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Corticosteroids in Pregnancy

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Corticosteroids refer to a group of hormones made within the adrenal cortex. Since these hormones play a critical role in maintaining carbohydrate reserves, they are often referred to as glucocorticoids and these words are often used interchangeably. The excess or deficiency of these hormones affects virtually every tissue in the body.

Corticosteroids were synthesized for their anti-inflammatory properties about fifty years ago (Reinisch et al, 1978). They are commonly used during pregnancy to reduce the immune response in allergic or inflammatory diseases, such as asthma, lupus, rheumatoid arthritis, or skin diseases. Other indications include: promoting fetal lung maturity, treating infertility and maintaining pregnancy, or as replacement hormone therapy. Corticosteroids all cross the placenta, but some corticosteroids are more readily inactivated than others (Roubenoff et al, 1988). Prednisone and cortisone are the preferred medication for treating maternal disease, since they have shorter half lives, while dexamethasone and betamethasone are used if the fetus requires specific treatment, such as for respiratory distress.

Physicians may be wary of prescribing corticosteroids because animal studies in rodents and rabbits have demonstrated that high doses consistently cause cleft palate (Walker, 1971; Pinsky and DiGeorge, 1965; Walker, 1967). Human studies, most of which rely on retrospective data, show varied and conflicting results. The association between corticosteroids and oral clefting remains controversial. Case reports include a spectrum of various defects such as cataracts, cyclopia, interventricular septal defect, gastroschisis, cleft lip, hydrocephalus, coarctation of the aorta, clubfoot; thus, no pattern of malformation has been established. Clinical observations suggest that corticosteroid use may be associated with low birth weight, intrauterine growth retardation, and in some cases, stillbirth has been reported (Reinisch et al, 1978; Warrell and Taylor, 1968). Schatz et al (1997) reported that mothers who took oral corticosteroids for asthma had an increased risk for preeclampsia. Studies have also been complicated by oral versus inhaled versus topical doses. When assessing reports of pregnancy outcome, such as low birth weight or prematurity, it is important to keep in mind the effect of maternal disease, such as lupus and asthma, both of which have been associated with increased risk for adverse outcomes. This RISK/NEWSLETTER will discuss the major types of corticosteroids.

General Studies

Although various types of corticosteroids are available, few studies have looked at the teratogenic potential of each one separately. Most of the studies analyzed the various drugs together, making it difficult to assess the teratogenic risk for a specific medication. In addition, women are often prescribed corticosteroids as part of a regimen of various medication combinations, so there may be some synergistic effect that is difficult to ascertain. While there have been mixed findings in regards to oral clefting, available studies do not suggest an overall increase in malformations after in utero exposure to corticosteroids. In published cases, the rate of malformations for therapeutic corticosteroid use was

4.4% (Roubenoff et al, 1988). No cleft palate defects were noted in 26 babies exposed to high doses of prednisone throughout pregnancy for treatment of maternal lupus (Fine et al, 1981). The Michigan Medicaid surveyed newborns exposed to prednisone (N=236), prednisolone (N=143), and methylprednisone (N=222). The data found no association between corticosteroid use and congenital defects, except perhaps for prednisolone, which had a 7.7% incidence for total number of birth defects. No cases of oral clefting were reported (Briggs et al, 1998). Fraser and Sajoo (1995) surveyed the available literature from 1952-1994 and found 457 exposed patients, in which the frequency of malformations was 3.5%. Although single case reports may reflect reporting bias, the two cases of cleft palate observed was higher than the 0.2 cases expected, and a possible association could not be excluded.

