WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 7, Issue 12, 480-493 Review Article ISSN 2278 – 4357

IS FLUCONAZOLE SAFE DURING PREGNANCY

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Article Received on
29 Sept. 2018,

Revised on 19 Oct. 2018,
Accepted on 09 Nov. 2018

DOI: 10.20959/wjpps201812-12760

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ABSTRACT

Introduction: Fluconazole is an azole antifungal agent used for the treatment of various indications like Coccidioidomycosis, cryptococcal meningitis, peritonitis and a wide range of candidial infections namely oropharyngeal candidiasis, esophageal candidiasis and vaginal candidiasis. Despite its limited safety profile during pregnancy, pregnant women are prescribed with this drug. **Aim**: This study aims to review all possible events like stillbirths, spontaneous abortions, congenital malformations and changes in Ano-Genital Distance in male offspring (AGD) among fluconazole exposed pregnant women. **Methods**: Literature from December 1992 to 2018 was reviewed regarding fluconazole induced teratogenic events during and after pregnancy including case reports, cross-sectional studies, prospective cohort, non-interventional observational cohort, preliminary study registries raised historical cohorts and many of its kind. **Results**: There seems to be a positive evidence for the occurrence of congenital abnormalities in infants, born to pregnant women who took high dose oral fluconazole (400- 800mg daily), but safer with 150mg oral fluconazole; spontaneous abortion in pregnant women who took a cumulative 150-300mg of oral fluconazole dose and a decrease in Ano-Genital Distance which may result in less masculinity among male off-springs. **Conclusion**: Although further studies are needed to establish a possible relationship between the occurrence of spontaneous abortions and reduced AGD with fluconazole, clinicians must be cautious regarding the use of fluconazole during pregnancy and to be used only when benefits outweigh the risk until safety profile is proved.

KEYWORDS: Fluconazole, Pregnancy, Safety, Congenital abnormalities, Still Births.

INTRODUCTION

Though many new discoveries and inventions are being emerged in our day-to-day sophisticated lives, the term "pregnancy" still remains a mystery to mankind. Pregnancy is a state/phase in the woman where she is vulnerable to a wide range of infections particularly fungal infections and coccidioidomycosis which could be life-threatening if left untreated. In general, as pregnant woman are excluded from participating in clinical trials, very little or no data is available to categorize a particular medication/therapy as to be safe or unsafe. Hence analyzing risk vs benefit ratio on the available data, prior to administration of drug in pregnant women is a fundamental role of any healthcare provider.[1,2] Even a minor error in either prescribing, dispensing or administering the wrong drug or dose could lead to spontaneous abortions, stillbirths, congenital malformations, prematurity, organ loss e.t.c.[2] Fluconazole is an azole antifungal agent which disrupts the cell membrane by inhibiting cytochrome p-450 enzymes and is being used in pregnant woman for a variety of indication since a very long time.[3-7] Other drugs under this category are Itraconazole, Voriconazole, Posaconazole, Ketoconazole and Isavuconazole.[8,9] A single dose of 150mg fluconazole is prescribed for vaginal candidiasis and higher doses are prescribed for a patient with systemic infections with variable duration.[6] Fluconazole penetrates into the cerebrospinal fluid well, hence it is used in coccidiomycosis and coccidioidal meningitis as well.[7,10,11] Ever since the first case report of fluconazole in 1992, there has been a lot of uncertainty in the view of various healthcare professionals whether fluconazole is safe during pregnancy or not?[12] This review provided the answer to the ever lasted question "IS FLUCONAZOLE SAFE DURING PREGNANCY?"

ANIMAL TOXICOLOGICAL STUDY

As a part of clinical trials, animal studies are generally performed in various animal models. Abnormalities in maternal weight gain and placental weights were seen.[13] When doses of 25 mg/kg and 50 mg/kg were used in pregnant rats (dams) in organogenesis phase, the rat infants (pups) had supernumerary ribs, renal pelvis dilation, and delays in fetal ossification. But none of the effects was seen at a dose of 5 or 10 mg/kg. And at a dose of 80 – 320 mg/kg i.e., 20-60 times the human dose, the pups had rib abnormalities like wavy ribs, cleft palates and abnormal craniofacial ossification (High-dose Fluconazole effects). These data may state that teratogenic events are dose-related. As these effects are seen during the period of organogenesis, these were thought to be due to the estrogen synthesis inhibition and hence considered as embryo-fetotoxic and teratogenic in rats.[3,6,13] Fluconazole exposure in cultured

