

Normal pregnancy outcomes in a population-based study including 2968 pregnant women exposed to budesonide

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Background: Inhaled corticosteroids are recommended as first-line therapy for pregnant women with moderate to severe asthma, although the effects on pregnancy outcome are uncertain. A low compliance with the recommendations might lead to inadequate control of asthma, which has been associated with adverse outcomes both for the mother and the infant.

Objective: To investigate whether the reported use of inhaled budesonide (Pulmicort) during pregnancy influences birth outcome.

Methods: Data were derived from the Swedish Medical Birth Register, which includes 99% of births in Sweden. During 1995 to 1998, 293,948 newborn infants were identified. Pregnancy outcomes were compared for mothers in Sweden reporting asthma medication usage with those reporting no asthma medication usage.

Results: The 2968 mothers who reported use of inhaled budesonide during early pregnancy gave birth to infants of normal gestational age, birth weight, and length, with no increased rate of stillbirths or multiple births. The rate of caesarean births was higher among mothers who used asthma medication during their pregnancy than among the control group.

Conclusions: The use of inhaled budesonide in Sweden is not linked with any clinically relevant effects associated with pregnancy outcome. (*J Allergy Clin Immunol* 2003;111:736-42.)

Key words: Asthma, inhaled corticosteroids, budesonide, pregnancy, growth

Asthma is a common and potentially serious complication of pregnancy, and severe asthma may be associated with increased maternal and/or fetal mortality rates.¹ Inadequate control of asthma during pregnancy has been associated with adverse outcomes, such as higher rates of prematurity, intrauterine growth retardation, lower birth weight, perinatal death, and preeclampsia, which may be due to fetal hypoxia.^{2,3} Asthma that is controlled during pregnancy, however, has been associated with outcomes that are not significantly different from those of the nonasthmatic population.⁴⁻⁶ Treatment guidelines there-

fore emphasize the importance of maintaining asthma control during pregnancy, and inhaled glucocorticoids are recommended as first-line regular therapy in pregnant women with moderate to severe asthma.⁷

Nevertheless, inhaled glucocorticoids are labeled with a pregnancy warning, based on reproductive toxicologic studies in animals in which a teratogenic effect (cleft palate) as well as intrauterine growth retardation were observed.⁸⁻¹⁰ Whether these effects are relevant in human beings is controversial.¹⁰⁻¹⁷ In a systematic review of studies investigating the risk of congenital malformations (associated with asthma treatment during the first trimester of pregnancy), only three eligible studies met the quality criteria.¹⁸ One study did not include inhaled corticosteroids, another included 137 pregnant women exposed to beclomethasone,¹⁹ and a further study included 2014 pregnant women exposed to budesonide.²⁰ None of the studies reported a significant increase in the proportion of congenital malformations with the use of inhaled corticosteroids.

Later, the budesonide study was extended from 2014 cases to a total of 2534 exposed pregnancies,²¹ in which the rate of congenital malformations among infants exposed to budesonide during early pregnancy was the same as that for all newborn infants during the same period (3.6%). The value of this epidemiologic data and the totality of safety and efficacy data available have been recognized by the American College of Allergy, Asthma, and Immunology and by the American College of Obstetricians and Gynecologists.⁷ In a joint statement, they list budesonide as one of two inhaled glucocorticoids of choice for use during pregnancy and a particularly good choice for those women who require high-dose inhaled glucocorticoid therapy because budesonide should maximize adherence and minimize systemic effects. Furthermore, budesonide is the only inhaled glucocorticoid assigned a category B pregnancy rating by the US Food and Drug Administration (ie, no risk in controlled animal studies or sufficient clinical safety data in pregnancy). However, the effect of inhaled glucocorticoids on the rates of preterm births, stillbirths, multiple births, and caesarean births as well as on birth weight and length is still unknown.