Corticosteroids and clefting

Data from three retrospective epidemiological studies have examined the association of oral clefting with exposure to corticosteroids during pregnancy. The Malformation Drug Exposure Surveillance Project (MADRE) compared congenital malformations with 1st trimester drug exposures from six different countries (Australia, France, Israel, Italy, Japan, and South America). Seven out of 1448 infants with facial clefts (CL, N=5; CL±CP, N=2) were exposed to systemic corticosteroids (Briggs update, June 1999). The Hungarian Case-Control Surveillance of Congenital Abnormalities found no significant association between oral corticosteroid treatment and congenital anomalies, with 1.55% of 20,830 malformed infants exposed to corticosteroids during the first trimester compared to 1.41% of 35,727 controls (Cziezel and Rockenbauer, 1997). This study looked at ointment, spray, and systemic exposures; the systemic exposures were primarily dexamethasone, prednisolone, and cortisone. A significantly higher use of both systemic and ointment corticosteroids use in the first month of gestation was found in the three cases of cleft lip with or without cleft palate (Odds ratio:5.88; CI 1.7-20.32). The case-control Spanish Collaborative Study of Congenital Malformations surveyed 1,184 cases of liveborns with nonsyndromic clefts and examined systemic exposures to prednisolone, hydrocortisone, prednisone, and triamcinolone. After controlling for four potential confounding factors (maternal smoking, family history of first degree relatives with clefts, maternal hyperthermia, and first trimester exposure to anticonvulsants, benzodiazepenes, metronidazole, or sex hormones), the authors concluded that prenatal exposure to a corticosteroid carried a six times greater risk for cleft lip with or without cleft palate.

The incidence of cleft lip with or without cleft palate is about 1 to 2 per 1000, and the incidence of cleft lip is 1 per 2500 in the general population. The criticism of the above studies is that the findings of cleft lip with or without cleft palate could be in part due to chance. Closer inspection of the data, however, lends more credence to the suggestion that corticosteroid exposure may be associated with a higher incidence of oral clefting. The critical period in pregnancy for oral palate formation is between the 8th and 11th weeks of gestation based on the last menstrual period. For indications of corticosteroid use that is not essential to maternal health, it may be prudent to discuss with the patient other options during the specific period of palate formation.

The main confounding variables in these studies are maternal disease and the effect of other maternal medication use. In evaluating the risks versus benefits of corticosteroids, the important factor to keep in mind is the importance of maternal of health in any pregnancy outcome. In addition, the route of exposure is important in determining the risk of a medication to pregnancy. Topical preparations are less systemically available than oral or inhaled doses, and thus are unlikely to reach the fetus in exposures great enough to cause an increased risk for congenital defects. Consideration should be taken when prescribing corticosteroid use in the first trimester of pregnancy, since the safety of these drugs remains controversial.

Reproductive data on specific corticosteroids

Hydrocortisone/Cortisone (Cortef, Hydrocortone)

The inactive precursor, cortisone has half-life of 8-12 hours (Melby, 1977), and is reduced by the liver to hydrocortisone. Hydrocortisone is used for a variety of purposes. It is most typically used topically to treat eczema or other related skin diseases, and has also been found effective in treating hyperemesis gravidarum. The following studies cited are based on systemic exposures; no reproductive studies on topical exposure to hydrocortisone are available.

As with other corticosteroids, hydrocortisone and cortisone exposure in pregnant mice and rabbits have shown an increased incidence of cleft palate and other pregnancy complications, such as IUGR, and shortening of the head and mandible (Fraser et al, 1951). Human doses are lower, especially if a topical preparation is used. A study by Czeizel et al (1997) identified 191 women exposed to topical cortisone during pregnancy and found no significant increase in birth defects. The Collaborative Perinatal Project followed women exposed to hydrocortisone (N=21) and cortisone (N=34) in the first trimester. While the number of exposure is limited, no increase in congenital malformations was found. Various case reports of birth defects exist but no pattern of defects was evident. In summary, it is unlikely that a topical exposure to hydrocortisone and its inactive precursor, cortisone, significantly increases the risk for oral clefts or other types of birth defects.

Prednisolone/Prednisone (Blephamide, predlone)

Prednisolone, the active metabolite of prednisone, has a half life of 12 – 36 hours (Melby, 1977), and is widely used to treat collagen-vascular diseases (rheumatoid arthritis) and as an immunosuppressant. It is also used to treat pregnant women with antiphospholipid antibodies.

An early study reported an increased risk for stillbirths following prednisone therapy (Warrell, 1968). Increased infant mortality has not been confirmed by other studies, and the findings have been largely attributed to the risks inherent in maternal disease such as lupus. Reinisch et al (1978) looked at prednisone use for infertility and maintenance of pregnancy. In 14% of prednisone exposed pregnancies, the babies were small for dates, i.e., less than 2,500 grams, as compared to 1.5% of controls. Fine et al (1981) followed 26 babies who were exposed primarily to prednisone during organogenesis as a result of maternal lupus. No cases of cleft palate were noted; low prevalence of congenital abnormalities was found. Immunosuppression was a concern for these neonates of mothers treated with prednisone, since the babies had reduced thymic size and transient lowered lymphocyte counts.

