Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment—Update 2004 Evidence Tables

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Table 1. Effects of bronchodilators—beta-agonists on maternal health and fetal outcomes when used to treat asthma during pregnancy.

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 1: Alexander, Mather, Dines 1997 Preclinical inhalation exposure system to test metered-dose aerosol reformulation, HFA-134a (1,1,1,2-tetrafluoroethane), and to determine if this is an acceptable method for conducting inhalation teratology studies	**x Animal** New Zealand white rabbits Age: At least 15 weeks old on day 1 of pregnancy Gestation: 8 days at time of exposure Animals removed if negative progesterone assay at day 8	**Purpose/Objective:** To develop a snout-only inhalation exposure system as part of a developmental program for testing metered-dose pharmaceutical aerosol reformulations with HFA-134a (1,1,1,2-tetrafluoroethane), a potential replacement propellant for metered-dose inhalers; to determine if exposure using this technique is an acceptable method for conducting inhalation teratology studies to meet the regulatory requirements for preclinical safety evaluation.				Maternal: Only maternal effects were reported. Both drugs were absorbed into systemic circulation; plasma concentration was within normal biological variation. Fetal: Fetal effects were not described.	Only minor effects on body weight were reported; reduced body weight during acclimatization, reversed following completion of exposure.	No maternal findings at necropsy related to the method of exposure or to treatment with drugs. Data confirm that the technique is an acceptable method for conducting inhalation teratology studies to meet regulatory requirements for preclinical safety evaluation.	Doses are estimated inhaled doses calculated by: RMV x T x C / BW where RMV = respired minute volume T = time of exposure C = chamber concentration BW = body weight
		Arm 1: **Salbutamol**	Total: 25	Total: 18	13 days acclimatization prior to exposure Exposure 1 hour / day on days 8–20 of pregnancy				
		A. Air control	5	4					
		B. HFA-134a control	5	4					
		C. Low dose (115 µg / kg)	5	3					
		D. Intermediate dose (223 µg / kg)	5	4					
		E. High dose (625 µg / kg)	5	3					
		Arm 2: **Salmeterol**	Total: 25	Total: 19					
		F. Air control	5	4					
		G. HFA-134a control	5	4					
		H. Low dose (29.1 µg / kg)	5	4					
		I. Intermediate dose (127 µg / kg)	5	3					
		J. High dose (317 µg / kg)	5	4					
Citation 2: Baker and Flanagan 1997 Case report	**x Human** Age: 34 years Race / Ethnicity: Not specified Pregnancy Trimester: 3rd (33 weeks) Severity: Hospital admission for pneumonia	**Purpose/Objective**: Not specified				Fetal: Fetal tachycardia (>200 beats / minute) was detected 3 hours after last dose. Biophysical profile score = 8 of 8. Fetal atrial flutter at 420 beats / minute with 2.1 conduction and rare 1:1 and 3:1 conduction. Spontaneous conversion to normal rate 8 hours after detection of fetal dysrhythmia.			Albuterol MDI inadvertently continued after initiation of albuterol nebulizer treatments on day 3; both treatments continued for 24 hours. Over that 24-hour period, the patient received 5 albuterol MDI doses and 5 albuterol nebulizer doses. Albuterol administration was stopped upon detection of fetal tachycardia. No further incidences of tachycardia were detected during the remainder of pregnancy after return to normal rhythm. Full-term infant was delivered, HR = 130–150 beats per minute; there were 2 normal ECGs during 4 days of monitoring during hospitalization.
		Arm 1: **Albuterol** • MDI: two 90-µg inhalations q4–6h • Nebulizer: 2.5 mg q4h	1	1	Days 1–3 Day 3 for 24 hours				

Key:

BW = body weight
C = chamber concentration
CI = confidence interval
FEV_1 = forced expiratory volume in 1 second
HFA = hydrofluoroalkane
HR = heart rate
D = incidence density
LMP = last menstrual period
MDI = metered dose inhaler
OR = odds ratio
RMV = respired minute volume
T = time of exposure

Table 1. Effects of bronchodilators—beta-agonists on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 3: Bracken, Triche, Belanger, et al. 2003 Prospective study	**x Human** Age: ≤24–≥35 years Race/Ethnicity: White/Asian: 1,496 (67.8%) African American: 209 (9.5%) Hispanic: 406 (18.4%) Other: 89 (4.0%) Pregnancy Trimester: ≤24 weeks Eligibility: Pregnant women ≤24 weeks gestation with history of physician-diagnosed asthma and random sample of nonasthmatic, pregnant women	**Purpose/Objective:** To examine whether asthma, asthma symptoms, or asthma therapy influences pregnancy outcomes (specifically, preterm delivery, intrauterine growth restriction [IUGR], gestational age, or birth weight) while controlling for other known risk factors.				Preterm delivery (adjusted associations):	IUGR (adjusted associations):		Exclusion criteria included being more than 24 weeks pregnant at interview, having insulin-dependent diabetes mellitus, not speaking English or Spanish, and intending to terminate pregnancy. Asthma symptoms were classified using the modified Global Initiative for Asthma (GINA) guidelines. Asthma treatment was classified using modified GINA guidelines. Asthma severity was determined by cross-classifying with the 2002 GINA grid on symptom and medication steps to derive 4 severity categories: intermittent, mild persistent, moderate persistent, and severe persistent. Gestational age was calculated as completed days from first day of LMP or doctor's estimated date of delivery if LMP was uncertain. Preterm delivery was defined as delivery before 37 weeks gestation. Fetal growth restriction was defined as below 10th percentile of birth weight for gestational age. Women with asthma symptoms but no asthma diagnosis are at particular risk of undermedication and of delivering IUGR infants.
		Arm 1: **Asthma diagnosis** Asthmatic Symptoms or medications No symptoms or medications Nonasthmatic Symptoms or medications No symptoms or medications	 872 778 98 1,333 449 884	 872 778 98 1,333 449 884	Length of study: 4/97–6/00 Length of treatment: Not specified	Not significantly associated with diagnosis of asthma.	Risk increased in symptomatic women (symptom steps 2 and 3) with NO diagnosis of asthma; linear trend OR = 31% (95% CI 4%, 65%). Risk also increased with severity (severity steps 3 and 4) in women with NO diagnosis of asthma; linear trend OR = 30% (95% CI 4%, 62%).		
		Arm 2: **Asthma symptoms** 0 (no symptoms) Step 1 Step 2 Steps 3 and 4	 992 750 305 158	 992 750 305 158		Not significantly associated with asthma symptoms.	Risk increased for women with daily symptoms (OR = 2.25, 95% CI 1.25, 4.06). Linear trend suggested increased risk (25% for each symptom step [95% CI 5%, 47%]).		
		Arm 3: **Asthma severity** 0 (no symptoms, no medications) Step 1 Step 2 Step 3 Step 4	 978 711 289 147 80	 978 711 289 147 80		Not significantly associated with asthma severity.	IUGR was associated with moderate persistent severity (OR = 2.01, 95% CI 1.11, 3.65). Risk declined in highest severity group, but overall linear trend was significant (20% increase for each step in severity [95% CI 4%, 38%]).		

Table 1. **Effects of bronchodilators—beta-agonists on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).**

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 3 (continued)		Arm 4: Asthma treatment				Preterm delivery increased with each increasing treatment step. OR for 2 controller medications = 3.67 (95% CI 1.11, 12.16). OR for 3 controller medications = 4.57 (95% CI 0.75, 24.63). Overall, 32% increased risk (95% CI 0%, 76%) for every increase in treatment step. Theophylline increased risk by 5% (95% CI 1%, 9%) for every increase in dose / month. Theophylline used once daily across pregnancy reduced gestation 1.11 weeks (p = 0.002). Oral steroid use increased risk by 11% (95% CI 3%, 18%) for every increase in dose / month. Oral steroids used daily across pregnancy reduced gestation 2.22 weeks (p = 0.001).	No increased risk by treatment step or for any specific medication type.		
		0 (no medication use)	1,657	1,657					
		Step 1	402	402					
		Step 2	108	108					
		Step 3	28	28					
		Step 4	10	10					
		Exposure:				Specific exposure risks:	Specific exposure risks:		
		• Short-acting bronchodilators	529	529		OR 1.01 (95% CI 1.00, 1.02)	OR 1.00 (95% CI 0.99, 1.01)		
		• Long-acting bronchodilators	64	64		OR 0.99 (95% CI 0.97, 1.02)	OR 1.00 (95% CI 0.99, 1.02)		
		• Leukotriene inhibitors	9	9		OR 1.00 (95% CI 0.87, 1.14)	OR 0.94 (95% CI 0.65, 1.36)		
		• Chromones	22	22		OR 1.01 (95% CI 0.98, 1.03)	OR N / A		
		• Theophylline	15	15		OR 1.05 (95% CI 1.01, 1.04)	OR 0.99 (95% CI 0.94, 1.05)		
		• Oral steroids	52	52		OR 1.11 (95% CI 1.03, 1.18)	OR 0.99 (95% CI 0.93, 1.05)		
		• Inhaled steroids	176	176		OR 0.99 (95% CI 0.98, 1.01)	OR 1.00 (95% CI 0.99, 1.01)		

Table 1. Effects of bronchodilators—beta-agonists on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 4: Rayburn, Atkinson, Gilbert, et al. 1994 Safety assessment	**x Human** Age: Mean 23.0 years, range 18–37 years Race/Ethnicity: Not specified Pregnancy Trimester: 3rd (mean 35.6 weeks, range 33–39 weeks) Eligibility: • Asthma requiring inhaler treatment • Interval between last dose and enrollment ≥6 hours	**Purpose/Objective:** To study effects of a standard dose of inhaled albuterol on short-term maternal and fetal circulations in pregnant women with asthma. Arm 1: **Albuterol MDI** Two inhalations of 0.5% solution Measurements prior to and at 15, 30, 60, and 120 minutes postdosing	12	12	2.25 hours	Maternal: Systolic blood pressure, diastolic blood pressure, heart rate: percent change from baseline was not significant over the course of measurement.	Uterine: Arcuate artery systolic/diastolic ratio: no statistically significant change from baseline. Umbilical artery systolic/diastolic ratio: no statistically significant change from baseline.	Fetal: Fetal aorta velocity: no decrease and no elevation of systolic/diastolic ratio. Fetal heart rate: unchanged.	Subjects' characteristics were not stated explicitly, but authors indicate that the study was approved by the Institutional Review Board and that "twelve women with asthma requiring inhaler treatment gave informed written consent."
Citation 5: Schatz, Zeiger, Harden, et al. 1997 Prospectively monitored cohort study	**x Human** Age: Not specified Race/Ethnicity: Not specified Pregnancy Trimester: 1st, 2nd (all subjects <28 weeks at entry) Eligibility: Pregnant subjects with asthma matched on basis of age, parity, and smoking status with pregnant nonasthmatic controls	**Purpose/Objective:** To assess safety of asthma medications, antihistamines, and decongestants in a prospectively monitored cohort of pregnant women with and without asthma. Arm 1: Exposure to **any asthma/allergy medication** at any time for total cohort: • β-agonists (inhaled or oral) • Theophylline • Cromolyn (inhaled, intranasal, ophthalmic) • Corticosteroids (oral, inhaled, or intranasal) • Antihistamines • Decongestants	1,904 (1,044 with asthma; 860 controls)	1,502 (824 with asthma; 678 controls)	Through delivery, all arms	Fetal effects: Major congenital malformations, 1st trimester: % Incidence (Exp. / Unexp.) **β-agonists 4.3 / 5.6** Theophylline 4.5 / 5.3 Cromolyn 6.0 / 5.0 Corticosteroids 6.9 / 4.9 Antihistamines 3.7 / 5.5 Decongestants 5.5 / 4.8 No significant relationship, p >0.05 for all comparisons	Fetal effects: Major congenital malformations, anytime: % Incidence (Exp. / Unexp.) **β-agonists 3.7 / 6.2** Theophylline 4.7 / 5.3 Cromolyn 6.2 / 4.9 Corticosteroids 6.1 / 4.9 Antihistamines 3.9 / 5.7 Decongestants 5.2 / 4.9 No significant relationship, p >0.05 for all comparisons		Drug exposure data in terms of incidence of malformations for all subjects (number of malformations): 1st Trimester: Exp. / Unexp.; Anytime: Exp. / Unexp. **β-agonists 488 / 1,000 / 557 / 823** Theophylline 292 / 1,208 / 429 / 1,061 Cromolyn* 151 / 1,348 / 243 / 1,247 Corticosteroids 204 / 1,295 / 297 / 1,190 Antihistamines 321 / 1,175 / 493 / 996 Decongestants 453 / 1,032 / 790 / 698 * Inhaled: 158; intranasal: 113; ophthalmic: 23 There were no significant relationships (all p >0.05) between β-agonists, cromolyn, antihistamines, or decongestants and increased incidence of any other adverse perinatal outcomes evaluated (data not shown). There were no significant relationships (all p >0.05) between specific medication use and increased incidence of small-for-gestational-age infants (data not shown). Results may be confounded by presence and severity of asthma.
		Arm 2: **Theophylline** exposure						Maternal effects: Preterm births: • 6.0% in exposed subjects • 3.6% in controls p = 0.034 Mean gestational age 33.08 ± 2.84 weeks in exposed subjects	

Table 1. Effects of bronchodilators—beta-agonists on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 5 (continued)		**Arm 3: Corticosteroid exposure** • Any route						Maternal effects: • Preterm births: 19/297 (64%) in exposed subjects, 45/1,195 (3.8%) in controls p = 0.045 (mean gestational age 32.74 ± 3.75 weeks in exposed subjects) • Preeclampsia: 34/296 (11.5%) in exposed subjects, 85/1,197 (7.1%) in controls, p = 0.013 • Low birth weight infants: 18/297 (6.1%) in exposed subjects, 40/1,197 (3.3%) in controls, p = 0.030	Following are results of multivariate analysis performed in pregnant subjects with asthma when significant univariate associations were identified between drug exposure and perinatal outcome variables: • Oral corticosteroids were independently associated with preeclampsia (p = 0.027, OR = 2.00 [95% CI 1.11, 3.61]), but inhaled steroids were not when controlled for other exposures. • When preeclampsia was included in the model for low birth weight, it was independently related (p = 0.025), but it did not substantially change demonstrated independent relationships with the African American race (p = 0.002) and lower weight gain during pregnancy (p <0.001) and lack of independent relationships with oral or inhaled corticosteroids or mean FEV_1. • African American race (p = 0.007) and lower weight gain during pregnancy (p = 0.001) but not theophylline or inhaled corticosteroids were associated with preterm birth.
		• Total inhaled (with or without oral steroids)						• Preterm births: 13/138 (9.4%) in exposed subjects, 51/1,354 (3.8%) in controls, p = 0.002 • Preeclampsia: 17/137 (12.4%) in exposed subjects, 102/1,356 (7.5%) in controls, p = 0.044 • Low birth weight infants: 11/138 in exposed subjects, 47/1,356 in controls, p = 0.009	
		• Inhaled only					Fetal effects: Incidence of major congenital malformations: • 5.4% in exposed subjects • 4.9% in controls	• Preterm births: 5/64 (7.8%) in exposed subjects, 59/1,428 (4.1%) in controls, p = NS • Preeclampsia: 7/64 (10.9%) in exposed subjects, 112/1,429 (7.8%) in controls, p = NS • Low birth weight infants: 3/64 (4.7%) in exposed subjects, 55/1,430 (3.8%) in controls, p = NS	
		• Oral					• 7.0% in exposed subjects • 4.9% in controls	• Preterm births: 10/130 (7.7%) in exposed subjects, 54/1,362 (4.0%) in controls, p = NS • Preeclampsia: 17/129 (13.2%) in exposed subjects, 102/1,364 (7.5%) in controls, p = 0.022, OR = 2.0 • Low birth weight infants: 11/130 (8.5%) in exposed subjects, 47/1,364 (3.4%) in controls, p = 0.005	

Table 1. Effects of bronchodilators—beta-agonists on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 6: Wilton, Pearce, Martin, et al. 1998 Postmarketing surveillance; noninterventional observational cohort study using prescription event monitoring	**x Human** Age: 14–48 years Race/Ethnicity: Not specified Pregnancy Trimester: 1st Eligibility: Exposure to newly marketed drugs during 1st trimester	**Purpose/Objective:** To determine proportion and nature of congenital anomalies in babies born to women exposed to newly marketed drugs during 1st trimester. Arm 1: 1st trimester exposures—all drugs	831	780	Not specified	Live births: 547 (70.1%) • Full-term: 513 (93.8%) – Single: 504 – Multiple: 9 • Premature: 34 (6.2%) – Single: 33 – Multiple: 1	Anomalies: 14 (1.8%) • Full-term: 12 (85.7%) – Single: 12 – Multiple: 0 • Premature: 2 (14.3%) – Single: 2 – Multiple: 0	Nonviable outcomes: 233 (29.9%) • Ectopic: 10 • Spontaneous abort: 94 • Missed abortion: 5 • Legal abortion: 120 • Intrauterine death: 4	Percentages were based on number of evaluable pregnancies. Conditions for which drugs prescribed were not reported. Mothers of 7 infants born with congenital anomalies had epilepsy and all were on multiple therapies; in 6 of these women, treatment included newer anti-epileptic drugs. Specific data on the 2 respiratory anti-asthmatics, salmeterol and nedocromil, are as follows:
		Arm 2: 1st trimester exposures—respiratory drugs (salmeterol, 65; nedocromil, 35; acrivastine, 33; cetirizine, 20; loratadine, 18)	171	162		Live births: 123 (75.9%) • Full-term: 120 (97.6%) – Single: 119 – Multiple: 1 • Premature: 3 (2.4%) – Single: 3 – Multiple: 0	Anomalies: 2 (1.2%) • Full-term: 2 (100%) – Single: 2 (1 salmeterol, 1 nedocromil) – Multiple: 0 • Premature: 0 (0%)	Nonviable outcomes: 39 (24.1%) • Ectopic: 2 (both salmeterol) • Spontaneous abort: 15 (7 salmeterol, 1 nedocromil) • Missed abortion: 0 • Legal abortion: 21 (4 salmeterol, 8 nedocromil) • Intrauterine death: 1	

	Salmeterol	Nedocromil
Number of pregnancies	93	84
Number stopped before LMP	22	44
1st trimester exposure	65	35
2nd/3rd trimester exposure	3	3
Unknown exposure time	3	2

For the 2 infants born with congenital anomalies in the respiratory drug class, in the first case (baby born with congenital heart disease), the mother was prescribed a new drug, nedocromil (along with aminophylline, steroids, and salbutamol); in the second case (baby born with Aarsgog syndrome), the mother was prescribed a new drug, salmeterol.

Three additional minor (nonreportable) anomalies were reported in live-born infants for an overall percentage rate of 2.2% (17 of 780) (article reports 2.5%); all were full-term births. No mother in this group was taking respiratory agents.

Table 1. Effects of bronchodilators—beta-agonists on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 7: Wilton and Shakir 2002 Postmarketing surveillance; noninterventional observational cohort study using prescription event monitoring	**x Human** Age (total): • M: 54.5 ± 18.6 years (range: 3–95 years) • F: 50.6 ± 19.0 years (range: 3–96 years) Race/Ethnicity: Not specified Pregnancy Trimester: (n = 33) 1st: 30 2nd: 2 3rd : 1 Eligibility: Formoterol Rx 1/96–3/98	**Purpose/Objective:** To monitor the safety of formoterol used under conditions of everyday general clinical practice in England, using postmarketing surveillance beginning as soon as the drug was marketed.				Formoterol effectiveness in total population: 77.2% (based on data from 3,484 of 4,513 patients for whom effectiveness information was given)	Most commonly reported non-respiratory events in terms of incidence density (ID) for total population: Figures given are for ID_1–ID_2, which equals arithmetic difference between ID for each event in month 1 (ID_1) and incidence density for each event in months 2–6 (ID_2) • Headache 3.6 • Tremor 4.8 • Nausea, vomiting 3.7 • Palpitation 3.9 • Cramp 2.9 • Dizziness 3.4	Reported reasons for formoterol discontinuance: 1,712 in 1,572 (27.2%) patients Deaths in total population: 190 (3.3% of cohort); cause of death was recorded for 186 • 74 respiratory (excluding carcinoma of lung) – 10 asthma – 39 COPD – 25 other • 66 cardiovascular • 37 lung or bronchial carcinoma • 9 various causes	No age recorded: n = 717. Events listed are those for which there is no null value for the 99% confidence interval around the point estimate of difference between event incidence in month 1 and event incidence in months 2–6; this indicates that rate of events in first month was significantly greater than that in months 2–6 and can be considered a signal of an adverse event associated with starting formoterol. The event with the highest overall ID was respiratory tract infections, but the first month ID was not significantly different from that in months 2–6, indicating that the event was unlikely to be associated with formoterol use. Rash was reported in 50 patients (0.9% of cohort), although it was not mentioned in Summary of Product characteristics; also there were 3 reports of photosensitivity (2 possibly related to formoterol), 1 report of paraesthesia, 2 reports of nightmares, and 2 reports of hallucinations assessed as possibly related to formoterol.
		Arm 1: Total population for whom formoterol prescribed	5,777 • 2,535 M • 3,212 F • 30 not recorded		Length of study: Data collected on formoterol Rx issued 1/96–3/98 Length of treatment: Data reviewed for 12-month period following 1st Rx				
		Arm 2: Pregnant women for whom formoterol prescribed	33	33 (known to still be taking formoterol after 12 months)		Births: • 25 live births – 5 premature births	Congenital anomalies: • 1 fetal heart rate anomaly (in premature infant) • Pyloric stenosis		
		Arm 3: Children for whom formoterol prescribed	258 (<18 years at time of 1st Rx)	51.8% (known still to be taking formoterol after 12 months) (actual number not reported)		Formoterol effectiveness: Not broken out for children	Suspected adverse events: None	Reported reasons for formoterol discontinuance: 94 events in 90/258 children (34.9% of children)	

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Table 2. Effects of bronchodilators—theophylline on maternal health and fetal outcomes when used to treat asthma during pregnancy.