Intrauterine growth retardation was reported by Reinisch et al¹⁰ among term newborn infants whose mothers had reported the use of oral corticosteroids (prednisone) for infertility treatment throughout the pregnancy. Prenatal treatment of congenital adrenal hyperplasia with dexamethasone, however, does not affect the pregnancy outcome.¹⁵⁻¹⁷

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The situation for pregnant women with asthma is therefore complicated because both inadequate control of asthma and treatment with glucocorticoids may affect the outcome of the newborn infant. Although inhaled glucocorticoids may result in lower systemic exposure than oral glucocorticoids, no large studies have been conducted in human beings to investigate the possible connection between inhaled glucocorticoids and pregnancy outcomes. In the current study, based on the Swedish Medical Birth Register data from 1995 to 1998, the association between reported use of inhaled budesonide during pregnancy and preterm birth, stillbirth, multiple birth, caesarean birth, birth weight, and birth length was determined.

METHODS

Information comprising asthma medication during pregnancy and pregnancy outcomes was derived from the Swedish Medical Birth Register, which was founded in 1973. This register contains detailed information on 99% of all births in Sweden (approximately 100,000 per year), including data on newborn infants. The register encompasses case sheet and record data from maternity clinics listing care received during parturition and examination of the newborn infant. This presupposes a similar system of case sheets and records throughout the country. During the first few years there was some variation, but by 1982 to 1983, full uniformity was attained.²²

In Sweden, all pregnant women receive free antenatal care. At their first visit to the antenatal center (weeks 10 through 12; record form 1) and during the rest of the pregnancy (record form 2), women are examined and interviewed by a midwife. From July 1994, midwives have reported which medication women were using, although information on duration and dose is often missing. Treatment names are listed as marketed names on the form but are assigned codes at a later date for data storage by using the Anatomical Therapeutic Chemical classification system. Copies of the resulting documentation (record forms 1 and 2) are sent to the National Board of Health and Welfare, where the data are entered onto a computer database.

Statistics

Comparisons in pregnancy outcomes were made between mothers who had reported use of different asthma medications during pregnancy (exposed) and those mothers in the study population who did not report use of asthma medication (nonexposed). Because the results were similar whether the comparisons were made between all women in the study population and exposed women or between unexposed women (excluding exposed women from the study population) and exposed women, the word "study population" is used in the text as the comparison group.

Statistical comparison of mean values was performed by means of the Student *t* test and 95% confidence intervals. A probability value of <5% indicated statistical significance. Because gestational age and the mother's size influence the size of fetus, both birth weight and length measurements were adjusted for these parameters in a separate analysis. Because the majority of pregnant women using inhaled corticosteroids had used budesonide, the analysis was focused on budesonide to obtain maximal power for conclusions regarding asthma treatments during pregnancy and their outcomes.

RESULTS

Study population

The total number of newborn infants in the Swedish Medical Birth Register for 1995 to 1998 was 298,880,

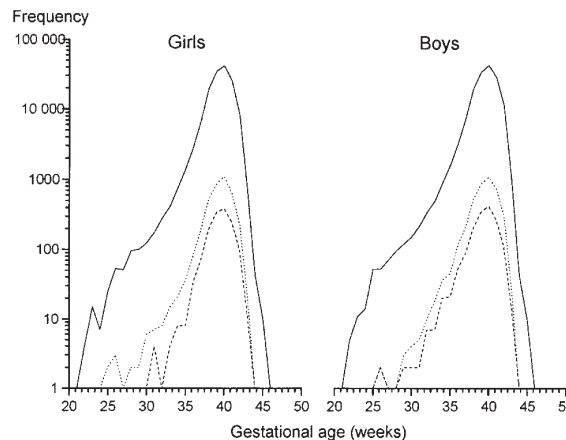


FIG 1. Distribution of gestational age for all girls and boys born in Sweden between 1995 and 1998 (—) and for those whose mothers reported use of inhaled budesonide (Pulmicort) in early pregnancy (· · ·) or asthma medication other than inhaled or oral glucocorticoids in early pregnancy (- - -). All multiple births and stillbirths are excluded.

after the number of multiple births (*n* = 4510) and stillbirths (*n* = 999) were excluded. Information regarding birth weight and length was obtained for 293,948 of these births (study population). Mothers recorded their use of asthma medication during early pregnancy (record form 1). Some 7719 (group A) used asthma medicines other than inhaled or oral glucocorticoids (adrenergics, xanthine derivatives, cromoglicates, or anticholinergics); 3364 used inhaled glucocorticoids as their only glucocorticoid treatment; 2968 used budesonide (group P1); whereas a further 103 (group P0) used oral glucocorticoids concomitant to treatment with budesonide. The use of budesonide during the whole pregnancy (record forms 1 and 2) was reported by 207 mothers (group P2) (Table I).

