Medicines Adverse Reactions Committee

Meeting date	11/06/2020	Agenda item	3.2.2
Title	**Fluconazole and use in pregnancy**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Fluconazole	Canesoral Capsule	Bayer New Zealand Limited
	Diflucan One Capsule	Johnson & Johnson (New Zealand) Limited
	Diflucan Powder for oral suspension	Pfizer New Zealand Limited
	Flonazol Capsule	Multichem NZ Limited
	Flucazole Capsule	Mylan New Zealand Limited
	Fluconazole Capsule	Mylan New Zealand Limited
	Fluconazole-Baxter Solution for infusion	Baxter Healthcare Limited
	Ozole Capsule	Douglas Pharmaceuticals Limited
Fluconazole; Clotrimazole	Canesoral Duo Combination	Bayer New Zealand Limited

PHARMAC funding	**Pharmaceutical Schedule:** Fluconazole (50 mg, 150 mg and 200 mg Capsule) Diflucan (10 mg/mL Powder for oral suspension) – Special Authority **Hospital Medicines List:** Fluconazole (50 mg, 150 mg and 200 mg Capsule) Diflucan (50 mg/5 mL Powder for oral suspension) Fluconazole-Baxter (2 mg/50 mL, 2 mg/100 mL vial, Solution for infusion))
Previous MARC meetings	8 September 2016 (167th meeting) – Fluconazole and use in pregnancy
Prescriber Update	MARC's Remarks: September 2016 Meeting (www.medsafe.govt.nz/profs/PUArticles/December%202016/MARC%20Remarks.htm
Classification	Prescription; except when specified as a restricted medicine Restricted; for oral use in medicines that have received the consent of the Minister or the Director-General to their distribution as restricted medicines and that are sold in the manufacturer's original pack containing 150 milligrams or less as a single dose for the treatment of vaginal candidiasis
Advice sought	**The Committee is asked to advise whether:** • The data sheets for fluconazole should be updated so that the information in the pregnancy section is harmonised. • The data sheets for fluconazole should be updated so that they include information in the pregnancy section on effects of low dose treatment including the results of the Bérard et al study [1]. • This topic requires further communication other that MARC's Remarks in *Prescriber Update*.

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1 PURPOSE

In February 2019, Bérard et al published a paper in the *Canadian Medical Association Journal* which concluded that any maternal exposure to fluconazole during pregnancy may increase the risk of spontaneous abortion and doses higher than 150 mg during the first trimester may increase the risk of cardiac septal closure anomalies [1]. Bérard et al aimed to assess the effect of exposure to low and high doses of fluconazole on the occurrence of spontaneous abortions, major congenital malformations and stillbirths [1].

The Committee previously considered fluconazole and use in pregnancy at the September 2016 meeting. At this meeting, the Committee's recommendations focussed on spontaneous abortions [Annexe 1].

The purpose of this paper is to review the data on fluconazole and its use in pregnancy. This paper will consider major congenital malformations and still births, as well as spontaneous abortions, as reported by Bérard et al [1].

2 BACKGROUND

2.1 Fluconazole

Fluconazole is a triazole medicine used to treat fungal infections [2]. It is effective against a broad spectrum of fungi including [2]:

- dermatophytes (tinea infections)
- yeasts (eg, candida and malassezia)
- systemic infections (eg, cryptococcosis and coccidioidomycosis).

Triazole antifungals inhibit fungal cytochrome P450-dependent lanosterol 14α-demethylase resulting in impaired sterol synthesis in fungal cell membranes and increased membrane permeability [3].

The information for fluconazole in the pregnancy section of the New Zealand Formulary is as follows [3]:

Human Data Suggest Risk (≥400 mg/day)

Human (and animal) Data Suggest Risk: The human data for the drug or drugs in the same class or with the same mechanism of action, and animal reproduction data if available, suggest that there may be a risk for developmental toxicity (growth restriction, structural anomalies, functional/behavioural deficits, or death) throughout pregnancy. Usually, pregnancy exposure should be avoided, but the risk may be acceptable if the maternal condition requires the drug.

Pregnancy summary

Although the data are very limited, the use of fluconazole during the 1st trimester appears to be teratogenic with continuous daily doses of 400 mg/day or more. The malformations may resemble those observed in the Antley-Bixler syndrome. The published experience with the use of smaller doses, such as those prescribed for vaginal fungal infections, suggests that the risk for adverse outcomes is low, if it exists at all. In those instances, in which continuous, high-dose fluconazole is the only therapeutic choice during the 1st trimester, the patient should be informed of the potential risk to her fetus.

2.2 Candida vulvovaginitis

There is an increased risk of candida vulvovaginitis during pregnancy [Annexe 1]. Vaginal candidiasis is not associated with adverse pregnancy outcomes [4].

Vulvovaginal candidiasis is one of the most common causes of vulvovaginal itching and discharge [4]. The disorder is characterised by inflammation in the setting of Candida species [4]. Treatment is indicated for the relief of symptoms [4].

The *UpToDate* database (www.uptodate.com/home) publishes the following information on the treatment for Candida vulvovaginitis in pregnancy:

Topical azole antifungals are first line treatment for Candida vulvovaginitis in pregnancy [4]. Oral fluconazole therapy does not appear to increase the risk of stillbirth or neonatal death, however the impact on birth defects is unclear [4]:

- Miscarriage – A cohort study of over 3,300 women who received 150 to 300 mg oral fluconazole between 7 and 22 weeks of pregnancy reported an approximately 50 percent increased risk of miscarriage in exposed women compared with either unexposed women or women treated with vaginal azole therapy [5]. Stillbirth risk did not differ among the groups, although stillbirth was a relatively rare outcome. A subsequent larger population cohort study that evaluated over 320,000 pregnancies reported exposure to oral fluconazole during early pregnancy was associated with a two- to threefold increased risk of miscarriage compared with no exposure (risk for doses of ≤150 mg and >150 mg, respectively) [1]. These studies contrast with two earlier, smaller cohort studies, totalling just over 1500 women, that did not report an association between oral fluconazole and miscarriage. As the larger studies likely had greater power to detect an increase in miscarriage risk, the authors recommend avoiding oral azole therapy for pregnant women, particularly in the first trimester.

- Birth defects – The impact of fluconazole on birth defects is unclear, in part because of the variability across studies for dose, timing of exposure, and method of exposure assessment and lack of consistency across the reported birth defects. Overall, the data appear reassuring for women who took low-dose fluconazole before realizing that they were pregnant, although an increased risk of specific anomalies cannot be definitively excluded.

  Initial case reports described a pattern of birth defects (abnormalities of cranium, face, bones, and heart) after first-trimester exposure to high-dose fluconazole therapy (400 to 800 mg/day). A Canadian population cohort study including over 220,000 pregnancies reported an 80 percent increased risk of cardiac septal closure anomalies following first trimester exposure to fluconazole at doses >150 mg, but no association was noted at doses up to 150 mg for overall congenital malformations or for cardiac septal defects [1]. A United States case-control study including over 31,000 mothers of children with birth defects reported an association with first-trimester fluconazole use and cleft lip with cleft palate and d-transposition of the great arteries, but the study was limited by exposure self-report and small total number of cases. Multiple smaller and earlier epidemiologic studies did not report an increased risk of birth defects after first-trimester use of a single low dose of fluconazole 150 mg, but the smaller size of these studies may have limited their ability to detect an outcome difference.

Comments:
Any relevant literature referred to in this section is discussed later in this report.

2.3 Usage

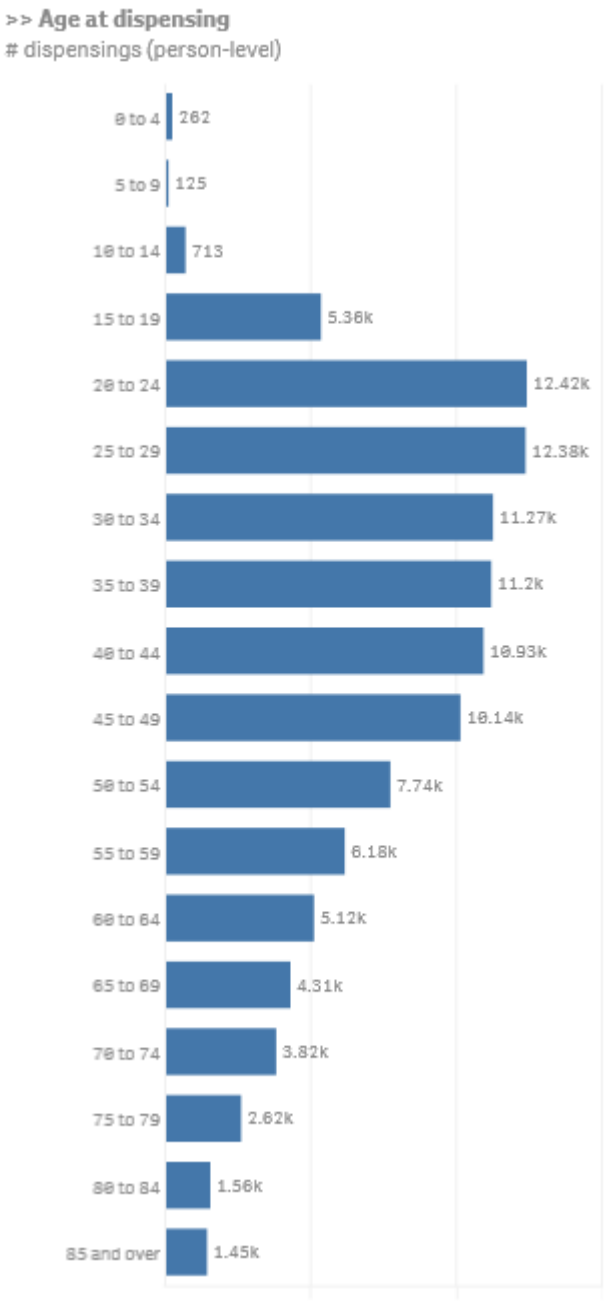
Table 1 below shows the number of people who received a dispensing of fluconazole from 2014-2018 [6].

