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Antifungals

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Antifungal use during pregnancy is common because pregnant women are more susceptible to fungal infections. In addition, pregnancy is more commonly associated with more serious systemic fungal infections, such as mycoses, that require treatment. There are three types of treatment that can be used for fungal infections: topical, vaginal and systemic/oral. The following review provides a summary of current data on the use of each type of fungal medication in pregnancy (over the counter medications and prescription medications are abbreviated in the sub-headings as (OTC) and (P) respectively).

TOPICAL THERAPY:

The use of antifungals in the topical treatment of infections of hair, skin and nails is common. Prescription and over the counter treatments are available for a variety of infections. To date, no topical antifungal treatments have been shown to be teratogenic during human pregnancy.

IMIDAZOLES: COLTRIMAZOLE-(OTC), KETOCONAZOLE-(P) and MICONAZOLE-(OTC)

Imidazoles are active in treating ringworm, tinea versicolor and cutaneous candidal infections. Animal studies have suggested teratogenicity of some imidazoles in high oral doses, but not with topical use. Topical agents are absorbed less by the body when compared to oral preparations, and have not been found to be teratogenic (King et al 1998). Jick (1999) reported on 492 women exposed to various topical azoles (ketoconazole, miconazole and econazole). A relative risk of 2.1 (95% CI 0.7-6.8) was not statistically significant for an increased risk of congenital malformations, when compared to matched controls. There is some suggestion that ketoconazole and miconazole could inhibit testosterone synthesis in utero, which could potentially inhibit genital development of a male fetus. However, this has not been documented in any controlled studies. Surveillance data from the Michigan Medicaid study reported by Rosa et al (1987, did not find an increased risk for congenital malformations with miconazole or clotrimazole use during pregnancy.

AMPHOTERICIN B-(P)

Topical use of amphotericin B has shown minimal absorption through the skin. Limited human surveillance data do not indicate any harm to mother or fetus, but relative safety is still unknown (King et al, 1998).

VAGINAL THERAPY:

Inflammation of the vagina is extremely common in the general population. Symptoms include soreness, irritation, and discharge. Differential diagnoses (excluding sexually transmitted diseases) for symptoms of vaginal irritation include candida vulvovaginitis (VVC), bacterial vaginosis (BV), trichomoniasis, and atrophic vaginitis. VCC is one of the most common fungal infections, affecting 50% of women by age 25. Some of the more common treatment options for the above-mentioned

conditions are described below; all of which are over the counter (OTC) with the exception of terconazole.

COLTRIMAZOLE- (OTC) Gyne-Lotrimin® Mycelex®

Clotrimazole is an OTC medication used to treat VVC. Clotrimazole is minimally absorbed (3-10%). The Michigan Medicaid Surveillance study reported on 1086 pregnancies exposed to clotrimazole during the first trimester (King et al, 1998). There were 74 pregnancies with a birth defect (RR=1.09, 95% CI 0.9-1.4), and 112 spontaneous abortions (RR=1.34, 95% CI 1.1-1.7). These data suggest a slight increase in spontaneous abortions, but no increase in birth defects, with first trimester exposure to clotrimazole. Clotrimazole is thought to be safe during the second and third trimesters of pregnancy (King et al, 1998). Czeizel et al (1999) studied the possible teratogenicity of clotrimazole for topical and vaginal therapy using a case-control surveillance study of 18,515 exposed pregnancies during three specific time intervals; first month, second and third month, and fourth through ninth month. Using 32,804 controls, they determined that clotrimazole use was not associated with an increase in congenital anomalies (OR=0.72, 95% CI 0.54-0.95). Further research has indicated that the use of clotrimazole may have a protective effect on preterm delivery. Czeizel and Rockenbauer (1999) determined that the use of clotrimazole during pregnancy significantly reduced the incidence of preterm births ($t=8.86$, $P<0.001$). These authors suggest that because clotrimazole effectively treats maternal infection, its use during pregnancy is indicated to eliminate maternal infection associated with prematurity.

MICONAZOLE-(OTC) Monistat®

Miconazole (monistat®) is one of the most commonly used over the counter medications for yeast infections. It is used topically (see above) and intravaginally for VVC treatment. Vaginal use has shown minimal systemic absorption (1.4%) (King et al, 1998). The Michigan Medicaid surveillance (Rosa et al 1987) reported on 2236 exposed pregnancies and 144 birth defects. These data do not support a significant increase in fetal malformations above the general population (RR=1.02, CI 0.9-1.2). The same surveillance study reported a slightly significant increase in spontaneous abortions in women who were prescribed miconazole 120 days before pregnancy loss, when compared with full term deliveries (RR=1.36, CI 1.1-1.6). Lack of controlled studies on the safety of miconazole use during pregnancy, however, does not provide an accurate estimate of potential risk.

