Cohort Study
Potential PURL Review Form
PURL Jam Version
Version #12 Sept 20, 2010

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

1. Citation	Mølgaard-Nielsen D, Svanström H, Melbye M, Hviid A, Pasternak B. Association Between Use of Oral Fluconazole During Pregnancy and Risk of Spontaneous Abortion and Stillbirth. JAMA. 2016 Jan 5;315(1):58-67.
2. Hypertext link to PDF of full article	http://www.ncbi.nlm.nih.gov/pubmed/26746458
3. First date published study available to readers	01/05/2016
4. PubMed ID	26746458
5. Nominated By	Sarah-Anne Schumann Other:
6. Institutional Affiliation of Nominator	Other Other:
7. Date Nominated	1/9/16
8. Identified Through	Other Other:
9. PURLS Editor Reviewing Nominated Potential PURL	Kate Rowland
10. Nomination Decision Date	1/20/16
11. Potential PURL Review Form (PPRF) Type	Cohort Study
12. Other comments, materials or discussion	
13. Assigned Potential PURL Reviewer	Anne Mounsey
14. Reviewer Affiliation	Other Other: UNC
15. Date Review Due	02/10/2016
16. Abstract	IMPORTANCE: Vaginal candidiasis is common during pregnancy. Although intravaginal formulations of topical azole antifungals are first-line treatment for pregnant women, oral fluconazole is often used despite limited safety information. OBJECTIVE: To study the association between oral fluconazole exposure during pregnancy and the risk of spontaneous abortion and stillbirth. DESIGN, SETTING, AND PARTICIPANTS: Nationwide register-based cohort study in Denmark, 1997-2013. From a cohort of 1,405,663 pregnancies, oral fluconazole-exposed pregnancies were compared with up to 4 unexposed pregnancies matched on propensity score, maternal age, calendar year, and gestational age (based on gestational age at first day of treatment with eligible controls surviving through this date). To test for confounding by indication, pregnancies exposed to intravaginal formulations of topical azoles were used as an additional comparator group. EXPOSURES:

Filled prescriptions for oral fluconazole were obtained from the National Prescription Register.
MAIN OUTCOMES AND MEASURES:
Hazard ratios (HRs) for spontaneous abortion and stillbirth, estimated using proportional hazards regression.
RESULTS:
Among 3315 women exposed to oral fluconazole from 7 through 22 weeks' gestation, 147 experienced a spontaneous abortion, compared with 563 among 13,246 unexposed matched women. There was a significantly increased risk of spontaneous abortion associated with fluconazoleexposure (HR, 1.48; 95% CI, 1.23-1.77). Among 5382 women exposed to fluconazole from gestational week 7 to birth, 21 experienced a stillbirth, compared with 77 among 21,506 unexposed matched women. There was no significant association between fluconazole exposure and stillbirth (HR, 1.32 [95% CI, 0.82-2.14]). Using topical azole exposure as the comparison, 130 of 2823 women exposed to fluconazole vs 118 of 2823 exposed to topical azoles had a spontaneous abortion (HR, 1.62 [95% CI, 1.26-2.07]); 20 of 4301 women exposed to fluconazole vs 22 of 4301 exposed to topical azoles had a stillbirth (HR, 1.18 [95% CI, 0.64-2.16]).
CONCLUSIONS AND RELEVANCE:
In this nationwide cohort study in Denmark, use of oral fluconazole in pregnancy was associated with a statistically significant increased risk of spontaneous abortion compared with risk among unexposed women and women with topical azole exposure in pregnancy. Until more data on the association are available, cautious prescribing of fluconazole in pregnancy may be advisable. Although the riskof stillbirth was not significantly increased, this outcome should be investigated further.

17. Pending PURL Review Date

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]

1 The study addresses an appropriate and clearly focused question.

☒ Well covered ☐ Not addressed
☐ Adequately addressed ☐ Not reported
☐ Poorly addressed ☐ Not applicable
Comments: Clear primary outcomes of spontaneous abortion and stillbirth when compared to fluconazole use in pregnancy.

2 The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.

☒ Well covered ☐ Not addressed
☐ Adequately addressed ☐ Not reported
☐ Poorly addressed ☐ Not applicable
Comments: Matched each exposed case to 4 unexposed pregnancies matched on propensity score, maternal age, calendar year, and gestational age.