Gestational age

Preterm birth is usually defined as <37 weeks' gestation (259 days). Mean ($\pm$ SD) gestational age was 39.4 ($\pm$ 1.7) weeks for all girls in the study population (Table I). Compared with this, the mean gestational age did not differ for girls in groups A and P1 but was 1 day shorter for girls in group P2 and 4 days shorter for girls in group P0 (Table I). For boys, the mean gestational age was 39.5 ($\pm$ 1.8) weeks in the study population (Table I). Compared with this, mean gestational age was 1 day shorter for boys in groups A and P1, 2 days shorter for boys in group P2, and 3 days shorter in group P0 (Table I). The distribution of gestational age for boys and girls was similar for all mothers compared with those mothers who reported use of budesonide (Fig 1).

Stillbirths

The rate of stillbirths among all mothers in the study population was similar to the rates in the other groups (A, P1, P0, and P2; Table II).

Asthma, rhinitis,
other respiratory
diseases

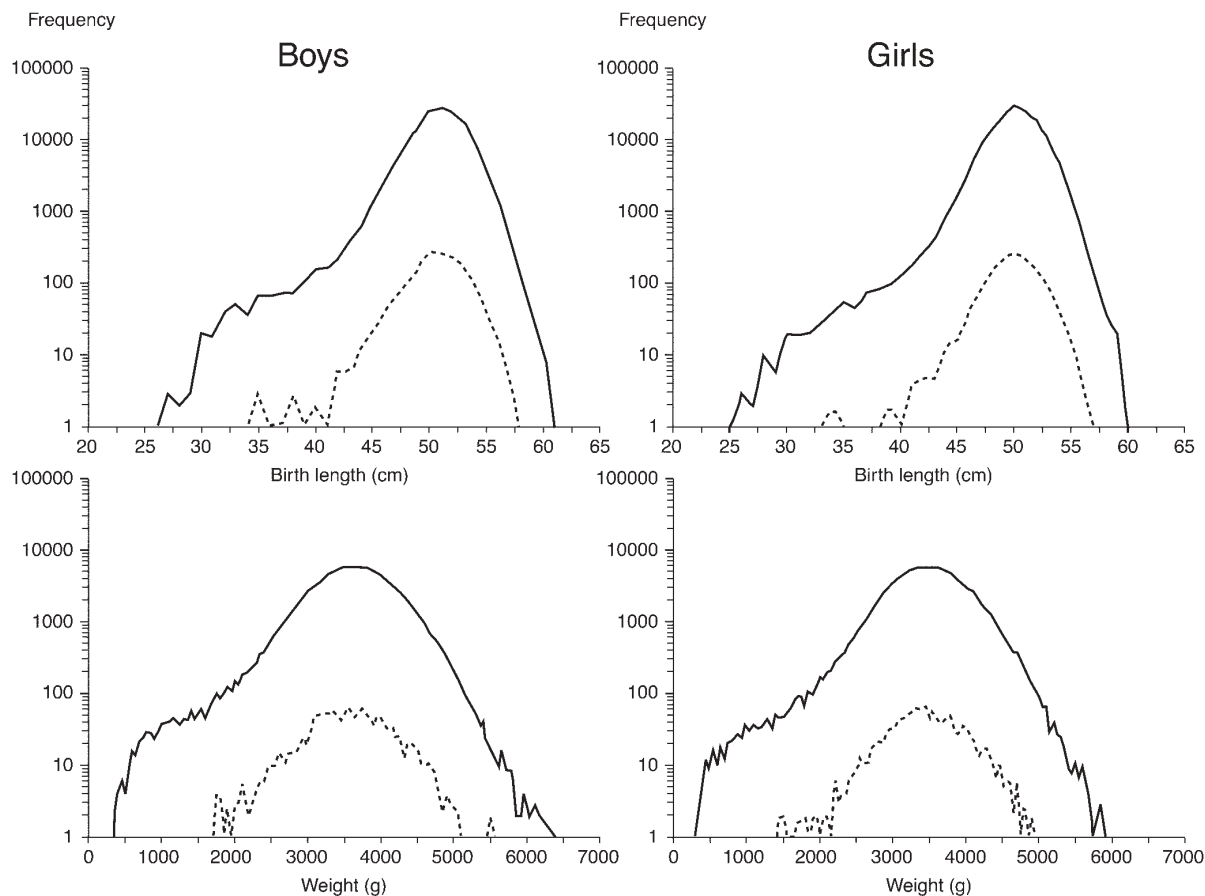


FIG 2. Distribution of birth weight and birth length for all girls and boys born in Sweden between 1995 and 1998 (—) and for those whose mothers reported use of inhaled budesonide (Pulmicort) during early pregnancy (---). All multiple births and stillbirths are excluded.

Multiple births

The rate of multiple births among all mothers in the study population was similar to the rates in the other groups (A, P1, P0 and P2) (Table II).

Caesarean births

The rate of caesarean births was slightly higher among asthmatic women (group A: 13.3% girls, 14.7% boys; group P1: 13.1% girls, 16.2% boys and group P2: 6.9% girls, 14.2% boys) than among all women in the study population (11.3% girls; 12.2% boys) (Table II). The highest rates were found in the P0 group (30.8% girls; 21.6% boys) (Table II).

