC: forced vital capacity; PC20: provocative concentration causing a 20% fall in FEV1.
Subjects subjectively rated their asthma as having improved, remained the same or worsened overall during pregnancy, compared to their pre-pregnancy state. In subjects whose asthma worsened, there was a significant increase in the number of days of wheezing and interference with sleep and activity between 25–32 weeks gestation. In asthmatic subjects who felt their asthma improved overall, there was a decrease in wheezing and little change in interference with sleep or activity between 25–32 weeks gestation. In all subjects, there was a fall in wheezing and interference with sleep and activity between 37–40 weeks. These changes highlight the importance of conducting trimester by trimester analyses of changes in asthma, as alterations at one time may not be the same as during another part of the pregnancy. Most subjects who felt their asthma worsened during pregnancy improved post-partum, with significantly fewer days of wheezing at 5–12 weeks post-partum compared with 29–32 weeks. Conversely, most subjects who felt their asthma improved during pregnancy worsened after pregnancy, with significantly more days of interference of activity in this period compared with 29–36 weeks gestation [97]. Of concern is the fact that 8% of subjects who stated that their asthma improved still had an emergency department presentation for asthma during pregnancy, which may have put their foetus at risk of poor outcomes. It is therefore not only females who have a subjective worsening of asthma during pregnancy that are clinically important and may benefit from improved asthma management strategies during pregnancy.

Some subjects were assessed in two successive pregnancies and 60% followed the same course of asthma in the second pregnancy as the first [97]. However, a substantial minority of patients did not follow the same course of asthma in subsequent pregnancies, suggesting that there must be a determinant of asthma that differed in the different pregnancies [97]. A further study from this group examined characteristics such as smoking, maternal body weight, foetal sex, season of delivery and nasal symptoms in pregnancy, to determine whether any of these factors may be causing the pregnancy-associated changes in asthma [100]. Season of pregnancy or delivery was not found to affect asthma progression [8, 100], suggesting that allergen exposure may not play a role in asthma alterations with pregnancy. Only the course of rhinitis during pregnancy correlated with the course of asthma during pregnancy [100]. Rhinitis worsened or improved in >50% of patients whose asthma had also worsened or improved, respectively [100]. The authors suggest that factors, such as IgE, which affect both the upper and lower airways, may be important in changes that occur in asthma during pregnancy [100]. Another group found that cockroach-specific IgE levels in serum were linked to clinical asthma during pregnancy, with significantly more days of interference of asthma during pregnancy that are clinically important and may benefit from improved asthma management strategies during pregnancy.

LAO and HUNGSBURG [11] reported that amongst treated asthmatics, 39% had no change, 30% had an increase and 31% had a decrease in the frequency and severity of symptoms or attacks during pregnancy. When compared with the group whose asthma did not change, females who reported an improvement in asthma during pregnancy had significantly higher per cent predicted PEF [11].

Data obtained from a cross-sectional survey of post-partum females in Western Australia indicated that during pregnancy, 16.4% of subjects experienced improved asthma and 35.4% experienced worsening asthma [6]. Wheezing or asthma attacks were experienced by 62% of females during pregnancy. A large number of asthmatics were also smokers in this study, although smoking was not related to the changes in asthma during pregnancy [6].

Recent work suggests that maternal asthma symptoms may be influenced by the foetus. In a blind prospective study, BERCROFT et al. [99] studied 34 pregnant mothers with moderate or severe asthma who were using regular treatments. Significantly more mothers pregnant with a female foetus reported shortness of breath, nocturnal waking and a worsening of cough and asthma in general, while mothers pregnant with a male foetus were more likely to report an improvement in asthma [99]. DODDS et al. [103] reported that re-analysis of their Canadian population-based study indicated that fewer asthmatic subjects pregnant with a male foetus required steroids for treatment (14%), compared with asthmatic subjects pregnant with a female foetus (20%) [1]. Although equal proportions of subjects pregnant with males or females used no drug treatment for asthma, there was a trend towards more subjects pregnant with a male using β₂-agonists alone (40% of subjects) compared with subjects pregnant with a female (35%), suggesting better managed asthma in the subjects pregnant with a male foetus [105]. It would be interesting to investigate whether foetal sex influences maternal asthma in a study with larger numbers.