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 1: Harris, Chapin, Lockhart, et al. 1992 Preclinical teratology screening study	**x Animal** Swiss Crl: CD-1 mice Age: 12–14 weeks Gestational Age: • Group A: treated before and throughout pregnancy • Group B: GD 8 at 1st exposure	**Purpose/Objective:** To design a short-term reproductive and developmental toxicity screen that would identify the toxicity of more potent chemicals; to identify the types of effects found; to determine if theophylline and ethylene glycol produce adverse effects; and to determine whether the screen could distinguish between developmental and reproductive toxicity.							Dose schedules: EGME: 0, 70, 250, and 700 mg/kg/day EG: 0, 250, 700, and 2,500 mg/kg/day BA: 0, 120, 400, and 1,200 mg/kg/day TH: 0, 20, 60, and 200 mg/kg/day Ethylene glycol methyl ether and boric acid resulted in significant effects on male reproduction and on group B females (number of litters, number of young). In this study, boric acid and ethylene glycol methyl ether were more toxic to reproductive systems than either theophylline or ethylene glycol.
		Arm 1: Group A Females treated SD 0–20 Males treated SD 3–20 Cohabitation SD 8–12 Treatments: EGME, EG, BA, and TH	10 males and 10 females at each dose level	10 males and 10 females at each dose level	Length of study: 26 days Length of treatment: Males: SD 3–20 Group A Females: SD 0–20 Group B Females: GD 8–14	Males: Body weight: • EG: 0.5% decrease in body weight at 2,500 mg/kg/day. • TH: 1.2% decrease in body weight at 200 mg/kg/day. Organ weight: • EGME at 250 and 700 mg/kg/day led to significant reduction in testis weight ($p < 0.05$). • BA at 400 and 1,200 mg/kg/day led to significant reduction in testis weight ($p < 0.01$). • EGME at 700 mg/kg/day led to significant reduction in epididymal sperm density and motility ($p < 0.05$).	Males: Histology: • Testes in EGME at 250 mg/kg/day groups showed extensive spermatocyte and spermatid cell loss; highest dose resulted in near-total germ cell loss. • The highest dose of BA caused exfoliation/disruption in >50% of tubules with up to 50% germ cell loss. • Theophylline produced milder changes in epithelium consisting primarily of asynchronous germ cell development and focal loss of 1 or more generations of germ cells.	Females: • EGME at 700 mg/kg/day produced significant decrease in pregnancies ($p < 0.05$). • EG at 2,500 mg/kg/day led to significantly fewer live implants and more dead implants.	
		Arm 2: Group B Females cohabited with males SD 0–3 Treated GD 8–14 Males untreated **Treatments:** EGME, EG, BA, and TH	10 males and 10 females at each dose level (same males used in both arms)	10 males and 10 females at each dose level (same males used in both arms)				Females: • EGME at 250 and 700 mg/kg/day significantly reduced number of deliveries and number of live pups ($p < 0.01$). • BA at 1,200 mg/kg/day significantly reduced number of deliveries and number of live pups ($p < 0.01$). • EG at 2,500 mg/kg/day produced significant decrease in total litter weight ($p < 0.05$).	

Key:

A = pregnant women with asthma not receiving theophylline
AT = pregnant women with asthma receiving theophylline
BA = boric acid
C = pregnant controls—no asthma, no theophylline
EG = ethylene glycol
EGME = ethylene glycol methyl ether
ER = emergency room
FEV = forced expiratory volume
FEV_1 = forced expiratory volume in 1 second
GD = gestation day
GR = growth rate
LBW = low birth weight
NOAELs = no observable adverse effect levels
OR = odds ratio
RACB = reproductive assessment by continuous breeding
PEFR = peak expiratory flow rate
s.c. = subcutaneous
SD = study day
TH = theophylline

Table 2. **Effects of bronchodilators—theophylline on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).**

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 2: Hart and Grimble 1990*a* Preclinical randomized study	**x Animal** Albino Wistar rats Age: Not specified Gestational Age: Day 0 at time of 1st exposure	**Purpose/Objective:** To investigate the effect of methylxanthines on lactational performance.							Caffeine and theobromine significantly enhanced litter growth, while theophylline produced no significant differences in litter growth. Body weight changes in dams generally showed no significant changes during pregnancy or lactation, although the caffeine group lost weight during lactation as opposed to weight gain in the other groups. Enhancement in pup growth did not involve increases in maternal food intake or maternal lipid mobilization.
		Arm 1: **Caffeine** 50 mg/kg/day in drinking water	5 dams	5 dams	Length of study: GD 0 through day 14 postpartum Length of treatment: GD 0 to delivery	Maternal food and fluid intake (mean g/dam or mL/dam/day; p vs. control): Caffeine: Pregnancy Food: 24 ± 1.3 Fluid: 32 ± 1.6 Lactation Food: 38 ± 1.6 Fluid: 57 ± 3.9 (p <0.01)	Litter weight: Caffeine: Day 3: 58 ± 1.8 g Day 13: 182 ± 2.1 g (p <0.01)		
		Arm 2: • **Theophylline** 1 mg/kg/day in drinking water	5 dams	5 dams		Theophylline: Pregnancy Food: 25 ± 1.1 Fluid: 32 ± 3.1 Lactation Food: 34 ± 0.7 Fluid: 47 ± 2.3	Theophylline: Day 3: 63 ± 3.3 g Day 13: 169 ± 7.6 g		
		• **Theobromine** 2 mg/kg/day in drinking water	**5 dams**	**5 dams**		Theobromine: Pregnancy Food: 23 ± 0.8 Fluid: 38 ± 3.5 Lactation Food: 36 ± 1.0 Fluid: 46 ± 4.2	**Theobromine:** **Day 3: 79 ± 6.0 g (p <0.05)** **Day 13: 195 ± 6.9 g (p <0.05)**		
		Arm 3: • **Combination** 50 mg caffeine, 1 mg theophylline, 2 mg theobromine/kg/day in drinking water	5 dams	5 dams		Combination: Pregnancy Food: 25 ± 0.9 Fluid: 35 ± 1.3 Lactation Food: 34 ± 1.2 Fluid: 57 ± 1.0 (p <0.001)	Combination: Day 3: 57 ± 2.1 g Day 13: 160 ± 3.04 g		
		• **Controls**	5 dams	5 dams		Controls: Pregnancy Food: 26 ± 1.1 Fluid: 33 ± 0.4 Lactation Food: 36 ± 3.4 Fluid: 45 ± 1.2	Controls: Day 3: 61 ± 3.6 g Day 13: 159 ± 6.1 g		

Table 2. Effects of bronchodilators—theophylline on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 3: Hart and Grimble 1990*b* Preclinical randomized study	**x Animal** Albino Wistar rats Age: Not specified Gestational Age: Day 0 at time of 1st exposure	**Purpose/Objective:** To investigate the effect of differential dose levels of methylxanthines on lactational performance, with respect to milk volume and composition and pup growth.							In the caffeine group, enhanced litter growth was due to a significant increase in milk volume, consequent to increased maternal food intake. In the theobromine group, only a weak association between increased litter weight and milk volume was shown. Neither theophylline nor the combination of methylxanthines had any effect on the volume or composition of milk.
		Arm 1: **Caffeine** 50 mg/kg/day in drinking water	5 dams	5 dams	Length of study: GD 0 through day 14 postpartum Length of treatment: GD 0 to delivery	Maternal food and fluid intake (mean g/dam or mL/dam/day; p vs. control): Caffeine: Pregnancy Food: 26 ± 0.9 Fluid: 37 ± 1.4 (p <0.05) Lactation Food: 40 ± 1.0 (p <0.01) Fluid: 66 ± 3.6 (p <0.05)	Litter weight and growth rate (GR): Caffeine: Day 3: 69 g Day 13: 213 g (p <0.01) GR: 14.4 g/day (p <0.005)	Milk volume in mL/dam/day (day 13): Caffeine: 53.9 ± 3.7 (p <0.05) No significant effect on protein, lactose, and triacylglycerol content was recorded.	
		Arm 2: • **Theophylline** 1 mg/kg/day in drinking water	5 dams	5 dams		Theophylline: Pregnancy Food: 23 ± 0.4 Fluid: 29 ± 2.5 Lactation Food: 34 ± 0.6 Fluid: 54 ± 6.1	Theophylline: Day 3: 63 g Day 13: 189 g GR: 12.6 g/day	Theophylline: 45.0 ± 2.4	
		• **Theobromine** 2 mg/kg/day in drinking water	5 dams	5 dams		Theobromine: Pregnancy Food: 24 ± 0.6 Fluid: 27 ± 0.8 Lactation Food: 36 ± 1.5 Fluid: 46 ± 1.7	Theobromine: Day 3: 66 g Day 13: 199 g (p <0.05) GR: 13.3 g/day	Theobromine: 51.7 ± 2.6 No significant effect of either on protein, lactose, and triacylglycerol content was reported.	
		Arm 3: • **Combination** 50 mg caffeine, 1 mg theophylline, 2 mg theobromine/kg/day in drinking water	5 dams	5 dams		Combination: Pregnancy Food: 27 ± 0.9 Fluid: 32 ± 1.9 Lactation Food: 40 ± 2.4 Fluid: 54 ± 3.8	Combination: Day 3: 60 g Day 13: 192 g GR: 13.3 g/day	Combination: 47.7 ± 3.8 No significant effect on protein, lactose, and triacylglycerol content was reported.	
		• **Controls**	5 dams	5 dams		**Controls:** **Pregnancy** **Food: 24 ± 0.9** **Fluid: 32 ± 1.5** **Lactation** **Food: 36 ± 0.6** **Fluid: 49 ± 1.5**	**Controls:** **Day 3: 66 g** **Day 13: 183 g** **GR: 11.7 g/day**	**Controls:** **45.3 ± 2.7**	

Table 2. Effects of bronchodilators—theophylline on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 4: Lamb, Gulati, Chambers, et al. 1997 Preclinical toxicity study	**x Animal** Swiss CD-1 mice Age: Not specified Gestational Age: Throughout pregnancy	**Purpose/Objective:** To test theophylline for its effects on reproduction and fertility in Swiss CD-1 mice using the RACB protocol.							Theophylline at these intake levels caused significant adverse reproductive effects in the absence of changes in parental body weight. Although alopecia may be taken as evidence of general toxicity, it is unlikely to "cause" the reproductive effects. The study did not address possibility that early exposure may adversely influence development of the reproductive system.
		Arm 1: **Theophylline** 0.075% weight by volume in feed (consumption estimate of ~ 126 mg/kg/day)	Not specified	Not specified	Length of study: Not specified Length of treatment: Throughout gestation (continuous cohabitation study)	General toxicity: • Body weight: — • Liver weight: — • alopecia: 20–25% (p <0.05 vs. controls)	Reproductive toxicity in treated males: • Seminal vesicle weight: — • Epididymal sperm density: —	Reproductive toxicity, birth parameters: • Number litters/pair: — • Number live pups/litter: decreased by 22% (p <0.05 vs. controls) • Cumulative days to litter: — • Pup weight/litter: —	
		Arm 2: **Theophylline** 0.15% weight by volume in feed (consumption estimate of ~ 260 mg/kg/day)	Not specified	Not specified		• Body weight: — • Liver weight: — • Alopecia: >50% (p <0.05 vs. controls)	• Seminal vesicle weight: — • Epididymal sperm density: —	• Number litters/pair: — • Number live pups/litter: decreased by 29% (p <0.05 vs. controls) • Cumulative days to litter: — • Pup weight/litter: —	
		Arm 3: **Theophylline** 0.30% weight by volume in feed (consumption estimate of ~ 500 mg/kg/day)	Not specified	Not specified		• Body weight: decreased 7% for males; increased 5% for females (p <0.05 vs. controls) • Liver weight: increased for both, 11% for females, unspecified for males (p <0.05 vs. controls) • Alopecia: >50% (p <0.05 vs. controls)	• Seminal vesicle weight: decreased by 19% (p <0.05 vs. controls) • Epididymal sperm density: reduced by 20% (p <0.05 vs. controls)	• Number litters/pair: reduced by 19% (p <0.05 vs. controls) • Number live pups/litter: decreased by 42% (p <0.05 vs. controls) • Cumulative days to litter: consistently greater (p <0.05 vs. controls) • Pup weight/litter: 6% decrease (p <0.05 vs. controls)	
Citation 5: León, Albasanz, Ruiz, et al. 2002 Preclinical study	**x Animal** Female Wistar rats Age: Not specified Gestational Age: Day 2 at time of 1st exposure	**Purpose/Objective:** To determine the effect of caffeine or theophylline administration throughout pregnancy on maternal and fetal brain adenosine A_1 receptors.							Assuming that 10 mg/kg caffeine/theophylline in rats corresponds to ~ 3.5 mg/kg in humans because of difference in metabolic body weight and half-lives, then the daily intake in study is equivalent to 2–3 cups of coffee per day in humans. B_{max} is an indicator of the number of receptors; K_d is an indicator of receptor affinity for caffeine or theophylline; K_i is an indicator of competitive binding affinity. Binding assays indicated a 30% decrease in total receptor numbers in maternal brain plasma membranes and a 50% decrease in fetal brain membranes. This was accompanied by a decrease in receptor affinity in maternal membranes; however, a significant increase in receptor affinity was detected in fetal membranes. This increase was associated with an increase in mRNA coding of the A_1 receptor in fetal brain membranes, but not in maternal membranes. Results suggest that maternal caffeine or theophylline intake modulates adenosine A_1 receptor in both mothers and fetuses.
		Arm 1: **Caffeine** 1 g/L in drinking water (mean intake = 83.2 ± 5.3 mg/kg/day)	Not specified	Not specified	Length of study: GD 2 to delivery Length of treatment: Same	Effect on brain plasma membrane binding: Maternal: B_{max} 97.65 ± 4.13 (p <0.001 vs. controls) K_d 0.364 ± 0.051 Fetal: B_{max} 28.93 ± 2.37 (p <0.001 vs. controls) K_d 0.400 ± 0.046 (p <0.005 vs. controls)	Effect on adenosine A_1 receptor competitive binding affinity for methylxanthines (K_i): Maternal: Caffeine 5.52 ± 1.18 (p <0.05 vs. controls) Theophylline 5.19 ± 2.98 Fetal: Caffeine 9.47 ± 3.38 (p <0.001 vs. controls) Theophylline 1.97 ± 0.09 (p <0.001 vs. controls and vs. caffeine)		

Table 2. **Effects of bronchodilators—theophylline on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).**

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 5 (continued)		Arm 2: **Theophylline** 1 g/L in drinking water (mean intake = 83.8 ± 2.2 mg/kg/day)	Not specified	Not specified		Maternal: B_{max} 97.00 ± 5.76 (p <0.001 vs. controls) K_d 0.384 ± 0.089 Fetal: B_{max} 33.53 ± 4.61 (p <0.001 vs. controls) K_d 0.341 ± 0.068 (p <0.001 vs. controls)	Maternal: Caffeine 11.40 ± 3.02 Theophylline 6.46 ± 4.90 Fetal: Caffeine 9.79 ± 7.48 (p <0.001 vs. controls) Theophylline 3.67 ± 1.00		
		Arm 3: **Controls** Tap water only (mean intake = 84.41 ± 5.5 mL/kg/day)	Not specified	Not specified		Maternal: B_{max} 139.91 ± 5.99 K_d 0.271 ± 0.083 Fetal: B_{max} 56.82 ± 4.25 K_d 1.027 ± 0.365	Maternal: Caffeine 7.96 ± 0.93 Theophylline 3.51 ± 0.72 (p <0.005 vs. caffeine) Fetal: Caffeine 51.84 ± 6.73 Theophylline 4.51 ± 0.15 (p <0.005 vs. caffeine)		
Citation 6: Lindström, Morrissey, George, et al. 1990 Preclinical teratology study	**x Animal** Sprague-Dawley (CD) rats; Swiss (CD-1) mice Age: Not specified Gestational Age: Day 6 at 1st exposure	**Purpose/Objective:** To determine the toxic and teratogenic effects of theophylline in rodents at several dose levels through oral administration during the period of organogenesis.							The corrected body weight gain equals weight at pregnancy termination minus initial weight and gravid uterine weight. Theophylline treatment was not associated with an increase in a particular malformation or group of malformations. There were developmental effects in rats at a dose (0.30%) that did not produce overt maternal toxicity, but adverse developmental effects in mice were observed at doses causing reduced maternal water consumption and body weight gain. It is possible that water deprivation contributed to the effects seen in mice. For maternal toxicity, the NOAELs were at 218 mg/kg/day for rats and 282 mg/kg/day for mice. For developmental toxicity, NOAELS were 124 mg/kg/day in rats and 282 mg/kg/day in mice. These NOAELs are approximately 10- to 30-fold greater than doses required to maintain clinically useful serum theophylline concentrations in humans.
		Arm 1: **Theophylline in rats** (percent admin in feed) • 0% (0 mg/kg/day) • 0.15% (124 mg/kg/day) • 0.20% (218 mg/kg/day) • 0.40% (259 mg/kg/day)	Treated 27 26 27 29	Pregnant 21 20 21 21	Length of study: From 1 day prior to mating through GD 20 (rats) or GD 17 (mice) Length of treatment: GD 6 to 15	Maternal weight measures: • Gestational weight gain, weight gain during treatment, and corrected body weight significantly decreased at 0.40% doses. • Gravid uterine weight and liver weight showed decreasing trend with increasing concentrations.	Maternal food and water consumption: • Food consumption decreased significantly in 0.40% group. • Water consumption increased significantly in all treatment groups.	Fetal parameters: • No differences in number of implantation sites/litter or number of implantation losses. • No significant changes in number of litters with resorptions or percent resorptions/litter. • Average male and female body weight/litter significantly decreased at 0.30 and 0.40% doses. • No increase in percent of fetuses malformed or in incidence of external, visceral, or skeletal malformations.	

Table 2. Effects of bronchodilators—theophylline on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 6 (continued)		Arm 2: **Theophylline in mice** (percent admin in water) • 0% (0 mg/kg/day) • 0.075% (282 mg/kg/day) • 0.15% (372 mg/kg/day) • 0.20% (396 mg/kg/day)	 35 34 37 35	 26 26 33 23		• Gestational weight gain and corrected weight gain significantly depressed at 0.15 and 0.20% doses. • Weight gain during treatment depressed only at 0.20%. • Gravid uterine weight was significantly less at 0.20%. • Absolute liver weight significantly decreased at 0.15 and 0.20% doses.	• Food consumption was not affected, although there was a trend toward increased consumption at 0.20%. • Water consumption decreased significantly at 0.15 and 0.20% doses.	• No differences in number of implantation sites/litter or number of implantation losses. • Percent of resorptions/litter significantly increased with increasing dose. • Among litters with live fetuses, average litter size was comparable to controls. • Average male and female body weight/litter significantly decreased at 0.15 and 0.20%. • Overall, percent of malformed fetuses/litter tended to increase, but there were no statistically significant pairwise comparisons with controls; however, there was a significant increase in number of litters with 1 or more fetuses showing external malformations.	
Citation 7: Shibata, Wachi, Kawaguchi, et al. 2000 Preclinical teratology and toxicity study	**x Animal** Mated female KbI: JW rabbits Age: 18 weeks Gestational Age: 6 days at 1st exposure	**Purpose/Objective:** To investigate the teratogenic and fetal toxicity of theophylline after i.v. administration to pregnant rabbits and the relationship to maternal plasma drug concentrations.							There were no statistically significant differences in the number of corpora lutea, implantations, live fetuses, implantation index, or sex ratio. No abnormalities were observed in the condition or appearance of amniotic fluid or placentas. There were no significant differences in incidence of visceral or skeletal anomalies or ossification. Maternal plasma theophylline levels on GD 18 were almost the same as those on day 6, indicating that there were differences due neither to gestational age nor to effects of 13 repeated administrations. Plasma theophylline concentrations GD 6–18 were ~ 106 **µg/mL in the 60 mg/kg/day group** in which teratogenic effects were observed; concentrations were ~ 56 **µg/mL for the** 30 mg/kg/day group where incidence of teratogenic effects were no greater than controls. It is suggested that the risk of teratogenic and fetal toxicity is dependent on dosage and that maternal (and fetal) plasma theophylline concentrations of 106 **µg/mL and above may** induce toxicity.
		Arm 1: **Theophylline** infusion 15 mg/kg/day at dose volume of 20 mL/kg	20 in fetal studies; 3 in plasma studies	18 in fetal studies; 3 in plasma studies	Length of study: 29 days Length of treatment: Days 6 through 18 of gestation	Maternal toxicity: • Significant decrease in food intake GD 7–21 ($p < 0.05$).	Fetal development: • Number of anomalies: 0	Maternal plasma theophylline concentrations: • GD 6: 29.16 ± 1.16 µg/mL • GD 18: 30.45 ± 3.96 µg/mL	
		Arm 2: **Theophylline** infusion 30 mg/kg/day at dose volume of 20 mL/kg	20 in fetal studies; 3 in plasma studies	18 in fetal studies; 3 in plasma studies		• A few animals showed polyuria following dosing.	• Number of anomalies: 2 (1 multiple, 1 cleft palate) • 14 occurrences of sutural bone vs. 3 in controls ($p < 0.05$)	• GD 6: 56.95 ± 6.52 µg/mL • GD 18: 54.76 ± 1.57 µg/mL	
		Arm 3: **Theophylline** infusion 60 mg/kg/day at dose volume of 20 mL/kg	20 in fetal studies; 3 in plasma studies	19 in fetal studies; 3 in plasma studies		• Significant decreases in body weight from GD 11 ($p < 0.01$). • Significant decrease in food intake GD 7–23 ($p < 0.01$). • Most exhibited sluggish startle reaction. • All exhibited dilation of auricular vessels and accelerated respiration during or following dosing; recovery within day. • Little or no feces in all animals, persisting 10 days or more in ½ the animals.	• Number of anomalies: 8 (8 cleft palate) • 74 fetuses with skeletal variations vs. 52 in controls, including 9 sutural bone occurrences and 63 occurrences of 13th rib ($p < 0.05$ for all) • Significant increase in number of late deaths (11.9 ± 16.3%) vs. 3.8 ± 13.3% in controls ($p < 0.05$)	• GD 6: 104.89 ± 8.68 µg/mL • GD 18: 106.39 ± 4.10 µg/mL	