Table 1: The number of people who received a dispensing of fluconazole from 2014-2018

Year	Fluconazole 50 mg Capsule	Fluconazole 150 mg Capsule	Fluconazole 200 mg Capsule	Fluoconazole 10 mg/mL Powder for oral suspension
2014	3699	20,422	1,708	121
2015	3654	20,378	1,553	123
2016	3565	20,829	1,599	131
2017	3409	21,095	1,446	144
2018	3424	22,776	1,298	143

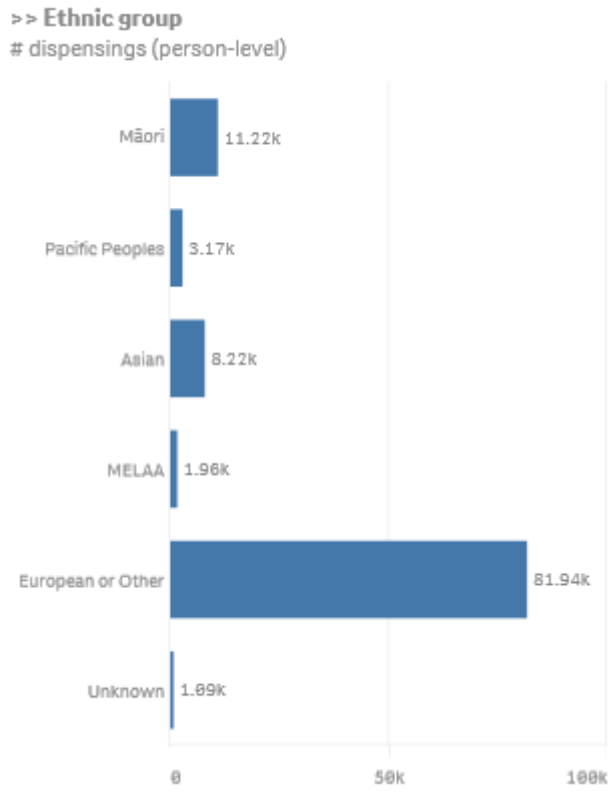
Figures 1 and 2 below show the age of women and ethnicity of people who received a dispensing of fluconazole from 2017-2019.

Figure 1: Age at dispensing of fluconazole (women only) from 2017-2019



Source: National Collections, Ministry of Health. 2020.

Figure 2: Dispensing of fluconazole by ethnicity from 2017-2019



Source: National Collections, Ministry of Health. 2020.

Comments:
The figures for the 150 mg capsule are much higher than the other dosage forms. The figures above do not include over-the-counter sales of fluconazole.

2.4 Previous Committee meeting and recommendations

2.4.1 September 2016 – 167th Committee meeting

In September 2016 the Committee considered fluconazole and its use in pregnancy [Annexe 1]. This review was triggered by the publication of a paper by Mølgaard-Nielsen et al in *The Journal of the American Medical Association* which concluded there is an association between the use of oral fluconazole in pregnancy and the risk of spontaneous abortion and stillbirth [5]. The effect of oral fluconazole was compared with unexposed women and women with topical azole exposure in pregnancy [5].

Due to the increased risk of vaginal candidiasis in pregnant women and the use of fluconazole in New Zealand at the time, Medsafe considered that these safety concerns should be reviewed by the Committee.

The minutes of the September 2016 meeting are available on the Medsafe website:

www.medsafe.govt.nz/profs/adverse/Minutes167.htm#3.2.2

Overall, the Committee considered that the Mølgaard-Nielsen et al study did not provide sufficient evidence to suggest that single low-dose fluconazole in pregnancy increases the risk of spontaneous abortion or stillbirth.

The Committee noted that the US Food and Drug Administration (US FDA) was, at the time, evaluating the results of the Mølgaard-Nielsen et al study.

The Committee recommended that the issue be reported back to the Committee at a future meeting once the US FDA's review and conclusion, following their evaluation of the Mølgaard-Nielsen et al study, was known. The Committee was also interested on any data on the bioavailability of azole antifungals when used vaginally, topically and orally.

2.4.2 December 2017 – 172nd Committee meeting

Updated information on fluconazole [Annexe 2] and the results of the US FDA review [Annexe 3] were presented to the Committee in December 2017.

The updated information provided by Medsafe [Annexe 2] included a summary of the US FDA's review and data on the bioavailability of azole antifungals when used vaginally, topically and orally as recommended by the Committee at the September 2016 meeting. In February 2017, the European Medicines Agency (EMA) published their recommendations from the Pharmacovigilance Risk Assessment Committee (PRAC) meeting of 6-9 February 2017 and a summary was also provided.

After reviewing evaluations on this topic carried out by international regulators, Medsafe noted that the US FDA have not recommended updates to product labelling whereas the EMA has regarding the risk of spontaneous abortion and stillbirth from the use of oral fluconazole.

The New Zealand data sheets had been updated since this was last discussed by the Committee and it included additional information on this risk in section 4.6 (fertility, pregnancy and lactation).

Comments:
The New Zealand data sheets were updated with additional information on the risk of spontaneous abortion and stillbirth from the use of oral fluconazole by the companies without a recommendation from the Committee.

2.5 Data sheets

2.5.1 New Zealand

Table 2 below shows the information on therapeutic indications, dose and pregnancy in the New Zealand data sheets.

Table 2: Information on indication, dose and pregnancy in the New Zealand data sheets

Name of product	Information in the data sheets published on the Medsafe website
Canesoral Capsule (150 mg) [7] Diflucan One Capsule (150 mg) [8] Flonazol Capsule (150 mg) [9] Flucazole Capsule (150 mg) [10] Ozole Capsule (150 mg) [11]	**4.1 Therapeutic Indications** [Name of product] given orally, is indicated for vaginal candidiasis.
	4.2 Dose and administration* [Name of product] is administered orally. **Adults** For vaginal candidiasis, [name of product] should be administered as a single oral dose. The median time to onset of symptom relief following a 150 mg single oral dose for the treatment of vaginal candidiasis is one day. The range of time to onset of symptom relief is one hour to nine days.
	4.6 Fertility, Pregnancy and Lactation Pregnancy (Category D) There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400 - 800 mg/day) fluconazole therapy for coccidiomycosis. The relationship between fluconazole use and these events is unclear.

Name of product	Information in the data sheets published on the Medsafe website
	Adverse foetal effects have been seen in animals only at high dose levels associated with maternal toxicity. [Name of product] should not be used in women who are pregnant, or in women of childbearing potential unless adequate contraception is employed.
Diflucan Powder for oral suspension (10 mg/mL, 40 mg/mL) [12] Fluconazole Capsule (50 mg, 100 mg, 150 mg and 200 mg) [13] Fluconazole-Baxter Solution for infusion (2 mg/mL) [14]	**4.1 Therapeutic indications** Diflucan/Fluconazole/Fluconazole-Baxter is indicated for the treatment of the following conditions: Cryptococcosis, including cryptococcal meningitis and infections of other sites (eg, pulmonary, cutaneous). Normal hosts, and patients with AIDS, organ transplants or other causes of immunosuppression may be treated. Diflucan/Fluconazole/Fluconazole-Baxter can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS. Systemic candidiasis including candidaemia, disseminated candidiasis and other forms of invasive candidal infection including infections of the peritoneum, endocardium and pulmonary and urinary tracts. Patients with malignancy, in intensive care units, receiving cytotoxic or immunosuppressive therapy, or with other factors predisposing to candida infection may be treated. Mucosal candidiasis. These include oropharyngeal, oesophageal, non-invasive bronchopulmonary infections, candiduria, mucocutaneous and chronic oral atrophic candidiasis (denture sore mouth). Normal hosts and patients with compromised immune function may be treated. Vaginal candidiasis, acute or recurrent. Prevention of fungal infection in immunocompromised patients considered at risk as a consequence of HIV infections or neutropenia following cytotoxic chemotherapy, radiotherapy or bone marrow transplant. [Fluconazole 50 mg and 150 mg capsules are also indicated for the treatment of] Dermatomycoses including tinea pedis, tinea corporis, tinea cruris, pityriasis versicolor & candidiasis.
	4.2 Dose and administration The daily dose of [name of product] should be based on the infecting organism, severity of the fungal infection and the patient's response to therapy. Most cases of vaginal candidiasis respond to single dose therapy. Therapy for those types of infections requiring multiple dose treatment should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection. Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require maintenance therapy to prevent relapse. Vaginal candidiasis [Name of product] should be administered as a single oral dose. Median time to onset of symptom relief following a 150 mg single oral dose for the treatment of vaginal candidiasis is one day. The range of time to onset of symptom relief is one hour to nine days.
	4.6 Fertility, Pregnancy and Lactation Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus. Effective contraceptive measures should be considered in women of child-bearing potential and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose. There have been reports of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400 mg/kg to 800 mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole use and these events is unclear. Adverse fetal effects have been seen in animals only at high dose levels associated with maternal toxicity. These findings are not considered relevant to fluconazole used at therapeutic doses. Case reports describe a distinctive and a rare pattern of birth defects among infants whose mothers received high-dose (400 mg/day to 800 mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include: brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.
Canesoral Duo Combination (Flucoazole Oral	**4.1 Therapeutic indications** Canesoral Duo is indicated for vaginal candidiasis.