**Changes in asthma treatment requirements during pregnancy**

The current authors have found evidence that maternal asthma worsens in the presence of a female foetus [30, 49]. Since their study found that the female foetus was particularly susceptible to reduced foetal growth in the presence of maternal asthma, it was questioned whether foetal sex may also be altering asthma. In females who were prescribed ICS, there was a significant increase in dose requirements from the first to third trimester only in those pregnant with a female foetus (n=41), suggesting an increase in maternal inflammatory pathways associated with asthma in the presence of a female foetus [30]. The current authors propose that factors derived from the male or female foetus may alter maternal asthma and could result from differences between male and female foetuses in protein or steroid expression, foetal gonadal or lung maturation, or differences in trafficking of foetal or placental cells or DNA from foetus to mother. The current authors also observed a significant rise in maternal circulating monocytes as pregnancy progressed in females who did not use ICS and were pregnant with a female foetus. This may be part of the mechanism explaining worsening maternal asthma during pregnancy with female foetal sex [30].

**Changes in lung function and airway hyperresponsiveness during pregnancy**

In 1976, SIMS et al. [104] performed lung function tests on asthmatic females during pregnancy and post-partum. They
found that there were no pregnancy-related changes in FEV1:vital capacity (VC) ratio in 12 nonasthmatic or 27 asthmatic females either at rest or during exercise [104]. BECKMANN [35] also reported no changes in peak flow measurements made in each trimester in 22 pregnant females with asthma.

JUNIPER et al. [105] demonstrated an overall improvement in airway responsiveness to methacholine challenge in the second trimester compared with pre-conception in 16 subjects, but no significant changes in FEV1 or FEV1:VC were observed. When individual data was examined, 11 subjects improved and five worsened during pregnancy and there was no relationship between airway responsiveness and serum progesterone or oestriol concentrations [105, 110].

WHITE et al. [106] examined changes in asthma during pregnancy using a symptom questionnaire and daily peak flow measurements. The results from subjective and objective measurements did not always agree, with 71% reporting a perception of improved asthma during pregnancy, and only 34% demonstrating an objective improvement in peak flow during the third trimester [106]. This study demonstrates the difficulty of classifying changes in asthma during pregnancy based on patient perception.

**Exacerbations of asthma during pregnancy**

Hospitalisation during pregnancy has been reported to occur in 1.6% and emergency room visits in 12.6% of asthmatic patients [97]. WENDEL et al. [111] reported that, with the use of objective pulmonary function tests, 62% of exacerbations during pregnancy required hospitalisation of the asthmatic patient. STENIUS-AARNIALA et al. [23] found that 9.3% of subjects had an acute asthma attack during pregnancy and this was more common in females who did not use ICS. Acute attacks were normally distributed around 21–24 weeks gestation. They concluded that a mild attack of asthma, if promptly treated does not affect pregnancy or perinatal outcome [23].

HENDERSON et al. [107] analysed data collected during the 1960s, where 2% of females with asthma were hospitalised and 15% experienced an acute exacerbation without hospitalisation. They found that strongly positive cockroach-specific IgE in serum was associated with an increased risk of exacerbations with status asthmaticus.

Several studies indicate that females with severe asthma are more likely to show signs of worsening asthma during pregnancy than females with milder asthma [8, 66, 96]. In a recent study, the relationship between asthma severity classification and subsequent changes in asthma during pregnancy was assessed in >1,700 pregnant asthmatics [66]. Exacerbations of asthma occurred in over half of all severe asthmatics, while only 12% of patients with mild asthma had exacerbations during pregnancy. Re-classification of asthma from mild to either moderate or severe occurred in 30% of patients, while only 25% of patients who were initially moderate or severe were later re-classified as mild. Asthma morbidity, encompassing hospitalisations, symptoms, steroid requirements and unscheduled doctor visits, was found to be closely related to the pregnancy classification of asthma severity and overall occurred in ~20% of subjects during pregnancy [66].