Table 2. Effects of bronchodilators—theophylline on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 8: Agarwal, Nanavati, Bhagwat, et al. 1998 Case report	**x Human** Age: 26 years Pregnancy trimester: 3rd (40 weeks) Asthma severity: Acute exacerbation unresponsive to salbutamol	**Purpose/Objective:** To report a case of transplacental aminophylline toxicity. Arm 1: **Aminophylline** (250 mg, i.v.) + hydrocortisone with no improvement, then 2 more 250-mg doses of aminophylline	1	1	Length of study: ~ 3–4 days Length of treatment: ~ 2 days, last dose 2 hours before delivery	Fetal effects: • Persistent fetal tachycardia (180–190 beats / minute) necessitating cesarean delivery. • Female newborn developed multifocal clonic convulsions within 3 minutes of birth, unresponsive to treatment. • Infant had supraventricular tachycardia, metabolic acidosis, normal blood pressure, and was neurologically comatosed. • Serum aminophylline levels 8.6 µg / mL at 1 hour. • Developed coffee-colored aspirate at 6 hours. • Expired 48 hours after birth.			Animal studies have shown that 28%–40% more unbound theophylline is present in pregnant rabbit and fetus than in nonpregnant adult rabbit, and transplacental transfer to intrauterine fetus occurs in less than 1 hour. In this case, the fetus was at risk for aminophylline toxicity because the mother received 3 doses of aminophylline, the last dose being 2 hours before delivery.
Citation 9: Bracken, Triche, Belanger, et al. 2003	**x Human** Age: ≤24–≥35 years Race / Ethnicity: White / Asian: 1,496 (67.8%) African American: 209 (9.5%) Hispanic: 406 (18.4%) Other: 89 (4.0%) Pregnancy Trimester: ≤24 weeks	**Purpose/Objective:** To examine whether asthma, asthma symptoms, or asthma therapy influence pregnancy outcomes (specifically, preterm delivery, intrauterine growth restriction [IUGR], gestational age, or birth weight) while controlling for other known risk factors. Arm 1: **Asthma diagnosis** (See Bronchodilators—β-agonists citation #3 for complete description of study arms)			Length of study: 4 / 97–6 / 00 Length of treatment: Not specified	Preterm delivery (adjusted associations): (See Bronchodilators—β-agonists citation #3 for complete description of outcomes)	IUGR: (See Bronchodilators—β-agonists citation #3 for complete description of outcomes)		Exclusion criteria included being more than 24 weeks pregnant at interview, having insulin-dependent diabetes mellitus, not speaking English or Spanish, and intending to terminate pregnancy. Asthma symptoms were classified using the modified Global Initiative for Asthma (GINA) guidelines. Asthma treatment was classified using modified GINA guidelines. Asthma severity was determined by cross-classifying with the 2002 GINA grid on symptom and medication steps to derive 4 severity categories: intermittent, mild persistent, moderate persistent, and severe persistent.
		Arm 2: **Asthma symptoms** (See Bronchodilators—β-agonists citation #3 for complete description of study arms)							

Table 2. Effects of bronchodilators—theophylline on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 9 (continued)	Eligibility: Pregnant women ≤24 weeks gestation with history of physician-diagnosed asthma and random sample of nonasthmatic, pregnant women	Arm 3: **Asthma severity** (See Bronchodilators—β-agonists citation #4 for complete description of study arms)							Gestational age was calculated as completed days from first day of LMP or doctor's estimated date of delivery if LMP was uncertain. Preterm delivery was defined as delivery before 37 weeks gestation. Fetal growth restriction was defined as below 10th percentile of birth weight for gestational age. Women with asthma symptoms but no asthma diagnosis are at particular risk of undermedication and delivering IUGR infants.
		Arm 4: **Asthma treatment** 0 (no medication use) Step 1 Step 2 Step 3 Step 4 Exposure: • Theophylline	 1,657 402 108 28 10 15	 1,657 402 108 28 10 15		Preterm delivery increased with each increasing treatment step. OR for 2 controller medications = 3.67 (95% CI 1.11, 12.16). OR for 3 controller medications = 4.57 (95% CI 0.75, 24.63). Overall, 32% increased risk (95% CI 0%, 76%) for every increase in treatment step. Theophylline increased risk by 5% (95% CI 1%, 9%) for every increase in dose / month. Theophylline used once daily across pregnancy reduced gestation 1.11 weeks (p = 0.002). Specific exposure risks: • Theophylline: OR 1.05 (95% CI 1.01, 1.09)	No increased risk by treatment step or for any specific medication type Specific exposure risks: • Theophylline: OR 0.99 (95% CI 0.94, 1.05)		

Table 2. Effects of bronchodilators—theophylline on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 10: Dombrowski, Schatz, Wise, et al. 2004 Prospective, double-blind, double placebo-controlled randomized clinical trial	**x Human** Age: Beclomethasone: 23.4 ± 5.7 years; Theophylline: 23.4 ± 5.4 years Race/Ethnicity: Beclomethasone: 64.9% African American; Theophylline: 59.7% African-American Pregnancy trimester (at randomization): Beclomethasone: 20.0 ± 4.7 weeks; Theophylline: 20.4 ± 4.8 weeks Eligibility: Mild persistent or moderate persistent asthma; singleton viable pregnancy; no major anomalies; <26 weeks gestation at randomization	**Purpose/Objective:** To compare the efficacy of inhaled beclomethasone dipropionate to oral theophylline for prevention of asthma exacerbations requiring medical intervention during pregnancy.				Primary outcome—at least 1 validated asthma exacerbation:	Study completion/compliance (p vs. theophylline):	Other asthma outcomes (p vs. theophylline):	Exclusion criteria for enrollment in this trial were: prenatal care or delivery planned elsewhere; imminent delivery; preeclampsia or gestational hypertension; current or history of epilepsy treated with medications; allergy or sensitivity to theophylline, inhaled steroids, or albuterol; treatment with oral corticosteroids for medical condition other than asthma; treatment with H_2-receptor antagonists; participation in other studies that might influence asthma control; previous or current participation in an asthma study; active pulmonary disease other than asthma; cardiac diseases (Class II–IV); pregestational diabetes; endocrine disorders requiring medication; sickle-cell disease; acute or chronic liver disease; inability to schedule an ultrasound; or inability to give informed written consent. Study used the National Asthma Education and Prevention Program's 1993 severity classification (modified in 1997) in which moderate asthma included mild persistent and moderate persistent asthma. Patients were also excluded if they had unstable or severe asthma (FEV_1 <60% predicted >4 hours postbronchodilator; or history of ≥1 hospitalization of at least 24 hours duration for asthma exacerbation since conception; or regular (daily or every other day) oral corticosteroids during the past 4 weeks; or need for ≥16 puffs inhaled corticosteroids/day; or requirement for >500 mg theophylline with ≥12 puffs/day of inhaled corticosteroids; or history of >4 courses of oral steroids in the previous year). Moderate asthma defined as symptoms for ≥8 days over past 4 weeks and/or FEV_1 60–80% predicted for >4 hours postbronchodilator; participants with mild asthma by symptoms and FEV_1 but who required regular medications for asthma control were also considered to have moderate asthma. No significant difference in proportion of asthma exacerbations in two arms, but beclomethasone cohort had significantly lower incidence of discontinuing study medications because of side effects. No significant differences in obstetric or perinatal outcomes between the two groups.
		Arm 1: **Beclomethasone** inhaler (4 puffs t.i.d. for ~ 504 µg/day) + placebo tablets on same schedule as theophylline tablets in Arm 2	199	194	Length of study: Randomization began 12/95, ended 2/00 Length of treatment: Through delivery	Beclomethasone 35/194 (18.0%), (p = 0.554, risk ratio 95% CI = 0.9 [0.6–1.3] vs. theophylline) Included: • 30/194 (15.5%) ER visits • 16/194 (8.2%) oral corticosteroids • 10/194 (5.2%) hospital admissions	Beclomethasone • Treatment failure: 11/194 (5.7%), p = 0.790, risk ratio 95% CI = 0.9 (0.4–2.0) • Discontinued medications due to side effects: 6/194 (3.1%), p = 0.016, risk ratio 95% CI = 0.3 (0.1–0.9) • Completed protocol: 136/194 (70.1%), p = 0.219, risk ratio 95% CI = 1.1 (0.9–1.3) • Proportion self-reported compliance: 0.691 ± 0.332 (p = 0.762) • Proportion measured compliance: 0.271 ± 0.281 (p = 0.333)	Beclomethasone • Proportion of study visits with FEV_1 <80% predicted: 0.231 ± 0.334 (p = 0.039) • Proportion of study visits with PEFR <80% predicted: 0.179 ± 0.283 (p = 0.149) • Average number of albuterol puffs/day: 1.4 ± 2.1 (p = 0.937) • Proportion reporting nocturnal symptoms: 0.138 ± 0.192 (p = 0.751) • Asthma symptoms at delivery: 36/192 (18.8%) (p = 0.696, risk ratio 95% CI = 1.1 [0.7–1.7])
		Arm 2: **Theophylline** tablets (initially 200 mg b.i.d. [a.m. and p.m.], then 300 mg b.i.d. after 3 days; total dose adjusted between 400 and 800 mg/day; target serum level 8–12 µg/mL) + placebo inhaler on same schedule as beclomethasone inhaler in Arm 1	199	191/190 (Delivery information not available for 1 patient with primary outcome information)		Theophylline 30/191 (20.4%) Included: • 36/191 (18.8%) ER visits • 21/191 (11.0%) oral corticosteroids • 15/191 (7.9%) hospital admissions	Theophylline • Treatment failure: 12/190 (6.3%) • Discontinued medications due to side effects: 17/190 (8.9%) • Completed protocol: 122/190 (64.2%) • Proportion self-reported compliance: 0.679 ± 0.349 • Proportion measured compliance: 0.356 ± 0.348	Theophylline • FEV_1 0.284 ± 0.221 (p = 0.039) • PEFR 0.214 ± 0.300 • Albuterol 1.5 ± 2.3 • Nocturnal 0.163 ± 0.229 • Sx at delivery 32/186 (17.2%)	

Table 2. **Effects of bronchodilators—theophylline on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).**

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 10 (continued)									It was expected that beclomethasone would be more efficacious because of greater anti-inflammatory effects, but possible explanation is that theophylline is bronchodilator + anti-inflammatory. Also, there are newer inhaled corticosteroids (e.g., fluticasone propionate and budesonide) that are more potent, require fewer puffs / day, and have less systemic absorption than beclomethasone; studies are needed to compare theophylline to these newer inhaled corticosteroids during pregnancy.
Citation 11: Neff and Leviton 1990 Prospective cohort study; review of data from Collaborative Perinatal Project	**x Human** Age: Not specified Race / Ethnicity: Not specified Pregnancy Trimester: Not specified Eligibility: Singleton pregnancies and data available on asthma status, theophylline administration, and stillbirth outcomes	**Purpose/Objective:** To assess to what extent theophylline receipt by pregnant women increases their risk of stillbirth. Arm 1: **Theophylline** administration for bronchial asthma during pregnancy	59,391 total pregnancies	51,830 singleton pregnancies (patients excluded because nonsingleton pregnancy, missing data on asthma status or stillborn status)	Length of study: Data on pregnancies from 1/1/59–6/30/66 Length of treatment: Not specified	Stillbirths, asthma and theophylline status: • Asthma, theophylline: Y 6, N 247, Risk ratio 0.8 • Asthma, no theophylline: Y 13, N 443 • No asthma, theophylline: Y 2, N 155, Risk ratio 0.7 • No asthma, no theophylline: Y 931, N 50,033			Theophylline ingested by pregnant women does not appear to increase their risk of delivering a stillborn infant. This applies both to women who had a diagnosis of asthma and to those who were not so labeled. Overall stillbirth rate was 1.8% (952 / 51,830). Power of 6 analyses ranged from 48.0% to 57.7%. Three limitations of the study: 1. The approximate 50% power is a consequence of a low incidence of stillbirth. 2. Details of theophylline dosage were not available to study. 3. Information on why a total of 157 women without a diagnosis of asthma received theophylline was not available to the study. Findings led to the conclusion that theophylline does not compromise fetal well-being and is not associated with any increased risk of stillbirth.
		Arm 2: **Theophylline** administration for acute asthma during pregnancy				Stillbirths, asthma and theophylline status: • Asthma, theophylline: Y 1, N 125, Risk ratio 0.2 • Asthma, no theophylline: Y 6, N 140 • No asthma, theophylline: Y 7, N 277, Risk ratio 1.3 • No asthma, no theophylline: Y 938, N 50,336			
		Arm 3: **Theophylline** administration for status asthmaticus during pregnancy				Stillbirths, asthma and theophylline status: • Asthma, theophylline: Y 1, N 20, Risk ratio 0.3 • Asthma, no theophylline: Y 3, N 14 • No asthma, theophylline: Y 7, N 382, Risk ratio 1.0 • No asthma, no theophylline: Y 941, N 50,462			

Table 2. Effects of bronchodilators—theophylline on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 12: Park, Schmer, Myers 1990 Case reports	**x Human** Age: 19, 29, and 32 years Race/Ethnicity: Not specified Pregnancy Trimester: All Asthma severity: Chronic	**Purpose/Objective:** To report cases of 3 infants with severe unusual congenital cardiovascular anomalies born to asthmatic mothers who had taken theophylline throughout pregnancy.							Important aspects of cardiovascular anomalies observed were their complex nature and wide spectrum, including double-outlet right ventricle, hypoplasia of left ventricle, aortic anomalies, and transposition of great arteries. It is especially noteworthy that truncus arteriosus and double-outlet right ventricle, induced frequently in animal experiments with theophylline, also were observed in humans. Three cases provide evidence linking use of theophylline with congenital anomalies in humans, though this evidence does not conclusively prove a direct cause-and-effect relationship.
		Arm 1: **Theophylline** • 900 mg daily orally for several years • Because of 1st trimester episode of status asthmaticus, hospitalized, treated with O_2, albuterol inhalation, terbutaline s.c. 0.25 mg, and theophylline, 300 mg b.i.d. initially, followed by aminophylline drip, 130 mg at 5 mg/kg/hour for 24 hours • Discharged on 3rd day, taking theophylline 300 mg t.i.d.	1	1	Length of study: Not specified Length of treatment: As described	Infant sex and birth weight: • Female, delivered at term • 7 lb 6 oz (3,318 g)	Cardiovascular anomalies: • Heart murmur • Isolated levocardia • Double-outlet right ventricle • Transposition of great arteries • Ventricular septal defect • Pulmonary stenosis • Hypoplasia of left ventricle and mitral valve	Other anomalies: • Rudimentary spleen • Dysplasia of right kidney • Hydronephrosis of left kidney	
		Arm 2: **Theophylline** 300 mg orally b.i.d. + albuterol inhaler q.i.d. throughout pregnancy	1	1		• Female, delivered at term • 7 lb 3 oz (3,234 g)	• Congestive heart failure • Poor peripheral perfusion • Hypoplasia of ascending aorta, aortic arch, and left ventricle • Atresia of mitral and aortic valves, consistent with hypoplastic left heart syndrome and total anomalous pulmonary venous connection into innominate vein • Infant died on third day of life		
		Arm 3: **Theophylline** • Asthmatic breathing since age of 3 • Because of mild wheezing, took theophylline 750 mg orally, and used albuterol inhaler 3–4/day throughout pregnancy	1	1		• Female, delivered at term • 8 lb 3 oz (3,684 g)	• Congestive heart failure • Coarctation of aorta • Large atrial septal defect • Patent ductus arteriosus		

Table 2. Effects of bronchodilators—theophylline on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 13: Schatz, Zeiger, Harden, et al. 1997 Prospectively monitored cohort study	**x Human** Age: Not specified Race / Ethnicity: Not specified Pregnancy Trimester: 1st, 2nd (all subjects <28 weeks at entry) Eligibility: Pregnant subjects with asthma matched on basis of age, parity, and smoking status with pregnant nonasthmatic controls	**Purpose/Objective:** To assess safety of asthma medications, antihistamines, and decongestants in a prospectively monitored cohort of pregnant women with and without asthma.							Drug exposure data in terms of incidence of malformations for all subjects (number of malformations): 1st Trimester / Anytime Exp. Unexp. Exp. Unexp. β-agonists 488 1,000 557 823 **Theophylline 292 1,208 429 1,061** Cromolyn* 151 1,348 243 1,247 Corticosteroids 204 1,295 297 1,190 Antihistamines 321 1,175 493 996 Decongestants 453 1,032 790 698 * Inhaled: 158; intranasal: 113; ophthalmic: 23 There were no significant relationships (all p >0.05) between β-agonists, cromolyn, antihistamines, or decongestants and increased incidence of any other adverse perinatal outcomes evaluated (data not shown). There were no significant relationships (all p >0.05) between specific medication use and increased incidence of small-for-gestational-age infants (data not shown). Results my be confounded by presence and severity of asthma. The following are results of multivariate analysis performed in pregnant subjects with asthma when significant univariate associations were identified between drug exposure and perinatal outcome variables: • Oral corticosteroids were independently associated with preeclampsia (p = 0.027, OR = 2.00 [95% CI 1.11, 3.61]), but inhaled steroids were not when controlled for other exposures. • When preeclampsia was included in the model for low birth weight, it was independently related (p = 0.025), but it did not substantially change demonstrated independent relationships with African American race (p = 0.002) and lower weight gain during pregnancy (p <0.001) and lack of independent relationships with oral or inhaled corticosteroids or mean FEV_1. • African American race (p = 0.007) and lower weight gain during pregnancy (p = 0.001) but not theophylline or inhaled corticosteroids were associated with preterm birth.
		Arm 1: Exposure to **any asthma/allergy medication** at any time for total cohort: • β-agonists (inhaled or oral) • Theophylline • Cromolyn (inhaled, intranasal, ophthalmic) • Corticosteroids (oral, inhaled, or intranasal) • Antihistamines • Decongestants	1,904 (1,044 with asthma; 860 controls)	1,502 (824 with asthma; 678 controls)	Through delivery, all arms	Fetal effects: Major congenital malformations, 1st trimester: % Incidence Exp. Unexp. β-agonists 4.3 5.6 **Theophylline 4.5 5.3** Cromolyn 6.0 5.0 Corticosteroids 6.9 4.9 Antihistamines 3.7 5.5 Decongestants 5.5 4.8 No significant relationship, p >0.05 for all comparisons	Fetal effects: Major congenital malformations, anytime: % Incidence Exp. Unexp. β-agonists 3.7 6.2 **Theophylline 4.7 5.3** Cromolyn 6.2 4.9 Corticosteroids 6.1 4.9 Antihistamines 3.9 5.7 Decongestants 5.2 4.9 No significant relationship, p >0.05 for all comparisons		
		Arm 2: **Theophylline** exposure						Maternal effects: Preterm births: • 6.0% in exposed subjects • 3.6% in controls p = 0.034 Mean gestational age 33.08 ± 2.84 weeks in exposed subjects	
		Arm 3: **Corticosteroid** exposure (See Bronchodilators—β-agonists citation #5 for complete description of study arms)				(See Bronchodilators—β-agonists citation #5 for complete description of outcomes)			

Table 2. Effects of bronchodilators—theophylline on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 14: Stenius-Aarniala, Riikonen, Teramo 1995 Case-control study	**x Human** Age (mean): AT: 29.2 A: 28.6 C: 28.9 Race/Ethnicity: Not specified Pregnancy Trimester: All Eligibility: Consecutive women with asthma referred to pulmonary medicine and maternity outpatient clinics for regular checkups	**Purpose/Objective:** To study the influence of theophylline treatment on the course of pregnancy and delivery and on maternal and infant health.							The prepregnancy value of theophylline plasma concentration was accepted if the dose remained unchanged, but if the dose changed during pregnancy, only recent values were accepted. Of the 3.8% malformations (~ 8) in the AT group, 3 were born to women receiving theophylline in the first trimester. Results indicate that theophylline treatment using moderate doses can be considered safe during the second and third trimesters, but safety in first trimester with regard to teratogenicity remains to be determined.
		Arm 1: **Theophylline (AT)** • 1st trimester: mean 506.5 ± 180 mg diurnal dose, orally • 2nd, 3rd trimester: mean 476 ± 179.5 mg diurnal dose, orally	121 91	121 91	Length of study: 1982–1990 Length of treatment: Varied as shown, but no information on duration of theophylline treatment prior to pregnancy	Maternal characteristics and concomitant treatment: • Percent exacerbations: 16.8 (p <0.001 vs. A)** • Inhaled β_2-agonist: 99.0% (p <0.003 vs. A) • Inhaled budesonide or beclomethasone: 83.0% (p <0.001 vs. A) • Course of oral corticosteroid therapy: 36% (p <0.001 vs. A) • Continuous oral corticosteroid therapy: 5.3% (p <0.01 vs. A)	Pregnancy complications: • Preeclampsia: 15.6% (p <0.003 vs. C) • Intrahepatic cholestasis of pregnancy: 3.3% • Bleeding during 2nd trimester: 2.4% (p <0.05 vs. C)	Neonatal effects: • Jaundice: 15.2% (p <0.03 vs. A, p <0.05 vs. C) • Malformations: 3.8%	
		Arm 2: **No theophylline (A)**	292*	292*		• Percent exacerbations: 4.1** • Inhaled β_2-agonist: 92.0% • Inhaled budesonide or beclomethasone: 52.0% • Course of oral corticosteroid therapy: 9.3% • Continuous oral corticosteroid therapy: 0.3%	• Preeclampsia: 10.5% • Intrahepatic cholestasis of pregnancy: 3.4% (p <0.04 vs. C) • Bleeding during 2nd trimester: 1.7% (p <0.01 vs. C)	• Jaundice: 7.6% • Malformations: 1.0%	
		Arm 3: **Controls (C)**	237	237			• Preeclampsia: 6.4% • Intrahepatic cholestasis of pregnancy: 0.43% • Bleeding during 2nd trimester: 6.8%	• Jaundice: 7.8% • Malformations: 0.8%	

* Group included 12 women not treated with maintenance dose of oral theophylline, but who were given theophylline parenterally over 1–2 days for exacerbations during pregnancy.