Birth weight

Low birth weight infants are usually defined as <2500 g. Mean ($\pm$ SD) birth weight was 3500 ($\pm$ 530) g for girls and 3630 ($\pm$ 570) g for boys in the study population (Table I). All babies in the study population were compared, and differences in gestational age and mother's height were adjusted. The resulting mean observed birth weight was slightly lower in group A (by 20 g for girls and by 10 g for boys) and group P1 (40 g for girls and 20

g for boys) and higher in group P2 (50 g for girls and 10 g for boys) (Table I). The largest differences were observed in group P0 (10 g higher for girls and 160 g lower for boys) (Table I).

For both boys and girls, distribution of birth weight was similar for the various groups (Figs 2 and 3), and there was no statistically significant difference in the correlations between birth weight and length (Fig 3). Because of the large number of observations for all boys and girls, a random sample of all births had to be chosen for illustration of the correlation between birth weight and length. The reported use of budesonide by mothers throughout pregnancy was not associated with differences in mean birth weight compared with all mothers in the study population (Table I and Fig 2).

Birth length

Mean ($\pm$ SD) birth length was 50.0 ($\pm$ 2.4) cm for girls and 50.8 ($\pm$ 2.5) cm for boys in the study population (Table I). Comparing all babies in the study population and having adjusted for differences in gestational age and mother's height, there were no observed differences in length for the various groups (A, P1, P2, and P0) (Table I). For both male and female newborn populations, the