NYSTATIN - Mycostatin®

Nystatin is a polyene antifungal and is available over the counter. Vaginal preparation is the only type of application available due to toxicity by IV or oral administration. Nystatin is poorly absorbed systemically after topical or mucosal application. Specific use of nystatin has not been studied during pregnancy. Animal studies do not show an increase in congenital malformations (Rosa et al, 1987). Surveillance studies by the Collaborative Perinatal Project and Collaborative Drug Surveillance program did not find an increase of congenital malformation with first trimester use. Rosa et al (1987) reported data from the Michigan Medicaid study on women who received prescriptions for nystatin during the first trimester of pregnancy. Of 848 pregnant women, 66 deliveries were linked to birth defects. Their results were not statistically significant for an increase in birth defects over the general population (RR=1.25, CI 0.97-1.6). Surveillance by the Michigan Medicaid study did not show a significant increase in spontaneous abortions (SAB) in women who were prescribed nystatin 120 days prior to pregnancy loss when compared to full term deliveries (RR=0.87, CI 0.6-1.2). Although these data do not suggest a risk to human pregnancy, the lack of controlled human studies makes it difficult to establish relative safety.

OTHER IMIDAZOLES

Butoconazole –(OTC) Femstat®

Butoconazole is minimally absorbed systemically (5.5%). Clinical trials suggest relative safety with use during the second and third trimesters of pregnancy (King et al, 1998). However, these data are not from controlled studies and therefore, butoconazole should be used with caution during pregnancy.

Tioconazole-(OTC) VagistatÒ

Tioconazole is minimally absorbed systemically (5%-16%). Clinical trials suggest relative safety with use during the second and third trimesters of pregnancy (King et al, 1998). However, these data are not from controlled studies and therefore, tioconazole should be used with caution during pregnancy.

Terconazole- (P) TerazolÒ

Tioconazole is thought to have negligible systemic absorption. There are currently no human data to determining safety during pregnancy. (King et al, 1998)

SYSTEMIC THERAPY:

Systemic (oral/IV) antifungal medications are used to treat serious fungal infections, such as meningitis. Cryptococcal meningitis is an infection that apparently does not cross the placenta (Chen et al, 1996), but failure to treat can compromise maternal health and thus the health of the fetus. Because of their toxicity, use of systemic antifungals during pregnancy is limited to life-threatening infections. There is relatively little data on the more potent systemic antifungals. However, the triazole class of systemic antifungals (including fluconazole and itraconazole) are less toxic alternatives and therefore have been studied more commonly in pregnant women. This review will concentrate on oral and IV preparations of systemic antifungal medications that have been well studied during pregnancy. This comparison will highlight differences in toxicity and how they affect pregnancy.

TRIAZOLES

ITRACONAZOLE –(P) (Oral- SporanoxÒ) Itraconazole is another azole preparation that is related to ketoconazole and fluconazole and is used orally to treat fungal infections. Jick (1999) reported on 88 women exposed to oral itraconazole; however, dose was not reported. When compared to matched controls, itraconazole exposed women had a relative risk of only 0.6 (95% CI 0.2-1.6) of having a baby with congenital anomalies. Other data on the use of oral itraconazole during pregnancy is limited to case reports, which have also failed to suggest an increased risk for fetal birth defects.