3 The study indicates how many of the people asked to take part did so, in each of the groups being studied

☒ Well covered ☐ Not addressed
☐ Adequately addressed ☐ Not reported
☐ Poorly addressed ☐ Not applicable
Comments: Figure 1.

4 The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.

☐ Well covered ☐ Not addressed
☐ Adequately addressed ☐ Not reported
☐ Poorly addressed ☒ Not applicable
Comments: This was a cohort study; thus the review looked at historical cases and the outcome measures of spontaneous abortion and stillbirth were used in the matched groups.

5 What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?

For spontaneous abortion: 4/3,319 (0.1%). For stillbirth: 5/5,387 (<0.1%). The matched control pregnancies were completed based on criteria as stated above. For every exposed pregnancy, 4 unexposed pregancnies were matched.

6 Comparison is made between full participants and those lost to follow up, by exposure status.

☐ Well covered ☐ Not addressed
☐ Adequately addressed ☐ Not reported
☐ Poorly addressed ☒ Not applicable
Comments: Those excluded from the study were excluded due to not having unexposed matches.

7 The outcomes are clearly defined.

☒ Well covered ☐ Not addressed
☐ Adequately addressed ☐ Not reported
☐ Poorly addressed ☐ Not applicable
Comments: Analysis included for both spontaneous aborition and stillbirth were measured and clearly defined.

8 The assessment of outcome is made blind to exposure status

☐ Well covered ☐ Not addressed
☐ Adequately addressed ☐ Not reported
☐ Poorly addressed ☒ Not applicable
Comments: Exposure status was needed in order to find propensity scored matches.

9 Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.

☐ Well covered ☐ Not addressed
☐ Adequately addressed ☐ Not reported
☐ Poorly addressed ☒ Not applicable
Comments: Given the retrospective nature of this study, exposed pregnancies needed to be compared with unexposed matches.

10 What are the key findings of the study?

Spontaneous abortions occurred in 147/3,315 fluconazole exposed pregnancies compared to 563/13,246 unexposed, matched pregnancies ([HR]1.48; 95%CI, 1.23-1.77). When compared to topical azole use, spontaneous abortions occurred in 130/2,823 pregnancies vs 118/2823 pregnancies respectively ([HR] 1.62; 95%CI 1.26-2.07). Stillbirths occurred in 21/5,382 fluconazole exposed pregnancies as compared to 7/21,506 unexposed, matched pregnancies ([HR] 1.32; 95%CI, 0.82-2.14). If exposed to higher doses of fluconazole (300mg vs 150mg), the hazard ratios for stillbirth were 0.99 (95%CI, 0.56-1.74) and 4.10 (95%CI, 1.89-8.90) respectively.

11 How was the study funded? Any conflicts of interest? Any reason to believe that the results may be influenced by other interests?

Funded by Danish Medical Research Council. The Danish Medical Council had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preperation, review, or approval of the manuscript; and decision to submit the manuscript for publication. No reason to think that there was any conflict of interest from the authors. No reason to believe the results were influenced.

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]

Citation Instructions

For UpTo Date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS as editor & current year as publication year.

EXAMPLE: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert dated modified if given.} Accessed February 12, 2009. {whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at: http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009.{search date}

1. DynaMed excerpts

2. DynaMed citation/access date

Title. Author. In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated: . Accessed

3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

4. UpToDate excerpts

Treatment of pregnant women is primarily indicated for relief of symptoms. Vaginal candidiasis is not associated with adverse pregnancy outcomes. We suggest application of a topical imidazole (clotrimazole or miconazole) vaginally for seven days. There is less information about the pregnancy safety profile of terconazole, a triazole, than for imidazoles. Vaginal nystatin is another option. As discussed above, a pessary is available in some parts of the world. One or two pessaries of 100,000 units nystatin are inserted into the vagina nightly for 14 days . Alternatively, a suppository can be prepared by a compounding pharmacy. Potential side effects include burning, redness, and irritation.

During pregnancy, we avoid oral azole therapy, particularly during the first trimester, because its impact on miscarriage risk is unclear and high doses appear to increase the risk of birth defects. Since topical therapy is an effective alternative to oral dosing, we prefer vaginal treatment until more data are available to support the safety of low dose oral treatment.