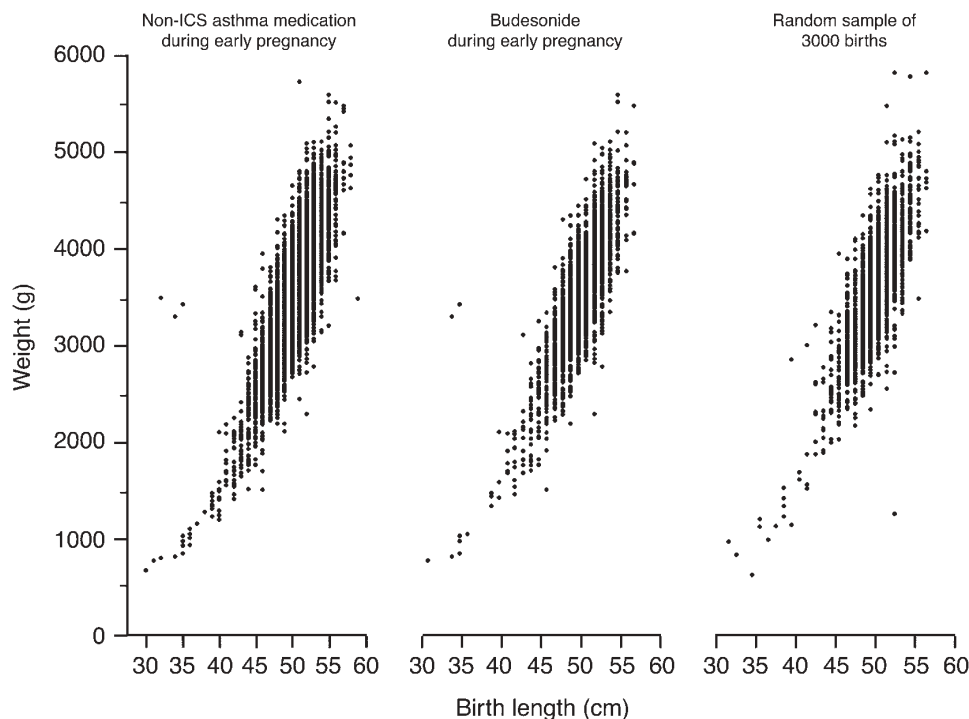


FIG 3. Scatterplot of birth weight and birth length for all babies born in Sweden between 1995 and 1998 whose mothers reported use of asthma medication other than inhaled or oral glucocorticoids, whose mothers reported use of inhaled budesonide (Pulmicort) during early pregnancy, and a random sample of all births. All multiple births and stillbirths are excluded.

distribution of birth length was similar for the groups (Figs 2 and 3). The reported use of budesonide by mothers throughout pregnancy was not associated with differences in mean birth length when compared with all mothers in the study population (Table I and Fig 2).

DISCUSSION

Practitioners have been reluctant to prescribe inhaled glucocorticoids to pregnant women because of the general fear of prescribing any medication during pregnancy and because of concerns raised by the labels warning that maternal side effects and adverse perinatal outcomes may result from any type of steroid administration. In addition, some patients are reluctant to take their medication even when prescribed for fear of potential negative effects on the fetus. This may in turn increase the effect of asthma on the fetus and increase the risk of adverse outcomes such as higher rates of prematurity, intrauterine growth retardation, lower birth weight, perinatal death, and preeclampsia.²³

The current study, which is the largest to date observing the use of inhaled glucocorticoids and pregnancy outcomes, shows that mothers who reported the use of 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 used in the current study were probably less than recommended because real-life use of inhaled glu-

corticoids tends to be lower than that prescribed.²³ These results cannot be applied to other inhaled glucocorticoids because the systemic effects of different inhaled glucocorticoids vary as the result of differences in potency and the bioavailability of compounds and their metabolites.^{24,25} It should also be considered that some inhaled glucocorticoids are 9-fluorinated or 9-halogenated and thus may be inactivated less by the placenta than other synthetic glucocorticoids.²⁶

Pregnancy induces a series of changes in maternal hormones, including increased cortisol levels, which facilitate the flow of nutrients to the growing fetus.²⁷ The placenta, however, protects the fetus from high maternal endogenous glucocorticoids. It is believed that placental 11- β -hydroxysteroid dehydrogenase type 2, which catalyzes the metabolism of cortisol, carries out this function.²⁸⁻³⁰ Thus the fetus is only exposed to low cortisol levels in the first stage of pregnancy, before its own endogenous production begins.^{31,32}

The enzyme 11- β -hydroxysteroid dehydrogenase type 2 also plays a role for synthetic glucocorticoids to cross the placenta and exert a pharmacologic effect on the fetus. This enzyme metabolizes synthetic glucocorticoids such as prednisolone, whereas 9-fluorinated glucocorticoids such as dexamethasone are inactivated to a much lesser extent.²⁶ This is the pharmacologic background for the use of dexamethasone in the treatment of pregnancy at risk of congenital adrenal hyperplasia. Treatment with dexamethasone (20 μ g/kg per day) in the first trimester

