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REVIEW

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

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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

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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 little available 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].

BAHNA and BJERKEDAL [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 HUENGSBURG [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 premature 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

TABLE 1 Historical cohort studies examining the effect of maternal asthma on pregnancy outcomes

Author yr [ref]	Population study yrs	Asthma definition	Sample size	ICS use	Poor outcomes associated with asthma	Poor outcomes not associated with asthma
Gordon *et al*., 1970 [9]	USA	Actively treated asthma	30861 (all) 277 (asthma)	Prior to ICS	Perinatal death (severe asthma)	Low birth weight
Bahna and Bjerkedal, 1972 [10]	Norway 1967–1968	Mother's health documented by midwife or physician in birth registry	112530 (control) 381 (asthma)	Prior to ICS	Pre-term delivery, low birth weight, hyperemesis, haemorrhage, toxemia, induced/complicated labour, neonatal mortality	
Lao and Huengsburg, 1990 [11]	Hong Kong 1984–1987	History of asthma	87 (control) 87 (asthma)	11% used beclomethasone	Low birth weight (mothers not receiving treatment for asthma), C-section (mothers using bronchodilators)	
Perlow *et al*., 1992 [12]	USA 1985–1990	Asthma diagnosis reported in perinatal database	130 (control) 81 (asthma)	Unclear	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)	Pre-eclampsia, chronic hypertension, congenital malformations, IUGR
Lehrer *et al*., 1993 [13]	USA 1987–1991	Asthma history or asthma requiring treatment	22680 (control) 1435 (asthma history), 136 (asthma with treatment)	136 used ICS	Pregnancy-induced hypertension	
Demissie *et al*., 1998 [14]	USA 1989–1992	Asthma diagnosis recorded in database	9156 (control) 2289 (asthma)	Unknown	Pregnancy-induced hypertension, pre-eclampsia, low birth weight, pre-term delivery, congenital malformations	Post-partum haemorrhage
Alexander *et al*., 1998 [1]	Canada 1991–1993	Completed on prenatal records or maternal admission forms	13709 (control) 817 (asthma)	Unclear	Antepartum and post-partum haemorrhage	C-section, gestational diabetes, pre-term delivery, pregnancy-induced hypertension
Kallen *et al*., 2000 [15]	Sweden 1984–1995	Recorded by midwife	36985 (all pregnant females) 15512 (asthma)	Unknown	Pre-term delivery, low birth weight, post-term birth, infant death	Congenital malformations
Wen *et al*., 2001 [16]	Canada 1989–1996	Diagnosis recorded in database	34688 (control) 8672 (asthma)	Unknown	Pre-term labour, pre-eclampsia, pregnancy-induced hypertension, antepartum and post-partum haemorrhage, premature rupture of membranes, C-section	Foetal death
Liu *et al*., 2001 [17]	Canada 1991–1996	Diagnosis recorded in database	8772 (control) 2193 (asthma)	Unknown	Small for gestational age, pregnancy-induced hypertension, chorioamnionitis, pre-eclampsia, pre-term delivery	Congenital malformations
Olesen *et al*., 2001 [18]	Denmark 1991–1996	Primiparae females with diagnosis of asthma and purchase of prescription drugs for asthma	8717 (control) 303 (asthma)	22.5% used ICS	Small for gestational age (theophylline users), reduced birth weight and length (mothers who reduced intensity of drug treatment during pregnancy)	Congenital malformations
Norjavaara and de Verdier, 2003 [19]	Sweden 1995–1998	Self-report	293948 (all) 2968 (asthma)	All used budesonide	C-section	Still birth, congenital malformations, reduced birth weight, reduced gestational length

ICS: inhaled corticosteroid; C-section: caesarean section; IUGR: intrauterine growth restriction.

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 2 Prospective cohort studies examining the effect of maternal asthma on pregnancy outcomes

Author yr [ref]	Population study yrs	Asthma definition	Sample size	ICS use	Active patient management	Poor outcomes associated with asthma	Poor outcomes not associated with asthma
Dombrowski *et al*., 1986 [20]	USA 1982–1985	Not specified	116 (control) 153 (asthma; 85 theophylline)	Unknown	No		Pre-eclampsia (reduced incidence in theophylline users within asthma group)
Stenius-Aarniala *et al*., 1988 [21]	Finland 1978–1982	ATS criteria [22]	198 (control) 181 (asthma)	Some females used beclomethasone <400 μg·day^{-1}	Yes	Pre-eclampsia, C-section	Induction of labour, reduced length of gestation, reduced birth weight, perinatal mortality, congenital malformations
Stenius-Aarniala *et al*., 1996 [23]	Finland 1982–1992	ATS criteria [22]	237 (control) 504 (asthma)	Budesonide or beclomethasone used by 70% of subjects	Yes	Elective C-section, pre-eclampsia (mothers with no acute attack *versus* control)	Gestational diabetes, pre-term labour and delivery, perinatal mortality, congenital malformations, placenta previa, premature rupture of membranes
Doucette and Bracken, 1993 [24]	USA 1980–1982	Self-reported history or diagnosis recorded in medical records	3859 (control) 32 (asthma)	Unknown	No	Pre-term labour (history of asthma in previous 12 months), pre-term delivery (respiratory problem during pregnancy)	Low birth weight
Schatz *et al*., 1995 [25]	USA 1978–1990	Clinical diagnosis during pregnancy, including pulmonary function tests	486 (control) 486 (asthma)	8% used ICS	Yes		Pre-term labour, pre-eclampsia, gestational diabetes, low birth weight, congenital malformations
Jana *et al*., 1995 [26]	India 1983–1992	ATS criteria [22]	364 (control) 182 (asthma)	Beclomethasone used by some subjects	Yes	Low birth weight (asthma requiring hospitalisation)	Pre-term delivery, perinatal mortality,
Minerbi-Codish *et al*., 1998 [27]	Israel 1993–1994	Symptom history	77 (control) 101 (asthma)	23% used ICS	No		Hypertension, low birth weight, pre-term delivery, low Apgar score
Sobande *et al*., 2002 [28]	Saudi Arabia 1997–2000	Acute asthma in emergency room	106 (control) 88 (asthma)	Unknown	Not prior to ER presentation	Pre-eclampsia, C-section perinatal mortality, induction of labour, congenital malformations	
Mihrshahi *et al*., 2003 [29]	Australia 1997–1999	Self-reported doctor or hospital diagnosis	271 (control) 340 (asthma)	31% used ICS	No	Hypertension	Gestational diabetes, labour and delivery complications, low birth weight
Murphy *et al*., 2003 [30]	Australia 1998–2002	Doctor diagnosis	44 (control) 138 (asthma)	67% used ICS	Yes	Reduced birth weight (female neonates from mothers not using ICS)	
Bracken *et al*., 2003 [31]	USA 1997–2001	Doctor diagnosis and/or symptoms during pregnancy	1333 (control) 872 (asthma)	Some subjects used ICS	No	Pre-term delivery (with oral steroids and theophylline), IUGR (mothers classified as mild or moderate persistent severity)	
Triche *et al*., 2004 [32]	USA 1997–2001	Doctor diagnosis and/or symptoms during pregnancy	1052 (control) 656 (asthma)	Some subjects used ICS	No	Pre-eclampsia (mothers classified as moderate or severe persistent symptoms)	
Dombrowski *et al*., 2004 [33]	USA 1994–1999	Doctor diagnosis	881 (control) 873 (mild asthma), 814 (moderate asthma), 52 (severe asthma)	ICS used by 21% of moderate/severe groups	Yes	Neonatal sepsis (mild asthma), C-section (moderate/severe asthma), pre-term delivery <37 weeks (oral steroid users)	Pre-term delivery (<32 weeks)