** Values given are those in Table 3 of the article; abstract indicates AT group had 19% exacerbations and A group had 6%.

Table 2. Effects of bronchodilators—theophylline on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 15: Wendel, Ramin, Barnett-Hamm, et al. 1996 Prospective randomized controlled trial	**x Human** Age: 22 ± 5 years Race/Ethnicity: Hispanic: 46% African American: 42% White: 10% Pregnancy Trimester: 2nd–3rd (22.7 ± 9.1 weeks) Eligibility: Asthma exacerbation prompting visit to ER or prenatal clinic and requiring inhaled bronchodilator therapy FEV <70% predicted after initial therapy	**Purpose/Objective:** To study the effect of inhaled steroids on asthma exacerbations in pregnancy.							84 pregnant women initially enrolled in the study; 12 patients overall were lost to followup. However, data (except for obstetric complications) are recorded in numbers of exacerbations, and the number of women experiencing exacerbations in each of the groups is not specified. Patients in inpatient groups 1 and 2 underwent a second randomization at discharge into Groups A and B. Obstetric complications relate to all patients, both those in initial outpatient group and those in both inpatient groups. General population appears to refer to obstetric population at the institution where the study was performed.
		Arm 1: **Outpatient group** (FEV >70% predicted after initial isoetharine therapy); patients discharged with no other therapy indicated Outpatient followup only	40 exacerbations (number of subjects not specified)	33 exacerbations (number of subjects not specified)	Duration: Through delivery			Maternal: All patient groups (n = 72): Obstetric complications: • Pregnancy hypertension (n = 12) increased 13% of general population • Cesarean sections (n = 21) increased 17% over general population • Other complications not outside range of those in general population	
		Arm 2: **Inpatient group 1** (FEV <70% predicted after initial isoetharine therapy) • Albuterol MDI q4h • IV methylprednisolone 1 mg/kg q8h; max single dose = 80 mg • IV aminophylline 5 mg/kg loading dose, then 0.5 mg/kg maintenance dose until 10–20 µg/dL therapeutic level achieved	33 exacerbations (number of subjects not specified)	Not specified		Maternal: Aminophylline (group 1): no effect on response time; no decrease in length of stay.			
		Arm 3: **Inpatient group 2** (FEV <70% predicted after initial isoetharine therapy) • Albuterol MDI q4h • IV methylprednisolone 1 mg/kg q8h; max single dose = 80 mg (For additional data relating to stratification of inpatient group 2, see Inhaled Steroids citation #13)	32 exacerbations (number of subjects not specified)	Not specified		Data relating to outcomes in stratified inpatient group are shown at Inhaled Steroids citation #13.			

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Table 3. Effects of cromolyn on maternal health and fetal outcomes when used to treat asthma during pregnancy.

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 1: Bracken, Triche, Belanger, et al. 2003 Prospective study	**x Human** Age: ≤24–≥35 years Race / Ethnicity: White / Asian: 1,496 (67.8%) African American: 209 (9.5%) Hispanic: 406 (18.4%) Other: 89 (4.0%) Pregnancy Trimester: ≤24 weeks Eligibility: Pregnant women ≤24 weeks gestation with history of physician-diagnosed asthma and random sample of nonasthmatic, pregnant women	**Purpose/Objective:** To examine whether asthma, asthma symptoms, or asthma therapy influence pregnancy outcomes (specifically, preterm delivery, intrauterine growth restriction [IUGR], gestational age, or birth weight) while controlling for other known risk factors.							
		Arm 1: **Asthma diagnosis** (See Bronchodilators—β-agonists citation #3 for complete description of study arms)			Length of study: 4 / 97–6 / 00 Length of treatment: Not specified	Preterm delivery (adjusted associations): (See Bronchodilators—β-agonists citation #3 for complete description of outcomes)	IUGR: (See Bronchodilators—β-agonists citation #3 for complete description of outcomes)		Exclusion criteria included being more than 24 weeks pregnant at interview, having insulin-dependent diabetes mellitus, not speaking English or Spanish, and intending to terminate pregnancy. Asthma symptoms were classified using the modified Global Initiative for Asthma (GINA) guidelines. Asthma treatment was classified using modified GINA guidelines. Asthma severity was determined by cross-classifying with the 2002 GINA grid on symptom and medication steps to derive 4 severity categories: intermittent, mild persistent, moderate persistent, and severe persistent. Gestational age was calculated as completed days from first day of LMP or doctor's estimated date of delivery if LMP was uncertain. Preterm delivery was defined as delivery before 37 weeks gestation. Fetal growth restriction was defined as below 10th percentile of birth weight for gestational age. Women with asthma symptoms but no asthma diagnosis are at particular risk of undermedication and of delivering IUGR infants.
		Arm 2: **Asthma symptoms** (See Bronchodilators—β-agonists citation #3 for complete description of study arms)							
		Arm 3: **Asthma severity** (See Bronchodilators—β-agonists citation #3 for complete description of study arms)							
		Arm 4: **Asthma treatment** 0 (no medication use) Step 1 Step 2 Step 3 Step 4 Exposure: • Chromones	 1,657 402 108 28 10 22	 1,657 402 108 28 10 22		Preterm delivery increased with each increasing treatment step. OR for 2 controller medications = 3.67 (95% CI 1.11, 12.16). OR for 3 controller medications = 4.57 (95% CI 0.75, 24.63). Overall, 32% increased risk (95% CI 0%, 76%) for every increase in treatment step. Specific exposure risks: • Chromones: OR 1.01 (95% CI 0.98, 1.03).	No increased risk by treatment step or for any specific medication type Specific exposure risks: • Chromones: N / A		

Key:
FEV = forced expiratory volume
FEV_1 = forced expiratory volume in 1 second
LMP = last menstral period
N / A = not applicable
OR = odds ratio

Table 3. Effects of cromolyn on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 2: Schatz, Zeiger, Harden, et al. 1997 Prospectively monitored cohort study	**x Human** Age: Not specified Race/Ethnicity: Not specified Pregnancy Trimester: 1st, 2nd (all subjects <28 weeks at entry) Eligibility: Pregnant subjects with asthma matched on basis of age, parity, and smoking status with pregnant nonasthmatic controls	**Purpose/Objective:** To assess safety of asthma medications, antihistamines, and decongestants in a prospectively monitored cohort of pregnant women with and without asthma.							Drug exposure data in terms of incidence of malformations for all subjects (number of malformations): * Inhaled: 158; intranasal: 113; ophthalmic: 23 There were no significant relationships (all p >0.05) between β-agonists, cromolyn, antihistamines, or decongestants and increased incidence of any other adverse perinatal outcomes evaluated (data not shown). There were no significant relationships (all p >0.05) between specific medication use and increased incidence of small-for-gestational-age infants (data not shown). Results may be confounded by presence and severity of asthma. The following are results of multivariate analysis performed in pregnant subjects with asthma when significant univariate associations were identified between drug exposure and perinatal outcome variables: • Oral corticosteroids were independently associated with preeclampsia (p = 0.027, OR = 2.00 [95% CI 1.11, 3.61]) but inhaled steroids were not when controlled for other exposures. • When preeclampsia was included in the model for low birth weight, it was independently related (p = 0.025), but it did not substantially change demonstrated independent relationships with African American race (p = 0.002) and lower weight gain during pregnancy (p <0.001) and lack of independent relationships with oral or inhaled corticosteroids or mean FEV_1. • African American race (p = 0.007) and lower weight gain during pregnancy (p = 0.001) but not theophylline or inhaled corticosteroids were associated with preterm birth.
		Arm 1: Exposure to **any asthma/allergy medication** at any time for total cohort: • β-agonists (inhaled or oral) • Theophylline • Cromolyn (inhaled, intranasal, ophthalmic) • Corticosteroids (oral, inhaled, or intranasal) • Antihistamines • Decongestants	1,904 (1,044 with asthma; 860 controls)	1,502 (824 with asthma; 678 controls)	Through delivery, all arms	Fetal effects: Major congenital malformations, 1st trimester: % Incidence (Exp. / Unexp.) β-agonists 4.3 / 5.6 Theophylline 4.5 / 5.3 **Cromolyn 6.0 / 5.0** Corticosteroids 6.9 / 4.9 Antihistamines 3.7 / 5.5 Decongestants 5.5 / 4.8 No significant relationship, p >0.05 for all comparisons	Fetal effects: Major congenital malformations, any time: % Incidence (Exp. / Unexp.) β-agonists 3.7 / 6.2 Theophylline 4.7 / 5.3 **Cromolyn 6.2 / 4.9** Corticosteroids 6.1 / 4.9 Antihistamines 3.9 / 5.7 Decongestants 5.2 / 4.9 No significant relationship, p >0.05 for all comparisons		
		Arm 2: **Theophylline** exposure (See Bronchodilators—β-agonists citation #5 for complete description of study arms)				(See Bronchodilators—β-agonists citation #5 for complete description of outcomes)			
		Arm 3: **Corticosteroid** exposure (See Bronchodilators—β-agonists citation #5 for complete description of study arms)				(See Bronchodilators—β-agonists citation #5 for complete description of outcomes)			

	1st Trimester Exp.	1st Trimester Unexp.	Anytime Exp.	Anytime Unexp.
β-agonists	488	1,000	557	823
Theophylline	292	1,208	429	1,061
Cromolyn*	**151**	**1,348**	**243**	**1,247**
Corticosteroids	204	1,295	297	1,190
Antihistamines	321	1,175	493	996
Decongestants	453	1,032	790	698

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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(4):739–52.

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Table 4. Effects of inhaled corticosteroids on maternal health and fetal outcomes when used to treat asthma during pregnancy.

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 1: Rotschild, Solimano, Sekhon, et al. 1997 Preclinical randomized study	**x Animal** Female Sprague-Dawley rats Age: Not specified Gestation: 12 days at time of 1st exposure	**Purpose/Objective:** To study the effect of triamcinolone acetonide administered during the early phase of lung growth and development, with emphasis on branching morphogenesis, using an in vivo model to see whether pulmonary hypoplasia results and to examine its nature.				Fetal: Cleft palate: 69/80	Various weight parameters: Maternal weight: Initial loss in body weight was found, then a slower increase than in controls. Fetal weight: Modest gain was found between days 15 and 17, then an increase between days 18 and 21, but less than controls (to ~ 60% of control weights). Placental weight: Weight increased throughout period, but less than in controls. Amniotic fluid weight: Little increase was found.	Fetal pulmonary effects: Peripheral airway count: Increased exponentially with gestational age; was significantly higher than controls on days 17–18 ($p < 0.001$). Pole to pole: Increased exponentially with gestational age; was significantly lower than controls days 17–18 ($p < 0.05$ on day 17, $p < 0.001$ on day 18). Ratio dry lung weight/body weight: 0.025 (evidence of pulmonary hypoplasia). Branching morphology: Diminished monopodial branching from segmental airways was found; but dichotomous branching increased. Histology: Accelerated differentiation of peripheral airway epithelium resulted in increased tissue maturation and increased cellular differentiation of peripheral airspaces.	
		Arm 1: 0.6 mg/kg i.m. TA 1 time/day on days 12,13, and 14 of gestation (study group)	14 rats producing 158 fetuses	Same	Length of study: Days 1–21 of gestation				

Key:

AA = arachidonic acid
B = bifurcation
b.i.d. = twice per day
BA = inhaled steroid treatment at various times
C = cross
CI = confidence interval
D = division
df = degrees of freedom
ER = emergency room
FEV = forced expiratory volume
FEV_1 = forced expiratory volume in 1 second
g = grams
ICU = intensive care unit
i.m. = intramuscular
IS = inhaled steroid treatment
L-656,224 = a benzofuran-class orally active lipoxygenase inhibitor
LBW = low birth weight
LMP = last menstrual period
MDI = metered dose inhaler
NICU = neonatal intensive care unit
NIS = no inhaled steroid treatment
NS = not significant
OR = odds ratio
PCD = postcoital day
PEF = peak expiratory flow
q4h = every four hours
q8h = every eight hours
s.c. = subcutaneous
Sh = shortness
Su = supernumerary
TA = triamcinolone acetonide
vol = volume
χ^2 = chi^2

Table 4. Effects of inhaled corticosteroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 1 (continued)		Arm 2: 0.6 mg/kg i.m. saline on days 12,13, and 14 of gestation (controls)				Cleft palate: 1/100	Maternal weight: Little change between days 25 and 17, then a steady increase to day 21. Fetal weight: Modest gain occurred between days 15 and 17, then an increase between days 18 and 21. Placental weight: Weight increased throughout the period. Amniotic fluid weight: Sharp increase was reported to day 18, then only a small further increase.	Peripheral airway count: Increased exponentially with gestational age. Pole to pole: Increased exponentially with gestational age. Ratio dry lung weight/body weight: 0.06 Branching morphology: Normal monopodial branching from segmental airways occurred with no increase in dichotomous branching. Histology: Normal cell differentiation pattern was found in peripheral airways.	
Citation 2: Sakamoto, Nakamura, Handa, et al. 1991 Preclinical controlled study	**x Animal** JcI: ICR Female mice Age: Not specified Gestational Age: 11 days at time of exposure	**Purpose/Objective:** To determine the effect of triamcinolone acetonide on rugal development and possible involvement of variant rugae in induction of cleft palate.							Number of implants, frequency of dead embryos, number of live embryos, and body weight of live embryos were not significantly different between treated and untreated embryos. No external abnormalities other than cleft palate were found in either 14- or 15-day triamcinolone-treated groups. Formation of secondary palate was considerably delayed in the 14-day-treated-embryos compared to controls. All but 1 of the 15-day-treated-embryos showed unfused secondary palate, whereas all but 1 of the control embryos showed completed formation of the secondary palate. Variant rugae were classed into five groups: B: bifurcation Sh: shortness D: division C: cross Su: supernumerary Shorter crown-rump length of the treated embryos was considered attributable to extensive body flexure found in those embryos.
		Arm 1: 10.0 mg/kg i.m. TA in aqueous suspension; embryos were analyzed on day 14.	5	4 mice producing 49 embryos	Length of study: Days 1–15 of gestation	Fetal: Crown-rump length: 10.09 ± 0.4 mm p <0.05 over the 14-day controls	Fetal: Number of variant palatal rugae: 22 embryos (44.9%) showing 39 variant rugae p <0.01	Fetal: Variant rugae types: B: 15 (38.5%) D: 4 (10.3%) Su: 8 (20.5%) Sh: 9 (23.1%) C: 3 (7.7%)	
		Arm 2: 10.0 mg/kg i.m. TA in aqueous suspension; embryos were analyzed on day 15.	5	5 mice producing 69 embryos		Crown-rump length: 13.1 ± 0.5 mm p <0.05 over the 15-day controls	Number of variant palatal rugae: 18 embryos (20.2%) showing 28 variant rugae	Variant rugae types: B: 16 (57.1%) D: 6 (21.2%) Su: 3 (10.7%) Sh: 3 (10.7%) C: 0 (0.0%)	
		Arm 3: Untreated controls; embryos were analyzed on day 14.	6	6 mice producing 89 embryos		Crown-rump length: 11.7 ± 0.4 mm	Number of variant palatal rugae: 13 embryos (26.5%) showing 24 variant rugae p <0.05	Variant rugae types: B: 0 (0.0%) D: 4 (16.7%) Su: 8 (33.3%) Sh: 9 (37.5%) C: 3 (12.5%)	

Table 4. Effects of inhaled corticosteroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 2 (continued)		Arm 4: Untreated controls; embryos were analyzed on day 15.	5	5 mice producing 75 embryos		Crown-rump length: 14.1 ± 0.5 mm	Number of variant palatal rugae: 10 embryos (11.2%) showing 12 variant rugae	Variant rugae types: B: 0 (0.0%) D: 6 (50.0%) Su: 3 (25.0%) Sh: 3 (25.0%) C: 0 (0.0%)	Authors speculated that formation of variant rugae was associated with disturbance of normal epithelial-mesenchymal interaction. The relationship between increased appearance of variant rugae and failure of palatal shelf elevation was examined, but no direct evidence was obtained.
Citation 3: Wise, Vetter, Anderson, et al. 1991 Preclinical randomized controlled study	**x Animal** Nulliparous Sprague-Dawley rats Age: ~ 11 weeks on day 1 of pregnancy Gestational Age: 11 or 14 days at time of 1st exposure	**Purpose/Objective:** To examine effects of arachidonic-acid-cascade inhibitors in rats; if agents cause decreases in anogenital distance in association with hypospadias, this is significant for future developmental toxicity studies of agents that could affect the cascade.							L-656,224 (7-chloro-2-[(4-methoxyphenyl) methyl]-3-methyl-5-propyl-4-benzofuranol) is a benzofuran-class orally active lipoxygenase inhibitor. Data indicate that Sprague-Dawley rats are much less sensitive to the effects of aspirin and glucocorticoids on anogenital distance; therefore, prostaglandins are unlikely to be primary mediators of androgen-initiated external masculinization in this rat strain.
		Arm 1: • TA: 0.05 mg/kg s.c. once/day • TA: 0.10 mg/kg s.c. once/day • Control 1: TA-vehicle 2 mL/kg s.c. 1 time/day • Aspirin: 75 mg/kg oral gavage vol 5 mL/kg once/day • Aspirin: 150 mg/kg oral gavage vol 5 mL/kg once/day • L-656,224: 1,000 mg/kg oral gavage vol 5 mL/kg once/day • L-656,224: 2,000 mg/kg oral gavage vol 5 mL/kg once/day • Control 2: aspirin/ L-656,224 vehicle oral gavage vol 5 mL/kg once/day	10 rats per treatment group	Same	Length of study: Day 11 of gestation to day 58 postpartum Length of treatment: Rats were exposed to treatments on days 11–19 of gestation	Fetal: Congenital anomalies: • Anomalous external genitalia were found in all pups in both TA treatment groups (0.05 mg/kg and 0.10 mg/kg) on PCD 23: genital tubercle flattened; thinned, glossy strip of flattened skin between tubercle and anus. • Malformations were found in 12 of 90 pups examined in the TA 0.10 mg/kg group (2 cleft palate; 10 omphalocele) vs. 0–1 malformations in all other groups of 123–150 pups each. • Male anogenital distance on PCD 23 was reduced 11% below control for the TA 0.05 mg/kg group ($p < 0.01$) and 19% for the TA 0.10 mg/kg group ($p < 0.001$).	Preweaning pups: • 4.7 live pups/litter (45.3%) were born in TA 0.10 mg/kg treatment group vs. 12.1–14.8 live pups/litter (93.3–100%) for all other treatment groups ($p < 0.001$). • On PCD 23, pup weight was reduced by 35.4% and 46.2% below controls in females treated with TA 0.05 mg/kg and TA 0.10 mg/kg, respectively ($p < 0.001$). • On PCD 23, pup weight was reduced by 35.7% and 45.7% in males treated with TA 0.05 mg/kg and TA 0.10 mg/kg, respectively ($p < 0.001$). – There was slight, but not significant, decrease in PCD 23 pup weight for males and females in both LCD-656,224 treatment groups (1,000 mg/kg and 2000 mg/kg).	Postweaning pups: Anatomic: (Examination of pups was from culled litters in TA 0.05 mg/kg, control 1, control 2, aspirin 150 mg/kg, and L-656,224 2000 mg/kg groups.) • Vaginal canalization in TA 0.05 mg/kg group was slightly decreased compared with control group 1 (64% vs. 83%) on postnatal day 37. • No evidence was found of irreversible alterations of external genitalia or testes descent for pups in any treatment group examined at 8 weeks.	

Table 4. Effects of inhaled corticosteroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 3 (continued)		Arm 2: • TA: 0.1 mg/kg s.c once/day • TA: 0.1 mg/kg s.c. + 100 mg/kg AA s.c. once/day • TA: 0.25 mg/kg s.c once/day • TA: 0.25 mg/kg s.c. + 100 mg/kg AA s.c. once/day • AA: 100 mg/kg (0.11 mL/kg) s.c. once/day • Vehicle: 2mL/kg s.c. once/day	6 rats in each TA treatment group; 8 rats in remaining 2 groups	Same	Length of study: Days 11–20 of gestation Length of treatment: Rats were exposed to treatments on days 14–19 of gestation	Maternal: Body weight gain: • Significant decrease occurred for both TA 0.1 mg/kg and TA 0.1 mg/kg + AA 100 mg/kg groups (4- and 6-gm gains vs. 73- and 76-gm gains in vehicle and AA-only groups, respectively), days 14–20 of gestation. • Presence of AA exhibited a statistically significant protective effect in TA 0.25 mg/kg groups (19-gm loss for TA + AA vs. 28-gm loss for TA-only, days 14–16 of gestation). (p value was not given.)	Fetal: Congenital anomalies: • Anomalous external genitalia were similar to those in Study 1 in essentially all pups in all drug-treated groups. • Micrognathia was present in 59% of pups in the TA 0.25 mg/kg group; addition of AA greatly reduced occurrence to 4%; no micrognathia was present in any other groups. • Omphalocele was present in 55% of pups in TA 0.25 mg/kg group; addition of AA only slightly reduced occurrence to 35%; only 1 pup had omphalocele in the TA 0.10 group, and none in AA-only and vehicle groups.	Fetal: Fetal weights: Fetal weights were reduced by 17% and 52% below the vehicle group for both TA groups, 0.10 and 0.25 mg/kg, respectively; AA slightly attenuated weight loss to 41% in TA 0.25 mg/kg group. Congenital anomalies: Male anogenital distance on gestational day 20 was significantly reduced (p <0.001) in both TA-only groups (0.10 mg/kg and 0.25 mg/kg), 34% and 39%, respectively, below the vehicle control.	
		Arm 3: • Aspirin: 150 mg/kg/day orally • Aspirin: 300 mg/kg/day orally • Vehicle: 5 mL/kg/day	2 groups of 5 rats 2 groups of 7 rats 1 group of 10 rats	Same Same Same	Length of study: Not specified Length of treatment: Days 14–19 of gestation	Maternal: 55% decrease in maternal weight gain occurred between gestational days 14 and 20 in 300 mg/kg aspirin group (data were not shown).	Fetal: Fetal weight was significantly reduced (p <0.05) in 300 mg/kg aspirin group (15% and 16% below control in males and females, respectively).		