Name of product	Information in the data sheets published on the Medsafe website
Capsule 150 mg, Clotrimazole Topical Cream 10 mg/g) [15]	The cream can also be used for relief of external itching/irritation and the management of Candida vulvovaginitis or infection of the peri-anal area.
	4.2 Dose and administration The fluconazole capsule must be used as a single dose treatment only. One fluconazole 150 mg capsule, swallowed whole, in a single dose.
	4.6 Fertility, Pregnancy and Lactation Pregnancy (Category D) There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400 - 800 mg/day) fluconazole therapy for coccidiomycosis. The relationship between fluconazole use and these events is unclear. Adverse foetal effects have been seen in animals only at high dose levels associated with maternal toxicity. Canesoral Duo should not be used in women who are pregnant, or in women of childbearing potential unless adequate contraception is employed

*The wording in the Canesoral data sheet [7] is slightly less. It states Canesoral must be used as a single dose treatment only and for adults, one capsule should be swallowed whole in a single dose.

Comments:

The dose for all products to treat vaginal candidiasis is a single 150 mg oral dose. Only the Fluconazole-Baxter data sheet states that 150 mg can be administered as a single dose once weekly, when topical therapy has failed [14].

The data sheets for Canesoral, Diflucan One, Flonazol, Flucazole, Ozole and Canesoral Duo all state that the product should not be used in pregnancy unless adequate contraception is employed. However, more recent research is not included in the information.

The data sheets for Diflucan Powder for oral suspension, Fluconazole and Fluconazole-Baxter state that Use in pregnancy should be avoided **except** in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus. These data sheets include more information on the 150 mg dose (ie, reports of spontaneous abortion ands congenital abnormalities as a single or repeated dose in the first trimester).

The information in the product information from other jurisdictions is described in section 3.3 of this report.

3 SCIENTIFIC INFORMATION

3.1 Published literature

The published literature considered in the following section is the result of a literature search from September 2016 (the last time the Committee considered this topic) to the present day.

3.1.1 Cottreau and Barr. 2016 [16]

This article, by Cottreau and Barr, reviews the current literature for the use of antiviral and antifungals, the pharmacokinetics of these agents, and their safety in pregnancy.

Cottreau And Barr state that if untreated, viral and fungal infections can have harmful effects on both maternal and fetal health. Therefore, understanding the use and risks of these medications in pregnancy is vital to provide appropriate care.

This literature review found:

- Fluconazole readily crosses the placenta and has been shown to be teratogenic and embryotoxic at high doses in rats.

- Prolonged administration during pregnancy and high doses (400–800 mg/day) have been associated with major congenital anomalies when used in the first trimester.
- Four infants whose mothers received high-dose fluconazole (200–400 mg/day) for prolonged periods were found to have congenital abnormalities characterised by skeletal, cranial, and functional abnormalities. The nature of these birth defects suggests that the teratogenic effect may occur early in the first trimester and has been confirmed by at least one animal study.
- Several studies support the risk of low-dose fluconazole during pregnancy, especially when used for short durations [5].
- One recent cohort study identified an association between oral fluconazole during pregnancy and the risk of spontaneous abortion [5]. Women who were exposed to either low-dose (150–300 mg) or high-dose (350–5600 mg) fluconazole during 7 through 22 weeks' gestation were matched to unexposed pregnancies. Fluconazole-exposed women had a significantly increased risk of spontaneous abortion compared with unexposed women (147 of 3315 and 563 of 13,246 women, respectively; hazard ratio [HR] 1.48, 95% CI 1.23–1.77). No significant differences were seen in the incidence of stillbirth overall (HR 1.18, 95% CI 0.64–2.16). Women who received high-dose fluconazole had a significantly higher rate of stillbirth (HR 4.10, 95% CI 1.89–8.90), although the study was based on a small number of cases (n=7). For that reason, the authors state that the study results should be interpreted with caution.
- Another population based, case-control study assessed first-trimester fluconazole use among deliveries that took place between 1997 and 2011. Of the 43,257 births assessed, only 50 reported exposure to fluconazole; of those 50 births, 44 were born with birth defects and 6 without. Most of the women reported using fluconazole for vulvovaginal candidiasis (36 of 50 [72%]), and the remaining women did not include an indication. Fluconazole use in the first trimester was associated with cleft lip with cleft palate (OR 5.53, 95% CI 1.68–18.24) and D-transposition of the great arteries (OR 7.56, 95% CI 1.22–35.45).

Cottreau And Barr concluded their review on fluconazole with the recommendations from the US FDA in 2016:

'Because of the animal and human findings, the US FDA reclassified fluconazole from a Pregnancy Category C to a Pregnancy Category D drug when used for all indications except treatment of vaginal candidiasis (a single dose of 150 mg), which remains in Pregnancy Category C. Doses of >300 mg should be contraindicated throughout pregnancy due to the teratogenic effect seen in multiple studies, and lower doses should be avoided in the first trimester if possible.'

Comments:

This review included the Mølgaard-Nielsen et al study presented to the Committee at the September 2016 meeting [5].

It is unclear what Cottreau And Barr mean by the comment 'Several studies support the risk of low-dose fluconazole during pregnancy, especially when used for short durations' (ie, whether they mean low risk or benefit).

Pregnancy is not a contraindication in any of the New Zealand data sheets.

The New Zealand data sheets for Canesoral, Diflucan One, Flonazol, Flucazole, Ozole and Canesoral Duo all include Pregnancy Category D.

The data sheets for Diflucan Powder for oral suspension, Fluconazole and Fluconazole-Baxter do not mention a category. These data sheets mention use in the first trimester and reports of spontaneous abortion, congenital abnormalities and birth defects.

Category C and D are described in the Australian categorisation system for prescribing medicines in pregnancy (which is slightly different to the US FDA classification above, but the classification used in the New Zealand data sheets) and mean:

Category C

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Category D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

For further details refer to the Australian Therapeutic Goods Administration (TGA) website: www.tga.gov.au/australian-categorisation-system-prescribing-medicines-pregnancy

3.1.2 Mogensen et al. 2017 [17]

Mogensen et al discuss that conazoles have anti-androgenic properties and prenatal exposure in rodents is associated with a shorter (less masculine) anogenital distance (AGD) in male offspring. Mogensen et al hypothesised, in this preliminary study, that prenatal exposure to antifungal medication may change anogenital distance in male offspring. They state that to their knowledge this has never been studied in humans.

Method

In the Odense Child Cohort, pregnant women residing in Odense municipality, Denmark, were recruited at gestational age 8–16 weeks between 2010 and 2012. Of the eligible 2,421 mother-child pairs, 812 mother-son pairs were included. Questionnaire data on medicine use were collected in first and third trimester and a physical examination at age three months was performed.

Ano-scrotal distance; measured from the centre of anus to the posterior base of scrotum (AGDas). Ano-cephalad distance; measured from the centre of anus to the cephalad insertion of the penis (AGDap) and penile width; measured at the base of the penis.

Results

Eighty seven women had used antifungal medicine during pregnancy. Maternal use of oral fluconazole (n = 4) was associated with a 6.4 mm shorter AGDas (95% CI: -11.9;-0.9) in the male offspring. Use of antifungal vaginal tablets (n = 21), was associated with a non-significantly shorter AGDas (−1.9 mm; 95% CI: -4.3; 0.5) whereas exposure to vaginal cream (n = 23) was not associated to AGDas. Use of antifungal medicine in the window of genital development between 8 and 14 weeks of gestation was associated with a larger reduction in AGDas than exposure outside this window. Antifungal medicine intake was not associated with AGDap and penil width.

Conclusion

Mogensen et al hypothesise that maternal use of conazole antifungal medication during pregnancy may affect the masculinisation of male offspring. If confirmed, pregnant women should be advised to use antifungal medicine with caution.

Comments:

This study, like the Mølgaard-Nielsen et al study [5], was carried out in Denmark.

The four pregnant women taking fluconazole orally gave birth to boys with a significantly shorter AGD. The small number of women means that this study is hypothesis generating and further research is required.

3.1.3 Pasternak at al. 2018 [18]

Pasternak at al investigated whether fluconazole use during pregnancy is associated with stillbirth and neonatal death.

Method

Nationwide register data were used to identify all pregnancies with singleton live births and stillbirths in Sweden (July 2006-December 2014) and Norway (January 2005-December 2015). Pasternak at al excluded pregnancies with missing maternal personal identification number, missing or implausible gestational age, non-residence in the country, prescription for fluconazole within 28 days before conception, and prescription for any non-fluconazole oral azole antifungal between 28 days before conception and delivery.