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 (Ig)E levels, rather than paternal asthma or IgE [40–42]. Therefore, as well as the immediate implications of poor pregnancy outcomes 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 lymphocytes within the first day of life, compared with those of nonasthmatic mothers [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 β_2-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 hyperbilirubinemia [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 discharge register (1984–1995) in Sweden. Asthmatic females 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 placentae 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 β_2-agonist; 2) inhaled steroid; 3) systemic β_2-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 medication 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 β_2-agonist. This study was limited by a lack of information regarding compliance and the reasons for alterations 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, prescription 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

labour was not associated with increased serum IgE or altered response to inhaled methacholine challenge in the mother [52].

Due to their retrospective nature, the main disadvantage of these studies is a lack of information regarding the clinical course of asthma and its treatment. In particular, asthma is often defined as a history of asthma diagnosis, rather than 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].

APTER *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].

MABIE *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 rates, 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 β_2-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.

DOMBROWSKI *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 (FEV_1) and birth weight [59]. Subjects with an FEV_1 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 FEV_1 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 β_2-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].

SOBANDE *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 β_2-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 underestimation 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 β_2-agonists alone and 31% used ICS. This study was complicated by the fact that several (21 of 271) nonasthmatics were using β_2-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 FEV_1 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 β_2-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

lifetime 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 ($FEV_1 \geqslant 80\%$ predicted, not taking daily asthma medications, similar to intermittent asthma by GINA guidelines), 814 females with moderate asthma (FEV_1 60–79%, using one or more daily asthma medications, similar to mild and moderate persistent) and 52 females with severe asthma ($FEV_1 < 60\%$, may be using oral corticosteroids, more severe than severe 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 DOMBROWKSI *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, and 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

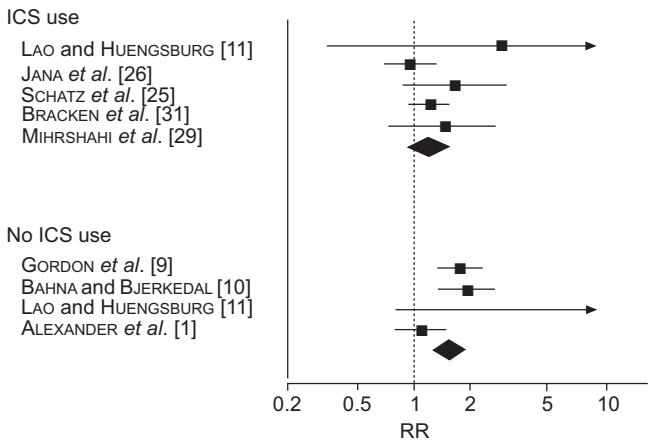

FIGURE 1. Meta-analysis examining the risk of low birth weight infants from asthmatic and nonasthmatic pregnancies. Studies are grouped based on whether some or all subjects used inhaled corticosteroids (ICS use) or whether none of the subjects used inhaled corticosteroids (no ICS use). RR: relative risk.

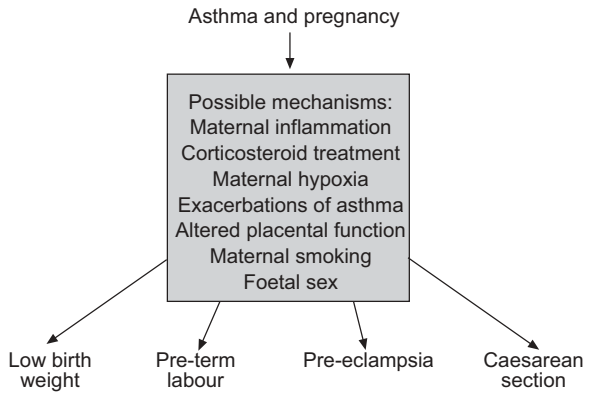

FIGURE 2. The effects of maternal asthma on pregnancy outcome.

between the RRs did not reach statistical significance (ratio of RRs 0.63, 95% CI 0.46–0.86 [71]).