mouse embryos at a dose of 0 tLg/ml and 25 tLg/ml, no statistical significance in abnormalities were seen but at a concentration of 50 tLg/ml and 75 tLg/ml, the development of morphological characteristics (Morphogenesis/ontogenesis) was impaired and was statistically significant.[13] When a high dose of nearly 700 mg/kg is given to pregnant mice, an interesting thing was noted. The frequency of cleft palate in mice infants was more when the drug was exposed on the 10th day of gestation rather than exposure on other days. By this, we may conclude that time of exposure of fluconazole plays a crucial role in the incidence of teratogenicity.[4] The drug crosses the placenta in rabbits as well and is embryotoxic.[2] Measurement of anogenital distance (AGD) is characteristically performed in animal studies. The decrease in length of genital is in accordance with the amount of androgen exposed in-utero which in several cases can result in de-masculinization.[14,15] Animal studies performed in rats, mouse, mice, and rabbits showed that the exposure of fluconazole to the pregnant woman may harm the fetus, but the outcome in humans is just hypothetical.

First ever reported human case-1992

The first-ever reported case on Fluconazole teratogenicity was in 1992 reported by Lee et al. In 1987, a woman from Bakersfield CA was diagnosed with Disseminated Coccidiomycosis during her first pregnancy (8th month). As a part of therapy, she was treated with IV and Intrathecal Amphotericin B and delivered a healthy baby during the treatment course and was continuing the same treatment till May 1990 and then the treatment was changed to Fluconazole when she started to experience arachnoiditis as a side effect to Amphotericin B. When Fluconazole therapy was initially started with 400 mg PO OD she was not conceived then. Later when she became pregnant, an ultrasound report was taken at her 23 weeks of pregnancy, which was quite normal and the existence of fluconazole in therapeutic concentrations both in the serum and CSF was reported. She underwent a cesarean section and delivered a live born premature female infant with grossly dysmorphic features. Infant weighed 1145 g(low birth weight), her APGAR scores were of 0 and 6.[3] Radiographic findings include: craniosynostosis, brachycephaly, humoral-radial fusion, craniosynostosis, frontal cranioschisis, sagittal, thin long bones bowed tibia and femur, bilateral femoral fractures an incomplete thumb, short toes, radiohumeral synostosis and upper and, lower extremity contractures. Autopsy reports include: hypoplasia of nasal bones, cleft palate, contractures of both upper and lower extremities, an incompletely formed right thumb, medial deviation of both feet, shortened toes, cranioschisis of the frontal bones, and craniostenosis of the sagittal suture and was reported by Lee and colleagues[1,3,4] These

findings were analogous to a genetic disorder called "Antley-Bixler Syndrome (ABS), a rare congenital disorder of craniosynostosis as skeletal abnormalities.. As this event is the first of its kind- teratogenic event reported under fluconazole, there was a lot of discrepancy as to whether this event was attributed by Fluconazole or ABS.[3,13,16-19]

Subsequently, after this event, the woman became less and less compliant with the fluconazole therapy (400mg OD), which is evident by her sub-therapeutic levels of fluconazole in the body. During the treatment period she became pregnant for the third time and gave birth to a male infant, but with neither dysmorphic features nor malformations. After the events reported by Lee and his colleagues, parsley and his colleagues reported the 2 more events of the same kind: the first one is the sibling of the events reported by Lee, After 3rd delivery the same woman started being compliance with the fluconazole (400mg OD) as evident by the serum therapeutic levels of drug in the body. She was found to be pregnant at 28 weeks of gestation and the therapy was discontinued. A female infant was born with cleft palate, tracheomalacia, low ears, a rudimentary epiglottis, femoral bowing, proptosis, clavicular fracture, thin wavy ribs, a ventricular septal defect and pulmonary artery hypoplasia and died at the age of 3 months. On and off presence of dysmorphic features for the same lady at difference in therapy (1st pregnancy: Amphotericin- no abnormality; 2nd pregnancy: Compliance with Fluconazole – dysmorphic features; 3rd pregnancy: non-compliant with fluconazole – healthy infant; 4th pregnancy: fluconazole -4 months of gestation- dysmorphic features) and compliance had led to the curiosity as whether Fluconazole is truly a teratogen or not?.[1,13]