FULCONAZOLE-(P) (IV and Oral - DiflucanÒ) Triazole used to treat systemic fungal infections (candidiasis, cryptococcosis, coccidioidomycosis and meningitis) penetrates the CNS and is present in high concentrations in the cerebral spinal fluid (CSF). Animal studies have shown teratogenic effects when fluconazole is administered at high doses (20-40X the normal human dose), including structural and craniofacial anomalies. Lee et al (1992) reported 3 patients exposed prenatally to fluconazole. These patients showed a pattern of Antley-Bixler-like malformations. Pursley et al (1995) reported 3 patients (2 siblings) exposed to high oral doses throughout the first trimester (400mg/day for first 24 weeks, 400mg/day for first 4 months, 800mg/day for first 7 weeks). These patients exhibited craniofacial, skeletal, and cardiac anomalies. One of the three patients was reported to have the previous diagnosis of Antley-Bixler syndrome. They concluded that fluconazole is teratogenic in humans and it is likely that other related azoles are also teratogenic. Kyrieckos and Bartley (1997) reported a single patient with fetal exposure to fluconazole in the first 9 weeks gestation [400mg/day (0-4/5 weeks gestation), 800mg/day (4/5- 9 weeks gestation)] for a maternal meningitis infection. Amphotericin B 50mg (3x/week) was also given over the next three months with fluconazole treatment resuming at 22 weeks (1200mg/day). This patient also presented with Antley-Bixler-like phenotype. Although this pregnancy was complicated with many other medications besides the two antifungals, Kyrieckos and Bartley (1997) concluded that fluconazole is teratogenic capable of producing Antley-Bixler-like phenotype when women are exposed to high doses for long duration in early pregnancy.

Antley-Bixler phenotype includes the following features: brachycephaly, depressed nasal bridge, dysplastic ears, frontal bossing, midfacial hypoplasia, pear shaped nose, proptosis, large anterior fontanelle, long philtrum, craniosynostosis, choanal stenosis/atresia, femoral bowing, radiohumeral synostosis, femoral fracture, thin ribs, multiple contractures, long palms and fingers, camptodactyly, rockerbottom feet, cardiac defects, cleft palate and early death.

Inman et al (1994) studied 60 pregnancies [6 SAB, 11 TAB, 44 births (1 set of twins)] of women with vaginal candidiasis. All but one had single oral exposures of 150mg (time of exposures not ascertained) of fluconazole. No fetal abnormalities were found in any of the 44 live born infants. They concluded that low doses of oral fluconazole for the treatment of vaginal candidiasis during pregnancy does not increase the risk for fetal malformations.

Masroiacovo et al (1996) performed a prospective cohort study from the Italian Teratogen Information Service (ITIS). Of the women exposed to fluconazole, 90.7% was for oral treatment of vaginal candidiasis. The majority of the women were exposed to single low doses (oral) of fluconazole (median 200mg) during the first trimester. The only significant difference between exposed and control groups was an increased therapeutic abortion (TAB) rate in the exposed group. With these results they concluded that single low doses of fluconazole during the first trimester are not associated with an increased risk for SAB, stillbirth or congenital anomalies.

Sorensen et al (1999) performed a retrospective study of 165 women who had received fluconazole prescriptions just before or during pregnancy, and compared them to 13,327 women that did not receive prescriptions. Their study found no increase in congenital malformations with single exposures to fluconazole before conception or during pregnancy. However, this study has many confounding variables primarily receiving a prescription does not ensure that the medication was taken. This is a large source of bias in the study.

Jick (1999) reports on 234 women of which 92% were exposed to single 150 mg doses of fluconazole. When compared to 492 matched controls, a relative risk of 1.1 (95% CI 0.4-3.3) for congenital abnormalities was calculated. Three of their patients exposed to high doses exhibited limb deformities that suggested a pattern of malformations. These data suggest possible teratogenicity of fluconazole at high dose.

IMIDAZOLES

KETOCONAZOLE-(P) (oral - Nizoral[®])

Numerous problems have been reported with the use of systemic ketoconazole during pregnancy. It has been shown to be teratogenic and embryotoxic at high doses in animals, with additional data to suggest prolonged gestation. Ketoconazole crosses the placenta and is thought to inhibit gonadal and adrenal steroid synthesis in humans. It has been suggested that ketoconazole use during pregnancy could inhibit sexual differentiation, although to date there are not human data to prove such an association (King et al 1998). McGregor and Pont (1990) indicated that therapeutic doses (200mg and 400mg/day) have not been associated with a major block in steroid synthesis.

Ketoconazole is also used to treat Cushing syndrome. Two case reports of treatment for Cushing's are the only data on human exposure during pregnancy. No adverse outcomes were reported. In Amado et al (1990) treatment was administered during the third trimester, when the sex of the fetus was already identified. In the second case report (Berwaerts et al, 1999) the patient received ketoconazole therapy from 1-3 weeks and 7-37 weeks of pregnancy. The pregnancy ended in a vaginal delivery at 37 weeks of a normally developed male infant. From this case report, Berwaerts et al (1999) argue that ketoconazole is safe to administer during pregnancy. However, lack of data still make it difficult to establish safety.