Asthma requiring hospitalisation [26] and lack of ICS use in females with mild asthma [30] emerge as risks for low birth weight in prospective cohort studies (table 2). Historical cohort studies (table 1) conducted prior to ICS use [10], or where subjects were either not on any preventer treatment [11] or reduced their use of ICS during pregnancy [18], also support the conclusion that ICS medication may protect against low birth weight in pregnant females with asthma. Pre-term labour or delivery is associated with the use of oral steroids [31, 33] and theophylline [31], or having a respiratory problem during the pregnancy [24], suggesting that this may be an effect of more severe asthma or asthma exacerbations. Data from case-control studies have also demonstrated that an asthma attack in the previous 12 months is a risk factor for pre-term delivery [52]. The risk for pre-eclampsia may increase in females with moderate-to-severe persistent asthma symptoms during pregnancy [32], whereas the use of theophylline reduces the risk of pre-eclampsia [20]. The effect of acute asthma attacks during pregnancy on pre-eclampsia is unclear, as one study found an effect [28], while another prospective cohort study did not [23]. The use of ICS by females in prospective or historical cohort studies did not appear to be related to the development of pre-eclampsia.

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 (PO_2) is a feature of acute severe asthma or status asthmaticus [72–74] and a small decrease in maternal PO_2 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 O_2 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 11β-hydroxysteroid dehydrogenase type 2 (11β-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 collected from females with moderate and severe asthma, but unaffected in placentae from mild asthmatics compared with nonasthmatic controls [62]. These results indicate that altered placental blood flow may contribute to reduced foetal growth in moderate and severe asthmatics, 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 11β-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

[87, 88]. Moreover, elevated maternal serum levels or placental gene expression of inflammatory cytokines has also been associated with IUGR [81, 89–92]. BOWDEN *et al*. [78] found that females with active inflammatory arthritis during pregnancy had smaller babies at birth compared with healthy control subjects or subjects whose disease was in remission. These data indicate that active inflammation during pregnancy may 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 placentae 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 concentrations [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 pregnancy 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 hyperresponsiveness. 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

Study type and author yr [ref]	Population study years	Sample Size	Method for assessing asthma changes	Asthma worse	Asthma unchanged	Asthma improved
Changes in asthma symptoms during pregnancy						
WILLIAMS, 1967 [8]	UK	210 (asthma)	Examination of hospital records	24%	34%	42%
GLUCK AND GLUCK, 1976 [96]	USA	47 (asthma)	Symptoms (wheeze) and/or medication requirements	43%	43%	14%
GIBBS *et al.*, 1984 [98]	England	67 (asthma)	Self-report of overall changes	14%	30%	33%
SCHATZ *et al.*, 1988 [97]	USA 1978–1984	336 (asthma)	Daily symptom diaries and subjective classification of overall changes	35%	33%	28%
LAO and HUENGSBURG, 1990 [11]	Hong Kong 1984–1997	87 (asthma)	Frequency and severity of symptoms/ attacks and third trimester PEF	30%	39%	31%
BEECROFT *et al.*, 1998 [99]	England	34 (asthma)	Questionnaire on symptoms and treatment	41%	32%	27%
KURINCZUK *et al.*, 1999 [6]	Australia 1995–1997	79 (asthma)	Self-report of overall changes in breathing	35%	35%	16%
KIRCHER *et al.*, 2002 [100]	USA 1978–1984	671 (asthma)	Daily symptom diaries and subjective classification of overall changes	36%	26%	34%
BECKMANN, 2002 [101]	Internet survey	166 (asthma)	Self-report of overall changes	41%	14%	35%
Changes in asthma treatment during pregnancy						
FEIN and KAMIN, 1964 [102]	USA	50 (atopy) 23 (asthma)	Overall change in treatment	21%	67%	12%
MURPHY *et al.*, 2003 [30]	Australia 1998–2002	71 (asthma)	Change in ICS use from first to third trimester	ICS increased with female foetus		
DODDS *et al.*, 1999 [103]	Canada 1991–1993	817 (asthma)	Use of β_2-agonists and steroids	Steroid use greater with female foetus		
Changes in lung function or airway hyperresponsiveness						
SIMS *et al.*, 1976 [104]	England 1973–1974	12 (control) 27 (asthma)	Serial spirometry (FEV_1 and FVC)		No changes with pregnancy	
JUNIPER *et al.*, 1989 [105]	Canada	16 (asthma)	Airway hyperresponsiveness to methacholine and spirometry and medications use		Overall no alteration	Overall PC_{20} improved in second trimester
WHITE *et al.*, 1989 [106]	England	31 (asthma)	Questionnaire (perception of symptoms), daily bronchodilator use and peak flow	6% (subjective)	23% (subjective)	71% (subjective) 34% (peak flow)
Asthma exacerbations during pregnancy						
STENIUS-AARNIALA *et al.*, 1996 [23]	Finland 1982–1992	504 (asthma)	Acute attack of asthma not controlled by normal rescue medications	9.3%		
HENDERSON *et al.*, 2000 [107]	USA 1960–1965	1564 (asthma)	Exacerbation and hospitalisation or acute asthma without hospitalisation	2% hospitalised 15% acute asthma		
SCHATZ *et al.*, 2003 [66]	USA 1994–2000	1739 (sub-divided into mild, moderate and severe asthma)	Exacerbations (emergency department visits, unscheduled doctor visits, oral steroids or hospitalisation)	12% (mild), 26% (moderate), 52% (severe)		

ICS: inhaled corticosteroid; PEF: peak expiratory flow; FEV_1: forced expiratory volume at one second; FVC: forced vital capacity; PC_{20}: provocative concentration causing a 20% fall in FEV_1.

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 effect 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 severity during pregnancy, and may be useful as a predictive measure [107]. Early studies from GLUCK and GLUCK [96] also found a correlation between increased serum IgE and worsening asthma during pregnancy.

LAO and HUENGSBURG [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, BEECROFT *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 β_2-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 [103]. 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 23% 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 β_2-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 β_2-adrenoreceptor 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 β_2-adrenoreceptor 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 β_2-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 oestradiol 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].

