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Acne and Pregnancy

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A variety of medications are prescribed for the treatment of acne, some taken orally, others topically. When assessing the possible risk of these medications during pregnancy, the route of the exposure is important to consider. Topical creams and gels are less systemically available than medicines taken orally, ultimately meaning that the fetus is exposed to less of the medication. As with any decision about medication during pregnancy, the potential risks must be weighed against its benefits for the patient. Since there are various acne medications available, it may be possible for a woman to find a combination of medications that is both effective and does not put her pregnancy at risk for major malformations. This newsletter examines various medications used in the treatment of acne.

Common medications

Benzoyl Peroxide (Benzac, Benzamycin, Beroxyl, Desquam, Triaz, Vanoxide)

Benzoyl peroxide is a topical treatment for acne that has antibacterial effects and induces skin peeling. About 5% of each topical dose is absorbed systemically. There are not any animal or human reproductive studies on benzoyl peroxide, and therefore its potential teratogenic risk is undetermined. However, benzoyl peroxide is commonly used, and there are no case reports about benzoyl peroxide and birth defects in the literature. This, combined with its topical exposure, provides some reassurance that the risk of malformations is likely to be low.

Hydrocortisone (Vanoxide-HC; w/ benzoyl peroxide)

Hydrocortisone is a corticosteroid used topically to treat acne and other dermatologic conditions. There have been no reproductive studies on topical exposures to hydrocortisone specifically, and as such its risk in pregnancy is undetermined.

A literature review of oral cortisol exposures during pregnancy did not find an increased risk for malformations in the exposed group, but it was found that the exposed group did have an increased risk for prematurity and other complications for the mother and fetus (Aron et al., 1990). The doses in the studies reviewed were presumably much larger than a dose from a topical exposure. Fraser et al. (1995) surveyed 468 women exposed to all corticosteroids in general, and noted no significant increase in birth defects. However, this study did note an increase in cleft palate versus that expected (2 vs. 0.2). Because an increase in clefting has been observed in mice exposed to corticosteroids (Fraser et al., 1951), this finding is of potential concern.

Most other studies of oral and inhaled corticosteroids have not found a significant increase in birth

defects or in clefts specifically (Czeizel and Rockenbauer, 1997; Fitzsimons et al., 1986; Rodriquesz-Pinella and Martinez-Frias, 1998; Schatz et al., 1997). Finally, a retrospective study by Czeizel et al. (1997) followed 191 women exposed to topical cortisone during pregnancy and found no significant increase in birth defects. In summary, although there is a potential connection between oral corticosteroids and cleft palate identified in the human and animal studies by Fraser et al. (1951 and 1995), it is unlikely that a topical exposure to hydrocortisone significantly increases the risk of birth defects, including oral clefts.

Salicylic Acid (Sal Ac)

Salicylic acid is used to treat acne, warts and other dermatological problems. There are no studies specifically looking at topical salicylic acid in pregnancy. Oral salicylic acid (aspirin) has not been associated with an increase in malformations if used during the first trimester, but use in late in pregnancy has been associated with bleeding, especially intracranial bleeding (Rumack et al., 1981). The risks of aspirin late in pregnancy are probably not relevant for a topical exposure to salicylic acid, even late in the pregnancy, because of its low systemic levels. Topical salicylic acid is common in many over-the-counter dermatological agents, and the lack of adverse reports suggests a low teratogenic potential.

Antibiotics/Anti-infectives

Erythromycin (A/T/S 2% acne gel, Benzamycin, Emgel, Erycette, T-Stat, Theramycin)

Erythromycin is an antibiotic that is commonly prescribed in pregnancy. Although often taken orally to treat infection, it is also used topically for acne. Erythromycin crosses the placenta minimally; the fetal blood concentration is only 2-10% of the maternal serum concentration, and the medication is quickly metabolized by the body. Takaya et al. (1965) found no increased malformations in mice exposed to 1-20 times the human dose. Human studies on erythromycin have all examined oral exposures. Retrospective studies of 79 and 6972 women exposed in first trimester had no significant increase in birth defects (Heinonen et al., 1977; Briggs, 1998). Jick et al. (1981) examined the prescription records of women exposed to erythromycin during the first trimester and also found no increase in birth defects (n=100-200). Because of these studies and the fact that this medication is commonly prescribed, it is generally assumed that topical erythromycin does not pose a significant increased risk for birth defects.