Table 4. Effects of inhaled corticosteroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 4: Alexander, Dodds, Armson 1998 Population-based retrospective cohort study	**x Human** Age: Nonasthmatic pregnant women: 28.4 ± 5.1 years Asthmatic pregnant women, no medication: 26.1 ± 5.7 years Asthmatic pregnant women, using β-agonists only: 26.7 ± 5.5 years Asthmatic pregnant women, using steroids, with or without other medications: 28.9 ± 5.9 years Race / Ethnicity: Not specified Pregnancy Trimester: Not specified Eligibility: All women living in the county delivering at city hospital	**Purpose/Objective:** To determine whether adverse perinatal outcome is associated with asthma or asthma medication use during pregnancy.				Maternal hemorrhage:	Maternal hypertension:	Infant complications:	Overall, 5.8% of pregnant women were identified as being asthmatic; the prevalence increased each year, from 4.8% in 1991 to 6.9% in 1993. Study groups differed significantly according to maternal age: mean age at delivery among nonasthmatic pregnant women was higher than that in the asthmatic, no medication use and the asthmatic, β-agonist use groups. Risk of antepartum and postpartum hemorrhage increased in asthmatic women, independent of medication usage. Increased incidence of neonatal hyperbilirubinemia and borderline increased risk of pregnancy-induced hypertension may be complications of steroid use or may be related to poorly controlled asthma. Did not differentiate oral from inhaled corticosteroid use.
		Arm 1: **ß-agonist** use by pregnant women with asthma	303	303	Length of study: 1/1/91–12/31/93 Length of treatment: Not specified	• Antepartum: 23 (10%), OR 1.2 (95% CI 0.8, 1.9) • Postpartum: 25 (12.9%), OR 1.5 (95% CI 1.0, 2.4)	• Pregnancy-induced: 26 (11.1%), OR 1.0 (95% CI 0.7, 1.5)	• No statistically significant differences were found between any asthma group and incidence of respiratory distress syndrome, low birth weight, or congenital anomalies. • Infants in the steroid group were at significantly increased risk for hyperbilirubinemia.	
		Arm 2: **Steroid** use by pregnant women with asthma	139	139		• Antepartum: 16 (15.2%), OR 2.2 (95% CI 1.3, 3.7) • Postpartum: 12 (14.3%), OR 1.7 (95% CI 1.0, 3.2)	• Pregnancy-induced: 19 (18.1%), OR 1.7 (95% CI 1.0, 2.9)		
		Arm 3: • **No medication** use by pregnant women with asthma	375	375		• Antepartum: 32 (11.6%), OR 1.4 (95% CI 1.0, 2.1) • Postpartum: 36 (15.3%), OR 1.9 (95% CI 1.3, 2.7)	• Pregnancy-induced: 40 (13.7%), OR 1.3 (95% CI, 0.9, 1.8)		
		• **Nonasthmatic** pregnant women	13,709	13,709		• Antepartum: 83 (8.0%), (Reference Group) Postpartum: 1,046 (9.3%), (Reference Group)	• Pregnancy-induced: 1,147 (10.5%), (Reference Group)		

Table 4. Effects of inhaled corticosteroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 5: Bracken, Triche, Belanger, et al. 2003 Prospective study	**x Human** Age: ≤24–≥35 years Race / Ethnicity: White / Asian: 1,496 (67.8%) African American: 209 (9.5%) Hispanic: 406 (18.4%) Other: 89 (4.0%) Pregnancy Trimester: ≤24 weeks Eligibility: Pregnant women ≤24 weeks gestation with history of physician-diagnosed asthma and random sample of nonasthmatic, pregnant women	**Purpose/Objective:** To examine whether asthma, asthma symptoms, or asthma therapy influence pregnancy outcomes (specifically, preterm delivery, intrauterine growth restriction [IUGR], gestational age, or birth weight) while controlling for other known risk factors.							Exclusion criteria included being more than 24 weeks pregnant at interview, having insulin-dependent diabetes mellitus, not speaking English or Spanish, and intending to terminate pregnancy. Asthma symptoms were classified using the modified Global Initiative for Asthma (GINA) guidelines. Asthma treatment was classified using modified GINA guidelines. Asthma severity was determined by cross-classifying with the 2002 GINA grid on symptom and medication steps to derive 4 severity categories: intermittent, mild persistent, moderate persistent, and severe persistent. Gestational age was calculated as completed days from first day of LMP or doctor's estimated date of delivery if LMP was uncertain. Preterm delivery was defined as delivery before 37 weeks gestation. Fetal growth restriction was defined as below 10th percentile of birth weight for gestational age. Women with asthma symptoms but no asthma diagnosis are at particular risk of undermedication and of delivering IUGR infants.
		Arm 1: **Asthma diagnosis** (See Bronchodilators—β-agonists citation #3 for complete description of study arms)			Length of study: 4 / 97–6 / 00 Length of treatment: Not specified	Preterm delivery (adjusted associations): (See Bronchodilators—β-agonists citation #3 for complete description of outcomes)	IUGR: (See Bronchodilators—β-agonists citation #3 for complete description of outcomes)		
		Arm 2: **Asthma symptoms** (See Bronchodilators—β-agonists citation #3 for complete description of study arms)							
		Arm 3: Asthma severity **(See Bronchodilators—β-agonists citation #3 for complete description of study arms)**							
		Arm 4: **Asthma treatment** 0 (no medication use) Step 1 Step 2 Step 3 Step 4 Exposure: • Inhaled steroids	 1,657 402 108 28 10 176	 1,657 402 108 28 10 176		Preterm delivery increased with each increasing treatment step. OR for 2 controller medications = 3.67 (95% CI 1.11, 12.16). OR for 3 controller medications = 4.57 (95% CI 0.75, 24.63). Overall, 32% increased risk (95% CI 0%, 76%) for every increase in treatment step. Specific exposure risks: Inhaled steroids: OR 0.99 (95% CI 0.98, 1.01).	No increased risk by treatment step or for any specific medication type Specific exposure risks: Inhaled steroids: OR 1.00 (95% CI 0.99, 1.01).		

Table 4. Effects of inhaled corticosteroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 6: Dombrowski, Brown, Berry 1996 Retrospective cohort study	x **Human** Age in years: • Arm 1: 26 ± 7 • Arm 2: 25 ± 6 • Arm 3: 26 ± 7 Pregnancy Trimester: 1st–3rd Race/Ethnicity: Percent African American • Arm 1: 80% • Arm 2: 79% • Arm 3: 68% Eligibility: Pregnant asthmatic subjects	**Purpose/Objective:** To report preliminary experience with inhaled triamcinolone acetonide.							4 inhaled triamcinolone subjects were treated with theophylline in each trimester; 7 inhaled beclomethasone subjects were treated with theophylline in each trimester; none of the theophylline subjects received either triamcinolone or beclomethasone. Some subjects in all 3 groups were treated with systemic steroids in all trimesters. The triamcinolone group trended toward larger birth weights, but differences between triamcinolone group birth weights and those in the beclomethasone or theophylline groups were not significant.
		Arm 1: **Inhaled triamcinolone acetonide**, but not inhaled beclomethasone dipropionate	16	15 (8 used in 1st trimester, 13 in 2nd trimester, 13 in 3rd trimester)	Length of study: 7/92–10/95 Length of observation: Through delivery	Maternal asthma exacerbations: Hospital admissions for asthma exacerbations: 5 (33%) p <0.05 compared with beclomethasone	Neonatal birth status: Birth weight (g): 3,300 ± 678 Gestational age (weeks): 39.2 ± 2.0 Apgar: 5 min: 8.8 ± 0.9 Cord arterial pH: 7.27 ± 0.07 NICU days: 2.7 ± 7.0		
		Arm 2: **Inhaled beclomethasone dipropionate**, but not inhaled triamcinolone acetonide	14	14 (5 used in 1st trimester, 9 in 2nd trimester, 10 in 3rd trimester)		11 (79%) p <0.05 compared with triamcinolone	Birth weight (g): 2,798 ± 759* Gestational age (weeks): 38.0 ± 3.1 Apgar: 5 min: 8.6 ± 0.9 Cord arterial pH: 7.24 ± 0.11 NICU days: 4.8 ± 9.4 *Not significant compared with triamcinolone group		
		Arm 3: **Oral theophylline**	25	25		7 (28%) p not significant compared with triamcinolone	Birth weight (g): 2,984 ± 526* Gestational age (weeks): 37.8 ± 3.9 Apgar: 5 min: 8.7 ± 0.6 Cord arterial pH: 7.24 ± 0.29 NICU days: 6.2 ± 17.0 *Not significant compared with triamcinolone group		

Table 4. Effects of inhaled corticosteroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 7: Dombrowski, Schatz, Wise, et al. 2004 Prospective, double-blind, double placebo-controlled randomized clinical trial	**x Human** Age: Beclomethasone: 23.4 ± 5.7 years; Theophylline: 23.4 ± 5.4 years Race/Ethnicity: Beclomethasone: 64.9% African American; Theophylline: 59.7% African American Pregnancy Trimester (at Randomization): Beclomethasone: 20.0 ± 4.7 weeks; Theophylline: 20.4 ± 4.8 weeks Eligibility: Mild persistent or moderate persistent asthma; singleton viable pregnancy; no major anomalies; <26 weeks gestation at randomization	**Purpose/Objective:** To compare the efficacy of inhaled beclomethasone dipropionate to oral theophylline for prevention of asthma exacerbations requiring medical intervention during pregnancy.				Primary outcome—at least 1 validated asthma exacerbation	Study completion/compliance (p vs. theophylline):	Other asthma outcomes (p vs. theophylline):	Exclusion criteria for enrollment in this trial were: prenatal care or delivery planned elsewhere; imminent delivery; preeclampsia or gestational hypertension; current or history of epilepsy treated with medications; allergy or sensitivity to theophylline, inhaled steroids, or albuterol; treatment with oral corticosteroids for medical condition other than asthma; treatment with H_2 receptor antagonists; participation in other studies that might influence asthma control; previous or current participation in an asthma study; active pulmonary disease other than asthma; cardiac diseases (Class II-IV); pregestational diabetes; endocrine disorders requiring medication; sickle-cell disease; acute or chronic liver disease; inability to schedule an ultrasound; or inability to give informed written consent. Study used the National Asthma Education and Prevention Program's 1993 severity classification (modified in 1997) in which moderate asthma included mild persistent and moderate persistent asthma. Patients were also excluded if they had unstable or severe asthma (FEV_1 <60% predicted >4 hours post-bronchodilator); or history of ≥1 hospitalization of at least 24 hours duration for asthma exacerbation since conception; or regular (daily or every other day) oral corticosteroids during the past 4 weeks; or need for ≥16 puffs inhaled corticosteroids/day; or requirement for >500 mg theophylline with ≥12 puffs/day of inhaled corticosteroids; or history of >4 courses of oral steroids in the previous year. Moderate asthma defined as symptoms for ≥8 days over past 4 weeks and/or FEV_1 60–80% predicted for >4 hours post-bronchodilator; participants with mild asthma by symptoms and FEV_1 but who required regular medications for asthma control were also considered to have moderate asthma. No significant difference in proportion of asthma exacerbations in 2 arms, but beclomethasone cohort had significantly lower incidences of discontinuing study medications because of side effects. No significant differences in obstetric or perinatal outcomes between the 2 groups.
		Arm 1: **Beclomethasone** inhaler (4 puffs t.i.d. for ~ 504 µg/day) + placebo tablets on same schedule as theophylline tablets in Arm 2	199	194	Length of study: Randomization began 12/95, ended 2/00 Length of treatment: Through delivery		Beclomethasone • Treatment failure: 11/194 (5.7%), p = 0.790, risk ratio 95% CI = 0.9 (0.4–2.0) • Discontinued medications due to side effects: 6/194 (3.1%), p = 0.016, risk ratio 95% CI = 0.3 (0.1–0.9) • Completed protocol: 136/194 (70.1%), p = 0.219, risk ratio 95% CI = 1.1 (0.9–1.3) • Proportion self-reported compliance: 0.691 ± 0.332 (p = 0.762) • Proportion measured compliance: 0.271 ± 0.281 (p = 0.333)	Beclomethasone • Proportion of study visits with FEV_1 <80% predicted: 0.231 ± 0.334 (p = 0.039) • Proportion of study visits with PEFR <80% predicted: 0.179 ± 0.283 (p = 0.149) • Average number of albuterol puffs/day: 1.4 ± 2.1 (p = 0.937) • Proportion reporting nocturnal symptoms: 0.138 ± 0.192 (p = 0.751) • Asthma symptoms at delivery: 36/192 (18.8%) p = 0.696, risk ratio 95% CI = 1.1 (0.7–1.7)	
		Arm 2: **Theophylline** tablets (initially 200 mg b.i.d. [a.m. and p.m.], then 300 mg b.i.d. after 3 days; total dose adjusted between 400 and 800 mg/day; target serum level 8–12 µg/mL) + placebo inhaler on same schedule as beclomethasone inhaler in Arm 1	199	191/190 (Delivery information not available for 1 patient with primary outcome information)			Theophylline • Treatment failure: 12/190 (6.3%) • Discontinued medications due to side effects: 17/190 (8.9%) • Completed protocol: 122/190 (64.2%) • Proportion self-reported compliance: 0.679 ± 0.349 • Proportion measured compliance: 0.356 ± 0.348	Theophylline • FEV_1 0.284 ± 0.221 (p = 0.039) • PEFR 0.214 ± 0.300 • Albuterol 1.5 ± 2.3 • Nocturnal 0.163 ± 0.229 • Sx at delivery 32/186 (17.2%)	

Table 4. Effects of inhaled corticosteroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 7 (continued)									**It was expected that beclomethasone would be more efficacious because of greater anti-inflammatory effects, but possible explanation is that theophylline is bronchodilator plus anti-inflammatory. Also, there are newer inhaled corticosteroids (e.g., fluticasone propionate and budesonide) that are more potent, require fewer puffs/day, and have less systemic absorption than beclomethasone; studies needed to compare theophylline to these newer inhaled corticosteroids during pregnancy.**
Citation 8: Källén, Rydhstroem, Åberg 1999 Prospective study using birth registry information	**x Human** Age: ≤19–40+ years Race/Ethnicity: Not specified Pregnancy Trimester: "Early pregnancy" Eligibility: Pregnant asthmatic subjects	**Purpose/Objective:** To study possible teratogenic risks with use of the inhaled glucocorticoid, budesonide, in early pregnancy.							Congenital anomalies among all infants born 1995–1999 amounted to 3.5% based on data from the Swedish Birth Registry. Of 76 infants with congenital abnormalities (75 + 1 for whom details were obtained outside the study), 41 were classed as having major structural defects and 35 as having minor defects. 2 slightly unusual malformations were observed: 1 Poland syndrome and 1 unilateral lower jaw anomaly.
		Arm 1: Use of inhaled budesonide in early pregnancy	2,014 infants	2,014 infants	Not specified	Fetal congenital anomaly rate: Congenital abnormalities by maternal age group: Age / Number / % ≤19 / 4/79 / 5.1 20–24 / 18/419 / 4.3 25–29 / 24/678 / 3.5 30–34 / 18/590 / 3.1 35–39 / 9/208 / 4.3 40+ / 2/40 / 5.0 75/2,014 / 3.8 χ^2 for heterogeneity (3 df) = 3.4, p = 0.85; 95% CI 2.9, 4.6	Specific major anomalies: • Orofacial cleft: 4/41 (expected from population rate = 3.3); risk ratio = 1.2 (94% CI 0.3, 3.1) • Heart defect: 15/41* (expected = 17–18) • Chromosomal abnormalities: 5/41 • Other structural defects: 16/41 *Data taken from table 2 in article; text says 18 cardiac defects.		
Citation 9: Murphy, Zakar, Smith, et al. 2002 Controlled clinical study	**x Human** Age: ~ 25 to ~ 28 years Race/Ethnicity: Not specified Pregnancy Trimester: Recruited in 1st	**Purpose/Objective:** To determine in pregnancies complicated by asthma whether there are any changes in mRNA, protein, or 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) activity; to assess whether these changes are associated with rises in fetal cortisol and alterations in placental pathways regulated by cortisol (CRH mRNA) or the fetal hypothalamic-pituitary-adrenal axis (fetal estriol concentrations); and to determine whether 11β-HSD2 activity is associated with neonatal birth weight centile.							Asthma severity was assessed by a combination of FEV_1, PEF, daytime symptoms, nocturnal and morning symptoms, bronchodilator use, and hospitalizations. Control groups = pregnant, nonasthmatic women. Inhaled glucocorticoid dose was summarized as mean daily dose of beclomethasone dipropionate or equivalent, where 1 µg **beclomethasone** dipropionate considered equal to 1 µg budesonide and to 0.5 µg **fluticasone propionate.** Nil use was no inhaled glucocorticoid use. Low use was <400 µg/day; **moderate use was** 400–1,500 µg/day; **high use was >1,500 µg/day.**
		Arm 1: Subjects were grouped by severity of asthma (control, mild, moderate, or severe)	Control: 25 Mild: 46 Moderate: 20 Severe: 36	Same	Length of study: Through delivery	Birth weight centile: • Decreased in moderate and severe asthma.		11β-HSD2 activity: • No significant difference was found in activity between asthmatic subjects and controls. • Mean 11β-HSD2 protein levels in subjects with severe asthma were significantly higher than in controls ($p < 0.05$).	

Table 4. Effects of inhaled corticosteroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 9 (continued)	Eligibility: Pregnant asthmatic and nonasthmatic women from prenatal clinic	Arm 2: Subjects were grouped by inhaled glucocorticoid use (control, nil, low, moderate, high)	Control: 25 Nil: 30 Low: 16 Moderate: 32 High: 24	Same		Birth weight centile: • Was significantly lower in nil group compared to control ($p < 0.05$). • Corresponds to a 25% reduction in birth weight centile vs. controls and 17% reduction vs. infants from mothers who used inhaled glucocorticoids at all.	Fetal cortisol: • Significantly increased in nil use group compared to control ($p < 0.05$); dose-dependent restoration to control with increased concentration of inhaled glucocorticoid intake. Fetal estriol: • Significantly reduced in nil group compared to control and glucocorticoid users ($p < 0.05$). • Inversely correlated with fetal cortisol in all groups ($p < 0.005$).	11β-HSD2 activity: • Significant reduction in enzyme activity occurred in subjects in the nil-use category compared with control and low-use ($p < 0.02$) and moderate- and high-use subjects ($p < 0.01$). • Mean 11β-HSD2 protein levels in the nil and high-use subjects were significantly higher than in controls ($p < 0.05$).	Oral glucocorticoid intake was not quantified. Inhaled glucocorticoid intake for treatment of asthma was associated with improved placental function and fetal outcome, suggesting that inflammatory factors associated with asthma may be detrimental to fetal growth and development in these pregnancies.
Citation 10: Norjavaara and de Verdier 2003 Population-based study using birth registry information	**x Human** Age: Not specified Race / Ethnicity: Not specified Pregnancy Trimester: "Early pregnancy" Eligibility: Pregnant asthmatic subjects	**Purpose/Objective:** To investigate whether reported use of inhaled budesonide during pregnancy influences birth outcome.	298,880 total newborns; mothers in following groups:	Study population of newborns = 293,948	Length of study: 1995–1998	Maternal: Cesarean births in study population: Girls: Number 16,132, % 11.3; Boys: Number 18,487, % 12.2	Newborns: Average birth weight (g) in study population: Girls: 3,500 ± 530; Boys: 3,630 ± 570	Newborns: Birth weight <1,000g in study population: Girls: Number 205, % 0.1; Boys: Number 216, % 0.1	Mothers who reported use of inhaled budesonide during pregnancy gave birth to babies of normal gestational age, birth weight, and length, with no increased rate of stillbirths or multiple births. Doses of budesonide reported in the current study were probably less than recommended doses, as real-life use tends to be lower than prescribed. Asthma severity is a possible confounding effect: inadequate control of asthma is associated with adverse outcomes such as higher prematurity rates, intrauterine growth retardation, low birth weight, perinatal death, and preeclampsia. Results of the current study on concomitant use of oral glucocorticoids were probably confounded by a severity of maternal asthma that necessitated use of both budesonide and oral glucocorticoids.
		Arm 1: Group A: Mothers using any asthma medication other than oral or inhaled glucocorticoids	A = 7,719			Group A: 498, 13.3; 584, 14.7 $p < 0.001$	Group A: 3,460 ± 550; 3,600 ± 580 $p < 0.001$ (girls) $0.001 < p < 0.01$ (boys)	Group A: 4, 0.1; 5, 0.1	
		Arm 2: Group P_1: Mothers using inhaled budesonide in early pregnancy	P_1 = 2,968			Group P_1: 184, 13.1; 252, 16.2 $0.01 < p < 0.05$ (girls) $p < 0.001$ (boys)	Group P_1: 3,450 ± 560; 3,570 ± 600 $0.001 < p < 0.01$ (girls) $p < 0.001$ (boys)	Group P_1: 3, 0.3; 2, 0.1	
		Group P_2: Mothers using inhaled budesonide during whole pregnancy	P_2 = 207			Group P_2: 7, 6.9; 15, 14.2 No p value given	Group P_2: 3,500 ± 500; 3,600 ± 550 No p value given	Group P_2: —, —; —, —	
		Arm 3: Group P_0: Mothers using inhaled budesonide and oral glucocorticoids in early pregnancy	P_0 = 103			Group P_0: 16, 30.8; 11, 21.6 $0.01 < p < 0.05$ (girls) $p < 0.001$ (boys)	Group P_0: 3,430 ± 660; 3,340 ± 590 No p value given for girls $0.001 < p < 0.01$ (boys)	Group P_0: 0, 0.0; 0, 0.0	