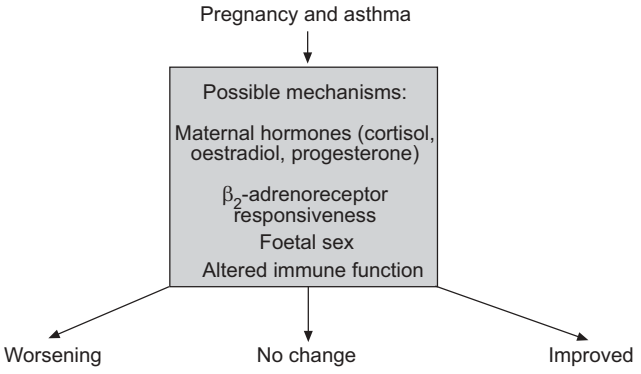

FIGURE 3. Changes in asthma during pregnancy.

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 oestradiol 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 DERBES 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.

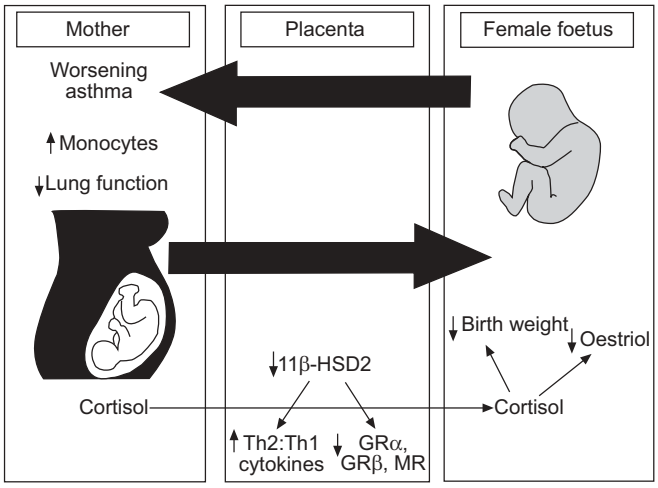

FIGURE 4. The interactions between mother, placenta and foetus in pregnancies complicated by asthma. 11β-HSD2: 11β-hydroxysteroid dehydrogenase type 2; GR: glucocorticoid receptor; Th2: T-helper cell type 2; Th1: T-helper cell type 1; MR: mineralocorticoid receptor.

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 β_2-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 β_2-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 β_2-agonists, such as salmeterol and eformoterol, 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.

REFERENCES

1 Alexander S, Dodds L, Armson BA. Perinatal outcomes in women with asthma during pregnancy. *Obstet Gynecol* 1998; 92: 435–440.
2 Demissie K, Marcella SW, Breckenridge MB, Rhoads GG. Maternal asthma and transient tachypnea of the newborn. *Pediatrics* 1998; 102: 84–90.
3 Kwon HL, Belanger K, Bracken MB. Asthma prevalence among pregnant and child bearing-aged women in the United States: estimates from national health surveys. *Ann Epidemiol* 2003; 13: 317–324.
4 Peat JK. Epidemiology and the changing prevalence of asthma. *In*: Walls RS, Jenkins CR, eds. Understanding asthma. Sydney, MacLennan and Petty, 2000; pp. 11–19.
5 Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998; 351: 1225–1232.
6 Kurinczuk JJ, Parsons DE, Dawes V, Burton PR. The relationship between asthma and smoking during pregnancy. *Women Health* 1999; 29: 31–47.
7 Schaefer G, Silverman F. Pregnancy complicated by asthma. *Am J Obstet Gynecol* 1961; 82: 182–191.
8 Williams DA. Asthma and pregnancy. *Acta Allergol* 1967; 22: 311–323.
9 Gordon M, Niswander KR, Berendes H, Kantor AG. Fetal morbidity following potentially anoxigenic obstetric conditions. VII. Bronchial asthma. *Am J Obstet Gynecol* 1970; 106: 421–429.
10 Bahna SL, Bjerkedal T. The course and outcome of pregnancy in women with bronchial asthma. *Acta Allergol* 1972; 27: 397–406.
11 Lao TT, Huengsburg M. Labour and delivery in mothers with asthma. *Eur J Obstet Gynecol Reprod Biol* 1990; 35: 183–190.
12 Perlow JH, Montgomery D, Morgan MA, Towers CV, Porto M. Severity of asthma and perinatal outcome. *Am J Obstet Gynecol* 1992; 167: 963–967.
13 Lehrer S, Stone J, Lapinski R, *et al.* Association between pregnancy-induced hypertension and asthma during pregnancy. *Am J Obstet Gynecol* 1993; 168: 1463–1466.
14 Demissie K, Breckenridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. *Am J Respir Crit Care Med* 1998; 158: 1091–1095.
15 Kallen B, Rydhstroem H, Aberg A. Asthma during pregnancy- a population based study. *Eur J Epidemiol* 2000; 16: 167–171.
16 Wen SW, Demissie K, Liu S. Adverse outcomes in pregnancies of asthmatic women: results from a Canadian population. *Ann Epidemiol* 2001; 11: 7–12.
17 Liu S, Wen SW, Demissie K, Marcoux S, Kramer MS. Maternal asthma and pregnancy outcomes: a retrospective cohort study. *Am J Obstet Gynecol* 2001; 184: 90–96.
18 Olesen C, Thrane N, Nielsen GL, Sorensen HT, Olsen J. A population-based prescription study of asthma drugs during pregnancy: changing the intensity of asthma therapy and perinatal outcomes. *Respiration* 2001; 68: 256–261.
19 Norjavaara E, de Verdier MG. Normal pregnancy outcomes in a population-based study including 2,968 pregnant women exposed to budesonide. *J Allergy Clin Immunol* 2003; 111: 736–742.
20 Dombrowski MP, Bottoms SF, Boike GM, Wald J. Incidence of preeclampsia among asthmatic patients lower with theophylline. *Am J Obstet Gynecol* 1986; 155: 265–267.
21 Stenius-Aarniala B, Piirila P, Teramo K. Asthma and pregnancy: a prospective study of 198 pregnancies. *Thorax* 1988; 43: 12–18.
22 Pulmonary terms and symbols. A report of the ACCP-ATS Joint Committee on Pulmonary Nomenclature. *Chest* 1975; 67: 583–592.
23 Stenius-Aarniala BS, Hedman J, Teramo KA. Acute asthma during pregnancy. *Thorax* 1996; 51: 411–414.
24 Doucette JT, Bracken MB. Possible role of asthma in the risk of pre-term labor and delivery. *Epidemiology* 1993; 4: 143–150.
25 Schatz M, Zeiger RS, Hoffman CP, *et al.* Perinatal outcomes in the pregnancies of asthmatic women: a prospective controlled analysis. *Am J Respir Crit Care Med* 1995; 151: 1170–1174.
26 Jana N, Vasishta K, Saha SC, Khunnu B. Effect of bronchial asthma on the course of pregnancy, labour and perinatal outcome. *J Obstet Gynaecol* 1995; 21: 227–232.
27 Minerbi-Codish I, Fraser D, Avnun L, Glezerman M, Heimer D. Influence of asthma in pregnancy on labor and the newborn. *Respiration* 1998; 65: 130–135.
28 Sobande AA, Archibong EI, Akinola SE. Pregnancy outcome in asthmatic patients from high altitudes. *Int J Gynaecol Obstet* 2002; 77: 117–121.
29 Mihrshahi S, Belousova E, Marks GB, Peat JK. Pregnancy and birth outcomes in families with asthma. *J Asthma* 2003; 40: 181–187.
30 Murphy VE, Gibson PG, Giles WB, *et al.* Maternal asthma is associated with reduced female fetal growth. *Am J Respir Crit Care Med* 2003; 168: 1317–1323.
31 Bracken MB, Triche EW, Belanger K, Saftlas A, Beckett WS, Leaderer BP. Asthma symptoms, severity, and drug therapy: a prospective study of effects on 2205 pregnancies. *Obstet Gynecol* 2003; 102: 739–752.
32 Triche EW, Saftlas AF, Belanger K, Leaderer BP, Bracken MB. Association of asthma diagnosis, severity, symptoms, and treatment with risk of preeclampsia. *Obstet Gynecol* 2004; 104: 585–593.
33 Dombrowski MP, Schatz M, Wise R, *et al.* Asthma during pregnancy. *Obstet Gynecol* 2004; 103: 5–12.
34 Fisher ES, Whaley FS, Krushat WM, *et al.* The accuracy of Medicare's hospital claims data: progress has been made, but problems remain. *Am J Public Health* 1992; 82: 243–248.
35 Beckmann CA. The effects of asthma on pregnancy and perinatal outcomes. *J Asthma* 2003; 40: 171–180.
36 Papageorgiou AN, Colle E, Farri-Kostopoulos E, Gelfand MM. Incidence of respiratory distress syndrome