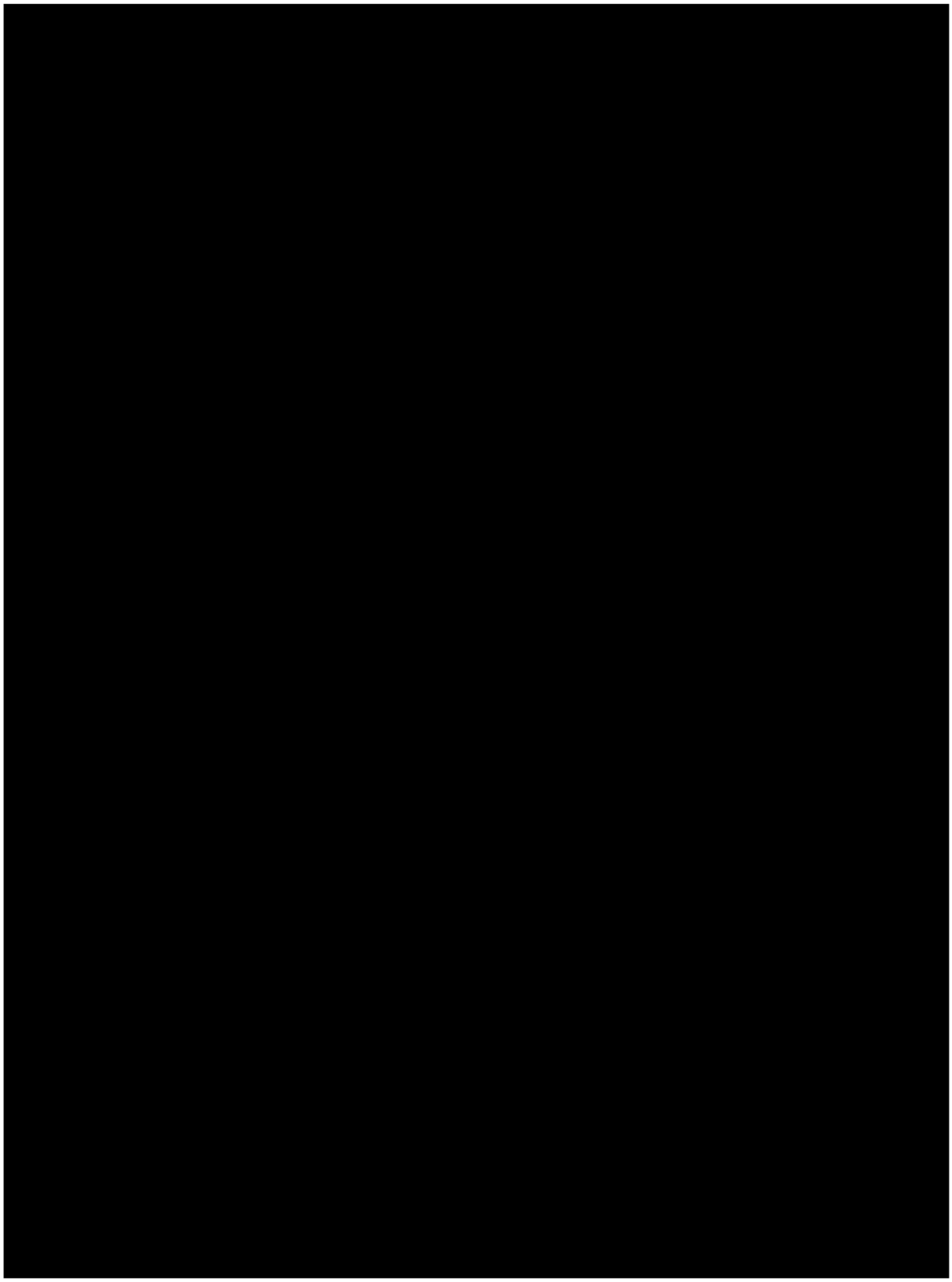
The primary outcomes were stillbirth (fetal loss after 22 completed weeks; except during July 2006-June 2008 in Sweden, when it was defined as after 28 completed weeks) and neonatal death (0-27 days after live birth) associated with any fluconazole exposure at any time during pregnancy, as defined by filled prescriptions. Secondary analyses investigated outcomes by fluconazole dose.

Using logistic regression, propensity scores were estimated in each country data set. Fluconazole-exposed and unexposed pregnancies were matched (1:10) on age and propensity scores. A distinct matched cohort was created for analyses of stillbirth (based on live births and stillbirths) and neonatal death (based on live births). The cohort for analysis of stillbirth also included gestational day at fluconazole exposure as a matching criterion. Following matching, data from the two countries were pooled for analysis. Sensitivity analyses restricted to Sweden were conducted including a broader set of covariates in the propensity score. Cox and Poisson regression were used to estimate HRs for stillbirth and risk ratios (RRs) for neonatal death, respectively.

Results

From a cohort of 1,485,316 pregnancies (852,959 in Sweden and 632,357 in Norway), 10,669 exposed and 106,690 unexposed pregnancies were included in the matched analysis of stillbirth, and 10,640 exposed and 106,387 unexposed pregnancies in the matched analysis of neonatal death. Baseline characteristics were well balanced between groups. Table 3 below shows the baseline characteristics of women included in the cohort.

[redacted]



There were 2.7 stillbirths per 1,000 exposed pregnancies and 3.6 per 1,000 unexposed pregnancies (HR, 0.76 [95% CI, 0.52-1.10]), and 1.2 neonatal deaths per 1000 exposed pregnancies and 1.7 per 1,000 unexposed pregnancies (RR, 0.73 [95% CI, 0.42-1.29]). Table 4 below shows the associations between use of fluconazole during pregnancy and risk of still birth and neonatal death.

[redacted]

Results were similar for doses of 300 mg or less and for more than 300 mg. Sensitivity analyses with a broader set of covariates in the propensity score were consistent with the primary analyses.

Discussion

In this cohort study, fluconazole use in pregnancy was not associated with significantly increased risks of stillbirth or neonatal death. To Pasternak et al's knowledge, the outcome of neonatal death has not been reported previously. An increased risk of stillbirth suggested by the Danish study for any fluconazole exposure or for doses more than 300 mg was not confirmed. This study included twice the number of fluconazole-exposed pregnancies from two countries, although the number exposed to higher doses was still small. However, in both studies, confidence intervals were wide and, for any exposure, neither result was statistically significant. The previous result may have been due to chance.

The possibility of confounding cannot be excluded. Of concern would be unmeasured confounders that could bias results toward no increased risk. Filled prescriptions were used to define drug exposure; any non-use of fluconazole would bias results toward the null.

Pasternak at al conclude that although the data on fluconazole use in pregnancy suggest no increased risk of stillbirth, additional studies should be conducted and the collective body of data scrutinised by drug authorities before recommendations to guide clinical decision making are made, and weighed against the benefits of therapy.

Comments:

This study was presented as a research letter in JAMA. It did not support the findings from the Mølgaard-Nielsen et al study which concluded there is an association between the use of oral fluconazole in pregnancy and the risk of spontaneous abortion and stillbirth [5].

This study did not include time preceding spontaneous abortion or induced abortion.

Pasternak el al suggest more studies should be conducted.

3.1.4 Bérard et al. 2019 [1]

Bérard et al aimed to assess the effect of exposure to low and high doses of fluconazole during pregnancy on the occurrence of spontaneous abortions, major congenital malformations and stillbirths by conducting three nested case-control studies.

Method

The study population included pregnant women insured by the Quebec Prescription Drug Insurance program continuously for ≥ 12 months before and during pregnancy.

Quebec Pregnancy Cohort data sources included the medical claims database, Quebec Prescription Drug Insurance database, hospitalisation archive database and Quebec Statistics database. The Quebec Pregnancy Cohort is updated every three years. The latest data available are from 2015. Individual-level information was obtained from province-wide databases and linked using personal identifiers.

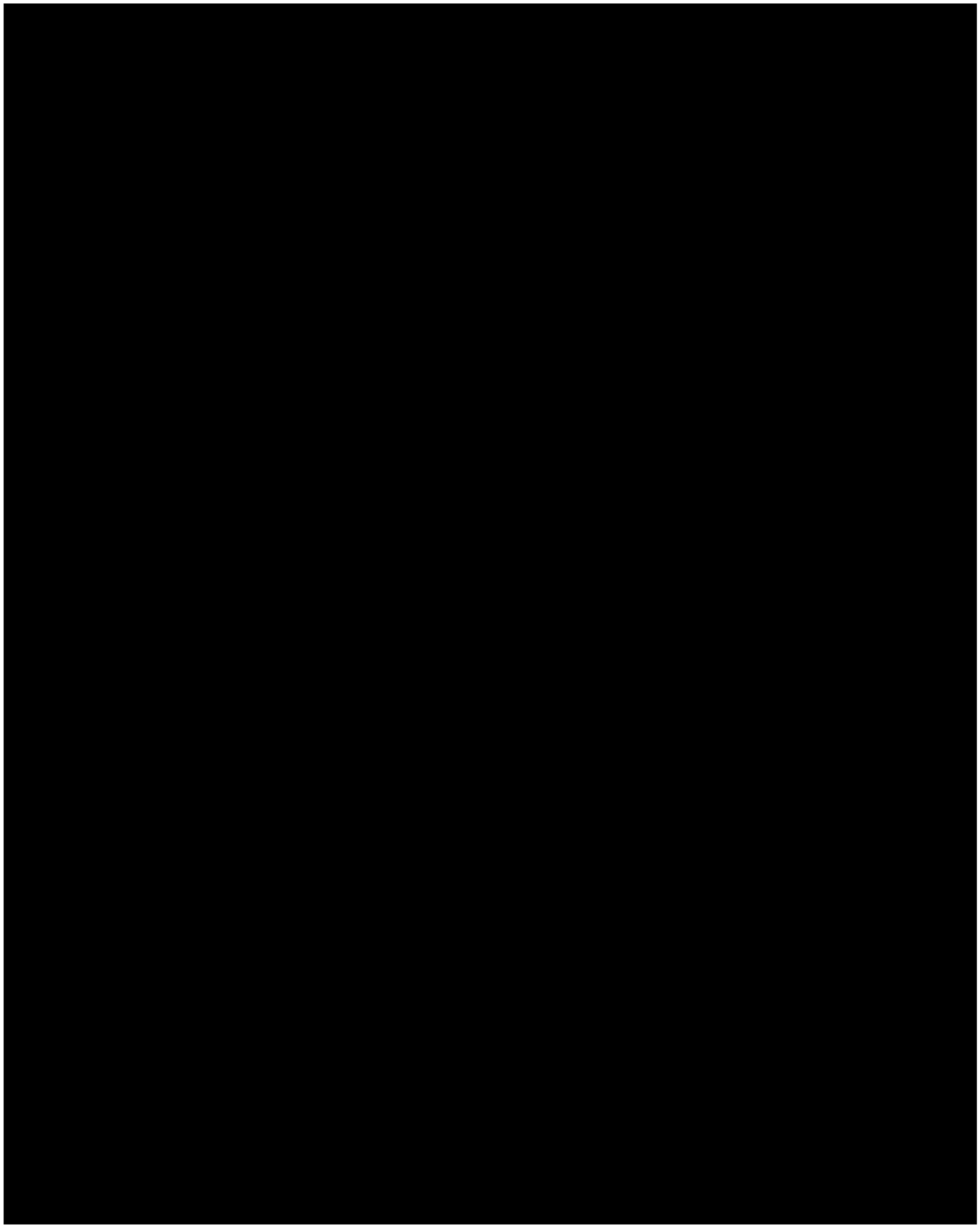
Within the Quebec Pregnancy Cohort (1998–2015), Bérard et al identified women exposed to low- (≤ 150 mg) and high-dose (> 150 mg) fluconazole, and women who were not exposed. For each case of spontaneous abortion or stillbirth, up to five controls were randomly selected using an incidence density sampling method matched on gestational age at diagnosis of spontaneous abortion or stillbirth (index date) and the year of the last menstrual period. For cases of major congenital malformation, Bérard et al considered all liveborn babies as controls. Generalised estimation equation models were used to analyse the three main outcomes separately.