Miscarriage: A cohort study of over 3300 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. Stillbirth risk did not differ among the groups, although stillbirth was a relatively rare outcome. This study contrasts with two prior cohort studies totaling just over 1500 women that did not report an association between oral fluconazole and miscarriage. As the larger study may have had greater power to detect an increase in miscarriage risk, we prefer to avoid oral azole therapy until more data are available.

Birth defects: Case reports have described a pattern of birth defects (abnormalities of cranium, face, bones, and heart) after first trimester exposure to high dose therapy (400 to 800 mg/day). The magnitude of the teratogenic risk is unknown. First trimester use of a single, low dose of fluconazole 150 mg to treat vaginal yeast infection has not been associated with an increased risk of birth defects overall in one large epidemiologic study (7352 pregnancies) and in several smaller epidemiologic studies. In the large nationwide cohort study, there was no overall risk of embryopathy associated with exposure to cumulative fluconazole doses of 150, 300, or 350 to 6000 mg during the first trimester nor with exposure to oral itraconazole or ketoconazole. Although these data are reassuring for women who took low dose fluconazole before realizing that they were pregnant, an increased risk of specific anomalies cannot be definitively excluded

5. UpToDate citation/access date

Always use Basow DS as editor & current year as publication year.
Title. Candida vulvovaginitis Author. Sobel In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: January 11, 2016. AccessedFebruary 12, 2016

6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

Oral azole therapy in pregancy should be avoided and first-line therapy should be topical azole therapy.

7. PEPID PCP excerpts www.pepidonline.com

Treatment should be with clotrimazole or miconazole: 200 mg intravaginally x 7 nights, and oral antifungals are contraindicated in treatment for vulvovaginal candidiasis.

username: fpinauthor
pw: pepidpcp

8. PEPID citation/access data	Author. French LTitle. Vulvovaginal Candidiasis In: PEPID [database online]. Available at: http://www.pepidonline.com. Last updated: September 2012. AccessedFebruary 12, 2016
9. PEPID content updating	1. Do you recommend that PEPID get updated on this topic? ☐ Yes, there is important evidence or recommendations that are missing ☒ No, this topic is current, accurate and up to date. If yes, which PEPID Topic, Title(s): 2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (EB) that should be updated on the basis of the review? ☐ Yes, there is important evidence or recommendations that are missing ☒ No, this topic is current, accurate and up to date. If yes, which Evidence Based Inquiry(HelpDesk Answer or Clinical Inquiry), Title(s):
10. Other excerpts (USPSTF; other guidelines; etc.)	
11. Citations for other excerpts	
12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)	

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer; Revised by the Pending PURL Reviewer as needed]

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity?	Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly) ☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7
2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?	
3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians?	Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly) ☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7
4. If 4.3 was coded as 4, 5, 6, or 7, lease provide an explanation.	
5. Practice changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice?	Give one number on a scale of 1 to 7 (1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice) ☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

Many primary care physicians take care of prenatal patients, and this recent analysis of a relatively common medication could impact and change treatment recommendations and counseling of patients. Many physisicans may opt for oral azole therapy given ease of treatment and compliance; however, this has associations with adverse outcomes.

7. Applicability to a Family Medical Care Setting:
Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention?

Give one number on a scale of 1 to 7
(1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

8. If you coded 4.7 as a 4, 5, 6 or 7, please explain. .

9. Immediacy of Implementation:
Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market?

Give one number on a scale of 1 to 7
(1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.

11. Clinical meaningful outcomes or patient oriented outcomes:
Are the outcomes measured in the study clinically meaningful or patient oriented?

Give one number on a scale of 1 to 7
(1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

12. If you coded 4.11 as a 4, 5, 6, or 7, please explain why.

13. In your opinion, is this a Pending PURL?
Criteria for a Pending PURL:

- Valid: Strong internal scientific validity; the findings appears to be true.
- Relevant: Relevant to the practice of family medicine
- Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in

Give one number on a scale of 1 to 7
(1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

medical care settings and seems different than current practice. • Applicability in medical setting: • Immediacy of implementation	
14. Comments on your response in 4.13	This recent study and evaluation seems to provide the most up-to-date treatment options for a relatively common diagnosis in pregnancy.

