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**VIGILANCE ON USE OF DRUGS, HERBAL PRODUCTS AND FOOD SUPPLEMENTS
DURING PREGNANCY: FOCUS ON FOSFOMYCIN.**

Running Title: Vigilance on use of Fosfomycin during pregnancy

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Abstract

Urinary tract infection (UTI) is defined as a common bacterial infection that can lead to significant morbidity such as stricture, fistula, abscess formation, bacteraemia, sepsis, pyelonephritis and kidney dysfunction with a mortality rates reported of 1% in men and 3% in women because of development of pyelonephritis. UTIs are more common in women and the 33% of them, requires antimicrobials treatment for at least 1 episode by the age of 24 years. UTIs are the most common infections observed during pregnancy and up to 30% of mothers with not treated asymptomatic bacteriuria may develop acute pyelonephritis which consequently can be associated to adverse maternal and fetal outcomes. All bacteriuria in pregnancy should be treated with antimicrobial treatments being safe for both the mother and the fetus. Approximately one every four women receives prescription of antibiotic treatment during pregnancy, nearly 80% of all the prescription medications during gestation. Use of fosfomycin to treat cystitis in pregnancy generally considered safe and effective. Even though use on antibiotics for urinary tract infections is considered generally safe for the fetus and mothers, this opinion is not based on specific studies monitoring the relationship of between urinary infections, consumption of antibiotics and pregnancy outcomes. On this basis we decided to analyze data from the database of our multicenter study PHYTOVIGGEST, reporting data from 5362 pregnancies, focusing on use of fosfomycin. Principal outcomes of pregnancy in women treated with fosfomycin were taken in consideration. Women who have been treated with urinary antibiotics during the pregnancy were 183. With respect to the total number of pregnancies of our sample, these women represented the percentage of 3.49 % (187/5360). Analysis of different outcomes of pregnancy such as gestational age, neonatal weight and neonatal Apgar index did not show any significant difference. At the same time analysis of data of pregnancy complicancies (such as, urgent cesarean delivery, use of general anesthesia, need to induce labour) did not show any difference in women taking fosfomycin during pregnancy and those not taking it. Our data, based on a large number of pregnancies, confirm the safety use of fosfomycin use in pregnancy.

Keywords: Fosfomycin, fosfomycin in pregnancy, urinary infection in pregnancy.

JUST ACCEPTED

Introduction

Urinary tract infection (UTI) is defined as a common bacterial infection that can lead to significant morbidity such as stricture, fistula, abscess formation, bacteraemia, sepsis, pyelonephritis and kidney dysfunction with a mortality rates reported of 1% in men and 3% in women because of development of pyelonephritis [1]. UTIs are more common in women and the 33% of them, requires antimicrobials treatment for at least 1 episode by the age of 24 years [2-4]. Among the infections observed during pregnancy, UTI are the most common [5]. Bacteriuria in pregnancy is represented

as asymptomatic bacteriuria (from 2% to 10% of pregnancies), infections of the lower urinary tract (cystitis 2%), or infections of the upper urinary tract (pyelonephritis). It has been observed that up to 30% of mothers with not treated asymptomatic bacteriuria, may develop acute pyelonephritis [6]. Developing pyelonephritis in pregnancy, is associated to adverse maternal and fetal outcomes. All bacteriuria in pregnancy should be treated, and antimicrobial treatments in pregnancy should be safe for both the mother and the fetus [7]. Approximately one every four women will be prescribed an antibiotic treatment during pregnancy, nearly 80% of prescription medications. Untreated urinary tract infections such as UTIs or sexually-transmitted infections (STIs) are associated with significant fetal risk such as spontaneous abortion, prematurity, and low birth weight [8,9]. Antibiotic exposure during pregnancy has been associated with both short-term (e.g., congenital abnormalities) and long-term effects (e.g., changes in gut microbiome, asthma, atopic dermatitis) in the newborn. However, it is estimated that only for 10% of medications data related to safe and effective use in pregnancy are available. Antibiotics such as beta-lactams, vancomycin, nitrofurantoin, metronidazole, clindamycin, and fosfomycin are generally considered safe and effective in pregnancy. The antibiotics fluoroquinolones and tetracyclines are generally avoided in pregnancy [10]. Even though use of antibiotics for urinary tract infections is considered generally safe for the fetus and mother, this opinion is not based on specific studies monitoring the relationship about urinary infections, consumption of antibiotics and pregnancy outcomes. On this basis we decided to analyze data from the database of the multicenter study PHYTOVIGGEST related to urinary antibiotics use in pregnancy and to focus on fosfomycin, because it was the antibiotic used by women of our sample for UTIs. In the present article principal outcomes of pregnancy in women using fosfomycin were taken in consideration.

Fosfomycin is in use since the early 1970s, initially as an intravenous preparation of the disodium salt and later as an oral formulation of fosfomycin trometamol. Today, its primary use is as an oral treatment for UTIs [11-12] as fosfomycin trometamol for treatment by single dose oral therapy of uncomplicated UTIs (acute cystitis) in women caused by *Escherichia coli* and *Enterococcus faecalis*. Because of the superficial nature of cystitis and the lack of advantages with longer treatments, single dose therapy has gained wide acceptance as the preferred method of treatment. Various clinical trials have indicated that fosfomycin trometamol is a suitable antibiotic for lower UTI, being relatively free of side effects [13], however, no evidence was purchased about the safety of fosfomycin treatment of UTIs in pregnancy. On this basis we investigated on the possible effects of fosfomycin taken for treatment of UTIs on principal outcomes in pregnancy.