Results

Within a cohort of 441,949 pregnancies, 320,868 pregnancies were included in the analyses of spontaneous abortions, 226,599 of major congenital malformations and 7,832 of stillbirths. Most (69.5%) women exposed to fluconazole in pregnancy received the common single therapeutic dose of 150 mg (low dose). The remainder received a dose of > 150 mg (high dose). Use of oral fluconazole during early pregnancy was associated with an increased risk of spontaneous abortion compared with no exposure (adjusted odds ratio [OR] for 345 cases exposed to low-dose treatment 2.23, 95% confidence interval [CI] 1.96–2.54; adjusted OR for 249 cases exposed to high-dose treatment 3.20, 95% CI 2.73–3.75).

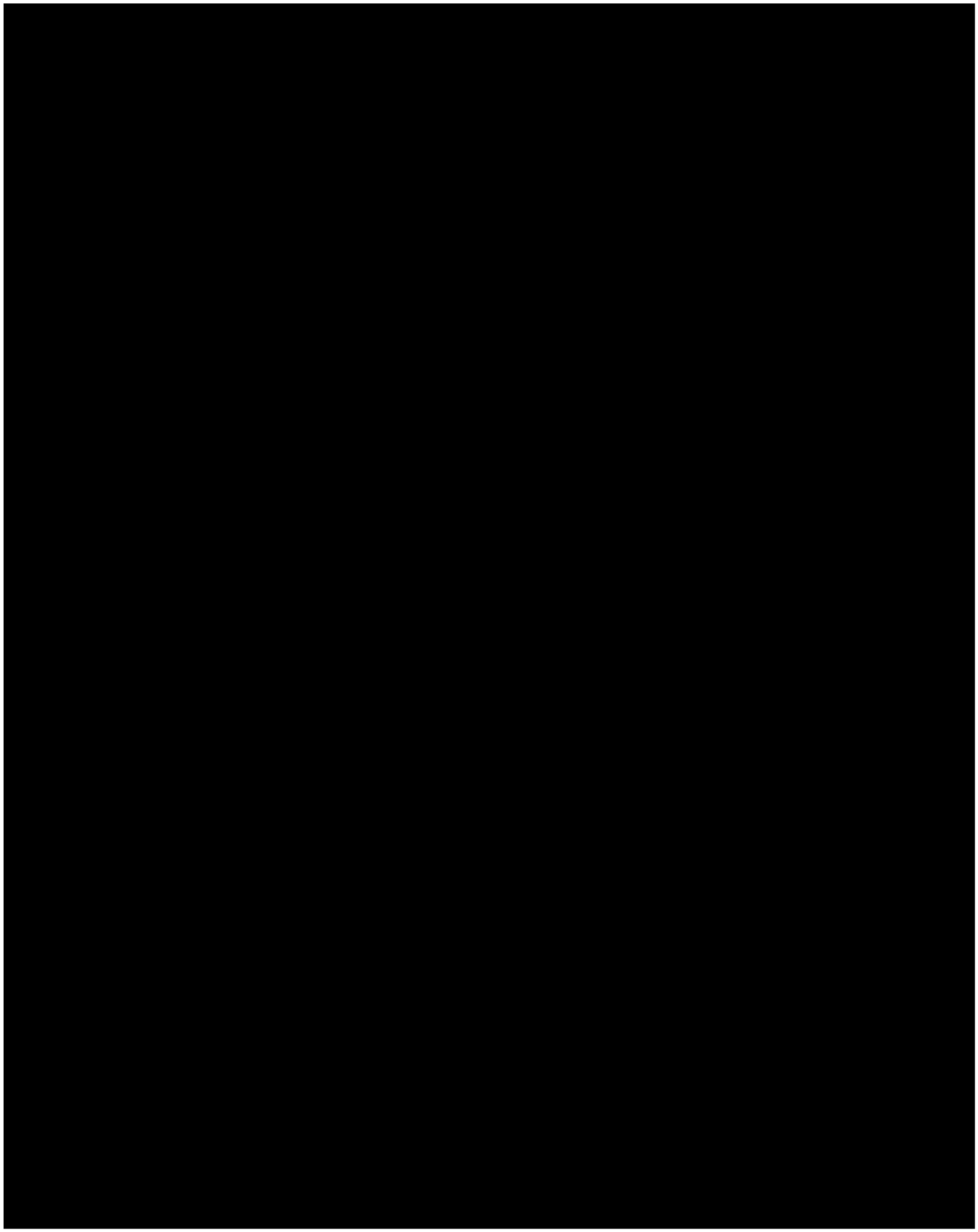
Table 5 below shows the association between the use of oral fluconazole and other antibiotics during early pregnancy and the risk of spontaneous abortion.

[redacted]

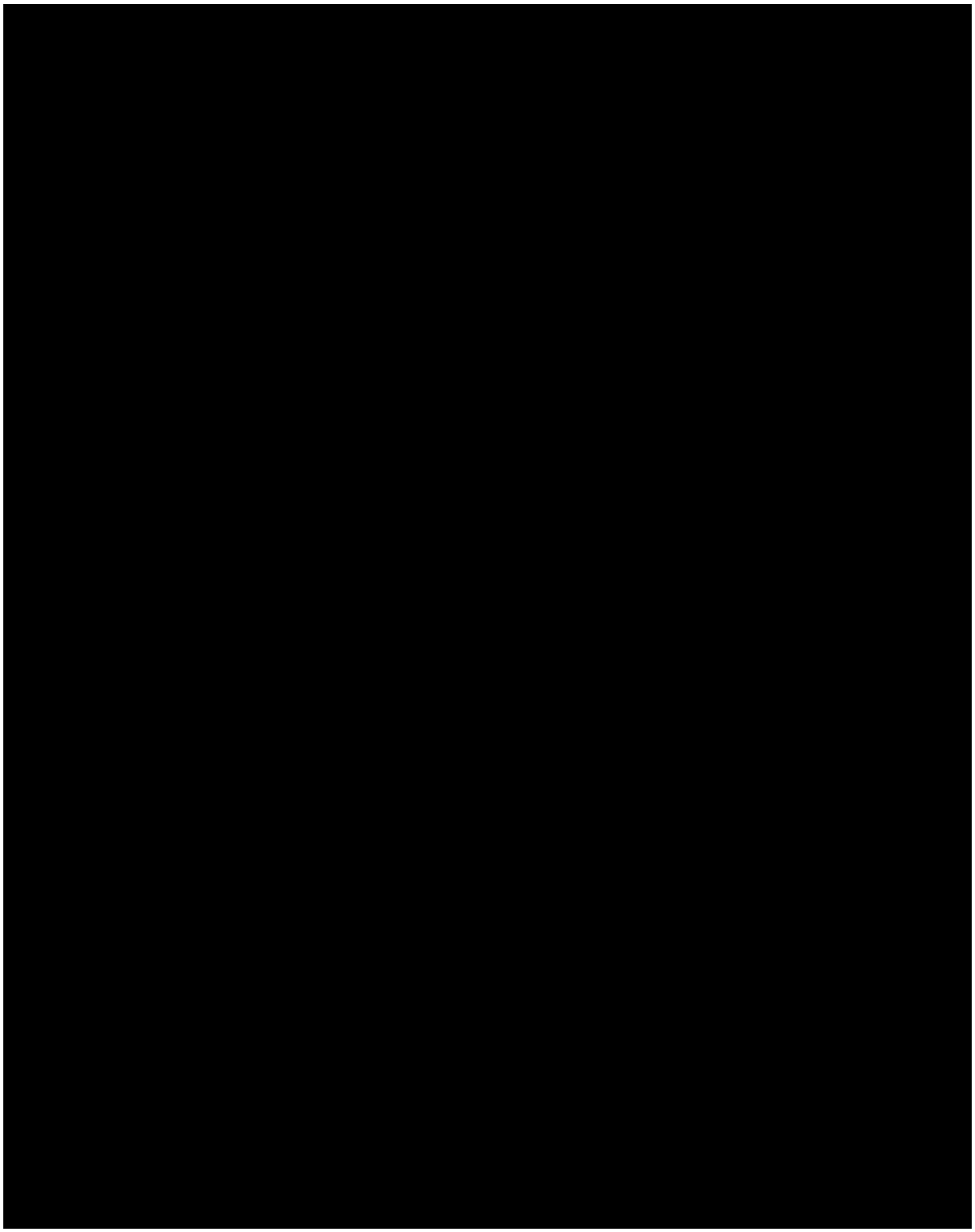


Exposure to fluconazole during the first trimester did not increase the risk of overall major congenital malformations. However, exposure to a high dose during the first trimester was associated with an increased risk of cardiac septal closure anomalies (adjusted OR 1.81, 95% CI 1.04–3.14; 13 exposed cases) compared with no exposure. Refer to 6 and Table 7 below.