The second event included a 25-year-old female from California was diagnosed with coccidioides immitis in 1986, in the due course she was started with fluconazole 800mg OD. She was known to be pregnant at 7 weeks of gestation and was subsequently she was given counselling and was advised to discontinue fluconazole. As Intrathecal amphotericin B is excluded as an option for her, she was ok to continue using Fluconazole during her pregnancy. At 38 weeks of gestation she underwent cesarean delivery and gave birth to an male infant weighing 1878g, cyanotic, brachycephaly, supraorbital ridge hypoplasia, bitemporal narrowing, open cranial sutures, maxillary hypoplasia, bowed femurs, thin ribs, long bones, his joints had limited range of motion, femur fractured while trying to measure the length and hypoplastic facial bones. Teratology of Fallot, patent ductus arteriosus, right

and left pulmonary artery hypoplasia, a patent foramen ovale and a large ventricular septal defect was showed by Echocardiogram (ECG).[1,13]

INMAN et,al-1994: A Prescription-Event Monitoring (PEM) –Retrospective cross-sectional was a study conducted in 1994 at United kingdom by Inman et, al to evaluate the safety and efficacy of fluconazole in a pregnant woman who took for the treatment of vaginal candidiasis during or before conception. Almost 289 women were divided into 3 groups depending on the dose taken. Group 1 consists of 275 pregnant women who received a single 150 mg dose. Group 2 consists of 3 women who received multiple 50 mg doses. And group 3 consists of 11 pregnant women who received multiple 150 mg doses. A follow-up study was conducted and the questionnaires were answered and given back by the health care providers. Fluconazole drug safety and efficacy data were compared with 32 other drugs. Total of 5 fetal abnormalities was reported from Group 1 and none from group 2 and 3. Malformations reported when exposure of fluconazole and their Last Menstrual Period (LMP) were taken in to account are as follows: bilateral nephrosis (12 weeks pre-LMP), hooded prepuce and minimal hypospadias (15 weeks pre-LMP), proximal hypospadias and bifid scrotum (8 weeks pre-LMP) minor finger webbing and 3 short fingers on the other hand (1 week pre-LMP) and a stillbirth along with Edwards Syndrome, syndrome with trisomy 18 and cardiac abnormalities. (26 weeks pre –LMP).[1,6,10,20]

Mastroiacova et al-1996: Mastroiacova et al performed a prospective cohort study among pregnant woman's who visited/contacted one of the three Teratology Information Service centers in Italy. After 3 months of exposure i.e., 1st trimester with fluconazole, their pregnancy outcomes were assessed. 226 woman who was exposed to fluconazole in the first trimester were compared to 452 women not exposed to a teratogen as controls. Majority of the pregnant woman took single 150 mg dose. Parameters assessed in this study were induced abortions, miscarriages, stillbirths, congenital anomalies, prematurity, low birth weight, cesarean section, and long hospital stay. Malformation rate among fluconazole exposed and unexposed groups was not significantly different (4.0% vs 4.2%). Induced abortions among exposed and unexposed were significant with Odds Ratio (OR) of 5.06 and for other variables like miscarriage (OR-1.21), stillbirths (OR- 0.36), congenital anomalies (OR- 1.07), prematurity (OR- 1.73), low birth weight (OR- 0.92), cesarean section (OD- 0.91) and long hospital stay (OR- 0.87) were insignificant.[1,6,10]

Sorensen et al-1999: Sorensen et al conducted a population-based follow-up study during January 1, 1991 to 31 December 1996 in Denmark. They recognized 165 women using Pregnancy Outcome Section of the North Jutland Pharmacoepidemiological Prescription Database, Danish Medical Birth Registry (DMBR) and Regional Hospital Discharge Registry who took at least a single dose of fluconazole either before or during pregnancy. The objective of the study was to study the birth outcomes in infants like congenital malformations, low birth weight and preterm delivery among fluconazole exposed (165) and unexposed pregnant women (13,327). As there was no exact data on the dose, it was assumed that everyone took a single dose of fluconazole. Among 121 pregnant women who used fluconazole during in 1st trimester, 4 were born with congenital malformations including congenital dislocation, of the hip, lacrimal stenosis, partial syndactyly, and ventricular septum deficiency (prevalence: 3.3%). Among 13,327 pregnant women who used fluconazole during in 1st trimester, 697 were born with congenital malformations (prevalence: 5.2%). The low birth weight infants among fluconazole exposed and unexposed were 2.0% and 1.6% respectively and there was no significantly higher incidence of preterm deliveries among fluconazole than the unexposed (6.6% vs 5.7%). This study did not consider the spontaneous abortions that occurred after detecting malformations during prenatal diagnosis and the study does not have the power to detect the risk of malformations that are of more than 1.8 fold.[12,10]