following antenatal betamethasone: role of sex, type of delivery, and prolonged rupture of membranes. *Pediatrics* 1981; 67: 614–617.
37 Torday JS, Nielsen HC, Fencl Mde M, Avery ME. Sex differences in fetal lung maturation. *Am Rev Respir Dis* 1981; 123: 205–208.
38 Schatz M, Zeiger RS, Hoffman CP, Saunders BS, Harden KM, Forsythe AB. Increased transient tachypnea of the newborn in infants of asthmatic mothers. *Am J Dis Child* 1991; 145: 156–158.
39 Shohat M, Levy G, Levy I, Schonfeld T, Merlob P. Transient tachypnoea of the newborn and asthma. *Arch Dis Child* 1989; 64: 277–279.
40 Sears MR, Holdaway MD, Flannery EM, Herbison GP, Silva PA. Parental and neonatal risk factors for atopy, airway hyper-responsiveness, and asthma. *Arch Dis Child* 1996; 75: 392–398.
41 Johnson CC, Ownby DR, Peterson EL. Parental history of atopic disease and concentration of cord blood IgE. *Clin Exp Allergy* 1996; 26: 624–629.
42 Liu CA, Wang CL, Chuang H, Ou CY, Hsu TY, Yang KD. Prenatal prediction of infant atopy by maternal but not paternal total IgE levels. *J Allergy Clin Immunol* 2003; 112: 899–904.
43 Littner Y, Mandel D, Sheffer-Mimouni G, Mimouni FB, Deutsch V, Dollberg S. Nucleated red blood cells in infants of mothers with asthma. *Am J Obstet Gynecol* 2003; 188: 409–412.
44 Weinstein RE, Gurvitz M, Greenberg D, *et al.* Altered cerebral dominance in atopy and in children of asthmatic mothers. *Ann N Y Acad Sci* 1992; 650: 25–29.
45 Kelly YJ, Brabin BJ, Milligan P, Heaf DP, Reid J, Pearson MG. Maternal asthma, premature birth, and the risk of respiratory morbidity in schoolchildren in Merseyside. *Thorax* 1995; 50: 525–530.
46 Schatz M, Harden K, Kagnoff M, Zeiger RS, Chilingar L. Developmental follow-up in 15-month-old infants of asthmatic vs. control mothers. *Pediatr Allergy Immunol* 2001; 12: 149–153.
47 Szczeklik A, Milner PC, Birch J, Watkins J, Martin JF. Prolonged bleeding time, reduced platelet aggregation, altered PAF-acether sensitivity and increased platelet mass are a trait of asthma and hay fever. *Thromb Haemost* 1986; 56: 283–287.
48 Szczeklik A, Schmitz-Schumann M, Krzanowski M, Virchow C Sr. Delayed generation of thrombin in clotting blood of atopic patients with hayfever and asthma. *Clin Exp Allergy* 1991; 21: 411–415.
49 Clifton VL, Murphy VE. Maternal asthma as a model for examining fetal sex-specific effects on maternal physiology and placental mechanisms that regulate human fetal growth. *Placenta* 2004; 25, Suppl. A, S45–S52.
50 Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. *Obstet Gynecol* 1999; 93: 392–395.
51 Sorensen TK, Dempsey JC, Xiao R, Frederick IO, Luthy DA, Williams MA. Maternal asthma and risk of pre-term delivery. *Ann Epidemiol* 2003; 13: 267–272.
52 Kramer MS, Coates AL, Michoud MC, *et al.* Maternal asthma and idiopathic pre-term labor. *Am J Epidemiol* 1995; 142: 1078–1088.
53 Corchia C, Bertollini R, Forastiere F, Pistelli R, Perucci C. Is maternal asthma a risk factor for low birth weight? Results of an epidemiologic survey. *Eur J Epidemiol* 1995; 11: 627–631.
54 Apter AJ, Greenberger PA, Patterson R. Outcomes of pregnancy in adolescents with severe asthma. *Arch Intern Med* 1989; 149: 2571–2575.
55 Mabie WC, Barton JR, Wasserstrum N, Sibai BM. Clinical observations on asthma and pregnancy. *J Matern Fetal Med* 1992; 1: 45–50.
56 Greenberger PA, Patterson R. The outcome of pregnancy complicated by severe asthma. *Allergy Proc* 1988; 9: 539–543.
57 Stenius-Aarniala B, Riikonen S, Teramo K. Slow-release theophylline in pregnant asthmatics. *Chest* 1995; 107: 642–647.
58 Dombrowski MP, Schatz M, Wise R, *et al.* Randomized trial of inhaled beclomethasone dipropionate *versus* theophylline for moderate asthma during pregnancy. *Am J Obstet Gynecol* 2004; 190: 737–744.
59 Schatz M, Zeiger RS, Hoffman CP. Intrauterine growth is related to gestational pulmonary function in pregnant asthmatic women. Kaiser-Permanente Asthma and Pregnancy Study Group. *Chest* 1990; 98: 389–392.
60 Miller HC, Hassanein K. Diagnosis of impaired fetal growth in newborn infants. *Pediatrics* 1971; 48: 511–522.
61 Brar HS, Rutherford SE. Classification of intrauterine growth retardation. *Semin Perinatol* 1988; 12: 2–10.
62 Clifton VL, Giles WB, Smith R, *et al.* Alterations of placental vascular function in asthmatic pregnancies. *Am J Respir Crit Care Med* 2001; 164: 546–553.
63 Murphy VE, Zakar T, Smith R, Giles WB, Gibson PG, Clifton VL. Reduced 11beta-hydroxysteroid dehydrogenase type 2 activity is associated with decreased birth weight centile in pregnancies complicated by asthma. *J Clin Endocrinol Metab* 2002; 87: 1660–1668.
64 National Asthma Campaign: Asthma management handbook. Sydney, National Asthma Council Australia, 1996.
65 National Institute of Health: Guidelines for the diagnosis and management of asthma. Bethesda, National Heart, Lung and Blood Institute, 1997.
66 Schatz M, Dombrowski MP, Wise R, *et al.* Asthma morbidity during pregnancy can be predicted by severity classification. *J Allergy Clin Immunol* 2003; 112: 283–288.
67 Barnes NC, Marone G, Di Maria GU, Visser S, Utama I, Payne SL. A comparison of fluticasone propionate, 1 mg daily, with beclomethasone dipropionate, 2 mg daily, in the treatment of severe asthma. International Study Group. *Eur Respir J* 1993; 6: 877–885.
68 Global Initiative for Asthma. 2002. Global strategy for asthma management and prevention. National Institutes of Health. NIH publication 02-3659.
69 Bracken MB, Triche EW. Asthma during pregnancy. *Obstet Gynecol* 2004; 103: 1001–1002.
70 Cugell DW, Frank NR, Gaensler EA, Badger TL. Pulmonary function in pregnancy. I. Serial observations in normal women. *Am Rev Tuberc* 1953; 67: 568–597.
71 Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003; 326: 219.
72 Tai E, Read J. Blood-gas tensions in bronchial asthma. *Lancet* 1967; 1: 644–646.