MICONAZOLE-(NP) (IV)

Miconazole use in IV form has not been studied in human pregnancy. Animal studies do not show teratogenicity in high doses, but it has been reported to be embryotoxic and to prolong pregnancy. Due to limited data, adverse maternal side effects, and the availability of other systemic antifungals, miconazole should be avoided during pregnancy (King et al, 1998).

OTHER SYSTEMICS

METRONIDAZOLE (P) Metronidazole is an antimicrobial agent that is primarily used to treat protozoan infections. There has been controversial evidence regarding its use during pregnancy. However, more recent epidemiological studies have led to more conclusive support for its use during pregnancy. Previously, it was hypothesized that metronidazole could increase the risk for birth defects and possibly for cancer due to its mutagenic capabilities. Olson Robbie et al (1983) reviewed the use of metronidazole in obstetrical practices. Their literature substantiated that metronidazole crosses the placenta and is found in high concentrations in fetal tissue and amniotic fluid. Their study reports on 597 women exposed to oral metronidazole during pregnancy for a treatment period of 7 to 10 days. When compared to 283 untreated controls, there were no significant differences in stillbirths or prematurity. There was no evidence to suggest teratogenicity. Their paper suggested further studies on the carcinogenesis of metronidazole were needed. Burtin et al (1995) did a meta-analysis on the safety of metronidazole use during pregnancy. They reported on 7 studies (6 prospective of 253 first trimester exposed women and 1 retrospective of 1083 exposed women) in which there was no increased risk for teratogenicity with metronidazole use during pregnancy (OR=0.93, 95% CI, 0.73-1.18). Czeizel and Rockenbauer (1998) did a case-control study on the use of oral metronidazole during the various times of pregnancy (first month, second to third month and fourth to ninth months). Their data did not suggest an overall increase in congenital abnormalities between cases and controls (OR=1.12, 95% CI, 0.83-1.50) with second and third month exposures. However, certain birth defects were found at a slightly higher incidence in the case populations, and exposure throughout pregnancy did show a slight increase in congenital anomalies (OR=1.25, 95% CI, 1.11-1.42). Cleft lip with or without cleft palate and neural tube defects were increased with first month exposures, poly/syndactyly, anal atresia/stenosis, and hydrocephaly were increased with second and third month exposures and cardiovascular congenital abnormalities were increased in the case population with exposures between the 4th and 9th months. These data can be explained by embryology. The most critical timing for heart development is between the 3rd and 9th weeks. The authors did suggest that due to the retrospective nature of the study, these findings were possibly due to confounding factors. Caro-Paton et al (1997) did a meta-analysis on the teratogenicity of metronidazole. They looked at all cohort and case-control studies that estimated a risk of congenital malformations after metronidazole exposure during pregnancy. They concluded that first trimester exposure to metronidazole does not significantly increase the risk for congenital abnormalities (OR=1.08, 95% CI, 0.9-1.29). The nature of this study did not allow for analysis of specific birth defects. In general, data do not suggest an overall increase in congenital anomalies with metronidazole use during pregnancy. However, even though some studies examined second and third trimester exposures, there are no data regarding the risk for prematurity, low birth weight or stillbirth associated with metronidazole use during that period of pregnancy.

The question of increased cancer risk in children exposed to metronidazole during pregnancy has been studied by Purushottam et al (1998). They studied a retrospective cohort of children under the age of 5. In their study they did not find an increased risk for tumor development (leukemia, neuroblastoma, CNS tumors, and other cancers) in children exposed prenatally to metronidazole when compared to non-exposed controls. Further analysis of the carcinogenicity of metronidazole has not shown an increase in risk for tumor formation in women followed 20 years after treatment for vaginal trichomoniasis (Beard et al; 1998). These findings were based on 771 women, and did not show

evidence for mutagenic properties of metronidazole treatment.

Similarly to clotrimazole, metronidazole has also been thought to be protective against preterm labor be induced by maternal infection. In a placebo controlled trial by McDonald et al (1997), pregnant women using metronidazole had a significantly reduced risk for preterm labor when compared to the placebo group in two categories: women who previously had experienced preterm labor, and women with previous preterm labor that also had bacterial vaginosis. This study did not find a significant difference between treatment and control populations in women without any history of preterm labor (infection or no infection).