TABLE I. Gestational age, weight, and length at birth for all girls and boys born between 1995 and 1998 in Sweden and for those whose mothers reported use of asthma medication during pregnancy

Category	Total number	Gestational age (wk): mean $\pm$ SD	Birth weight (g): mean $\pm$ SD	Birth length (cm): mean $\pm$ SD
Girls				
All	143,017†	39.4 $\pm$ 1.7	3,500 $\pm$ 530	50.0 $\pm$ 2.4
Reported use of asthma medication other than glucocorticoids in early pregnancy (group A)	3,743	39.4 $\pm$ 1.8	3,460 $\pm$ 550*** (3,480)	49.9 $\pm$ 2.6*** (49.9)
Reported use of inhaled budesonide (Pulmicort) in early pregnancy (group P1)	1,409	39.4 $\pm$ 1.8	3,450 $\pm$ 560** (3,460)	49.8 $\pm$ 2.6*** (49.8)
Reported use of inhaled budesonide during the whole pregnancy (group P2)	101	39.2 $\pm$ 1.5	3,500 $\pm$ 500 (3,550)	50.0 $\pm$ 2.0 (50.3)
Reported use of inhaled budesonide and oral glucocorticoids in early pregnancy (group P0)	52§	38.8 $\pm$ 1.9*	3,430 $\pm$ 660 (3,510)	49.5 $\pm$ 2.8 (49.9)
Boys				
All	150,931	39.5 $\pm$ 1.8	3,630 $\pm$ 570	50.8 $\pm$ 2.5
Reported use of asthma medication other than glucocorticoids in early pregnancy (group A)	3,976§	39.4 $\pm$ 1.8**	3,600 $\pm$ 580** (3,620)	50.7 $\pm$ 2.5* (50.8)
Reported use of inhaled budesonide in early pregnancy (group P1)	1,559	39.3 $\pm$ 2.0***	3,570 $\pm$ 600*** (3,610)	50.6 $\pm$ 2.6*** (50.8)
Reported use of inhaled budesonide during the whole pregnancy (group P2)	106	39.2 $\pm$ 1.9	3,600 $\pm$ 550 (3,640)	50.8 $\pm$ 2.4 (51.1)
Reported use of inhaled budesonide and oral glucocorticoids in early pregnancy (group P0)	51	39.1 $\pm$ 2.2	3,340 $\pm$ 590** (3,470)	49.8 $\pm$ 2.2** (50.1)

Values adjusted for differences in mother's height and gestational age are given in parentheses. Evaluated at mother's height = 166.21 (166.26) cm and gestational age = 39.42 (39.48) weeks for girls and (boys).

*.01 < *P* < .05; **.001 < *P* < .01; ****P* < .001 (*t* test of all infants vs infants in group A or P1 or P2 or P0).

†Information on gestational age missing for *n* = 130.

§Information on gestational age missing for *n* = 1.

||Information on gestational age missing for *n* = 148.

TABLE II. Birth weight less than 1000 g and caesarean, twin, and stillbirths for all girls and boys born between 1995 and 1998 in Sweden and for those whose mothers reported use of asthma medication during pregnancy

	All				Asthma medication other than inhaled glucocorticoids in early pregnancy (group A)				Inhaled budesonide (Pulmicort) in early pregnancy (group P1)				Inhaled budesonide during the whole pregnancy (group P2)				Inhaled budesonide + oral glucocorticoids in early pregnancy (group P0)			
	Girls		Boys		Girls		Boys		Girls		Boys		Girls		Boys		Girls		Boys	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Birth weight <1000 g	205	0.1	216	0.1	4	0.1	5	0.1	3	0.3	2	0.1	—	—	—	—	0	0.0	0	0.0
Caesarean births	16,132	11.3	18,487	12.2	498	13.3***	584	14.7***	184	13.1*	252	16.2***	7	6.9	15	14.2	16	30.8***	11	21.6*
Mean age (wk)	38.5		38.7		38.3		38.7		38.3		38.4		38.1		38.1		37.8		39.4	
Multiple births	2,184	1.5	2,326	1.5	60	1.6	53	1.3	22	1.6	19	1.2	1	1.0	3	2.8	0	0.0	0	0.0
Stillbirths	485	0.3	514	0.3	14	0.3	3	0.1*	4	0.3	1	0.1	0	0.0	0	0.0	0	0.0	1	2.0
Total	143,017		150,931‡		3,743		3,976†		1,409		1,559		101		106		52‡		51	