[redacted]



[redacted]



No association was found between exposure to fluconazole during pregnancy and the risk of stillbirth.

Discussion

Any maternal exposure to fluconazole during pregnancy may increase the risk of spontaneous abortion and doses higher than 150 mg during the first trimester may increase the risk of cardiac septal closure anomalies.

Bérard et al comment that, although this is consistent with animal studies, it could also be a chance finding or a result of unmeasured confounding. Therefore, this study requires replication. They found that use of antibiotics during pregnancy was independently associated with the risk of spontaneous abortion, which is consistent with the results of a previous study.

Bérard et al describe the main limitation of their study is missing information on potential confounders such as smoking, use of over-the-counter folic acid and alcohol intake.

Other potential confounders are as follows:

- sociodemographic variables at the last menstrual period
- maternal chronic comorbidities
- use of health care resources
- lifestyle variables
- pregnancy-related variables.

Comments:

This study triggered this report to the Committee. The study is consistent with the results from the Mølgaard-Nielsen et al and the Pasternak et al studies and supports including information about major congenital malformations among pregnancies exposed to high-dose fluconazole during the first trimester in the data sheet.

The women taking high doses of fluconazole indicates the infections are severe which could potentially increase the risk of spontaneous abortion (as a confounding factor).

It would have been helpful if more baseline information and characteristics were provided so we could see if potential confounders were controlled for.

Induced abortions were not included in the analysis of spontaneous abortion, as they had been in the Mølgaard-Nielsen et al study.

Fluconazole is available over-the-counter in New Zealand as a restricted medicine so there is a potential risk of drug resistance (which could increase the risk of spontaneous abortion). Also, it is not clear if high dose was a high single dose, continuous treatment or repeat treatment done shortly after first treatment (which may indicate resistance).

3.1.5 Zhang et al. 2019 [19]

In a systematic review and meta-analysis, Zhang et al aimed to evaluate the pregnancy outcomes associated with exposure to oral fluconazole during the first trimester of pregnancy.

Method

A systematic literature search was conducted to identify relevant studies published from inception until April 2019. The selection criteria included relevant English-language citations using the terms oral fluconazole and pregnancy in humans. The analysis included six studies.

Two reviewers independently abstracted data and assessed study quality.

Results

Oral fluconazole use during the first trimester of pregnancy was marginally associated with an increased risk of congenital malformations (odds ratio [OR] 1.09, 95% CI 0.99–1.2, P = 0.088; n = 6 studies), whereas in the subgroup analysis, this association existed only for high-dose users (>150 mg) (OR 1. 19, 95% CI 1.01–1.4, P = 0.039; n = 2). Exposure to fluconazole also increased the risk of heart malformations (OR 1.31, 95% CI 1.09–1.57, P = 0.003; n = 4), cardiac septal defects (OR 1.3, 95% CI 1.1–1.67, P = 0.047; n = 3), and tetralogy of Fallot (OR 3.39 95%CI 1.71–6.74, P < 0.001; n = 2) in the offspring. In addition, exposure to fluconazole was

significantly associated with an increased risk of spontaneous abortion (OR 1.99, 95% CI 1.38–2.88, P < 0.001; n = 3).

Figure 3 below shows the risk of congenital malformations in relation to oral fluconazole exposure during the first trimester of pregnancy.

[redacted]

Discussion

Zhang et al concluded oral fluconazole use during the first trimester of pregnancy appears to be associated with heart malformations and spontaneous abortion, but a causal link cannot be proven.

Zhang et all comment that current evidence suggests generally small risks of heart malformations and spontaneous abortion. However, low dose (150 mg) oral fluconazole use during the first trimester of pregnancy does not appear to increase the risk of congenital malformations. Therefore, their findings might not warrant a recommendation to prohibit oral fluconazole therapy for fungal infection during the first trimester of pregnancy.

Comments:
This review included the Bérard et al [1] and Mølgaard-Nielsen et al studies [5].

3.1.6 Liu et al. 2020 [20]

Liu et al conducted a systematic review and meta-analysis to assess the risk of adverse fetal outcomes after exposure to oral antifungal agents during pregnancy.

Method

PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to October 2018. The selection criteria included cohort studies and case–control studies investigating fetal outcomes following maternal exposure to oral antifungal agents.

Two reviewers independently assessed studies for inclusion, assessed risk of bias and extracted data. Pooled estimates were calculated for the frequency of adverse fetal outcomes.

Results

Overall, eight cohort studies and one case–control study were included.

The oral antifungal agents used during pregnancy were fluconazole and itraconazole. The data indicated that oral fluconazole exposure during pregnancy might slightly increase the risk of congenital heart defects and limb defects relative to the general population; oral itraconazole during pregnancy might increase the risk of eye defects. No difference was found between oral fluconazole/itraconazole exposure and non-exposure in the risk of other birth defects, spontaneous abortion, or stillbirth.

Five studies involving 1,163,149 pregnant women compared the risk of birth defects between pregnant women exposed to fluconazole and unexposed women. The pooled data showed no significant increase in risk (RR, 0.99; 95% CI, 0.46–2.12; I2=0). Figure 4 below shows the risk of birth defects among pregnant women using fluconazole during pregnancy versus unexposed pregnant women.

[redacted]

Four studies reported specific categories of birth defects after maternal exposure to fluconazole during pregnancy (see Table 8 below).

[redacted]

[redacted]

Congenital heart defects were the most common type with a frequency of 1.52% (95% CI, 1.28–1.81), which was higher than the value for the general population published by EUROCAT (0.77%; 95% CI, 0.76–0.78).16 The second was limb defects with a frequency of 0.62% (95% CI, 0.48–0.78), which was slightly higher than the EUROCAT value (0.56%; 95% CI, 0.53–0.58). The frequencies of other birth defects were essentially similar to the constituent ratios of malformations published by EUROCAT.

Two studies involving 27,612 pregnant women compared the frequency of spontaneous abortion between maternal exposure to fluconazole during pregnancy and non-exposure.

The pooled data showed no significant difference between the oral fluconazole group and non-exposure group in the incidence of spontaneous abortion (RR, 1.15; 95% CI, 0.32–4.1; I2=0%).

Three studies involving 41,179 pregnant women reported stillbirth as an outcome. The pooled data showed no significant difference between the oral fluconazole group and non-exposure group in the incidence of spontaneous abortion (RR, 1.09; 95% CI, 0.22–5.41; I2=0%)

Discussion

Oral fluconazole or itraconazole may not increase the risk of birth defects. Nonetheless, the risk of congenital heart defects and limb defects after fluconazole exposure and eye defects after itraconazole exposure should be cautiously investigated.

Comments:
This review included the Mølgaard-Nielsen et al study [5]. Interestingly, the Bérard et al study was not included [1].

3.1.7 Zhu et al. 2020 [21]

In a recent population based cohort study, Zhu et al examined the risk of congenital malformations associated with exposure to oral fluconazole at commonly used doses (typically 150 – 600 mg) in the first trimester of pregnancy for the treatment of vulvovaginal candidiasis.

Method

Zhu et al conducted a cohort study of pregnancies publicly insured in the United States, with data from the nationwide Medicaid Analytic eXtract from 2000 to 2014. Participants were pregnancies of women enrolled in Medicaid from three or more months before the last menstrual period to one month after delivery, and infants enrolled for three or more months after birth. The use of fluconazole and topical azoles was established by requiring one or more prescriptions during the first trimester of pregnancy.

Exclusions were:

- pregnancies with a chromosomal abnormality or exposure to a known teratogenic drug during the first trimester
- an inpatient diagnosis of a fungal infection between 90 days before the last menstrual period (baseline) and the end of the first trimester (because inpatient treatment is not captured in the Medicaid Analytic eXtract, which could lead to misclassification of exposure)
- diagnoses of oropharyngeal or esophageal candidiasis, cryptococcal meningitis, or systemic candidiasis during the baseline and first trimester (because Zhu et al were interested in the safety of fluconazole at commonly used therapeutic doses for vulvovaginal candidiasis)
- diagnoses of HIV infection, malignancy, or transplant during the baseline and first trimester (because fluconazole is used for prophylaxis in immunocompromised patients).

The main outcome measures were the risk of musculoskeletal malformations, conotruncal malformations, and oral clefts (primary outcomes), associated with exposure to oral fluconazole, diagnosed during the first 90 days after delivery.

Results

The study cohort of 1,969,954 pregnancies included 37,650 (1.9%) pregnancies exposed to oral fluconazole and 82,090 (4.2%) pregnancies exposed to topical azoles during the first trimester.

The risk of musculoskeletal malformations was 52.1 (95% confidence interval 44.8 to 59.3) per 10,000 pregnancies exposed to fluconazole versus 37.3 (33.1 to 41.4) per 10,000 pregnancies exposed to topical azoles.

The risks of conotruncal malformations were 9.6 (6.4 to 12.7) versus 8.3 (6.3 to 10.3) per 10,000 pregnancies exposed to fluconazole and topical azoles, respectively; risks of oral clefts were 9.3 (6.2 to 12.4) versus 10.6 (8.4 to 12.8) per 10,000 pregnancies, respectively.

The adjusted relative risk after fine stratification of the propensity score was 1.30 (1.09 to 1.56) for musculoskeletal malformations, 1.04 (0.70 to 1.55) for conotruncal malformations, and 0.91 (0.61 to 1.35) for oral clefts overall.