73 Karetzky MS. Blood studies in untreated patients with acute asthma. *Am Rev Respir Dis* 1975; 112: 607–613.

74 Rudolf M, Riordan JF, Grant BJ, Maberly DJ, Saunders KB. Arterial blood gas tensions in acute severe asthma. *Eur J Clin Invest* 1980; 10: 55–62.

75 Beck SA. Asthma in the female: hormonal effect and pregnancy. *Allergy Asthma Proc* 2001; 22: 1–4.

76 McClure JH, James JM. Oxygen administration to the mother and its relation to blood oxygen in the newborn infant. *Am J Obstet Gynecol* 1960; 80: 554–556.

77 Skomsvoll JF, Ostensen M, Irgens LM, Baste V. Obstetrical and neonatal outcome in pregnant patients with rheumatic disease. *Scand J Rheumatol* 1998; 107: 109–112.

78 Bowden AP, Barrett JH, Fallow W, Silman AJ. Women with inflammatory polyarthritis have babies of lower birth weight. *J Rheumatol* 2001; 28: 355–359.

79 Skomsvoll JF, Baste V, Irgens LM, Ostensen M. The recurrence risk of adverse outcome in the second pregnancy in women with rheumatic disease. *Obstet Gynecol* 2002; 100: 1196–1202.

80 Brabin BJ. An analysis of malaria in pregnancy in Africa. *Bull World Health Organ* 1983; 61: 1005–1016.

81 Moormann AM, Sullivan AD, Rochford RA, *et al.* Malaria and pregnancy: placental cytokine expression and its relationship to intrauterine growth retardation. *J Infect Dis* 1999; 180: 1987–1993.

82 Sullivan AD, Nyirenda T, Cullinan T, *et al.* Malaria infection during pregnancy: intrauterine growth retardation and pre-term delivery in Malawi. *J Infect Dis* 1999; 179: 1580–1583.