Krmery et al (1996) reported the case of a 24-year-old pregnant woman diagnosed with Torulopsis glabrata fungemia. After developing intolerance to amphotericin B on her very first day of therapy, she was started with fluconazole therapy from her 14th week of gestation at a dose of 600mg daily for 21 days. She gave birth to a healthy baby at 41 weeks of gestation with no congenital malformations even after 18 months of follow-up.[4,10]

Wiesinger et al. (1996) reported a case of a 24-year-old pregnant woman with a history of candida albicans sepsis, endophthalmitis, and oral and genital mucous candida infection. As the use of amphotericin B is not a suitable option for her, intravenous (IV) Fluconazole treatment is started at a dose of 400 mg daily (10 mg/kg) for a period of 16 days and oral dose for the next 34 days. A healthy female infant with no congenital malformations was born after 39 weeks of gestation.[10]

Aleck and Bartley (1996) reported a case of a 24-year-old woman with coccidioidal meningitis who initially started treatment with fluconazole 400 mg daily and the dose eventually was increased to 800 mg daily. At this point of time, after 4 weeks of high dose therapy, she was known to be pregnant (9 weeks of gestation). Hence the physician discontinued the treatment with fluconazole and started using amphotericin B. But unfortunately as her clinical condition was not up to the mark and use of amphotericin B is of no added advantage, hence at her 22 weeks of gestation she discontinued it and was re-administered with high dose fluconazole (1200 mg daily). She gave birth to a male infant at 31 weeks of gestation who had soft calvarium, mild exorbitism, widely separated cranial sutures, hemangioma on tip of the nose, bilateral radiohumeral synostosis, dysplastic hips and posteriorly angulated ears with overfolded helices.[10,22]

A U.S based national birth defects prevention prospective case-control study was conducted by Carter et al in which 7047 pregnant women 84 were exposed to antifungal agents. Among 84, only 12 women were exposed to fluconazole and the remaining were miconazole, terconazole, and clotrimazole. A small increase in hypoplastic left heart syndrome and an insignificant increase in a diaphragmatic hernia were recorded.[2]

A letter to the editor was sent by Campoori and Bonati (1997) in which a series of 16 pregnant women contacted the Drug Information Center (DIC) to know the possible teratogenic effects of fluconazole during pregnancy. These 16 pregnant women took fluconazole at a mean dose of 291 mg, median dose of 300mg and a range of 150-1000mg starting from 4 ± 6 weeks of their gestation period. These 16 women gave birth to 17 infants (15 single deliveries and a twin). Among these 17 infants, 16 were healthy and one among the twin had stillbirth. None of the infants had congenital malformations.[4,5,6,10]

Sanchez and Moya (1998) reported a case of 38-year-old women with vaginal candidiasis took single oral dose 150mg fluconazole right before conception. She presented to the clinic on her 12th week of pregnancy to have a prenatal diagnosis, and the reports were quite normal at that time. An ultrasound taken at her 32nd week of gestation showed severe hypoplasia of the cervica, vertebrae and occipital encephalocoele. A male infant was born after 39 weeks of gestation through caesarean section and the baby had encephalocoele. Echocardiography showed that both pulmonary artery and aorta emerged from right ventricle which is contradictory as aorta must emerge from the left ventricle. He later died on the 7th day after birth.[10,23]

Jick (1999) with the help of United Kingdom's General Practice Research Database, identified 492 pregnant women exposed to topical azoles, 88 were exposed to oral azoles excluding fluconazole and 234 were exposed to fluconazole and 1629 pregnant women with no exposure to fluconazole and other azole drugs. The Relative Risk of pregnant women exposed to Fluconazole- 1.1, oral azoles -2.1, topical azoles – 2.1 and unexposed – 0.6 in the first trimester. 92% of the women took a single 150mg fluconazole and no significant increases in the risk of congenital malformations were noted in infants compared to the unexposed.[6,10,21]

Elena Lopez et.al (2005) reported a case of a 30-year-old woman with a history of vaginal candidiasis and maternal human immunodeficiency virus (HIV) infection. She took multiple drugs during her pregnancy including fluconazole for a period of first 5 months at a dose of 400 mg/day and from then she used efavirenz, nevirapine, methadone, dapsone, pentamidine, and trimethoprim-sulfamethoxazole along with fluconazole until delivery. After 37 weeks of pregnancy, a male infant was born with multiple congenital anomalies and neonatal abstinence syndrome: Streptococcus pneumonia: bacteremia -related seizures. And at his 9 months of age, he was found to have hypoplastic supraorbital ridges, shallow orbital region, radioulnar synostosis, craniosynostosis secondary to coronal and lambdoidal suture closures, mild ptosis, contractures, shallow orbital region, moderate bilateral hearing loss, hypertelorism, bilateral metacarpophalangeal-proximal interphalangeal symphalangism of D2–D5, mild to moderately diffuse cerebral dysfunction and short first toe.[10,24]