The adjusted relative risks for musculoskeletal malformations, conotruncal malformations, and oral clefts overall, based on cumulative doses of fluconazole, are shown in Table 9 below.

Table 9: Adjusted relative risks for malformations based on cumulative doses of fluconazole

	Adjusted Relative risks with cumulative dose of fluconazole		
Malformation	**150 mg**	**> 150 mg up to 450 mg**	**> 450 mg**
Musculoskeletal malformations	1.29 (1.05 to 1.58)	1.24 (0.93 to 1.66)	1.98 (1.23 to 3.17)
Conotruncal malformations	1.12 (0.71 to 1.77)	0.61 (0.26 to 1.39)	2.30 (0.93 to 5.65)
Oral clefts	0.88 (0.55 to 1.40)	1.08 (0.58 to 2.04)	0.94 (0.23 to 3.82)

Discussion

Oral fluconazole use in the first trimester was not associated with oral clefts or conotruncal malformations, but an association with musculoskeletal malformations was found corresponding to a small adjusted risk difference of about 12 incidents per 10 000 exposed pregnancies overall.

Zhu et al comment that the strengths of the study include:

- the large sample size, which allowed them to examine the risk of rare malformations that have been suggested to be associated with fluconazole and specific dose groups; use of highly specific validated algorithms to define outcomes
- use of pharmacy prescriptions to calculate exposure, avoiding recall bias
- use of an active comparator group to reduce confounding by indication and other potential unmeasured confounders, and generate evidence more applicable to clinical decision making
- careful control for a broad range of potential confounding variables.

The limitations were described as despite the large study size, the number of outcomes for the least common malformations was relatively low, particularly in the subgroup analyses. Zhu et al were not were not able to determine if the women consumed the dispensed drug. Another limitation was potential residual confounding by unmeasured or poorly measured variables (eg, obesity or overweight) that could account for the increased risk.

Comments:

This study supports previous studies that oral fluconazole used in the first trimester may increase the risk of musculoskeletal malformations. However, it contests there may be an increased risk of conotruncal malformations, oral clefts and other specific types of malformations.

3.2 International Information

3.2.1 Australian Therapeutic Goods Administration (TGA)

The TGA reviewed the issue of fluconazole and use in pregnancy in 2013 and concluded that the Australian Product Information adequately described the risk.

Table 10 below shows the information on therapeutic indications, dose and pregnancy in the Australian Product Information of one example fluconazole product.

Table 10: Information on indication, dose and pregnancy in the Australian Product Information

Name of product	Information in the Australian Product Information
Difllucan Capsule 50 mg, 100 mg 150 mg and 200 mg, Intravenous infusion 2 mg/mL, Powder for oral suspension 50 mg/5 mL [22]	**4.1 Therapeutic Indications** DIFLUCAN, given orally, is indicated for: 1. Treatment of cryptococcal meningitis in patients who are unable to tolerate amphotericin B. NOTE: Data suggest that the clinical efficacy of DIFLUCAN is lower than that of amphotericin B in the treatment of the acute phase of cryptococcal meningitis. 2. Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with AIDS. 3. Treatment of oropharyngeal and oesophageal candidiasis in AIDS and other immunosuppressed patients. 4. Secondary prophylaxis of oropharyngeal candidiasis in patients with HIV infection. 5. Serious and life-threatening Candida infections in patients who are unable to tolerate amphotericin B. NOTE: It remains to be shown that DIFLUCAN is as effective as amphotericin B in the treatment of serious and life-threatening Candida infections. Until such data are available, amphotericin B remains the drug of choice. 6. Vaginal candidiasis, when topical therapy has failed. 7. Treatment of extensive tinea corporis, extensive tinea cruris and extensive tinea pedis infections in immunocompetent patients in whom topical therapy is not a practical treatment option. Usually, topical therapy should be attempted first because oral therapy has a less favourable ratio of benefits to risks. DIFLUCAN IV is indicated for the same conditions in adults and children but should be used only when DIFLUCAN cannot be administered orally.
	4.2 Dose and method of administration DIFLUCAN is normally administered orally. If oral administration is not possible, it may be administered by intravenous infusion at a rate not exceeding 200 mg/hour. Since oral absorption is rapid and almost complete, there is no need to change the daily dosage on transferring from the intravenous to the oral route or vice versa. **Adults** Vaginal candidiasis when topical therapy has failed: DIFLUCAN 150 mg should be administered as a single oral dose. In those patients who responded to treatment, the median time to onset of symptom relief was one day (range: 0.04 – 9 days) and to complete symptom relief was two days (range: 0.5 - 20 days).
	4.6 Fertility, Pregnancy and Lactation Use in pregnancy – Pregnancy Category D Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus. Effective contraceptive measures should be considered in women of child-bearing potential and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose. There have been reports of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester. There are no adequate and well-controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400 mg/kg to 800 mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole use

Name of product	Information in the Australian Product Information
	and these events is unclear. Adverse fetal effects have been seen in animals only at high dose levels associated with maternal toxicity. These findings are not considered relevant to fluconazole used at therapeutic doses. Case reports describe a distinctive and a rare pattern of birth defects among infants whose mothers received high-dose (400 mg/kg to 800 mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include: brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.

Comments:

The Australian Product Information states that use in pregnancy should be avoided.

It also includes similar information to New Zealand Data Sheets for Diflucan Powder for oral suspension, Fluconazole and Fluconazole-Baxter. Some of the similar information is:

> There have been reports of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester.

And

> Case reports describe a distinctive and a rare pattern of birth defects among infants whose mothers received high-dose (400 mg/kg to 800 mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include: brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.

The New Zealand data sheets for Canesoral, Diflucan One, Flonazol, Flucazole, Ozole and Canesoral Duo do not include this information.

3.2.2 Health Canada

Health Canada reviewed fluconazole and use in pregnancy in 2017 [23]. Their review was conducted in part because of the Mølgaard-Nielsen et al study.

Health Canada's review in 2017 found that a link between the use of non-prescription fluconazole and the risk of unwanted effects in pregnancy could not be made based on the available information [23]. Following the voluntary update of its product safety information by the Canadian Reference Product about the potential risk of pregnancy loss and birth defects, Health Canada recommended that the Canadian product information for all other non-prescription fluconazole products be updated in the same way [23]. Women continue to be advised to avoid the use of non-prescription fluconazole products while pregnant [23]. These products are also not recommended for use by women who are trying to become pregnant [23].

Table 11 below shows the information on therapeutic indications, dose and pregnancy in the Canadian Product Monograph of one example fluconazole product.

Table 11: Information on indication, dose and pregnancy in the Canadian Product Monograph

Name of product	Information in the Canadian Product Monograph
Difllucan Tablet 50 mg, 100 mg, Intravenous infusion 2 mg/mL, Powder for oral suspension 50 mg/5 mL [24]	**Indications and Clinical Use** DIFLUCAN (fluconazole) is indicated for the treatment of: 1. Oropharyngeal and esophageal candidiasis. DIFLUCAN is also effective for the treatment of serious systemic candidal infections, including urinary tract infection, peritonitis, and pneumonia. 2. Cryptococcal meningitis. 3. Prevention of the recurrence of cryptococcal meningitis in patients with acquired immunodeficiency syndrome (AIDS).

Name of product	Information in the Canadian Product Monograph
	Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.
	Dose and administration The daily dose of DIFLUCAN and the route of administration should be based on the infecting organism, the patient's condition and the response to therapy. For Systemic Candidiasis (Candidemia and Disseminated Candidal Infections): Adults - 200 mg to 400 mg once daily for a minimum of 4 weeks, and for at least 2 weeks following resolution of symptoms
	Use in Pregnancy DIFLUCAN (fluconazole) should not be used in pregnant women except in patients with severe or potentially life-threatening fungal infections in whom DIFLUCAN (fluconazole) may be used if the anticipated benefit outweighs the possible risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the fetus. There have been reports as well as observational studies that have suggested an increased risk of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with doses as low as 150 mg of fluconazole as a single or repeated dose during the first trimester. There have been reports of multiple congenital abnormalities in infants whose mothers were treated with high-dose (400 mg/day to 800 mg/day) fluconazole therapy for coccidioidomycosis (an unapproved indication). Exposure to fluconazole began during the first trimester in all cases and continued for three months or longer. Case reports describe a distinctive and rare pattern of birth defects among infants whose mothers received high-dose (400-800 mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.

Comments:

In the Adverse Reactions section of the Canadian Product Monograph, reactions are described in patients receiving a single dose for vaginal candidiasis. This dosing detail is not in the dose and administration section.

Canada only has 50 mg and 100 mg tablets – there is no 150 mg strength. Also, it seems that their indications do not include vaginal candidiasis. It is interesting that they have this information in the adverse reactions section.

The Canadian Product Monograph states that use in pregnancy should be avoided. It also includes similar information to New Zealand Data Sheets for Diflucan Powder for oral suspension, Fluconazole and Fluconazole-Baxter.

3.2.3 Medicine and Healthcare products Regulatory Agency (MHRA), UK

The MHRA reviewed fluconazole and use in pregnancy in 2016-17 as part of an EU review, following the publication of the Mølgaard-Nielsen et al study [25]. Their review concluded that the fluconazole product information should be updated to reflect the study findings [25].

Table 12 below shows the information on therapeutic indications, dose and pregnancy in the UK Summary of Product Characteristics (SmPC) of one example fluconazole product.