83 Aggarwal N, Sawhney H, Vasishta K, Chopra S, Bambery P. Pregnancy in patients with systemic lupus erythematosus. *Aust N Z J Obstet Gynaecol* 1999; 39: 28–30.

84 Fedorkow DM, Persaud D, Nimrod CA. Inflammatory bowel disease: a controlled study of late pregnancy outcome. *Am J Obstet Gynecol* 1989; 160: 998–1001.

85 Baird DD, Narendranathan M, Sandler RS. Increased risk of pre-term birth for women with inflammatory bowel disease. *Gastroenterology* 1990; 99: 987–994.

86 Fonager K, Sorensen HT, Olsen J, Dahlerup JF, Rasmussen SN. Pregnancy outcome for women with Crohn's disease: a follow-up study based on linkage between national registries. *Am J Gastroenterol* 1998; 93: 2426–2430.

87 McGaw T. Periodontal disease and pre-term delivery of low-birth-weight infants. *J Can Dent Assoc* 2002; 68: 165–169.

88 Teng YT, Taylor GW, Scannapieco F, *et al.* Periodontal health and systemic disorders. *J Can Dent Assoc* 2002; 68: 188–192.

89 Fried M, Muga RO, Misore AO, Duffy PE. Malaria elicits type 1 cytokines in the human placenta: IFN-g and TNF-a associated with pregnancy outcomes. *J Immunol* 1998; 160: 2523–2530.

90 Ida A, Tsuji Y, Muranaka J, *et al.* IL-18 in pregnancy: the elevation of IL-18 in maternal peripheral blood during labour and complicated pregnancies. *J Reprod Immunol* 2000; 47: 65–74.

91 Hayashi M, Ohkura T. Elevated levels of serum macrophage colony-stimulating factor in normotensive pregnancies complicated by intrauterine fetal growth restriction. *Exp Hematol* 2002; 30: 388–393.

92 Hahn-Zoric M, Hagberg H, Kjellmer I, Ellis J, Wennergren M, Hanson LA. Aberrations in placental cytokine mRNA related to intrauterine growth retardation. *Pediatr Res* 2002; 51: 201–206.

93 Namazy J, Schatz M, Long L, *et al.* Use of inhaled steroids by pregnant asthmatic women does not reduce intrauterine growth. *J Allergy Clin Immunol* 2004; 113: 427–432.

94 Bertrand JM, Riley SP, Popkin J, Coates AL. The long-term pulmonary sequelae of prematurity: the role of familial airway hyperreactivity and the respiratory distress syndrome. *N Engl J Med* 1985; 312: 742–745.

95 Chan KN, Noble-Jamieson CM, Elliman A, Bryan EM, Aber VR, Silverman M. Airway responsiveness in low birthweight children and their mothers. *Arch Dis Child* 1988; 63: 905–910.

96 Gluck JC, Gluck PA. The effects of pregnancy on asthma: a prospective study. *Ann Allergy* 1976; 37: 164–168.

97 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.

98 Gibbs CJ, Coutts II, Lock R, Finnegan OC, White RJ. Premenstrual exacerbation of asthma. *Thorax* 1984; 39: 833–836.

99 Beecroft N, Cochrane GM, Milburn HJ. Effect of sex of foetus on asthma during pregnancy: blind prospective study. *BMJ* 1998; 317: 856–857.

100 Kircher S, Schatz M, Long L. Variables affecting asthma course during pregnancy. *Ann Allergy Asthma Immunol* 2002; 89: 463–466.

101 Beckmann CA. A descriptive study of women's perceptions of their asthma during pregnancy. *MCN Am J Matern Child Nurs* 2002; 27: 98–102.

102 Fein BT, Kamin PB. Management of allergy in pregnancy. *Ann Allergy* 1964; 22: 341–348.

103 Dodds L, Armson BA, Alexander S. Use of asthma drugs is less among women pregnant with boys rather than girls. *BMJ* 1999; 318: 1011.

104 Sims CD, Chamberlain GV, de Swiet M. Lung function tests in bronchial asthma during and after pregnancy. *Br J Obstet Gynaecol* 1976; 83: 434–437.

105 Juniper EF, Daniel EE, Roberts RS, Kline PA, Hargreave FE, Newhouse MT. Improvement in airway responsiveness and asthma severity during pregnancy. A prospective study. *Am Rev Respir Dis* 1989; 140: 924–931.

106 White RJ, Coutts II, Gibbs CJ, MacIntyre C. A prospective study of asthma during pregnancy and the puerperium. *Respir Med* 1989; 83: 103–106.

107 Henderson CE, Ownby DR, Trumble A, DerSimonian R, Kellner LH. Predicting asthma severity from allergic sensitivity to cockroaches in pregnant inner city women. *J Reprod Med* 2000; 45: 341–344.

108 Gelber M, Sidi Y, Gassner S, *et al.* Uncontrollable life-threatening status asthmaticus- an indicator for termination of pregnancy by cesarean section. *Respiration* 1984; 46: 320–322.

109 Shanies HM, Venkataraman MT, Peter T. Reversal of intractable acute severe asthma by first-trimester termination of pregnancy. *J Asthma* 1997; 34: 169–172.

110 Juniper EF, Daniel EE, Roberts RS, Kline PA, Hargreave FE, Newhouse MT. Effect of pregnancy on airway responsiveness and asthma severity. Relationship to serum progesterone. *Am Rev Respir Dis* 1991; 143: S78.

111 Wendel PJ, Ramin SM, Barnett-Hamm C, Rowe TF, Cunningham FG. Asthma treatment in pregnancy: a randomized controlled study. *Am J Obstet Gynecol* 1996; 175: 150–154.

112 Clark SL. Asthma in pregnancy. National Asthma Education Program Working Group on Asthma and Pregnancy. National Institutes of Health, National Heart, Lung and Blood Institute. *Obstet Gynecol* 1993; 82: 1036–1040.