SECTION 4.1: Diving for PURLs
[optional for the potential PURL reviewer -if you wish to be the author on the summary]

1. Study Summary- Please summarize the study in 5-7 sentences	This cohort study was conducted to determine the association between oral fluconazole exposure during pregnancy and the risk of spontaneous abortion and stillbirth. Using the Medical Birth Register in Denmark, oral fluconazole-exposed pregnancies were compared with up to 4 unexposed pregnancies (matched on propensity score, maternal age, calendar year, and gestational age) and to pregnancies exposed to intravaginal formulations of topical azoles. From the cohort of 1,405,663 pregnancies 3,315 were exposed to fluconazole between 7 weeks and 22 weeks gestation. Primary outcomes included hazard ratios for spontaneous abortion (loss before 22 weeks) and stillbirth (loss after 23 weeks). .and Spontaneous abortions occurred in 147/3,315 fluconazole exposed pregnancies compared to 563/13,246 unexposed, matched pregnancies ([HR]1.48; 95%CI, 1.23-1.77). Compared to topical azole use, spontaneous abortions occurred in 130/2,823 pregnancies vs 118/2,823 pregnancies respectively ([HR] 1.62; 95%CI 1.26-2.07). Stillbirths occurred in 21/5,382 fluconazole exposed pregnancies as compared to 7/21,506 unexposed, matched pregnancies ([HR] 1.32; 95%CI, 0.82-2.14). If exposed to higher doses of fluconazole (150mg vs 300mg), the hazard ratios for stillbirth were 0.99 and 4.10 p=.002 respectively.
2. Criteria- note yes or no for those which this study meets	RELEVENT - yes VALID - yes CHANGE IN PRACTICE- yes MEDICAL CARE SETTING - yes IMMEDIATELY APPLICABLE - yes CLINICALLY MEANINGFUL - yes
3. Bottom Line- one –two sentences noting the bottom line recommendation	Use of oral fluconazole compared to topical imidazoles in pregnancy is associated with a higher rate of spontaneous abortion.
4. Title Proposal	Treating yeast infections in pregnancy? Think twice about fluconazole

SECTION 5: Editorial Decisions
[to be completed by the FPIN PURLs Editor or Deputy Editor]

1. FPIN PURLs editorial decision (select one)	☐1 Pending PURL Review—Schedule for Review ☐ 2 Drop ☐ 3 Pending PURL
3. Follow up issues for Pending PURL Reviewer	
3. FPIN PURLS Editor making decision	☐1 Bernard Ewigman ☐2 John Hickner ☐3 Sarah-Anne Schumann ☐4 Kate Rowland
4. Date of decision	

5. Brief summary of decision

SECTION 6: Survey Questions for SERMO, PURLs Instant Polls and Other Surveys [To be completed by the PURLs Survey Coordinator and PURLs Editor]

1. Current Practice Question for Surveys

2. Barriers to Implementation Question for Surveys

3. Likelihood of Change Question for Surveys

4. Other Questions for Surveys

SECTION 7: Variables for Secondary Database Analyses

1. Population: Age, gender, race, ethnicity

2. Diagnoses

3. Drugs or procedures

SECTION 8: Pending PURL Review Assignment [to be completed by PURLs Project Manager

1. Person Assigned for Pending PURL Review

2. Date Pending PURL Review is due

SECTION 9: Pending PURL Review [to be completed by the Pending PURL Reviewer]

1. Did you address the follow up issues identified at the PURL Jam (Section 5.2). Add comments as needed.

☐ Yes
☐ No
☐ Not applicable
Comments:

2. Did you review the Sermo poll & Instant Poll results (if available)? Add comments as needed.

☐ Yes
☐ No
☐ Not applicable
Comments:

3. Did you modify Sections 2, 3, or 4? Add comments as needed.

☐ Yes
☐ No
☐ Not applicable
Comments:

SECTION 10: PURL Authoring Template
[to be completed by the assigned PURL Author]

Author Citation Information (Name, Degrees, Affiliation)

1. Practice Changer

2. Illustrative Case

3. Background/
Clinical Context/Introduction/Current Practice/

4. Study Summary

5. What's New

6. Caveats

7. Challenges to Implementation

8. Acknowledgment Sentence

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If using UHC data:
We acknowledge Sofia Medvedev of University HealthSystem Consortium (UHC) in Oak Brook, IL for analysis of the National Ambulatory Medical Care Survey data.

9. References