Norgaard et. al-2008: A registry-based study was conducted by Norgaard et. al in Northern Denmark an extension to the study done by Sorensen at al. between 1991-2005 which included 1079 (0.6% of the total 171532 women who give stillbirth) woman who took at least a single dose of fluconazole during 1st trimester and gives birth to live infants. And this data is compared with 170,453 pregnant women who didn't take any fluconazole dose during pregnancy. Pregnant woman was recognized through D Danish Medical Birth Registry and the information on drug use, birth outcome and covariates from population-based healthcare databases. Among 1079 pregnant women who filled fluconazole in the prescription during the visit during the 1st trimester, 797 received fluconazole 150 mg, 235 received fluconazole 300mg, 24 received 350 mg fluconazole and 23 received 600mg fluconazole. 44 (4.1%) and 6152 (3.6%) infants were born with congenital anomalies among 1079 and 170453 pregnant women respectively. Among the 44 congenital anomalies, 10 were craniofacial

malformations with a prevalence of 0.6% compared with control 0.6%; 15 had congenital heart malformations (1.4% vs 1.0%); There was no significant increase in risk of preterm birth (adjusted Prevalence Odds Ratio- 1.0) or stillbirth (adjusted Prevalence Odds Ratio- 1.1) low birth weight (adjusted Prevalence Odds Ratio-1.1) compared to the control group. The only drawback of the study is that malformations that lead to either miscarriage or abortion were not included.[2,5,10,6]

Pregnancy category C to D

As pregnant women are an exemption among clinical trials, little or no data is available to conclude whether a dug is safe or not. Hence drugs are classified into categories like category A, B, C, D, and X depending on the evidence of animal studies and possible human exposure case reports. As discussed earlier fluconazole shows teratogenic effects when used in animal reproduction models and human exposure data shows that its exposure to higher doses causes fetal risk. Hence in August 2011, U.S Food and Drug Administration (FDA) issued a drug-safety announcement for the use of high dose long-term Fluconazole exposure during pregnancy. It re-classified the drug fluconazole from pregnancy category C to D for doses above 150 mg (excluding 150 mg doses) for the treatment of vaginal candidiasis. [Pregnancy category C means that the drug shows +ve evidence of risk to the fetus in animal reproduction studies but no adequate information on human effects. And category D means that +ve fetal risk to humans during post-marketing surveillance and must be used only when benefits exceed the risk.[25] By this, it states that a total dose of 300 mg is teratogenic and is contraindicated during pregnancy. And for single low doses like 150 mg i.e., ≤ 300 mg may not increase the risk of congenital malformations and can be used when after 1st trimester when no other drug alternative is found.[2,10,26]

Molgaard-Nielsen et al (2013) performed a registry-based cohort study during January 1, 1996, to March 31, 2011, among the Danish pregnant women who had either fluconazole or ketoconazole or itraconazole during their 1st-trimester prescriptions. The objective of the study is to find the risk of overall birth defects, related to antifungal azole drugs. A total of 9,76,000 liveborn infants with at least one drug exposure during birth (antenatal exposure) were recognized and among them 7352 children had antenatal exposure with fluconazole. They classified them into groups depending on the cumulative amount of drug dose exposed during or before pregnancy like 150 mg (56%), 300mg (31%) or 350-600 mg (31%). No overall increase in birth defects among fluconazole exposed group was seen. 210 birth defects

among 7352 fluconazole exposed (prevalence: 2.86%) and 25,159 birth defects among 9,68,236 unexposed pregnancies (prevalence: 2.60%). Though there was no significant increase in birth defects and congenital anomalies, this study showed that the risk of tetralogy of Fallot (TOF) is three times to that of the unexposed. 7 out of 7352 fluconazole exposed (prevalence 0.10%) and 287 out of 9,68,236 unexposed had tetralogy of Fallot (prevalence 0.03%). A subanalysis performed in this study found a significant association between Fluconazole exposure and hypoplastic left heart.[26,6] After the study got published, a letter to the editor was sent regarding the cons and pros of this study. That article discussed that the study mostly relates to the safety of 150 mg single dose fluconazole and is not that appropriate to consider higher doses as safe. This is evident by the fact that few of the values were marginally significant like the overall crude prevalence odds ratio for cumulative doses of 300 and above. Besides, few numbers of pregnant women are present in higher dose groups and the safety of fluconazole in higher doses cannot be confirmed by this study.[27]