113 Nelson-Piercy C. Asthma in pregnancy. *Thorax* 2001; 56: 325–328.

114 Lyons HA, Antonio R. The sensitivity of the respiratory center in pregnancy and after the administration of progesterone. *Trans Assoc Am Physic* 1959; 72: 173–180.

115 Lye SJ, Porter DG. Demonstration that progesterone ''blocks'' uterine activity in the ewe *in vivo* by a direct action on the myometrium. *J Reprod Fertil* 1978; 52: 87–94.

116 Tan KS, Thomson NC. Asthma in pregnancy. *Am J Med* 2000; 109: 727–733.

117 Tan KS, McFarlane LC, Lipworth BJ. Paradoxical down-regulation and desensitization of beta2-adrenoceptors by exogenous progesterone in female asthmatics. *Chest* 1997; 111: 847–851.

118 Vrieze A, Postma DS, Kerstjens HA. Perimenstrual asthma: a syndrome without known cause or cure. *J Allergy Clin Immunol* 2003; 112: 271–282.

119 Tan KS. Premenstrual asthma: epidemiology, pathogenesis and treatment. *Drugs* 2001; 61: 2079–2086.

120 Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? *Immunol Today* 1993; 14: 353–356.

121 Saito S, Sakai M, Sasaki Y, Tanebe K, Tsuda H, Michimata T. Quantitative analysis of peripheral blood Th0, Th1, Th2 and the Th1:Th2 cell ratio during normal human pregnancy and preeclampsia. *Clin Exp Immunol* 1999; 117: 550–555.

122 Saito S. Cytokine network at the feto-maternal interface. *J Reprod Immunol* 2000; 47: 87–103.

123 Margni RA, Zenclussen AC. During pregnancy, in the context of a Th2-type cytokine profile, serum IL-6 levels might condition the quality of the synthesized antibodies. *Am J Reprod Immunol* 2001; 46: 181–187.

124 Robinson DS, Hamid Q, Ying S, *et al.* Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. *N Engl J Med* 1992; 326: 298–304.

125 Lapa e Silva JR, Possebon da Silva MD, Lefort J, Vargaftig BB. Endotoxins, asthma, and allergic immune responses. *Toxicology* 2000; 152: 31–35.

126 Chaouat G, Zourbas S, Ostojic S, *et al.* A brief review of recent data on some cytokine expressions at the materno-foetal interface which might challenge the classical Th1/Th2 dichotomy. *J Reprod Immunol* 2002; 53: 241–256.

127 Ostensen M, Aune B, Husby G. Effect of pregnancy and hormonal changes on the activity of rheumatoid arthritis. *Scand J Rheumatol* 1983; 12: 69–72.

128 Ostensen M, Villiger PM. Immunology of pregnancy-pregnancy as a remission inducing agent in rheumatoid arthritis. *Transpl Immunol* 2002; 9: 155–160.

129 Gandevia B. A note on the course of bronchial asthma and vasomotor rhinitis during pregnancy. *Royal Melbourne Hospital Clinical Reports* 1953; 23: 72–74.

130 Rubio Ravelo L, Gago Rodriguez B, Almirall Collazo JJ, Bell Heredia L, Fernandez Fernandez L. Comparative study of progesterone, estradiol and cortisol concentrations in asthmatic and non-asthmatic women. *Allergol Immunopathol (Madr)* 1988; 16: 263–266.

131 Green B. Bronchial asthma as a complication of pregnancy. *JAMA* 1934; 102: 360–363.

132 Derbes VJ, Sodeman WA. Reciprocal influences of bronchial asthma and pregnancy. *Am J Med* 1946; 1: 367–375.

133 Williamson AC. Pregnancy concomitant with asthma or hay fever. *Am J Obstet Gynecol* 1930; 20: 192–197.

134 Hiddlestone HJH. Bronchial asthma and pregnancy. *NZ Med J* 1964; 63: 521–523.

135 Fitzsimons R, Greenberger PA, Patterson R. Outcome of pregnancy in women requiring corticosteroids for severe asthma. *J Allergy Clin Immunol* 1986; 78: 349–353.

136 Schatz M. Asthma during pregnancy: interrelationships and management. *Ann Allergy* 1992; 68: 123–133.

137 Schatz M, Zeiger RS, Harden KM, *et al.* The safety of inhaled beta-agonist bronchodilators during pregnancy. *J Allergy Clin Immunol* 1988; 82: 686–695.

138 Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L, Petitti D. The safety of asthma and allergy medications during pregnancy. *J Allergy Clin Immunol* 1997; 100: 301–306.

139 Mann RD, Kubota K, Pearce G, Wilton L. Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. *J Clin Epidemiol* 1996; 49: 247–250.

140 Burdon JG, Goss G. Asthma and pregnancy. *Aust NZ J Med* 1994; 24: 3–4.

141 Lipson A. Asthma and pregnancy- misleading and incorrect recommendation on the effect of medication on the foetus- and a remedy. *Aust NZ J Med* 1994; 24: 407–408.

142 Barron WM, Leff AR. Asthma in pregnancy. *Am Rev Respir Dis* 1993; 147: 510–511.

143 Cydulka RK, Emerman CL, Schreiber D, Molander KH, Woodruff PG, Camargo CAJ. Acute asthma among pregnant women presenting to the emergency department. *Am J Respir Crit Care Med* 1999; 160: 887–892.

144 Chambers K. Asthma education and outcomes for women of childbearing age. *Case Manager* 2003; 14: 58–61.

145 Liccardi G, Cazzola M, Canonica GW, D'Amato M, D'Amato G, Passalacqua G. General strategy for the management of bronchial asthma in pregnancy. *Respir Med* 2003; 97: 778–789.

146 Asthma Management Handbook. South Melbourne, National Asthma Council Australia Ltd, 2002.

147 Burton J, Reyes M. Breathe in breathe out. Controlling asthma during pregnancy. *AWHONN Lifelines* 2001; 5: 24–30.

148 Seyal AM. Asthma in the hospitalized obstetrical patient. *Clin Rev Allergy Immunol* 2001; 20: 327–339.