There is little evidence that labour and delivery themselves have any major effect on maternal asthma. If an acute attack occurs at this time, normal medication use is recommended [112]. The prospective study of 198 asthmatic females by STENIUS-AARNIALA et al. [21] found that 14% of patients with atopic asthma and 22% of patients with nonatopic asthma experienced asthma symptoms during labour. They reported that in all subjects, symptoms during labour were mild and well controlled by inhaled β2-agonists [21]. Similar data has been reported by other groups [26, 55] including SCHATZ et al. [97] where 10% of females experienced mild symptoms during labour and delivery. A larger multi-centre study found that asthma symptoms were present during labour in 17.9% of all patients, with 46% of subjects with severe asthma experiencing symptoms during labour [66].

**Mechanisms for the effect of pregnancy on maternal asthma**

The mechanisms that contribute to changes in asthma during pregnancy are not well understood, although increases in maternal circulating hormones, altered β2-adrenoceptor responsiveness or foetal sex may be involved (fig. 3).

The pregnancy-associated rise in serum-free cortisol may contribute to improvements in asthma during pregnancy [8, 113], since cortisol has anti-inflammatory properties. In addition, oestradiol and progesterone concentrations increase significantly during pregnancy [75]. Progesterone is known to contribute to increased minute ventilation during normal pregnancy [114] and is also a potent smooth muscle relaxant [115] and may, therefore, be expected to contribute to improved asthma during pregnancy. Alternatively, changes in β2-adrenoceptor responsiveness and airway inflammation as a result of circulating progesterone may contribute to worsening asthma during pregnancy [116]. TAN et al. [117] found that in female asthmatics, there was a desensitisation and down-regulation of lymphocyte β2-adrenoceptors following administration of medroxyprogesterone. Alterations in asthma associated with changes in sex steroid production during the menstrual cycle have previously been observed [98, 118], with up to 40% of females experiencing an exacerbation around the time of menstruation when progesterone and oestriol levels are low [119]. No correlation has been found between the occurrence of pre-menstrual asthma and the progression of asthma during pregnancy [8, 98].

**FIGURE 3.** Changes in asthma during pregnancy.
During pregnancy, exposure to foetal antigens, or alterations in immune function, may predispose some females to worsening asthma. Successful pregnancy has previously been described as a Th2 phenomenon [120–123], and asthma itself is primarily a Th2 mediated disease [124]. Although in both asthma and pregnancy, the distinction between Th2 and Th1 immune deviation is not definitive [125, 126], in this sense, asthma may be expected to become worse during pregnancy. Rheumatoid arthritis, a Th1 mediated inflammatory disease, is known to go into remission during pregnancy in 75% of patients [127, 128].

The fact that some females experience an improvement in asthma during pregnancy, while others experience a deterioration of asthma, and that different patterns are observed in different pregnancies in the same mother [97, 129], casts doubt on the contribution of these major common hormonal or immune changes of pregnancy. However, studies in nonpregnant females have shown that a high proportion of asthmatics have an abnormal concentration of either progesterone or oestriadiol compared with nonasthmatics, and these changes are not consistent across the entire group [130]. Such individual abnormalities may explain why the progression of asthma during pregnancy differs between females.

**Effect of foetal sex**

The possible influence of foetal sex on maternal asthma during pregnancy may not be a novel concept. In 1961, the following comment was made by SCHAEFER and SILVERMAN [7] in a discussion of his publication on seven cases of asthma in pregnancy: “There have been reports that asthma becomes worse only when the patient is pregnant with a female child and shows no change or gets better when she is pregnant with a male child”. These authors and others [8] did not find any data to support this statement in their own patients. However, reference to this older literature was also made by GREEN [131] in 1934 and DREBBES and SODEMAN [132] in 1946, who reviewed the non-English language literature dating back to the 1920s. In several studies, sex of the foetus had an effect on maternal asthma during pregnancy [132]. No consistent patterns were observed in these case series. Green suggested that where asthma attacks during pregnancy were associated with a particular foetal sex, the factor responsible came from the sexual organs of the foetus [131]. In 1930, WILLIAMSON [133] reported case histories of 13 females with asthma and 14 females with hay fever. Surprisingly, subjects had differing histories of urticaria during their pregnancies, which were related to the sex of the child [133]. A case series, from New Zealand in 1964, found no consistent overall change in asthma, dependent on the sex of the foetus in subjects with at least three previous pregnancies, with some subjects reporting worsening of asthma in several pregnancies with a male foetus, and others reporting worsening of asthma in several pregnancies with a female foetus [134]. The mechanisms leading to changes in asthma during pregnancy in the presence of a male or female foetus require further investigation.