Molgaard Neilsen (2016) conducted a Nationwide register-based cohort study in Denmark from 1997 – 2013 to analyze the relation between the risk of fluconazole exposure and spontaneous abortion and stillbirth. Among the total 1405663 pregnant women found in National Prescription Register, 3315 were exposed to oral fluconazole during 7 to 22 weeks of gestation and 5382 were exposed to oral fluconazole during 7 weeks to birth. 147 out of 3315 oral fluconazole exposed pregnant woman had spontaneous abortions (7-22 weeks) when compared with 563 out of 13246 unexposed pregnant women had an significant increase in risk of spontaneous abortions. 21 out of 5382 oral fluconazole exposed pregnant woman had spontaneous abortions (7 weeks to birth) when compared with 77 out of 21506 unexposed pregnant women had no significant risk of spontaneous abortion. And for the woman who used topical azole preparations during pregnancy, 2823 women were exposed to a topical azole. Among these 2823, 130 members exposed to topical fluconazole and 118 members exposed with a topical azole had spontaneous abortions. Women exposed to fluconazole and topical azoles had 20 and 22 stillbirths respectively. This study shows that there is a significant increase in spontaneous abortions among fluconazole exposed.**[28]**

FDA Drug safety communication

In April 2016 Food and Drug Administration (FDA) alerted the healthcare professionals regarding the risk of single low dose 150mg fluconazole and to be cautious while prescribing the drug to the pregnant woman till they review the Danish study data and make a conclusion.

In 2011 it reported that use of high dose fluconazole i.e., 400-800 mg OD in pregnant women could lead to congenital malformations in infants. Till then 150 mg dose was found to be safe, but as new data are being emerged regarding the risk during pregnancy, FDA stated that the use of fluconazole during pregnancy shall be on hold unless benefits outweigh risks.[29]

In 2017 a preliminary study was conducted to study the relationship between prenatal exposure to antifungal drugs and the change in anogenital distance among male offspring. Pregnant women from Odense municipality Denmark with 8-16 gestational weeks were included initially from 2010 and 2012. Finally, 812 mother-son duo were selected and were given 2 questionnaires regarding their drug use in 1st and 3rd trimesters. Ano-scrotal distance (AGDas) is the distance between the center of the anus and posterior base of the scrotum. Ano-cephalad distance (AGDap) is the distance between the center of the anus and cephalad insertion of the penis. And the width of the penis is measured at the base. Masculinization programming window (MPW) in humans was found to take place between 8-14 gestational weeks. Among 812 selected mothers, 87 (11%) took an antifungal drug during pregnancy. Measurement of anogenital distance and width of the penis was done by using standard vernier caliper. 6.4 mm shorter Ano-scrotal distance is noted among 4 male offspring whose mother took oral fluconazole 150mg single dose during pregnancy. And this is more valid for the women who took oral fluconazole during 8 and 14 gestational weeks. Whereas, use of anti-fungal vaginal tablets and vaginal cream had no significant decrease and no association in AGDas respectively. Thus a hypothetical relation was found between oral fluconazole use and AGB and this effect may be contributed by the fact that, the fetus being vulnerable to endocrine disruption this might influence genital distance among male offspring as evident by the animal toxicology studies. An insignificant decrease in AGDas is found among male offspring whose mother took both miconazole or clotrimazole vaginal tablets, and no association when used as vaginal creams. This is the first of its kind study to be performed and more data is essential to confirm this effect. But this study provides us a basic foundation for further studies.[15,30]

CONCLUSION

Fluconazole is an azole antifungal drug being used in pregnant women though discrepancy is persisting on its safety. Hence in this study, a comprehensive review is done and data from various sources are gathered. This study mainly aims to bring to the note of the clinicians and gynecologists as an awareness that the use of Fluconazole during may not be safe and the use

could lead to congenital malformations (high-dose 400-800mg OD) stillbirths (single 150 mg) and decrease in AGD among male offspring. But more clear data is needed to conclude the teratogenicity of 150 mg dose fluconazole and the effect of decreased AGD. Hence it is advisable to keep the use of fluconazole in hold until FDA confirms its safety.

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