Clindamycin (Cleocin)

Clindamycin is an antibiotic related to erythromycin and available both orally and topically for the treatment of acne. It has been studied in both mice and rats at doses up to 180 mg/kg/day without teratogenic effects (Weinstein et al., 1976; Philipson et al., 1976). The retrospective Michigan Medicaid study identified 647 women exposed to clindamycin in the first trimester (both oral and topical exposures) and did not note an increased risk for major malformations. Furthermore, a study of 104 women exposed to clindamycin in the second and third trimesters did not suggest an increased risk for prematurity or placental complications (McCormack et al., 1987). This medication is unlikely to significantly increase the risk for birth defects in either its oral or topical form.

Tetracycline

Tetracycline is an antibiotic taken orally to treat acne. This medication belongs to a family of antibiotics that includes minocycline and doxycycline. The half-life of tetracycline is 11-22 hours, so most of the medication is removed from the body in 5 days. Two retrospective studies found no increase in the incidence of major malformations when women were exposed to tetracycline in the first trimester (Heinonen et al., 1977; Briggs, 1998). However, discoloration of deciduous teeth and the crowns of permanent teeth was seen in children who were exposed to tetracycline after the fourth month of gestation. Studies performed by Cohlan et al. (1961), Kline et al. (1964) and Kutscher et al. (1966)

established that infants exposed to tetracycline in utero after the fourth month of gestation may have discoloration of deciduous ("baby") teeth, cavities, and enamel hypoplasia in their teeth. It is believed that tetracycline causes dental discoloration and bone depression because it acts on the calcification process in development. The critical period for calcification begins at four months' gestation and ends twelve months post-partum. Therefore, tetracycline should be avoided after the sixteenth week of gestation and throughout lactation.

The degree of dental staining appears to be proportional to the dose of the medication (Egerman et al., 1992). Cohan et al. (1961) also found that tetracycline caused long bone growth depression of 40% which normalized when the use of the medication was suspended.

Doxycycline and minocycline, two medications structurally-related to tetracycline, are also used to treat acne. These medications have not been as well-studied as tetracycline; it is, however, generally assumed that doxycycline and minocycline similarly affect the fetal calcification process. Therefore, these medications should also be avoided after the first trimester of pregnancy through the breastfeeding period.

Sodium Sulfacetamide (Sulfaset, Klaron, Novacet, Sebizon)

Sodium sulfacetamide is a topical anti-infective medication used to treat acne and seborrheic skin conditions. It belongs to the class of medications termed sulfonamides, and most reproductive studies examine sulfonamides as a class and in oral dosages, making it difficult to extrapolate the potential risk for a topical medication such as sulfacetamide.

The maternal use of sulfonamides near delivery can lead to newborn toxicity, resulting in anemia and jaundice and, theoretically, kernicterus, although this has yet to be documented in the literature. (Briggs, 1998). There have been two large retrospective studies of sulfonamide exposure, which involved 1445 and 3465 women exposed in the first trimester; neither study found an increased risk for malformations from the class in general (Heinonen et al., 1977; Briggs, 1998).

In contrast, other case controlled studies raised concerns about sulfonamide use in pregnancy. A 1971 case-control study by Nelson et al. determined the pregnancy exposures of 1369 patients, 468 of whom had babies with congenital malformations. They observed that significantly more mothers of the babies with birth defects took sulfonamides than the control mothers (Nelson et al., 1971). Saxon et al. (1975) looked retrospectively at 599 children born with oral clefts. The mothers of children with malformations in addition to the oral clefts were more likely to have taken sulfonamides than mothers of children with isolated oral clefts.

Because topical sulfacetamide has never been specifically studied to determine its potential teratogenic risk, one cannot definitively conclude that it does not cause birth defects. However, because it is topical and, for the most part, sulfonamides as a class do not appear to significantly increase the risk for birth defects, it is unlikely that topical sulfacetamide causes a significantly increased risk for malformations.

Breastfeeding while using sulfonamides is probably not a risk to a healthy infant. At most 1-2% of a maternal, oral dose of sulfonamides enters the breastmilk (Adair, 1938; Hac, 1939). However, sulfonamides can potentially cause anemia and jaundice in stressed, premature or hyperbilirubinemic infants. In addition, if an infant has G-6-PD deficiency breastfeeding should be avoided while taking sulfonamides, as sulfonamides act as oxidative stressors and can result in a hemolytic crisis.