There is likely to be a link between changes in maternal asthma and the increased risk of poor pregnancy outcomes. This has been suggested by several studies where worsening of asthma was associated with reduced birth weight [26, 30, 56]. Studies by the current authors have examined possible relationships between the mother’s asthma, placental function and foetal development (fig. 4). In the presence of a female foetus, the current authors found that maternal asthma worsens during pregnancy, as demonstrated by an increased requirement for ICS and a significant rise in circulating monocytes [30, 49]. These alterations in maternal asthma in the absence of corticosteroid therapy are associated with significantly reduced female birth weight and changes in placental function. Placental 11β-HSD2 activity is significantly reduced, which allows more maternally derived cortisol to reach the female foetus. Further changes in placental function, which may be due to the decrease in 11β-HSD2 activity, include a rise in the local Th2:Th1 cytokine mRNA ratio and decreased glucocorticoid and mineralocorticoid receptor expression. The changes in placental cortisol metabolism contribute to changes in the foetus, reducing growth in late gestation, and suppressing foetal hypothalamic-pituitary-adrenal axis function, as demonstrated by significantly reduced oestriol concentrations in female cord blood [30, 49]. Improvements in maternal asthma control during pregnancy may contribute to better foetal outcomes.

**THE TREATMENT AND MANAGEMENT OF ASTHMA DURING PREGNANCY**

Many studies confirm that better control of asthma is less likely to result in adverse outcomes than poorly controlled asthma [26, 55, 56, 135]. One study found that birth weight was decreased in asthmatics who had at least one asthma attack during pregnancy, compared with asthmatics who did not have an attack or require emergency therapy [56]. In addition to avoiding possible asthma triggers [136], treatments have an important role to play in controlling maternal asthma exacerbations and reducing inflammation during pregnancy.

There is extensive evidence for the safety of the major drug classes used to treat asthma during pregnancy, including short-acting β2-agonists [137, 138], theophylline [58, 138] and ICS [19, 50, 138]. The safety of oral steroids for asthma during pregnancy is less clear, as two large prospective cohort studies recently found an association between oral steroid use and an
increased risk of pre-term delivery [31, 33]. Information is also lacking on the safety of some of the newer inhaled corticosteroid drugs, such as fluticasone propionate, and no studies have addressed the use of combined inhaled corticosteroid and long-acting β2-agonist preparations in asthmatic pregnant females. The current authors found no alteration in foetal growth in subjects using beclomethasone, budesonide or fluticasone, compared with nonasthmatic controls [30, 63]. Recently, NAMAZY et al. [93] studied asthmatic females using beclomethasone, budesonide, fluticasone, triamcinolone or flunisolide and found no increases in SGA infants and no difference in mean birth weight in association with use of these medications. However, no control group was specifically recruited for this study, with all data compared to population averages [93]. No studies have specifically examined the use of the long acting β2-agonists, such as salmeterol and formoterol, either alone or in combination with ICS in asthmatics during pregnancy. An epidemiological study of salmeterol use in >15,000 patients, reported that among this population, there were 65 subjects who used salmeterol while pregnant [139]. While no adverse outcomes were reported, there was no information given about the analysis of outcomes or maternal asthma status, as this was not the primary aim of the study [139].