The Michigan Medicaid study retrospectively surveyed newborns exposed to prednisolone (N=143) and prednisone (N=236). Observed versus expected major malformations for each were as follows: 11/6 (7.7%) and 11/10 (4.7%). The data did not support an association between drugs and congenital defects, except perhaps for prednisolone use and total number of birth defects. The Motherisk Program in Toronto, a teratogen information service, prospectively followed 187 pregnant women exposed to prednisone for disease and 127 pregnant women exposed because of fertility treatment. In comparing the results to 188 control women, no statistically significant difference in rates of major malformations was found. However, in the exposed group, a cluster of cleft palate (3/455) was reported. Therefore, prednisone and its derivatives may present a small but statistically significant increased risk for cleft palate but they otherwise do not appear to be associated with adverse effects in mother or fetus.

Dexamethasone (Decadron, Maxidex)

Dexamethasone is a glucocorticoid most commonly used in the third trimester to reduce fetal respiratory distress, and is also found in some topical preparations. It is also used in the first trimester to treat the virilization associated with congenital adrenal hyperplasia, since it suppresses adrenal function.

The safety and effectiveness of dexamethasone therapy is debatable but most authors agree that this

treatment has been effective in some populations (Seckl et al, 1997). More importantly, this drug exposure is not associated with long term adverse effects in the offspring (Collaborative Group on Antenatal Steroid Therapy, 1984).

No human studies have been reported on dexamethasone use during early pregnancy, since it is primarily used in the third trimester. As found with other corticosteroids, the principle birth defect produced in animals is cleft palate; however, in rhesus monkeys, high doses of dexamethasone have induced cranial malformations (Jerome et al, 1988). Animal studies in rabbits have shown that dexamethasone use was associated with retinopathy of prematurity, although no proof of this association has been demonstrated in human populations (Batton et al, 1992). Concern that corticosteroid use could effect long-term central nervous system development arose because it was shown that rats' brains displayed a decrease in dendritic branching after hydrocortisone administration. Also, in rhesus monkeys, suppression of bodily growth and brain development, specifically the cerebellum, has been shown (Uno et al, 1990).

The long-term effects of dexamethasone therapy in babies may include increased fetal death, growth retardation, adult hypertension, and psychological effects (Seckl et al, 1997). The Collaborative Group on Antenatal Steroid Therapy followed for three years approximately 400 children who were part of a randomized trial to evaluate the efficacy and safety of antenatal dexamethasone for respiratory distress. The rationale for a three year follow up was that outcome in these first few years are less affected by environmental factors and therefore may more accurately reflect the effects of acute perinatal events. No statistically significant differences for head circumference and neurologic abnormalities between placebo and steroid groups were noted. In addition, no detectable growth, physical, motor, or developmental deficiencies within the first three years of life could be attributed to dexamethasone. The demonstrated benefits of dexamethasone use to reduce complications of respiratory distress seem to outweigh any potential risks for adverse effects. Due to its longer half life of 36 –54 hours (Melby, 1977), dexamethasone is generally not suggested for treatment of maternal disease. It may be prudent to use another more well-studied corticosteroid during the first and second trimesters.

Betamethasone (Diprosone, Celestone)

Betamethasone is a synthetic corticosteroid used to promote fetal lung maturation in the third trimester, and is also found in some topical preparations. Since betamethasone is an isomer of dexamethasone, the information on dexamethasone may also be relevant.

Betamethasone, like all the other glucocorticoids, has been associated with clefting in mice, rats, and rabbits, but it is also associated with an increased incidence of omphalocele and umbilical hernia in rats (Mosier et al, 1982; Ishimura et al, 1975). These studies show decreased cell number in the lung, and impaired myelination and cellular development of the central nervous system, as well as suppression of the immune system (MacArthur et al, 1981).

Several studies have followed prematurely-born children whose mothers were given betamethasone as part of a randomized, placebo control trial (MacArthur et al, 1981; Schmand et al, 1990; Doyle et al, 1989). No difference between placebo and steroid groups existed in cognitive or psychological development, and in physical growth. Schmand et al. (1990) found an increased number of hospital admissions due to infectious diseases in early childhood, possibly demonstrating some proof of immune system suppression in offspring due to antenatal betamethasone exposure. In one study, betamethasone was shown to mildly constrict the ductus arteriosus, but the findings were not clinically significant (Wasserstrum et al, 1989). In general, there seems to be no long-term side effects of betamethasone use in the third trimester. Like dexamethasone, betamethasone is typically not suggested for treatment of maternal disease; no studies have been reported to evaluate the risks of its use during the first and second trimesters.