Table 12: Information on indication, dose and pregnancy in the UK Summary of Product Characteristics

Name of product	Information in the UK Summary of Product Characteristics
	4.1 Therapeutic Indications

Name of product	Information in the UK Summary of Product Characteristics
Difllucan Capsule 150 mg [26]	Diflucan is indicated in adults for the treatment of: • Cryptococcal meningitis. • Coccidioidomycosis. • Invasive candidiasis. • Mucosal candidiasis including oropharyngeal, oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis. • Chronic oral atrophic candidiasis (denture sore mouth) if dental hygiene or topical treatment are insufficient. • Vaginal candidiasis, acute or recurrent; when local therapy is not appropriate. • Candidal balanitis when local therapy is not appropriate. • Dermatomycosis including tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal candida infections when systemic therapy is indicated. • Tinea unguinium (onychomycosis) when other agents are not considered appropriate.
	4.2 Posology and method of administration The dose should be based on the nature and severity of the fungal infection. Acute vaginal candidiasis – 150 mg single dose.
	4.6 Fertility, pregnancy and lactation An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester. There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400 - 800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear. Studies in animals have shown reproductive toxicity. Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary. Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

Comments:

The UK SmPC states that use in pregnancy should be avoided. It also includes similar information, although with less detail, to New Zealand Data Sheets for Diflucan Powder for oral suspension, Fluconazole and Fluconazole-Baxter.

3.2.4 United States Food and Drug Administration (US FDA)

The US FDA reviewed fluconazole and use in pregnancy in 2019 [27]. They published an update to their 2016 Drug Safety Communication which states the following [27]:

'Based on our reviews of several studies, FDA has determined that the available data do not provide conclusive evidence of an increased risk of miscarriage or stillbirth with a single 150 mg dose of oral fluconazole (Diflucan). We reviewed the 2016 study cited in this Drug Safety Communication and four additional epidemiological studies. We approved updated prescribing information in 2018 to include all available information on the use of fluconazole in women who are pregnant or breastfeeding. It adequately addresses the potential risk of harm to unborn babies. We will continue to monitor the safety of fluconazole as part of FDA's usual ongoing drug safety review and will communicate any new information to the public if it becomes available.'

Table 13 below shows the information on therapeutic indications, dose and pregnancy in the US Prescribing Information of one example fluconazole product.

Table 13: Information on indication, dose and pregnancy in the US Prescribing Information

Name of product	Information in the US Prescribing Information
Difllucan Tablet 50 mg, 100 mg 150 mg, 200 mg, Oral suspension 350 mg, 1400 mg [28]	**Indications and Usage** DIFLUCAN (fluconazole) is indicated for the treatment of: 1. Vaginal candidiasis (vaginal yeast infections due to Candida). 2. Oropharyngeal and esophageal candidiasis. In open noncomparative studies of relatively small numbers of patients, DIFLUCAN was also effective for the treatment of Candida urinary tract infections, peritonitis, and systemic Candida infections including candidemia, disseminated candidiasis, and pneumonia. 3. Cryptococcal meningitis.
	Dosage and Administration Vaginal candidiasis: The recommended dosage of DIFLUCAN for vaginal candidiasis is 150 mg as a single oral dose.
	4.6 Fertility, pregnancy and lactation Teratogenic Effects Potential for Fetal Harm: Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus. A few published case reports describe a pattern of distinct congenital anomalies in infants exposed in utero to high dose maternal fluconazole (400 to 800 mg/day) during most or all of the first trimester. These reported anomalies are similar to those seen in animal studies. Effective contraceptive measures should be considered in women of child-bearing potential who are being treated with DIFLUCAN 400 to 800 mg/day and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose. If DIFLUCAN is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the fetus. Spontaneous abortions and congenital abnormalities have been suggested as potential risks associated with 150 mg of fluconazole as a single or repeated dose in the first trimester of pregnancy based on retrospective epidemiological studies. There are no adequate and well-controlled studies of DIFLUCAN in pregnant women. (See WARNINGS: Potential for Fetal Harm.) Human Data Case reports describe a distinctive and rare pattern of birth defects among infants whose mothers received high-dose (400 to 800 mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease. These effects are similar to those seen in animal studies. Epidemiological studies suggest a potential risk of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester, but these epidemiological studies have limitations and these findings have not been confirmed in controlled clinical trials. Animal Data Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies at doses of 5 mg/kg, 10 mg/kg, and 20 mg/kg and at 5 mg/kg, 25 mg/kg, and 75 mg/kg, respectively. Maternal weight gain was impaired at all dose levels (approximately 0.25 to 4 times the 400 mg clinical dose based on body surface area [BSA] comparison), and abortions occurred at 75 mg/kg (approximately 4 times the 400 mg clinical dose based on BSA); no adverse fetal effects were observed. In several studies in which pregnant rats received fluconazole orally during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 mg/kg or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 mg/kg and 50 mg/kg and higher doses. At doses ranging from 80 to 320 mg/kg (approximately 2 to 8 times the 400 mg clinical dose based on BSA), embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate, and abnormal craniofacial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis, and parturition WARNINGS: Potential for Fetal Harm There are no adequate and well-controlled clinical trials of DIFLUCAN in pregnant women. Case reports describe a pattern of distinct congenital anomalies in infants exposed in utero to high dose maternal fluconazole (400 to

Name of product	Information in the US Prescribing Information
	800 mg/day) during most or all of the first trimester. These reported anomalies are similar to those seen in animal studies. If DIFLUCAN is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the fetus. Effective contraceptive measures should be considered in women of child-bearing potential who are being treated with DIFLUCAN 400 to 800 mg/day and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose. Epidemiological studies suggest a potential risk of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester, but these epidemiological studies have limitations and these findings have not been confirmed in controlled clinical trials.

Comments:

The US FDA's 2019 review included the Bérard et al study.

The Prescribing Information states that use in pregnancy should be avoided. It also includes similar information, although with much more detail, to New Zealand Data Sheets for Diflucan Powder for oral suspension, Fluconazole and Fluconazole-Baxter.

3.3 CARM data

The Centre for Adverse Reactions Monitoring (CARM) have received one report of a miscarriage associated with the use of fluconazole. The patient had been taking Flucazole (fluconazole) [redacted] and experienced a spontaneous abortion [redacted]. Minimal case details are available.

Comments:

This is the same case reported to the Committee at the September 2016 meeting. There have been no further reports in New Zealand.

4 DISCUSSION AND CONCLUSIONS

There is an increased risk of candida vulvovaginitis during pregnancy [Annexe 1]. Fungal infections can have harmful effects on both maternal and fetal health [16] which is why effective treatment is important. Fluconazole is a triazole medicine used to treat fungal infections [2]. Pregnant women are typically given one 150 mg oral dose of fluconazole.

This paper was triggered by the Bérard et al study [1] and reviews relevant data since the Committee's previous review (from September 2016 to the present day).

The information in the New Zealand data sheets varies. The data sheets for Canesoral, Diflucan One, Flonazol, Flucazole, Ozole and Canesoral Duo all state that the product should not be used in pregnancy, or in women of childbearing potential unless adequate contraception is employed. However, more recent research is not included in the information. Also, most of these data sheets are for products that are available as restricted medicines (ie, over-the-counter). Therefore, pharmacists should not be recommending these products for pregnant women (ie, what a pharmacist can provide is more restrictive than a doctor).

The data sheets for Diflucan Powder for oral suspension, Fluconazole and Fluconazole-Baxter state that Use in pregnancy should be avoided **except** in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus. These data sheets include more information on the 150 mg dose (ie, reports of spontaneous abortion and congenital abnormalities as a single or repeated dose in the first trimester).

The studies published in the literature and presented here are either cohort studies or systematic reviews and meta-analysis. Most concluded that more research is required on this topic.

The Bérard et al study adds to the available data on fluconazole use in pregnancy. The Bérard et al study concluded any maternal exposure to fluconazole during pregnancy may increase the risk of spontaneous abortion and doses higher than 150 mg during the first trimester may increase the risk of cardiac septal closure anomalies.

The study is consistent with the results from the Mølgaard-Nielsen et al and the Pasternak et al studies and supports including information about major congenital malformations among pregnancies exposed to high-dose fluconazole during the first trimester in the data sheet.

When considering international information and data sheets, it seems pertinent to update the New Zealand data sheets so that they contain the same information.

Suggested changes are as follows (in bold)

1. Indication: Vaginal candidiasis, **when topical therapy has failed** (as in the Australian Product information, apart from the Fluconazole-Baxter data sheet where this statement is included in the dosage section)
2. Pregnancy section (in the Canesoral, Diflucan One, Flonazol, Flucazole, Ozole and Canesoral Duo) data sheets):

   There have been reports of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester. (As in the Fluconazole data sheet.)

Other options would be to include more information in the New Zealand data sheets based on the findings of the Bérard et al study [1]. Suggested changes are as follows (in bold):

3. Pregnancy section of all New Zealand data sheets:

   Any maternal exposure to fluconazole during pregnancy may increase the risk of spontaneous abortion and doses higher than 150 mg during the first trimester may increase the risk of cardiac septal closure anomalies.

5 ADVICE SOUGHT

The Committee is asked to advise whether:

- The data sheets for fluconazole should be updated so that the information in the pregnancy section is harmonised.
- The data sheets for fluconazole should be updated so that they include information in the pregnancy section on effects of low dose treatment including the results of the Bérard et al study [1].
- This topic requires further communication other that MARC's Remarks in *Prescriber Update*.

6 ANNEXES

1. Medsafe. 2016. *Fluconazole and its use in pregnancy*. Wellington: Medsafe.
2. Medsafe. 2017. *Report on Standing Agenda Items - Oral fluconazole and the risk of spontaneous abortion and stillbirth*. Wellington: Medsafe.
3. FDA. 2017. *FDA Office of Surveillance and Epidemiology – Integrated Review: The association between use of oral fluconazole during pregnancy and the outcomes of spontaneous abortion and stillbirth*. USA: FDA. [**CONFIDENTIAL**]

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