Despite reports indicating the safety of corticosteroid use for asthma treatment during pregnancy, both pregnant subjects [101, 140, 141] and physicians [23, 113, 140–143] remain apprehensive about using these medications. A recent survey of 501 asthmatic females of child-bearing age reported that 82% of subjects who used ICS were concerned about their effects on the foetus [144]. However, subjects also felt concern about the consequences of discontinuing medication on their own health. Despite this, many were likely to discontinue medication while pregnant, without first seeking advice from their physician [144]. The problem of unfounded fears of the effects of asthma drugs on the foetus was acknowledged by the working group on asthma and pregnancy from the National Institutes of Health [112]. Publicity surrounding teratogenic effects of drug use in early pregnancy and concern about litigation contributes to these fears [142, 145]. A comparison of emergency department visits by pregnant and nonpregnant asthmatic females found that although there were similar symptom durations and peak expiratory flows in both groups, those who were pregnant were significantly less likely to be treated with systemic steroids either in the emergency department or following discharge from hospital [143]. In addition, the pregnant asthmatics were more likely to experience an ongoing exacerbation in the following two weeks compared with nonpregnant asthmatics [143]. These studies suggest that despite continuing advice that pregnant females with asthma should be treated in the same way as nonpregnant asthmatic females, this has not completely translated into clinical practice.

Existing data demonstrating the safety of ICS use for both the foetus and mother in asthmatic pregnancies [30, 63, 93] should facilitate further improvements in asthma management for pregnant females. Most recent reviews and recommendations on asthma management suggest treating asthma in pregnant females in a similar manner to nonpregnant females [112, 146], as preventing asthma exacerbations during pregnancy is critically important. Recent literature has also highlighted the importance of educating pregnant females about their asthma [145, 147, 148]. Education has numerous benefits, including improvement of patient adherence with medications [136]. These strategies are designed to result in the best possible outcome for both mother and foetus.

**FUTURE STUDIES**

Future studies of asthma and pregnancy should be focussed on the mechanisms that lead to poor outcomes for the foetus. Understanding the changes in asthma that occur in the mother could lead to improvements in monitoring and treatment adjustment and more effective asthma management in these females. Based on the current authors’ findings in the mother, placenta and foetus, factors derived from the female foetus may alter maternal asthma. The current authors have observed increased maternal monocytes and increased requirements for ICS in asthmatic subjects pregnant with a female foetus, suggesting a worsening of maternal asthma as gestation progresses [30]. These changes were associated with altered placental function, such as decreased placental 11β-HSD2 activity [63] and altered expression of glucocorticoid receptors and cytokines [49]. The current authors believe that reduced placental 11β-HSD2 activity contributes to reduced growth and altered hypothalamic-pituitary- adrenal development of the female foetus [30]. Future studies will focus on understanding systemic and airway inflammation in asthmatic females, and determining ways to monitor and modify asthma management and treatment during pregnancy.

**CONCLUSIONS**

Despite conflicting results of historical and prospective cohort studies, it is clear that maternal asthma is a risk factor for some poor pregnancy outcomes and that asthma itself may be altered by pregnancy. In particular, asthma requiring hospitalisation during pregnancy [26, 56], or asthma that is not treated with ICS [18, 30] may increase the risk of low birth weight. The greatest risk factor for pre-term labour and delivery, based on recent large prospective cohort studies, is oral steroid and theophylline use [31, 33]. Atopy has not been thoroughly investigated as a risk factor. Further work is needed to investigate the mechanisms, both maternal and placental, which contribute to changes in asthma during pregnancy and lead to pre-term delivery, reduced foetal growth and pre-eclampsia. The current authors’ approach has been to collect data simultaneously from the mother, placenta and foetus in asthmatic pregnancies, which is providing detailed information of the changes and interactions which occur in these pregnancies.

Although the paradigm has remained for decades that during pregnancy, asthma will worsen in one-third, remain the same in one-third and improve in one-third of females, no studies have examined whether this is primarily due to changes in asthma severity, asthma control or sudden exacerbations of asthma. It appears that from a patient perspective, there are unpredictable changes in asthma during pregnancy; however, the majority of studies that have addressed this question have not used objective measures of asthma, but rather categorised females based on their subjective opinion of the overall change in asthma they experienced. Clinically relevant outcomes, such as hospitalisations and exacerbations, have not been examined by many studies and even females who report an improvement in asthma may require emergency medical intervention for
asthma during pregnancy, which potentially puts both the mother and the foetus at risk. Future studies should attempt to understand changes in airway inflammation in pregnant females in asthma, which may lead to more effective treatment and targeted management of asthmatic females with improved outcomes for their babies.

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