*.01 < *P* < .05; **.001 < *P* < .01; ****P* < .001 (all infants vs infants in group A or P1 or P2 or P0; χ^2 test of prevalence of caesarean births, multiple births, and stillbirths).

of a pregnancy at risk of congenital adrenal hyperplasia has not been reported to significantly affect birth weight.¹⁵⁻¹⁷ The use of oral corticosteroids (10 mg per day prednisone) for treatment of infertility throughout pregnancy has, however, been associated with a reduction in mean birth weight of 500 g for girls and 300 g for boys among term newborn infants.¹⁰ Several factors may have influenced these results such as differences in the properties of glucocorticoids used, the treatment period,

study population, and sample sizes. The number of exposed pregnancies in these investigations was not of the same magnitude as in the current study.

The quality of information regarding the use of medication in the Swedish Medical Birth Register must allow for different sources of error to be identified.²¹ One error observed is underreporting, when the use of a medicine is not recorded. In these cases, pregnant women have either not reported the use of treatment or this informa-

tion has not been recorded. Thus, women reporting the use of a drug have used it, but the study population will also include women who have used the drug but not reported it. Such underreporting is of nominal importance, however, because the study population is so large. Underreporting appears to be more common when using record form 2 than using record form 1 because 2968 women reported using budesonide in record form 1, whereas 207 women reported use of budesonide in both record forms 1 and 2. It is reasonable to assume that several of the 2968 women who reported budesonide use in record form 1 also continued to take the treatment throughout the whole pregnancy. Another source of error is incomplete documentation during the registration process, which reduces the power and prolongs the time needed to collect sufficiently large amounts of data for possible injurious effects to be illustrated.

The results in the current study must be interpreted with caution because even small differences between means become statistically significant in large samples. Thus, it is important to distinguish between statistical significance and clinical relevance; for example, a statistically significant difference of ≤ 2 mm in birth length does not signify that it has any clinical relevance.

The rate of caesarean births is a surrogate parameter of disease severity that is associated with gestational age, birth weight, and birth length. The increased frequency of caesarean births among mothers who used asthma medication during their pregnancy can partly explain the small difference in crude mean weight, length, and gestational age detected in the newborn infants. Another explanation is confounded by asthma severity, because inadequate control of asthma is associated with adverse outcomes such as higher rates of prematurity, intrauterine growth retardation, low birth weight, perinatal death, and preeclampsia.^{2,3} Optimally, mothers with asthma of similar severity should be compared with and without budesonide treatment. In this study, similar distributions of birth length and weight among mothers with asthma either exposed or not exposed to budesonide indicate that this is a minor source of error. However, results of the current study on concomitant use of oral glucocorticoids are probably confounded by asthma severity.

In conclusion, two large population-based studies of budesonide taken during pregnancy have provided reassuring results. These studies detected neither an increased risk of congenital malformation (based on 2534 budesonide-exposed pregnancies)²¹ nor an increased rate of premature births, stillbirths, multiple births, or decreased birth weight or length (based on 2968 budesonide-exposed pregnancies). These results support guidelines acknowledging that budesonide is one of two inhaled glucocorticoids that should be chosen if inhaled glucocorticoid therapy is to be started for an asthmatic woman who is pregnant or likely to become pregnant. In addition, budesonide could be a particularly good choice for pregnant women requiring the use of high doses of inhaled glucocorticoids for effective asthma treatment.⁷ In some susceptible women, steroid intake may still be associated

with clinically relevant adverse effects. Therefore, it is important to use the lowest dose of inhaled glucocorticoids required to maintain asthma control, both in fertile pregnant and nonpregnant women.

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