Retinoids Isotretinoin (Accutane, Roaccutane)

Isotretinoin is an oral retinoid used to treat cystic acne. A known teratogen, this medication is contraindicated during pregnancy due to the characteristic malformations it causes. The pattern includes defects of the CNS, thymus, craniofacial and cardiovascular systems, as well as conotruncal

malformations. Isotretinoin is thought to affect initial differentiation and migration of cephalic neural crest cells, and the critical period for this medication is 2-5 weeks post conception. Because the teratogenicity of Accutane is fairly well-known, we have chosen to focus upon other common acne medications in this review, rather than summarizing the literature about isotretinoin (for more details, see RISK/NEWSLETTER 3/96). Despite the half-life of approximately 1 day (manufacturer insert), due to the teratogenicity of this medication it is recommended that isotretinoin be discontinued at least one month prior to attempting pregnancy (Braun et al., 1984; Benke, 1984; Rosa, 1983; McBride, 1985; Rizzo et al., 1991).

Tretinoin (Avita cream, Retin A)

Tretinoin is a component of various topical acne creams. Because this medication is related to isotretinoin, there is concern that tretinoin could potentially have similar teratogenic effects on the fetus. Two case reports have described infants born to women using topical tretinoin during the first trimester of pregnancy. The infants had malformations that mimic the birth defects associated with isotretinoin (Camera et al., 1992; Lipson et al., 1993). In contrast, a prospective cohort study failed to find an association between birth defects and 215 women exposed to tretinoin in the first trimester (Jick et al., 1993). Shapiro et al. (1997) did not find a significant increase in number of livebirths, SAB's, low birth weight, major malformations, duration of pregnancy, and cesarean sections in 94 women exposed to tretinoin versus controls.

A dose-response relationship potentially could play a role in the effects of tretinoin; it is of note that 5-31% of tretinoin is absorbed systemically, depending on whether the skin is healthy or dermatitic. Although prospective studies have shown no increase in congenital anomalies, the case reports and biological plausibility of the anomalies raise concern about this medication. While such risks are likely to be low given the low topical absorption, health professionals should encourage women to weigh the risk and benefits of tretinoin during pregnancy.

Adapalene (Differin Gel)

Adapalene is a retinoid used in a topical gel form for the treatment of acne. As such, there are theoretical risks for retinoid embryopathy. However, the manufacturer reports that only trace amounts of adapalene are absorbed from the skin (trace is defined as less than 0.25 ng/ml). The manufacturer's studies on pregnant rats and rabbits using doses 120-150 times the maximum human topical dose did not show an increased risk of adverse outcome or malformations. There has been one human case report of adapalene use during weeks 4-13 of pregnancy; the fetus had IUGR, anophthalmia and agenesis of the optic chiasm, and the pregnancy was aborted at 13 weeks (Autret et al., 1997). The anomalies seen in this pregnancy are not typical of those seen with other retinoid exposures. In addition, as with any case report, the malformations could be coincidental and unrelated to the adapalene. There have not been any other human studies or case reports to date. The overall risk of adapalene is undetermined because there have not been any human studies. However, because only trace amounts of the gel are absorbed into the skin, it is unlikely that doses large enough to induce malformations could reach a fetus.

Other medications

Azelaic Acid (Azelex)

Azelaic acid is a topical cream for acne. The manufacturer's studies in animals do not show an increase in malformations at doses much higher than the maximum human dose. There have not been any human reproductive studies to date. While it is reassuring that animal studies do not show teratogenicity and that the fetal dose is small because the medication is topical, the risk of azelaic acid is undetermined because there have been no human studies.

Conclusions/Summary

In summary, acne medications present a range of risks during pregnancy. Because of its proven teratogenicity, it is well known that isotretinoin (Accutane) should not be taken during pregnancy. Additionally, tetracycline and its derivatives should not be used after 16 weeks gestation due to its effects on calcium-containing tissue, particularly teeth. The risks of other medications such as tretinoin are less certain, while some commonly used medications, like benzoyl peroxide, do not appear to pose a significant risk for malformations. Because of the widely known teratogenic effects of isotretinoin, many women are wary of acne medications in general during pregnancy. However, there are a wide variety of medications available for the treatment of acne, many of which pose a minimal risk if applied topically during pregnancy.

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