Beclomethasone (Beclovent, Vancenase, Beconase)

Beclomethasone is the most commonly used inhaled corticosteroid in pregnancy to control the symptoms of asthma. Only about 10 to 20 percent of the inhaled dose of corticosteroid reaches the lungs (Glaxo group, 1980), and topically, it has almost no systemic activity. The aerosol dosage in an inhaled dose which is less than one sixth of an oral corticosteroid and controls symptoms as well or better than the oral preparations (Brompton Hospital, 1974)).

Two clinical human studies have investigated the pregnancy outcomes of women who received beclomethasone; some of these women also received prednisone for severe asthma. One study evaluated the outcome of 45 pregnancies, 33 of which were prospectively followed and 12 of which were retrospectively collected. Beclomethasone was used in the first trimester and throughout pregnancy. The overall risk for malformations was 2.3%; one infant had a cardiac malformation (Greenberger and Patterson, 1983). Fitzsimons et al (1986) reported the outcome of 56 pregnancies in which women with severe asthma were treated with prednisone and/or beclomethasone dipropionate. No maternal, neonatal deaths, or malformations occurred. The rate of low birth weight was 17.2%, compared to the general population's rate of 6.8%.

Twenty patients out of 600 in the Brompton Hospital/ Medical Research Council Collaborative Trial were exposed to beclomethasone throughout pregnancy. No malformations or abortions were described. The Michigan Medicaid Study surveyed 395 newborns that had been exposed to beclomethasone in the first trimester. A total of 16 (4.1%) major birth defects were observed and 16 were expected. The findings from these various studies do not support an association between beclomethasone use and congenital defects.

Triamcinolone (Azmecort, Nasacort)

Triamcinolone is a synthetic fluorinated corticosteroid typically used to treat asthma symptoms or for skin conditions. Depending on preparation, it can be administered orally, parenterally, topically, or by oral inhalation.

Triamcinolone is a potent teratogen in animals, producing cleft palate in pregnant mice, rabbits, and hamsters (Walker, 1965; 1967; 1969; Shah, 1976). In three species of nonhuman primates (bonnet monkeys, rhesus monkeys, and baboons), doses of triamcinolone acetonide at approximately 300 times the human dosage produced central nervous system and craniofacial malformations, as well as growth retardation (Parker and Hendrickz, 1983; Tarara et al, 1989). These findings, in particular the primate studies, have caused concern that triamcinolone may also produce human developmental effects similar to the teratogenic effects seen in animals.

There is limited human experience with triamcinolone exposure in pregnancy. The Collaborative Perinatal Project identified eight triamcinolone-exposed mother-child pairs in a group of 56 women who were exposed to first trimester corticosteroids; two infants had malformations (3.6%) in the entire group. Dombrowski et al (1996) reported pregnancy outcomes for 15 women treated with inhaled triamcinolone. No increase in adverse outcome or birth defects were noted; in fact, triamcinolone compared favorably with other medications in efficacy and safety. One case report of topical triamcinolone use for atopic dermatitis suggested that excessive use of this corticosteroid may be associated with severe intrauterine growth retardation in the exposed offspring (Katz et al, 1990). Although preliminary studies do not suggest an association of triamcinolone use with adverse outcomes, additional studies are ongoing to fully evaluate its safety for use during pregnancy.

Clobetasol and Fluocinodide (Cormax, Lidex)

Virtually no human data for use during pregnancy is available on these two topical corticosteroids typically used to treat psoriasis and other skin conditions. They are both considered "potent" topical preparations but since no information on their reproductive effects are available, their risk is

undetermined.

Summary

While most studies do not show a large teratogenic risk, the association with corticosteroid use and clefting cannot be excluded. Avoidance of such medication exposure during specific times may be important to discuss, particularly for indications in which the medication is not essential for maternal health. For maternal disease, derivatives of cortisone and prednisone are suggested since they are more readily inactivated by the placenta, as opposed to dexamethasone and betamethasone, which are more likely to reach the fetus in the active state. As with any medication, use of a corticosteroid must be weighed against the severity of maternal disease.

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