Table 4. Effects of inhaled corticosteroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 11: Schatz, Zeiger, Harden, et al. 1997 Prospectively monitored cohort study	**x Human** Age: Not specified Race/Ethnicity: Not specified Pregnancy Trimester: 1st, 2nd (all subjects <28 weeks at entry) Eligibility: Pregnant subjects with asthma matched on basis of age, parity, and smoking status with pregnant nonasthmatic controls	**Purpose/Objective:** To assess safety of asthma medications, antihistamines, and decongestants in a prospectively monitored cohort of pregnant women with and without asthma.							Drug exposure data in terms of incidence of malformations for all subjects (number of malformations): 1st Trimester / Anytime Exp. / Unexp. / Exp. / Unexp. β-agonists 488 / 1,000 / 557 / 823 Theophylline 292 / 1,208 / 429 / 1,061 Cromolyn* 151 / 1,348 / 243 / 1,247 Corticosteroids 204 / 1,295 / 297 / 1,190 Antihistamines 321 / 1,175 / 493 / 996 Decongestants 453 / 1,032 / 790 / 698 * Inhaled: 158; intranasal: 113; ophthalmic: 23 There were no significant relationships (all p >0.05) between β-agonists, cromolyn, antihistamines, or decongestants and increased incidence of any other adverse perinatal outcomes evaluated (data not shown). There were no significant relationships (all p >0.05) between specific medication use and increased incidence of small-for-gestational-age infants (data not shown). Results my be confounded by presence and severity of asthma. The following are results of multivariate analysis performed in pregnant subjects with asthma when significant univariate associations were identified between drug exposure and perinatal outcome variables: • Oral corticosteroids were independently associated with preeclampsia (p = 0.027, OR = 2.00 [95% CI 1.11, 3.61]) but inhaled steroids were not when controlled for other exposures. • When preeclampsia was included in the model for low birth weight, it was independently related (p = 0.025), but it did not substantially change demonstrated independent relationships with African American race (p = 0.002) and lower weight gain during pregnancy (p <0.001) and lack of independent relationships with oral or inhaled corticosteroids or mean FEV_1. • African American race (p = 0.001) and lower weight gain during pregnancy (p = 0.001) but not theophylline or inhaled corticosteroids wee associated with preterm birth.
		Arm 1: Exposure to **any asthma/allergy medication** at any time for total cohort: • β-agonists (inhaled or oral) • Theophylline • Cromolyn (inhaled, intranasal, ophthalmic) • Corticosteroids (oral, inhaled, or intranasal) • Antihistamines • Decongestants	1,904 (1,044 with asthma; 860 controls)	1,502 (824 with asthma; 678 controls)	Through delivery, all arms	Fetal effects: Major congenital malformations, 1st trimester: % Incidence Exp. / Unexp. β-agonists 4.3 / 5.6 Theophylline 4.5 / 5.3 Cromolyn 6.0 / 5.0 Corticosteroids 6.9 / 4.9 Antihistamines 3.7 / 5.5 Decongestants 5.5 / 4.8 No significant relationship, p >0.05 for all comparisons	Fetal effects: Major congenital malformations, any time: % Incidence Exp. / Unexp. β-agonists 3.7 / 6.2 Theophylline 4.7 / 5.3 Cromolyn 6.2 / 4.9 Corticosteroids 6.1 / 4.9 Antihistamines 3.9 / 5.7 Decongestants 5.2 / 4.9 No significant relationship, p >0.05 for all comparisons		
		Arm 2: **Theophylline** exposure (See Bronchodilators—β-agonists citation #5 for complete description of study arms)						(See Bronchodilators—β-agonists citation #5 for complete description of outcomes)	
		Arm 3: **Corticosteroid** exposure • Any route • Total inhaled (inhaled with or without oral corticosteroids)					Fetal effects:	Maternal effects: • Preterm births: 19/297 (64%) in exposed subjects, 45/1,195 (3.8%) in controls, p = 0.045 (mean gestational age 32.74 ± 3.75 weeks in exposed subjects) • Preeclampsia: 34/296 (11.5%) in exposed subjects, 85/1,197 (7.1%) in controls, p = 0.013 • Low birth weight infants: 18/297 (6.1%) in exposed subjects, 40/1,197 (3.3%) in controls, p = 0.030 • Preterm births: 13/138 (9.4%) in exposed subjects, 51/1,354 (3.8%) in controls, p = 0.002 • Preeclampsia: 17/137 (12.4%) in exposed subjects, 102/1,356 (7.5%) in controls, p = 0.044 • Low birth weight infants: 11/138 in exposed subjects, 47/1,356 in controls, p = 0.009	

Table 4. Effects of inhaled corticosteroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 11 (continued)		• Inhaled only					% incidence of major congenital malformations (inhaled only): Exposed 5.4 / Unexposed 4.9	• Preterm births: 5/64 (7.8%) in exposed subjects, 59/1,428 (4.1%) in controls, p = NS • Preeclampsia: 7/64 (10.9%) in exposed subjects, 112/1,429 (7.8%) in controls, p = NS • Low birth weight infants: 3/64 (4.7%) in exposed subjects, 55/1,430 (3.8%) in controls, p = NS	
		• Oral					% incidence of major congenital malformations (oral): Exposed 7.0 / Unexposed 4.9	• Preterm births: 10/130 (7.7%) in exposed subjects, 54/1,362 (4.0%) in controls, p = NS • Preeclampsia: 17/129 (13.2%) in exposed subjects, 102/1,364 (7.5%) in controls, p = 0.022, OR = 2.0 • Low birth weight infants: 11/130 (8.5%) in exposed subjects, 47/1,364 (3.4%) in controls, p = 0.005	
Citation 12: Stenius-Aarniala, Hedman, Teramo 1996 Prospective cohort study	**x Human** Age: • Mean 28.0 years (range 17–43 years) (acute asthma group) • Mean 28.9 years (range 16–44 years) (no acute asthma group) Race/Ethnicity: Not specified Pregnancy Trimester: Not specified Eligibility: Pregnant women with asthma followed and treated at hospital	**Purpose/Objective:** To investigate effect of acute attack of asthma during pregnancy on course of pregnancy or delivery or health of newborn infant, and to identify undertreatment as possible cause of exacerbations.							The incidence of preeclampsia was higher among women with asthma than among controls, but was not specifically high in the acute attack group. There was a high incidence of elective cesareans in the acute attack group and in women with asthma in general.
		Arm 1: Inhaled steroid treatment throughout (IS), at various times (BA), or not at all (NIS)	504 pregnant women with asthma	504 pregnant women with asthma	Length of study: 1/82–9/92 Duration of treatment: Through delivery	Maternal: Incidence of acute asthma attacks: No. of Patients / No. of Acute Attacks / % of Acute Attacks NIS: 177 / 31 / 17.5 IS: 257 / 10 / 3.9 BA: 70 / 6 / 8.6 χ^2 (NIS vs. IS group) = 17.3, p <0.0001 Risk of IS patients having attack = 22% that of NIS patients having attack (95% CI 0.11, 0.44) Risk of BA patients having an attack = 49% that of NIS patients having attack (95% CI 0.21, 1.12)			

Table 4. Effects of inhaled corticosteroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 12 (continued)		Arm 2: Effect of acute asthma on maternal health in 504 pregnant women with asthma	47 acute attack 457 nonacute attack 237 pregnant nonasthmatic controls				Maternal complications: No significant differences were found in incidence of preeclampsia, intrahepatic cholestasis of pregnancy, or gestational diabetes between acute attack patients and nonacute attack patients or controls. No significant differences were found in incidence of pregnancy complications between acute attack patients and nonacute attack or control groups.	Newborn outcomes: No significant differences were found in the incidence of congenital malformations, perinatal death, hypoglycemia, treatment in newborn ICU, or jaundice between births in acute attack patients and those in nonacute attack or controls. No significant differences were found in perinatal deaths, Apgar scores, or relative birth weights between births in acute attack patients and those in nonacute attack patients or control groups.	
Citation 13: Wendel, Ramin, Barnett-Hamm, et al. 1996 Prospective randomized controlled trial	**x Human** Age: 22 ± 5 years Race/Ethnicity: • Hispanic: 46% • African American: 42% • White: 10% Pregnancy Trimester: 2nd–3rd (22.7 ± 9.1 weeks) Eligibility: • Asthma exacerbation prompting visit to ER or prenatal clinic and requiring inhaled bronchodilator therapy • FEV <70% predicted after initial therapy	**Purpose/Objective:** To study the effect of inhaled corticosteroids on asthma exacerbations in pregnancy.						Maternal: All patient groups (n = 72): Obstetric complications: • Pregnancy hypertension (n = 12) increased 13% over general population. • Cesarean sections (n = 21) increased 17% over general population. • Other complications were not outside the range of those in the general population.	Initially, 84 pregnant women were enrolled in the study; 12 patients overall were lost to followup. However, data (except for obstetric complications) are recorded in numbers of exacerbations, and the number of women experiencing exacerbations in each of the groups is not specified. Patients in inpatient groups 1 and 2 underwent a second randomization at discharge into groups A and B. Obstetric complications relate to all patients, both those in initial outpatient group and those in both inpatient groups. The general population appears to refer to the obstetric population at the institution where the study was performed.
		Arm 1: **Outpatient group** (FEV >70% predicted after initial isoetharine therapy); patients discharged with no other therapy indicated Outpatient followup only	40 exacerbations (number of subjects not specified)	33 exacerbations (number of subjects not specified)	Duration: through delivery				
		Arm 2: Data for Arm 2 are shown at Bronchodilators—theophylline citation #15				Data for Outcomes from Arm 2 are shown at Bronchodilators—theophylline citation #15			
		Arm 3: **Inpatient group 2** (FEV <70% predicted after initial isoetharine therapy) • Albuterol MDI q4h • IV methylprednisolone 1 mg/kg q8h; maximum single dose = 80 mg	32 exacerbations (number of subjects not specified)	Not specified					

Table 4. Effects of inhaled corticosteroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 13 (continued)		2nd-level stratified randomization of groups 1 and 2 following discharge from hospital: Group A: • Albuterol MDI, 2 puffs q4h as needed • Oral methylprednisolone taper (initial 40 mg, decreased by 8 mg/day over 6 days)	31 exacerbations (number of subjects not specified)	27 (4 lost to followup; number of subjects not specified)					
		Group B: • Albuterol MDI, 2 puffs q4h as needed • Oral methylprednisolone taper (initial 40 mg, decreased by 8 mg/day over 6 days) • Beclomethasone MDI 4 puffs b.i.d.	34 exacerbations (number of subjects not specified)	33 (1 lost to followup; number of subjects not specified)			Maternal: Beclomethasone (Group B): 55% reduction in exacerbations and readmissions; 9 (33%) in Group A vs. 4 (12%) in Group B p = 0.047 OR 3.63 95% CI 1.01, 13.08		

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Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy.

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 1: Abbott, Diliberto, Birnbaum 1992 Preclinical developmental toxicity study	**x Animal** Pregnant C57BL/6N mice Maternal Age: Not specified Gestational Age: 10 days at 1st exposure	**Purpose/Objective:** To examine mechanisms of cleft palate induction by exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), retinoic acid (RA) + TCDD, and hydrocortisone (HC) + TCDD; to determine the effects of these exposures on the proliferation and differentiation of palatal cells and the relationship of these effects to those on growth factor expression.							
		Arm 1: TCDD 24 µg/kg, oral dose	Not specified	Not specified	Gestational day 10	Cleft palate: • 100% incidence. • No fusion occurred due to altered differentiation of medial epithelial cells.	Growth factor expression: Epithelial Cell Type Oral / Medial / Nasal TGF-α ↓* / ↓† / ↓* EGF = / = / = TGF-β_1 = / ↑* / ↑* TGF-β_2 = / ↑* / ↑* See key	Palatal organ culture: • Rat and human cells responded only at concentrations ~ 200-fold higher than required for C57Bl/6N. • Responsiveness diminished in serum-free culture. • ^{3}H-TCDD was distributed equally well in the presence or absence of FBS.	Effects on growth factor expression varied: • TCDD increased TGF-β_1 peptide levels in the absence of altered mRNA expression. • HC and HC + TCDD strongly induced both TGF-β_1 peptide and mRNA. • Increase in EGF after HC and HC + TCDD was not accompanied by increased mRNA. A palatal organ culture was used on medial epithelial cells; comparisons were made with cultured F344 rat and human palatal cultures. Induction of medial cell responses with 1% FBS-containing medium suggests that serum factor plays a role in *in vitro* activity. It remains to be seen if altered growth factor expression is a consequence of direct effects or is secondary to TCDD transcriptional regulation at other sites or posttranscriptional effects. Synergism between TCDD and RA or HC implies action through these pathways.
		Arm 2: • RA 100 mg/kg, oral dose • RA 40 mg/kg + TCDD 6 µg/kg, oral dose			Gestational day 10	• Doses for both TCDD and RA that were too low to induce cleft palate separately produced 100% incidence when combined. • Clefts induced by TCDD + RA were caused by growth inhibition rather than by altered differentiation.	Epithelial Cell Type RA: Oral / Medial / Nasal TGF-α ↑‡ / ↓* / = EGF = / = / = TGF-β_1 = / = / = TGF-β_2 = / = / ↑* RA + TCDD TGF-α ↓† / ↓† / ↓* EGF ↓† / = / = TGF-β_1 ↓† / ↓† / ↓* TGF-β_2 = / = / =		
		Arm 3: • HC 100 mg/kg/day, s.c. • HC 25 mg/kg/day, s.c. + TCDD 3 µg/kg/day, oral dose			Gestational days 10–13	• Doses for both TCDD and HC that were too low to induce cleft palate separately produced 100% incidence when combined. • Clefts induced by TCDD + HC were caused by growth inhibition rather than by altered differentiation.	Epithelial Cell Type HC: Oral / Medial / Nasal TGF-α = / = / = EGF ↑* / ↑* / ↑‡ TGF-β_1 ↑‡ / ↑‡ / ↑‡ TGF-β_2 = / = / = HC + TCDD TGF-α = / = / = EGF = / = / ↑† TGF-β_1 ↑* / ↑‡ / ↑‡ TGF-β_2 = / = / ↑*		

Key:

*	= p <0.5 significance relative to controls	BPA	= British Paediatric Association	ICD9	= International Classifaction of Diseases, 9th Revision	NA	= noradrenaline
=	= same	C	= controls	ICP	= isolated cleft palate	NS	= not significant
↑	= increase	CHD	= conotruncal heart defects	ICLP	= isolated cleft lip with or without cleft palate	NTD	= neural tube defects
↓	= decrease	CI	= confidence interval	ICU	= intensive care unit	OC	= orofacial clefts
†	= p <0.01 significance relative to controls	CL	= cleft lip	i.m.	= intramuscular	OR	= odds ratio
‡	= p <0.001 significance relative to controls	cm	= centimeters	i.v.	= intravenous	PTG_1	= prenatal treatment group 1
^{3}H-TCDD	= tritium-labeled TCDD	CYP1A1	= liver microsomal cytochrome P-450 mono-oxygenase	LD	= limb deficiencies	PTG_2	= prenatal treatment group 2
ACTH	= adrenocorticotropic hormone	EGF	= epidermal growth factor	LGA	= large for gestational age	RA	= retinoic acid
AGA	= appropriate for gestational age	F	= female	LMP	= last menstrual period	S	= steroid group
Ah	= aryl hydrocarbon	FBS	= fetal bovine serum	M	= male	s.c.	= subcutaneous
AhR	= aryl hydrocarbon receptor	FEV	= forced expiratory volume	MCLP	= multiple cleft lip with or without cleft palate	SGA	= small for gestational age
ANG II	= angiotensin II	FEV_1	= forced expiratory volume in 1 second	MCP	= multiple cleft palate	TCDD	= 2,3,7,8-tetrachlorodibenzo-p-dioxin
ARNT	= aryl hydrocarbon receptor nuclear translocator	GD	= gestational day	MRI	= magnetic resonance imaging	TGF-α	= transforming growth factor α
ATC	= Anatomical Therapeutic Chemical	GR	= glucocorticoid receptors	mRNA	= messenger ribonucleic acid	TGF-β_1	= transforming growth factor β_1
BP	= blood pressure	HC	= hydrocortisone	N	= nonsteroid group	TGF-β_2	= transforming growth factor β_2
				N/A	= not applicable	WHO	= World Health Organization

Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 2: Abbott, Harris, Birnbaum 1992 Preclinical randomized, controlled teratology study	**x Animal** Female C57BL/6N mice Maternal Age: 8–10 weeks at mating Gestational Age: 10 days at 1st exposure	**Purpose/Objective:** To extend the range of doses at which hydrocortisone (HC) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) interaction occurs and to compare the morphological, cellular, and molecular responses of palates to HC vs. HC + TCDD.							Extreme sensitivity, indicated by teratogenic effects at very low doses, suggests involvement of a receptor-mediated mechanism, possibly resulting in altered regulation of gene expression. Interaction between HC and TCDD results in a small palate resembling that induced by HC alone rather than the morphology typical of TCDD-induced clefting. Both compounds inhibited programmed cell death of medial epithelium, which instead differentiated into oral-like epithelium. Synergism between HC and TCDD may involve similar and potentially additive effects on regulators of proliferation and differentiation in the palate.
		Arm 1: • Vehicle • HC 1 mg/kg s.c. • HC 10 mg/kg s.c. • HC 1 mg/kg s.c. + TCDD 3 µg/kg oral gavage • HC 10 mg/kg s.c. + TCDD 3 µg/kg oral gavage • HC 25 mg/kg s.c. and TCDD 3 µg/kg oral gavage	8–11 dams in each treatment group; at least 10 embryos from 2–3 litters in each treatment group	Same	Gestational days 10–13	Cleft palate: • 0% in embryos given HC 1 mg/kg and 10 mg/kg • 54.5% (36/66) in embryos given HC 1 mg/kg and TCDD 3 µg/kg, p <0.01 • 89.7% (52/88) in embryos given HC 10 mg/kg and TCDD 3 µg/kg, p <0.01 • 99.1% (74/75) in embryos given HC 25 mg/kg and TCDD 3 µg/kg, p <0.01	Maternal effects: • Liver/body weight reduced in embryos given HC 10 mg/kg, p <0.05. • Liver/body weight increased in embryos given HC 1 mg/kg and TCDD 3 µg/kg and in embroyos given HC 10 mg/kg and TCDD 3 µg/kg, p <0.05.		
		Arm 2: • Vehicle • HC 100 mg/kg s.c. • HC 25 mg/kg s.c. + TCDD 3 µg/kg oral gavage	8–11 dams in each treatment group	Same		Morphologic: • Control: Of 37 embryos from 6 litters, 7 palates were not yet in contact and fusing (19%) at GD 14; by GD 18, all fused; at GD 14, medial epithelial periderm degenerated to single-cell thickness. • HC: Small palatal shelves occurred in 76/91 embryos (84%); shelves were not touching at medial edge on GD 14; periderm degeneration was inhibited. • HC + TCDD: Small palatal shelves occurred in 66/68 embryos (97%); shelves were not touching at medial edge on GD 14; periderm degeneration was inhibited; for both HC and HC + TCDD, the medial epithelium thickened, and accumulating glycogen-like material was not contained in vesicles.	Growth factor expression: Epithelial Cell Type HC / Oral / Medial / Nasal TGF-α: NS / NS / NS EGF: ↑* / ↑* / ↑‡ TGF-β1: ↑‡ / ↑‡ / ↑‡ TGF-β2: NS / NS / ↑* HC + TCDD TGF-α: NS / NS / NS EGF: NS / NS / ↑† TGF-β1: ↑* / ↑‡ / ↑‡ TGF-β2: NS / NS / ↑*	EGF receptor levels: Oral / Medial / Nasal HC: NS / ↑* / ↑‡ HC + TCDD: NS / NS / ↑‡	

Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 3: Abbott, Perdew, Buckalew, et al. 1994 Preclinical randomized, controlled teratology study	**x Animal** Pregnant C57BL/6N mice Maternal Age: 8–10 weeks at time of mating Gestational Age: 10 days at 1st exposure	**Purpose/Objective:** To examine the hypothesis that altered expression of aryl hydrocarbon (Ah) and glucocorticoid receptors (GR) are involved in the synergistic induction of cleft palate.							Data for controls and TCDD effects at 24 µg/kg are from a previous study.
		Arm 1: • TCDD 24 µg/kg, single oral dose • TCDD 3 µg/kg/day, oral dose	12 embryos from 3–4 litters in each treatment group	Same	Length of treatment: Gestational day 10 for single dose; gestational days 10–13 for multiple-dose groups	Ah receptor expression: • Expression decreased at both TCDD dose levels. • mRNA localization decreased at both TCDD dose levels.	GR expression: • TCDD at 3 µg/kg/day increased expression in 8 of 12 mesenchymal samples. • TCDD at 24 µg/kg caused GR localization patterns and levels similar to controls (nuclei and cytoplasm of nasal epithelia). • GR expressed predominantly in basal nuclei in litters exposed to TCDD at 3 µg/kg. • TCDD at 24 µg/kg increased mRNA in mesenchyme and appeared to increase mRNA in oral and medial epithelia.		
		Arm 2: • HC 25 mg/kg/day, s.c. • HC 100 mg/kg/day, s.c.				• HC at 25 mg/kg/day had no effect on expression. • HC at 100 mg/kg/day elevated expression, especially in the mesenchyme. • HC at both doses appeared to increase mRNA localization in both epithelial and mesenchyme; higher dose caused greater response.	• HC reduced GR expression in 8 of 12 palates at 25 mg/kg/day and in 7 of 12 palates at 100 mg/kg/day. • HC at 100 mg/kg/day increased mRNA in mesenchyme and appeared to increase mRNA in oral and medial epithelia.		
		Arm 3: HC 25 mg/kg/day, s.c. + TCDD 3 µg/kg/day, orally				• HC + TCDD increased expression relative to TCDD alone in 9 of 12 palatal epithelial samples and in 10 of 12 mesenchymal samples. • The combination strongly decreased mRNA levels, but Ah receptor protein was detected.	• HC + TCDD appeared to increase GR expression in mesenchyme in 5 of 12 samples. • The combination increased mRNA in mesenchyme and appeared to increase mRNA in oral and medial epithelia.		

Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 4: Abbott, Schmid, Brown, et al. 1999 Preclinical randomized, controlled teratology study	**x Animal** Pregnant C57BL/6N mice Maternal Age: Not specified Gestational Age: 12 days at time of exposure	**Purpose/Objective:** To provide quantitative observations of glucocorticoid receptor (GR) and aryl hydrocarbon receptor (AhR) expression.							CYP1A1 is capable of biotransforming xenobiotics, such as polycyclic hydrocarbons and halogenated aromatic hydrocarbons, into carcinogenic or mutagenic compounds. ARNT is considered to mediate effects of dioxin-like pollutants and aryl hydrocarbon signaling and toxicity by dimerizing with the ligand-activated AhR, forming a complex that binds specific DNA elements and alters transcription of target genes. The relative overall expression of genes was AhR >ARNT >GR; within individuals, expression of AhR and/or ARNT highly correlated with GR level.
		Arm 1: TCDD 24 µg/kg, oral dose	4 fetuses from each of 3 litters	Same	Length of treatment: Dams dosed at GD 12; fetuses collected at 4,12, and 24 hours postexposure	AhR expression: • TCDD did not significantly alter expression. • Expression was similar at 4 and 12 hours but increased significantly at 24 hours ($p < 0.05$) for both TCDD groups and controls.	CYP1A1 expression: • Significant rise 2–4 hours ($p = 0.02$); plateau 4–48 hours.		
		Arm 2: • TCDD 24 µg/kg, oral dose • HC 100 mg/kg s.c. • TCDD 3 µg/kg, oral dose + HC 25 mg/kg s.c.	6 fetuses from each of 3 litters	Same	Length of treatment: Dams dosed at GD 12; fetuses collected at 2, 4, 6, 12, 24, and 48 hours postexposure	• Expression was not significantly altered by TCDD at any time point. • Significant increase in expression occurred at 12 hours for all groups except HC ($p < 0.001$ controls and TCDD; $p = 0.005$ HC + TCDD; $p = 0.0676$ HC).	• TCDD produced a significant increase ($p = 0.005$) at 2 hours and induction significant at all later time points ($p < 0.001$).	GR expression: • TCDD, HC, or HC + TCDD had no significant effect at any of times examined. ARNT expression: • Increased significantly in control tissues from 4–12 hours and similarly in TCDD-treated tissues ($p < 0.001$); however, significant decrease occurred at 24 hours ($p < 0.001$). • Significant delay occurred in expression in HC- and HC + TCDD-treated tissues; control levels were not reached until 48 hours; expression actually decreased at 12 hours in each case ($p = 0.016$ and 0.013, respectively).	

Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 5: Dodic, May, Wintour, et al. 1998 Preclinical controlled study	**x Animal** Pregnant Merino ewes Maternal Age: Not specified Gestational Age: 22–29 days or 59–66 days	**Purpose/Objective:** To test the hypothesis that relatively brief prenatal treatment could have long-lasting deleterious consequences in a long-gestation mammal.							Pregnant ewes were transported from a farm to the study center, cannulated, treated, and returned to the farm, where they then lambed; control lambs were taken from sheep not exposed to stress of transportation or cannulation. Prenatal treatment at end of first month, but not at end of second month of gestation, resulted in lambs which had significantly higher blood pressures from 4–19 months of age.
		Arm 1: **Dexamethasone** infusion at 0.28 mg/kg/day for 48 hours at GD 22–29 (prenatal treatment group 1 [PTG1])	8 ewes giving birth to 9 lambs, (6 F, 3 M, including 1 set of twins)	6 female lambs	Length of treatment: 48 hours Length of study: Up to 560 days postdelivery	Basal mean arterial pressure in lambs: • At 104–124 days, BP was significantly higher in PTG1 vs. controls ($p < 0.05$). • At 285–323 days, BP was significantly higher in PTG1 vs. controls ($p < 0.05$). • At 558–568 days, BP was significantly higher in PTG1 vs. controls ($p < 0.05$) and also vs. PTG2 ($p < 0.05$). • BP changed significantly with age in controls ($p < 0.05$) and in PTG1 ($p < 0.001$), but not in PTG2.	BP responsiveness to NA, ANG II, and ACTH: • At 104–124 days, BP responsiveness was similar across all groups. • At 285–323 days, BP responsiveness was similar across all groups. • At 558–568 days, BP responsiveness was similar across all groups.	
		Arm 2: **Dexamethasone** infusion at 0.28 mg/kg/day for 48 hours at GD 59–66 (prenatal treatment group 2 [PTG2])	12 ewes giving birth to 11 lambs (7 F, 4 M)	7 female lambs					
		Arm 3: Control		7 female lambs					
Citation 6: Jobe, Wada, Berry, et al. 1998 Preclinical randomized controlled study	**x Animal** Sheep Age: Not specified Gestational Age: 104 days at 1st exposure	**Purpose/Objective:** To evaluate the effects of a single dose or three repeated doses of maternal betamethasone on fetal growth at preterm and term delivery in sheep.							All pregnant ewes were given 150 mg medroxyprogesterone, i.m., at GD 97–102 to minimize the occurrence of preterm labor and abortion induced by glucocorticoids in sheep. Sheep were divided into 2 groups: those delivered at 125 GD (preterm) and those delivered at 145 GD (term). Decreases in length and head size were less pronounced than decreases in weight in the 3-dose group; therefore, the 3-dose group lost weight out of proportion to length and head size; this effect was not noted in 1-dose group. The effect of a single dose at 104 GD, at both 125-day and 145-day delivery, and of 3 doses evaluated at term was proportionate to growth retardation in body size measurements, organ weights, organ DNA, and organ protein.
		Arm 1: **Betamethasone** 0.5 mg/kg i.m. GD 104, 111, and 118 (3 doses)	9: 125-day delivery; 8: 145-day delivery	9: 125-day delivery; 8: 145–day delivery	Length of study: 145 days Length of treatment: 1–3 days	Fetal losses: 125 days: 4 145 days: 6	Neonatal attributes: Hematocrit (percent): • 125 days: 30.0 ± 1.6 ($p < 0.05$ vs. controls) • 145 days: 40.5 ± 0.9 Biparietal diameter (cm): • 125 days: 4.9 ± 0.1 • 145 days: 5.6 ± 0.8 ($p < 0.05$ vs. controls) Frontal-occipital diameter (cm): • 125 days: 5.9 ± 0.1 • 145 days: 7.4 ± 1.0 ($p < 0.05$ vs. controls)	Neonatal body and organ weights: Body weight: • 125 days: 25% less than controls ($p < 0.05$ vs. controls and 1-dose group) • 145 days: 19% less than controls ($p < 0.05$) Organ weight: • 125 days: all organ weights decreased ($p < 0.05$) • 145 days: all except adrenals decreased ($p < 0.05$)	

Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 6 (continued)		Arm 2: **Betamethasone** 0.5 mg/kg i.m., GD 104; saline injections GD 111 and 118 (1 dose)	10: 125-day delivery; 8: 145-day delivery	10: 125-day delivery; 8: 145-day delivery		125 days: 1 145 days: 0	Hematocrit (percent): • 125 days: 33.5 ± 1.1 • 145 days: 42.0 ± 1.4 Biparietal diameter (cm): • 125 days: 5.0 ± 0.1 • 145 days: 5.9 ± 1.0 Frontal-occipital diameter (cm): • 125 days: 6.3 ± 0.1 • 145 days: 7.7 ± 0.7	Body weight: • 125 days: 11% <controls • 145 days: 14% less than controls (p <0.03) Organ weight: • 125 days: brain and liver decreased (p <0.06) • 145 days: kidney, brain, and liver decreased	Experiments were designed to address, in a large animal model, the effects of evolving clinical practice for women who are at risk of preterm delivery, of initiating prenatal glucocorticoid treatments at very early gestation (22 weeks), and repeating treatments at 7- to 10-day intervals.
		Arm 3: **Controls** saline injections GD 104, 111, 118	10: 125-day delivery; 7: 145-day delivery	10: 125-day delivery; 7: 145-day delivery		125 days: 0 145 days: 0	Hematocrit (percent): • 125 days: 37.9 ± 0.8 • 145 days: 43.4 ± 0.8 Biparietal diameter (cm): • 125 days: 5.4 ± 0.1 • 145 days: 6.1 ± 1.1 Frontal-occipital diameter (cm): • 125 days: 6.7 ± 0.1 • 145 days: 7.9 ± 1.0	Body weight: Specific weights not indicated	
Citation 7: Tangalakis, Lumbers, Moritz, et al. 1992 Preclinical randomized controlled study	**x Animal** Merino ewes Age: Not specified Gestational Age: 103 days or 130 days at 1st exposure	**Purpose/Objective:** To test the potential pressor effect of exogenous cortisol in the ovine fetus between 100 and 120 days when endogenous cortisol production is minimal and after 130 days when endogenous plasma cortisol starts to rise.							Angiotensin II and noradrenaline were administered randomly to the fetus in bolus i.v. doses of 0.2, 0.5, 1.0, and 2.0 µg on day 1 and following the 24-hour infusions on days 2 and 3. To let blood pressure and heart rate return to basal values, at least a 10-minute interval was allowed between consecutive doses. No significant changes in fetal heart rate occurred in either regimen. Basal blood pressure was higher in the mature group but did not increase further despite an increase in cortisol levels. Vascular responsiveness to angiotensin II, but not to adrenaline, was significantly enhanced following cortisol infusion at both ages.
		Arm 1: **Cortisol** in immature (103–120 days of gestation) fetuses: 3-day schedule: day 1, control day; day 2, 24-hour infusion of 0.9% saline; day 3, 24-hour infusion of cortisol at 100 µg/hour	13	13	Length of study: Not specified Length of treatment: 3 days	Blood pressure (systolic/diastolic): Day 1: 50.8 ± 1.3/31.7 ± 1.3 Day 2: 51.7 ± 1.5/30.1 ± 1.2 Day 3: 59.1 ± 1.4/34.7 ± 1.7 Significant increase occurred in both systolic and diastolic pressures as a result of cortisol infusion (p <0.001).	Effect of angiotensin II administered days 1–3: Day 1: No significant changes in blood pressure Day 2: No significant changes in blood pressure Day 3: Significant increase in systolic pressure (p <0.004) Slope of dose-response curve was significantly steeper (p <0.001 for systolic, p <0.05 for diastolic pressure).	Effect of noradrenaline administered days 1–3: Day 1: No significant changes in blood pressure Day 2: No significant changes in blood pressure Day 3: No significant changes in blood pressure	

Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 7 (continued)		Arm 2: **Cortisol** in mature (130–137 days of gestation) fetuses: 3-day schedule: day 1, control day; day 2, 24-hour infusion of 0.9% saline; day 3, 24-hour infusion of cortisol at 100 µg/hour	10	10		Day 1: 55.6 ± 0.8 / 34.7 ± 1.3 Day 2: 53.9 ± 1.4 / 34.3 ± 1.6 Day 3: 57.0 ± 1.6 / 34.9 ± 2.0 No significant increase in blood pressure occurred as a result of cortisol infusion.	Day 1: No significant changes in blood pressure Day 2: No significant changes in blood pressure Day 3: Increase in blood pressure Slope of the dose-response curve was significantly steeper (p <0.01 for systolic, p <0.05 for diastolic pressure).	Day 1: No significant changes in blood pressure Day 2: No significant changes in blood pressure Day 3: No significant changes in blood pressure	Exogenous cortisol contributes to regulation of fetal blood pressure in the immature fetus when other mechanisms have not developed. Cortisol might achieve this effect, in part, by enhancing vascular sensitivity to angiotensin II.
Citation 8: Uno, Eisele, Sakai, et al. 1994 Preclinical longitudinal study	**x Animal** Female rhesus monkeys Age: Not specified Gestational Age: 132 days at 1st exposure	**Purpose/Objective:** To examine longitudinal postnatal sequelae of prenatal brain damage resulting from exposure to dexamethasone in utero.							This paper also reviews the authors' earlier studies that examined the effects of prenatal glucocorticoids on hippocampal neurons. Four consecutive images of hippocampal formations, coronal segments posterior from uncus, were selected for examination. Familiarity between the caretaker and the mother-infant monkey pairs was established for 4 months prior to the study; thereafter, all handling and blood collections were done by the same caretaker. Stress blood samples were taken after the infant was separated from the mother and kept in small, dark cage for 30 minutes. The infant was returned to its mother after the sample was drawn. Results suggest that the hippocampus mediates negative feedback of cortisol release: lack or deficiency of hippocampal neurons attenuates this feedback, resulting in hypercortisolemia.
		Arm 1: **Dexamethasone** 5 mg/kg, multiple-doses	5	5	Length of study: 20 months Length of treatment: GD 132–133	Hippocampal MRI in 19- to 20-month-old infants: • Both average area and volume of hippocampal segments were reduced 20–30% from those in vehicle-treated animals. • Total brain volume of the two groups showed no significant difference, although female brains were ~ 10% smaller in volume compared to male brains in same age groups.	Plasma cortisol levels in 10-month-old infants (µg/dL): • 10 a.m.: 30.1 ± 2.5 • 2 p.m.: 23.3 ± 2.6 • 2:30 p.m. (post-stress): 51.4 ± 3.4 • 3:30 p.m.: 49.5 ± 5.6 • 4:30 p.m.: 28.7 ± 2.9		
		Arm 2: **Control vehicle**, in multiple doses	3	3			• 10 a.m.: 18.9 ± 1.3 • 2 p.m.: 18.1 ± 2.8 • 2:30 p.m. (poststress): 41.8 ± 0.9 • 3:30 p.m.: 23.2 ± 5.4 • 4:30 p.m.: 20.11 ± 1.2		

Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 9: Watanabe, Ishizuka, Nagao 1995 Preclinical randomized controlled teratogenicity study	**x Animal** Female Sprague-Dawley rats Maternal Age: 9 weeks at time of mating Gestational Age: 14 days at time of 1st exposure	**Purpose/Objective:** To study potential comparative teratogenicity of triamcinolone acetonide, prednisolone, and hydrocortisone in the induction of palatal slit and cleft palate in rats.							No explanation was given for different litter sizes for each group across outcome measures. All treatment groups showed a significant reduction in fetal body weight as compared to controls, suggesting a generalized growth retardation. Weight reduction was more pronounced with increased dosage. The most severely affected group was that treated with triamcinolone acetonide, in which frequencies of cleft palate and palatal slit were highest. It is suggested that the duration of growth inhibitory effects plays an important role in palatal defect induction. The most prevalent anomalies other than palatal defects were omphalocele and general edema, observed in both prednisolone and triamcinolone acetonide groups. Comparison of these results with those in earlier studies involving dexamethasone indicates that triamcinolone acetonide is the most potent palatal teratogen, followed by dexamethasone and prednisolone. Findings indicate that triamcinolone acetonide has a significantly higher potentiality for induction of palatal slit in rats, compared to prednisolone and hydrocortisone. Earlier studies indicate that this is true also in mice.
		Arm 1: **Prednisolone** s.c. administered at 2 mg/kg volume on GD 14 and 15			Length of study: 20 days (dams sacrificed on GD 20) Length of treatment: 2 days	Cleft palate/live fetuses:	Palatal slit/live fetuses:	Late resorptions/implants:	
		• 12.5 mg/kg/day • 25 mg/kg/day • 50 mg/kg/day	12 dams 14 dams 11 dams	12 dams 14 dams 11 dams		• 0/176 (0%) • 0/220 (0%) • 6/170 (3.41 ± 1.85%)	• 9/176 (5.77 ± 6.03%) • 9/220 (4.63 ± 2.18%) • 45/164 (27.51 ± 9.47%, p <0.01)	• 0/179 (0.0%) • 6/241 (2.61 ± 0.84%) • 5/188 (2.23 ± 1.54%)	
		• 100 mg/kg/day	9 dams	9 dams		• 13/123 (10.59 ± 7.38%, p <0.01)	• 87/110 (77.69 ± 7.52%, p <0.01)	• 19/145 (8.13 ± 3.72%, p <0.05)	
		Arm 2: **Triamcinolone acetonide** s.c. administered on GD 14 and 15							
		• 0.25 mg/kg/day • 0.50 mg/kg/day	10 dams 10 dams	10 dams 10 dams		• 0/157 (0%) • 13/153 (8.56 ± 6.60%, p <0.05)	• 0/157 (0%) • 30/140 (26.27 ± 8.55%, p <0.01)	• 10/176 (5.54 ± 1.93%) • 5/169 (2.89 ± 1.56%)	
		• 1.0 mg/kg/day	11 dams	11 dams		• 35/146 (26.06 ± 6.61%, p <0.01)	• 35/111 (42.65 ± 11.70%, p <0.01)	• 20/158 (15.72 ± 4.76%, p <0.05)	
		• 2.0 mg/kg/day	10 dams	10 dams		• 77/125 (58.34 ± 8.87%, p <0.01)	• 35/48 (80.46 ± 7.83%, p <0.01)	• 18/156 (11.38 ± 3.70%, p <0.05)	
		Arm 3: **Hydrocortisone** s.c. administered on GD 14 and 15, 100 mg/kg/day	17 dams	17 dams		• 0/252 (0%)	• 0/252 (0%)	• 0/277 (0%)	
		Controls	21 dams	21 dams		• 0/326 (0%)	• 0/326 (0%)	• 1/345 (0.25 ± 0.25%)	

Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 10: Bracken, Triche, Belanger, et al. 2003 Prospective study	**x Human** Age: ≤24–≥35 years Race/Ethnicity: White/Asian: 1,496 (67.8%) African American: 209 (9.5%) Hispanic: 406 (18.4%) Other: 89 (4.0%) Pregnancy Trimester: ≤24 weeks Eligibility: Pregnant women ≤24 weeks gestation with history of physician-diagnosed asthma and random sample of nonasthmatic, pregnant women	**Purpose/Objective:** To examine whether asthma, asthma symptoms, or asthma therapy influence pregnancy outcomes (specifically, preterm delivery, intrauterine growth restriction [IUGR], gestational age, or birth weight) while controlling for other known risk factors.							Exclusion criteria included being more than 24 weeks pregnant at interview, having insulin-dependent diabetes mellitus, not speaking English or Spanish, and intending to terminate pregnancy. Asthma symptoms were classified using the modified Global Initiative for Asthma (GINA) guidelines. Asthma treatment was classified using modified GINA guidelines. Asthma severity was determined by cross-classifying with the 2002 GINA grid on symptom and medication steps to derive 4 severity categories: intermittent, mild persistent, moderate persistent, and severe persistent. Gestational age was calculated as completed days from first day of LMP or doctor's estimated date of delivery if LMP was uncertain. Preterm delivery was defined as delivery before 37 weeks gestation. Fetal growth restriction was defined as below 10th percentile of birth weight for gestational age. Women with asthma symptoms but no asthma diagnosis are at particular risk of undermedication and delivering IUGR infants.
		Arm 1: **Asthma diagnosis** (See Bronchodilators—β-agonists citation #3 for complete description of study arms)			Length of study: 4/97–6/00 Length of treatment: Not specified	Preterm delivery (adjusted associations): (See Bronchodilators—β-agonists citation #3 for complete description of outcomes)	IUGR: (See Bronchodilators—β-agonists citation #3 for complete description of outcomes)		
		Arm 2: **Asthma symptoms** (See Bronchodilators—β-agonists citation #3 for complete description of study arms)							
		Arm 3: **Asthma severity** (See Bronchodilators—β-agonists citation #3 for complete description of study arms)							
		Arm 4: **Asthma treatment** 0 (no medication use) Step 1 Step 2 Step 3 Step 4 Exposure: • Oral steroids	 1,657 402 108 28 10 52	 1,657 402 108 28 10 52		Preterm delivery increased with each increasing treatment step. OR for 2 controller medications = 3.67 (95% CI 1.11, 12.16). OR for 3 controller medications = 4.57 (95% CI 0.75, 24.63). Overall, 32% increased risk (95% CI 0%, 76%) for every increase in treatment step. Oral steroids use increased risk by 11% (95% CI 3%, 18%). Oral steroids used daily across pregnancy reduced gestation 2.22 weeks (p = 0.001). Specific exposure risks: • Oral steroids: OR 1.11 (95% CI 1.03, 1.18)	No increased risk by treatment step or for any specific medication type Specific exposure risks: • Oral steroids: OR 0.99 (95% CI 0.93, 1.05)		

Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 11: Carmichael and Shaw 1999 Population-based case-control study	**x Human** Age: Not specified Race/Ethnicity: 91% English-speaking, 9% Spanish-speaking (no other breakout provided) Pregnancy Trimester: Not specified Eligibility: Infants or fetuses with specified congenital anomalies from all hospitals and counseling centers in a known geographic base and matched controls	**Purpose/Objective:** To examine the association between women's corticosteroid use during the periconceptional period (1 month before to 3 months after conception) and delivering infants with orofacial clefts, conotruncal heart defects, neural tube defects, and limb deficiencies.							
		Arm 1: **Corticosteroids** used in periconceptional period	552,611 total infants	552,529 infants 13 mothers reporting use of corticosteroids	Length of study: 1987–1989 Length of treatment: 1 month before to 3 months after conception	Birth defects among 13 corticosteroid users based on maternal interviews (% is % of total eligible cases): 9 oral clefts • 6 ICLP (1.7%), OR 4.3 (95% CI 1.1, 17.2) • 3 ICP (2.1%), OR 5.3 (95% CI 1.1, 26.5) 1 NTD (0.4%) 3 without birth defects			Mothers were interviewed by telephone 3.7–3.8 years after delivery. Percentages indicate those interviewed out of total number giving birth to an infant with specified anomaly reported in reviewed records. Corticosteroids used, conditions treated, and anomalies reported: Corticosteroid / Condition / Anomaly Unspecified / Crohn's disease / ICLP Prednisone / Asthma / ICLP Prednisone / Lupus / ICLP Cortisone / Pelvic inflammatory disease / ICLP Cortisone / Hives / ICLP Triamcinolone acet. / Poison oak / ICLP Cortisone / Ulcers and colitis / ICP Dexamethasone / Rash / ICP Cortisone/prednisone / Hives / ICP Cortisone/steroid injection / Back injury / NTD Hydrocortisone / Back pain / None Prednisone (2) / Asthma / None Corticosteroid use was associated with an increased risk of ICLP (OR 4.3, 95% CI 1.1, 17.2) and ICP (OR 5.3, 95% CI 1.1, 26.5). No increased risk was reported for other anomaly groups. This suggests that periconceptional corticosteroid use is associated with increase of delivering infants with isolated clefts. Study problems: • No information on timing, mode, and dose of exposure • Small sample size (n = 13) • Only 1 case of ICLP in asthmatic patient on prednisone and no dose of drug, timing, etc., given
		Arm 2: **General population**				Birth defects in general population based on maternal interviews (% interviewed out of total number giving birth to infants with anomalies): 662 oral clefts (85%) • 348 ICLP • 141 ICP • 99 MCLP • 74 MCP 207 CHD (87%) 265 NTD (84%) 165 LD (82%)			

Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 12: Czeizel and Rockenbauer 1997 Population-based case-control study	**x Human** Age: ~ 25 years Race/Ethnicity: Not specified Pregnancy Trimester: All Eligibility: Infants with specified congenital anomalies identified from birth registry records and matched controls	**Purpose/Objective:** To assess the teratogenic potential of oral and topical corticosteroid treatment during pregnancy.				Birth defects (cases):	Risk for specific defects with oral exposure:	No birth defects (controls):	Use of tablets was rare in the first trimester except in the first month. Maximum use occurred in the last trimester (to promote fetal maturation in pregnant women with threatened preterm birth). Maximum use of ointments was in the first month. 57 women were treated in the first trimester (24 in the birth defects group, 33 in the nonbirth defects group). Mean birth order was higher in the birth defects group than in the nonbirth defects group; the rate of threatened preterm births was high in both groups, but higher in the nonbirth defects group. Summary: Observed birth prevalence of posterior cleft palate as 0.47, while expected is 0.48 per 1,000. The study indicated that absolute risk is low. Treatment with corticosteroids in pregnancy presents little, if any, teratogenic risk to the fetus in humans.
		Arm 1: **Corticosteroid** exposure	1,008	1,008	Length of study: Registry records from 1980–1994 Length of treatment: Varied	392 (= 1.88% of 20,830 defects in total population, but 38.9% of all steroid exposures): • Oral/systemic: 322 (1.5%) • Ointment: 73 (0.35%) • Spray: 8 (0.04%)	• CLP = 24/1,223 (1.96%), OR = 1.27 (95% CI 0.82, 1.96) • Ear anomalies = 13/318 (4.09%), OR = 3.07 (95% CI 1.73, 5.45) • Posterior CP = 9/561 (1.60%), OR = 1.17 (95% CI 0.60, 2.29) • Cardiovascular anomalies = 74/3,969 (1.86%), OR = 1.22 (95% CI 0.94, 1.58) • Intestinal atresia, stenosis = 4/144 (2.78%), OR = 1.83 (95% CI 0.66, 5.09)	616 (= 1.72% of 35,727 total population without birth defects, but 61.1% of all steroid exposures): • Oral/systemic: 503 (1.41%) • Ointment: 118 (0.33%) • Spray: 11 (0.03%)	
		Arm 2: **No corticosteroid** exposure	55,549	55,549		20,438 (= 98.1% of 20.830 defects in total population)		35,111 (= 98.3% of 35,727 total population without birth defects)	
Citation 13: Park-Wyllie, Mazzotta, Pastuszak, et al. 2000 Prospective observational cohort study and meta-analysis	**x Human** Age: 25–36 years Race/Ethnicity: Not specified Pregnancy Trimester: 1st Eligibility: Pregnant women who had taken prednisone in 1st trimester	**Purpose/Objective:** To investigate the relative fetal safety of maternal prednisone therapy; in addition, to conduct a meta-analysis to determine the risk of steroid use for the fetus with respect to major malformations, especially oral clefts.				Birth defects (major anomalies):	Obstetric results:	Neonatal results:	The study population consisted of women who telephoned voluntarily for information about fetal safety/risk from use of prednisone by the mother during pregnancy; the control population voluntarily contacted the organization for information on fetal safety/risk from other drugs. The meta-analysis reviewed 10 articles (6 cohort studies, 4 case-control studies) culled from 455 articles retrieved from various databases and covering publication years 1962–1999. The current study was included in the set of 10. 3 of the 10 articles did not detail specific corticosteroids and dosages used by mothers. Mothers in the meta-analysis studies were being treated for multiple pathologies, including rheumatoid arthritis, asthma, Crohn's disease, systemic lupus erythematosus, etc. They were exposed to corticosteroids and other drugs in 4 of 10 studies. In 1 of these 4, the authors (Heinonen, et al.) did not separate major and minor fetal malformations. In the prospective study, the difference in the rate of major anomalies and in the AGA:SGA:LGA ratios was not significant.
		Arm 1: **Prednisone** exposure, 27 ± 29 mg/day; range 5–80 mg/day Therapeutic duration (weeks) 21 ± 16; exposure (13 weeks) 38.184 (21%)	184 mothers • asthma = 30 (16%) • 138 exposed in 1st trimester (75%)	184 mothers	Length of study: 1985–1995 Length of treatment: 21 ± 16 weeks	• 4 (3.6%), no significant difference	• Elective terminations: 16 (9%), p = 0.002 • Gestational age at delivery: 38 ± 3 weeks (p = 0.0001) • Premature births: 27 (17%), p = 0.0001	• Birth weight: 3,112 ± 684 gms (p = 0.0001) in exposed infants; no preponderance of SGA or LGA compared to nonexposed infants	
		Arm 2: **Controls** (unexposed)	188 mothers	188 mothers		• 3 (2%)	• Elective terminations: 2 (1%) • Gestational age at delivery: 39.5 ± 2 weeks • Premature births: 9 (5%)	• Birth weight: 3,428 ± 578 gms in nonexposed infants	
		Arm 3: **Meta-analysis** prednisone exposure range 2.5–100 mg/day			Publication years: 1962–1999 (2000 including current study)	• Summary OR with all cohort studies = 1.45 (95% CI 0.80, 2.60) • OR (removing Heinonen study) = 3.03 (95% CI 1.08, 8.54) • Summary OR for case-control studies examining oral clefts = 3.35 (95% CI 1.97, 5.69)		

Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 13 (continued)									Prednisone does not represent a major teratogenic risk at therapeutic doses, but, on the basis of the meta-analysis, it increases the risk of oral cleft 3.4-fold. Cumulative OR for the cohort and case-control studies showed nonsignificant increased risk of major malformations associated with steroids. However, it did show a greater than 3 times increased risk of oral clefts when the fetus was exposed in the first trimester. Note marked length of steroid use in prospective study.
Citation 14: Perlow, Montgomery, Morgan, et al. 1992 Case-control study	**x Human** Age: S: 28 ± 6 years NS: 29 ± 5 years C: 28 ± 5 years Race/Ethnicity: Not specified Pregnancy Trimester: All Eligibility: Pregnant asthmatic patients who delivered at the study hospital	**Purpose/Objective:** To determine the impact of asthma and its severity, as determined by medication requirements, on perinatal outcome.				Maternal:	Obstetric:	Neonatal:	Patients who were using over-the-counter drugs or prescription medications only on an as-needed basis were excluded. Perinatal outcome is compromised in pregnancy complicated by chronic medication-dependent asthma; although both steroid-dependent and nonsteroid-dependent women are at risk, steroid-dependent women seem to be at even greater risk than nonsteroid-dependent women. As indicated by the data in Outcomes column 1, steroid-dependent women with asthma were more than twice as likely to have an antepartum admission for asthma exacerbation and were admitted 5 times more often for >4 days when compared to nonsteroid-dependent women with asthma. Both asthmatic groups underwent cesarean section for fetal distress significantly more often than controls (Outcomes, column 2). Steroid-dependent women with asthma had a significantly higher frequency of admission for preterm labor and preterm delivery compared with nonsteroid-dependent women with asthma (Outcomes, column 2). Neonates born to women with asthma were significantly more likely to require neonatal ICU admission. Low birth weight significantly increased in steroid-dependent group compared to the nonsteroid-dependent group (Outcomes, column 3).
		Arm 1: **Steroid group (S):** pregnant, steroid-dependent asthmatics, requiring long-term administration of prescription steroid preparations; all patients used prednisone and other medications (theophylline, metaproterenol, terbutaline, cromolyn sodium, or other)	31	31	Length of study: 1/1/85–12/31/90 Length of treatment: Throughout pregnancy	• Diabetes mellitus: 9.7% (p = 0.01 vs. controls) • Gestational diabetes: 12.9% (p = 0.02 vs. controls) • Admission for asthma exacerbation: 71.0% (2.5 times greater than nonsteroid dependent admissions) • Admission for >4 days: 22.6% (5 times more than nonsteroid dependent)	• Cesarean section, overall: 38.7% • Cesarean section for fetal distress: 41.6% (p = 0.01 vs. controls) • Admission for preterm labor: 48.4% (p <0.0001 vs. controls) • Premature rupture of membranes: 25.8% (p <0.0001 vs. controls) • Delivery <37 weeks: 54.8% (p <0.0001 vs. controls)	• Birth weight <2500 gm: 45.2% (p <0.0001 vs. controls); 50% of steroid-dependent had SGA • Intrauterine growth retardation: 6.5% (p = 0.3 vs. controls) • Admissions to neonatal intensive care unit (ICU): 39.0% (p <0.0001 vs. controls)	
		Arm 2: **Nonsteroid group (NS):** pregnant, nonsteroid-dependent asthmatics, requiring prescription medications other than steroids; patients used theophylline, metaproterenol, terbutaline, cromolyn sodium, or other	50	50		• Diabetes mellitus: 2.0% • Gestational diabetes: 4.0% • Admission for asthma exacerbation: 30.0% • Admission for >4 days: 4.0%	• Cesarean section, overall: 56.0% (p = 0.002 vs. controls) • Cesarean section for fetal distress: 24.1% (p = 0.04 vs. controls) • Admission for preterm labor: 10.0% (p = 0.03 vs. controls) • Premature rupture of membranes: 10.0% (p = 0.04 vs. controls) • Delivery <37 weeks: 14.0% (p = 0.037 vs. controls)	• Birth weight <2500 gms: 14.0% (p = 0.06 vs. controls) • Intrauterine growth retardation: 8.0% (p = 0.09 vs. controls) • Admissions to neonatal ICU: 22.0% (p = 0.015 vs. controls)	

Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 14 (continued)		Arm 3: **Controls (C):** Pregnant women without asthma	130	130		• Diabetes mellitus: 0.0% • Gestational diabetes: 1.5% • Admission for asthma exacerbation: N/A • Admission for >4 days: N/A	• Cesarean section, overall: 30.0% • Cesarean section for fetal distress: 5.1% • Admission for preterm labor: 1.6% • Premature rupture of membranes: 1.6% • Delivery <37 weeks: 3.9%	• Birth weight <2500 gms: 4.6% • Intrauterine growth retardation: 1.5% • Admissions to neonatal ICU: 7.7%	No anomalies were observed in the steroid-dependent group, and 2 (ventriculoseptal defect and syndactyly) were observed in the nonsteroid-dependent group. No significant difference in frequency of congenital anomalies was identified. The study did not identify the length of time or the pregnancy trimester in which steroids were taken. It was not specified whether steroids were used at the time of conception.
Citation 15: Robert, Vollset, Botto, et al. 1994 Retrospective, case-control drug exposure-malformation surveillance report	**x Human** Age: Not specified Race/Ethnicity: Not specified Pregnancy Trimester: 1st Eligibility: All malformations with known 1st-trimester drug exposure in participating registries	**Purpose/Objective:** To look for deviations from a random distribution of drug exposures and malformations as part of the MADRE (Malformation Drug Exposure Surveillance) project							Reports in 1990–1991 came from 8 participating programs, all collecting exposure data retrospectively: • Australia—national population-based monitoring system • Central-East France—regional population-based system • Israel—hospital-based system • Italy—2, 1 hospital-based, the other a regional population-based monitoring system • Japan—2, both hospital-based programs • ECLAMC—Latin American collaborative study of congenital malformations, a clinical-epidemiological, hospital-based, case-control study Coding of malformations was based on the WHO International Classification of Diseases, 9th revision, adapted by the British Paediatric Association (ICD9/BPA). Drug coding was based on the Anatomical Therapeutic Chemical (ATC) classification system.
			1,448 cases of malformed infants collected in 2 years		Length of study: Report on 1st 2 years of study, 1991–1992	Key associations: Anticonvulsants: • And facial clefts (barbiturates): OR 4.10, p = 0.003 • And atrial septal defects (barbiturates and fatty acids): OR 2.34, p = 0.04 Benzodiazepines: • And facial clefts: OR 2.81, p = 0.03 • And cleft lip with or without cleft palate: OR 3.55, p = 0.01 Corticosteroids (systematic use): • And facial clefts – 7/132 cases (5.3%) – 2 cleft lip only; 5 cleft lip and cleft palate – p = 0.04; OR = 3.16 Thyroid hormones: • And cardiac septal defects: OR 4.10, p = 0.02 Seven infants were exposed to systemic corticosteroids in the first trimester, but there was no discussion of the length of exposure, dose, or timing relative to preconceptual use or diseases for which steroids were provided.		

Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 16: Rodríguez-Pinilla and Martinez-Frias 1998 Case-control study	**x Human** Age: Not specified Race/Ethnicity: Not specified Pregnancy Trimester: 1st Eligibility: All infants born with congenital anomalies in ~ 75 participating hospitals and controls	**Purpose/Objective:** To present the results of a large case-control study, conducted by the Spanish Collaborative Study of Congenital Malformations (ECEMC), on the use of corticosteroids during pregnancy and the presence of oral clefts in the newborn (nonsyndromic).							Maternal illness for steroids: • Addison's disease • Thrombocytopenia • Ulcerative colitis • Chronic sinusitis Key: Case 4: CL, CP+ = cleft lip + cleft palate, diaphragmatic hernia, and hypoplasia of left kidney Case 5: CL, CP+ = cleft lip + cleft palate, dysplastic ears, posterior fontanel, hemivertebra, ventricular hypertrophy, absent parathyroid gland, hypoplastic ovary, postaxial polydactyly, talipes Researchers cannot rule out that case 5 is trisomy 13, because karyotype could not be performed. Results of analysis were controlled for potential confounder factors such as maternal smoking, maternal hyperthermia, first-degree malformed relatives with cleft lip with or without cleft palate, and maternal treatment with antiepileptics, benzodiazepines, metronidazole, or sex hormones during first trimester of pregnancy. The safety of oral steroids in first trimester is controversial. The authors believe that corticosteroids in the first trimester should be restricted to life-threatening situations, diseases without any other safe alternative, or cases with replacement therapy.
		Arm 1: **Corticosteroids** and oral clefts	5/1,184 total oral clefts	5/1,184 total oral clefts	Length of study: 4/76–12/95	Exposure in oral cleft infant (5/1184) vs. other groups: OR p • Paired controls (5/1) 5.0 0.1 • Controls ± 45 days (5/9) 5.2 0.008 • Other anomalies (5/26) 3.2 0.03	Cleft lip (with or without cleft palate) in exposed infants vs. other groups (4/1184): OR p • Paired controls (4/1) 4.0 0.19 • Controls ± 45 days (4/5) 8.9 0.004 • Other anomalies (4/26) 4.7 0.01 First trimester oral steroid exposure increased risk of clef lip with or without cleft palate. OR = 6.55 (95% CI 1.44, 29.76) p = 0.015	Exposure data for 5 oral cleft cases: Anomaly Drug/dose Time exposed (1) CP: Prednisolone 40 mg (2 doses) 3rd month (2) CL: Hydrocortisone 40 mg/day Whole pregnancy (3) CL, CP: Prednisone 15–30 mg/day 1st month (4) CL, CP+: Prednisone 30 mg/day 1st trimester and 6–9 months (5) CL, CP+: Triamcinolone 8 mg/day 2nd month	
		Arm 2: **Corticosteroids** and other anomalies	26/19,459 total other anomalies	26/19,459 total other anomalies					
		Arm 3: **Corticosteroids** and no anomalies • Paired controls • Controls ± 45 days	1/1,173 9/11,120	1/1,173 9/11,120					

Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics: Arm	Number Enrolled	Number Evaluable	Treatment Duration	Findings: Outcome 1	Outcome 2	Outcome 3	Comments
Citation 17: Schatz, Zeiger, Harden, et al. 1997 Prospectively monitored cohort study	**x Human** Age: Not specified Race/Ethnicity: Not specified Pregnancy Trimester: 1st, 2nd (all subjects <28 weeks at entry Eligibility: Pregnant subjects with asthma matched on basis of age, parity, and smoking status with pregnant nonasthmatic controls	**Purpose/Objective:** To assess safety of asthma medications, antihistamines, and decongestants in a prospectively monitored cohort of pregnant women with and without asthma.							Drug exposure data in terms of incidence of malformations for all subjects (number of malformations): 1st Trimester Exp. / Unexp. / Anytime Exp. / Unexp. β-agonists 488 / 1,000 / 557 / 823 Theophylline 292 / 1,208 / 429 / 1,061 Cromolyn* 151 / 1,348 / 243 / 1,247 Corticosteroids 204 / 1,295 / 297 / 1,190 Antihistamines 321 / 1,175 / 493 / 996 Decongestants 453 / 1,032 / 790 / 698 * Inhaled: 158; intranasal: 113; ophthalmic: 23 There were no significant relationships (all p >0.05) between β-agonists, cromolyn, antihistamines, or decongestants and increased incidence of any other adverse perinatal outcomes evaluated (data not shown). There were no significant relationships (all p >0.05) between specific medication use and increased incidence of small-for-gestational-age infants (data not shown). Results my be confounded by presence and severity of asthma. Following are results of multivariate analysis performed in pregnant subjects with asthma when significant univariate associations were identified between drug exposure and perinatal outcome variables: • Oral corticosteroids were independently associated with preeclampsia (p = 0.027, OR 2.00 [95% CI 1.11, 3.61]) but inhaled steroids were not when controlled for other exposures. • When preeclampsia was included in the model for low birth weight, it was independently related (p = 0.025), but it did not substantially change demonstrated independent relationships with African American race (p = 0.002) and lower weight gain during pregnancy (p <0.001) and lack of independent relationships with oral or inhaled corticosteroids or mean FEV_1. • African American race (p = 0.001) and lower weight gain during pregnancy (p = 0.001) but not theophylline or inhaled corticosteroids were associated with preterm birth.
		Arm 1: Exposure **to any asthma/allergy medication** at any time for total cohort: • β-agonists (inhaled or oral) • Theophylline • Cromolyn (inhaled, intranasal, ophthalmic) • Corticosteroids (oral, inhaled, or intranasal) • Antihistamines • Decongestants	1,904 (1,044 with asthma; 860 controls)	1,502 (824 with asthma; 678 controls)	Through delivery, all arms	Fetal effects: Major congenital malformations, 1st trimester: % Incidence Exp. / Unexp. β-agonists 4.3 / 5.6 Theophylline 4.5 / 5.3 Cromolyn 6.0 / 5.0 Corticosteroids 6.9 / 4.9 Antihistamines 3.7 / 5.5 Decongestants 5.5 / 4.8 No significant relationship, p >0.05 for all comparisons	Fetal effects: Major congenital malformations, anytime: % Incidence Exp. / Unexp. β-agonists 3.7 / 6.2 Theophylline 4.7 / 5.3 Cromolyn 6.2 / 4.9 Corticosteroids 6.1 / 4.9 Antihistamines 3.9 / 5.7 Decongestants 5.2 / 4.9 No significant relationship, p >0.05 for all comparisons		
		Arm 2: **Theophylline** exposure (See Bronchodilators—β-agonists citation #5 for complete description of study arms)						(See Bronchodilators—β-agonists citation #5 for complete description of outcomes)	

Table 5. Effects of oral steroids on maternal health and fetal outcomes when used to treat asthma during pregnancy (continued).

Citation/ Study Type	Population	Study Characteristics				Findings			Comments
		Arm	Number Enrolled	Number Evaluable	Treatment Duration	Outcome 1	Outcome 2	Outcome 3	
Citation 17 (continued)		Arm 3: **Corticosteroid** exposure • Any route					Fetal effects:	Maternal effects: • Preterm births: 19/297 (64%) in exposed subjects, 45/1,195 (3.8%) in controls p = 0.045 (mean gestational age 32.74 ± 3.75 weeks in exposed subjects) • Preeclampsia: 34/296 (11.5%) in exposed subjects, 85/1,197 (7.1%) in controls, p = 0.013 • Low birth weight infants: 18/297 (6.1%) in exposed subjects, 40/1,197 (3.3%) in controls, p = 0.030	
		• Total inhaled (inhaled with or without oral corticosteroids)						• Preterm births: 13/138 (9.4%) in exposed subjects, 51/1,354 (3.8%) in controls, p = 0.002 • Preeclampsia: 17/137 (12.4%) in exposed subjects, 102/1,356 (7.5%) in controls, p = 0.044 • Low birth weight infants: 11/138 in exposed subjects, 47/1,356 in controls, p = 0.009	
		• Inhaled only					% incidence of major congenital malformations (inhaled-only): Exposed 5.4 Unexposed 4.9	• Preterm births: 5/64 (7.8%) in exposed subjects, 59/1,428 (4.1%) in controls, p = NS • Preeclampsia: 7/64 (10.9%) in exposed subjects, 112/1,429 (7.8%) in controls, p = NS • Low birth weight infants: 3/64 (4.7%) in exposed subjects, 55/1,430 (3.8%) in controls, p = NS	
		• Oral					% incidence of major congenital malformations (oral): Exposed 7.0 Unexposed 4.9	• Preterm births: 10/130 (7.7%) in exposed subjects, 54/1,362 (4.0%) in controls, p = NS • Preeclampsia: 17/129 (13.2%) in exposed subjects, 102/1,364 (7.5%) in controls, p = 0.022, OR = 2.0 • Low birth weight infants: 11/130 (8.5%) in exposed subjects, 47/1,364 (3.4%) in controls, p = 0.005	

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