FLUCYTOSINE-(P)

Flucytosine is limited to the treatment of yeast infections, and resistance is developed rapidly following treatment. Data suggest that flucytosine is teratogenic in rats at doses less than the normal human dose (mg/kg basis). Flucytosine is known to cross the placenta. Case reports of use during the second and third trimesters have not shown adverse outcomes (only 3 reports). Due to its mechanism of action, flucytosine has the potential to cause congenital defects in humans and is therefore contraindicated in pregnancy (King et al 1998).

GRISEOFULVIN-(P)

Griseofluvin is used to treat ringworm. It has been reported to be embryotoxic in animals and crosses the placenta in humans. There is some suggestion of an association between first trimester exposure and an increased incidence of conjoined twins (2 case reports), but further epidemiological studies failed to support these preliminary findings. Other data regarding the use of griseofluvin during pregnancy is limited to case reports. These limited findings specifically reported by the FDA might be associated with an increased risk for miscarriage, but these data have not been confirmed by controlled studies. However, due to limited information, it is suggested that griseofluvin use be avoided during pregnancy (King et al, 1998).

TERBINAFINE-(P)

To date there is minimal data on the use of terbinafine for fingernail and toenail infections during pregnancy. Animal studies reveal that there is no evidence for fetal harm. However, there have been no controlled studies on human use during pregnancy (King et al 1998).

POTASSIUM IODIDE -(P)

Oral iodides are used to treat cutaneous infections. In general, iodides are thought to be contraindicated in pregnancy because they have been associated with congenital goiter that can be fatal in newborns (King et al 1998).

AMPHOTERICIN B -(P)

Amphotericin B is a polyene antifungal that has been used for more than 30 years, with numerous adverse effects (transient azotemia, febrile reactions, shaking chills, nephrotoxicity, thrombophlebitis, electrolyte disorders and anemia). Amphotericin B is used to treat numerous types of infections including: histoplasmosis, blastomycosis, cryptococcosis, coccidioidomycosis, visceral leishmaniasis, and cryptococcal meningitis. Oral preparations of amphotericin B are still the chosen antifungal for severe infections. Amphotericin B is known to cross the placenta and enter the fetal circulation. It is also available in topical form for less severe infections but is minimally absorbed by the skin.

Oral/IV formulations of amphotericin B are commonly prescribed during pregnancy. King et al (1998) reviewed its use during pregnancy, and 26 additional cases of amphotericin B use during pregnancy. Because of the toxicity of amphotericin B, adverse maternal reactions were commonly reported which

included: anemia, acute nephrotoxicity, fever, chills, headache, nausea and vomiting. Fetal effects that were most commonly seen included: anemia, low birth weight, microcephaly, transient acidosis, increased serum creatine (SCr) levels, respiratory failure, transient maculopapular rash. Their review of the data concluded that Amphotericin B is the drug of choice for life threatening fungal infections during pregnancy. Its use in human pregnancy has not shown consistent adverse fetal effects. Maternal toxicity is common and pregnant women should be closely monitored if taking amphotericin B.

Lipid formulations have been more recently introduced into the treatment of fungal infections especially for women that are intolerant of amphotericin B (King et al, 1998). Abelcet is used for invasive fungal infections. Animal studies have not shown detrimental effects to the fetus with 0.64X the human dose. There is currently no human data on its use during pregnancy. Amphotec is prescribed primarily for aspergillosis infections. Animal studies have not shown detrimental effects to the fetus with 1.1X the human dose, however, there are currently no data on use during human pregnancy. Ambisome is used to treat febrile neutropenic patients, aspergillus, candida or cryptococcus species and visceral leishmaniasis treatment. Animal studies have shown significantly higher spontaneous abortion rate with 0.5-2X the human dose. One human case report of AmBisome treatment of Mediterranean visceral leishmaniasis (18mg/kg total dose) in a pregnant patient resulted in a normal pregnancy.

SUMMARY:

It is important to weigh the risks and benefits of any drug usage during pregnancy. In the context of antifungal medications, it is necessary to consider the potential risks to both mother and fetus if the infection goes untreated. Current literature does not address the risks of an untreated infection. If an infection worsens during pregnancy, a higher dose may be needed, which may affect the fetus. In general, there is a higher rate of relapse with certain infections when a woman is pregnant (especially candidal vaginitis). This can be important to consider when treating fungal infections in pregnant women. Overall, data differs on the various types of antifungals available. Choosing one that is favorable for treating the particular infection while considering the potential risks to the fetus is critical when managing the treatment of a pregnant woman.

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