Methods

Study design

An Italian multicenter observational study was conducted for a period of two years (2014-2015) in the maternity units of general hospitals. The study named PHYTO.VIG.GEST (Phytovigilance on gestation) since in origin designed for the investigation on phytotherapeutical products in pregnancy, was successively dedicated to the collection of data regarding all health products (food supplements, herbal supplements, medicinal products) used by pregnant women, including synthetic drugs. The study was sponsored by the Italian Medicines Agency and Assessorato alla Salute della Regione Siciliana (Italy). Hospital centers of three Italian regions (Emilia-Romagna, Sicily, Tuscany), were involved: 9 centers of gynecology and obstetrics located in hospitals of the Sicily region, 4 centers in Emilia-Romagna region and one center in the Tuscany region. The study was based on collection of data through the interview and clinical records of 5362 pregnant women about the consumption of health products including synthetic drugs during pregnancy and pregnancy outcomes. The study was approved by the local ethics committee (protocol number E 42/12 of the Ethic Committee of Azienda Ospedaliera Universitaria Policlinico "G. Martino", Messina (Italy).

Aims and design of the study were explained in details to all the women recruited before to obtain their written informed consent. Data were collected via a pre-structured questionnaire through a face-to-face interview carried out by five specially trained gynecologists and directly from clinical records. Interviews were performed 1-2 days after childbirth, just before discharge. Women unable to comprehend Italian language were excluded. Each interview lasted 25–30 min. The questionnaire consisted of 72 items, divided into five sections. Drugs and dietary and herbal supplement intake was investigated, including details such as brand name, dose, formulation, frequency, and timing of administration. All products were included following classification using the Italian Pharmaceutical Reference Book as possible. Moreover, data on pregnancy outcome (gestational age and newborn birthweight, sex, Apgar score, etc.) were collected from clinical records together with other information collected about the pregnancy and the delivery. Data on women's age, gestation, parity (nullipara or multipara), any previous pregnancies, labour onset (spontaneous or induced), type of delivery (spontaneous, operative vaginal, caesarean section), perineal outcome (intact perineum, labial or vaginal laceration only, first, second, third or fourth degree, or episiotomy) were collected. Data obtained from interviews were stored using an electronic database.

Results

Regarding the use and intake of health products and drugs of the 5362 mothers interviewed, 4569 (85.21%) reported that they had taken one or more health products including synthetic drugs at least once during their pregnancy. This percentage included 2143 (39.96%) women who took drugs and food supplements, a percentage of women that took only drugs 1769 (33%) and a percentage of women that took only food supplements 657 (12.25%). The questionnaire revealed that 793 (14.8%) women took no dietary supplements or synthetic drugs during their pregnancy.

Sociodemographic features of total sample and women assuming fosfomycin during pregnancy are showed in Table 1. Women who have been treated with antibiotics for UTIs during the pregnancy were 187. With respect to the total number of pregnancies of our sample, these women represented the percentage of 3.49 %. The only drug used was fosfomycin, the same antibiotic was used by all the pregnant women for UTIs. Analysis of different outcomes of pregnancy such as gestational age, neonatal weight or Apgar index did not show any significant difference. Statistical significant difference was observed about the number of frequency of urgent cesarean delivery performed in pregnant women of our sample. Urgent caesarean section is generally performed as quickly as possible in consequence of following cases: immediate threat to life of woman or fetus, not immediately life-threatening maternal or fetal compromise, needing early delivery but no maternal or fetal compromise and at a time to suit the woman and maternity team [14,15].

In our sample the rate of caesarean section was 29.9 %, while urgent caesarean section was performed in 684 women, 12.7% of the total sample. A similar percentage (12.8%) was observed in pregnant women taking fosfomycin subjected to urgent cesarean delivery (24/187) (Table 2). The largest part of urgent caesarean section was due to fetal compromise reported in the most of clinical records as generic fetal suffering. No serious adverse reaction was reported by women using fosfomycin during pregnancy.

Discussion

Current evidence and epidemiological data indicate that women take at least one prescription drug during pregnancy in a range between 65-94 %. Nearly 70% of women generally take a medication in the first trimester during organogenesis [15,16]. Antibiotics result to be about the 80% of all

prescription medications and approximately 20–25% of women receive an antibiotic prescription during pregnancy [5,17,18]. The most common infections encountered during pregnancy are UTIs (including pyelonephritis), sexually transmitted infections (STIs), and upper respiratory tract infections. Asymptomatic bacteriuria occurs in 2% to 10% of pregnant women and up to 30% of women will develop acute pyelonephritis if not treated. UTIs or STIs are considered to be associated with significant fetal risk including spontaneous abortion, preterm birth and low birth weight [6,8,9,19].

Non pharmacological approach represented by intake of cranberry-based products or other natural products is commonly adopted by women for prevention of UTIs [20], however, in our sample medicinal plants were poorly used during pregnancy and no pregnant woman used cranberry to treat cystitis.

Fosfomycin is a low molecular weight phosphonic acid derivative bactericidal antibiotic whose action is directed both to gram-negative and gram-positive bacteria. It acts by inhibiting phosphoenolpyruvate transferase, an enzyme involved in the initial stage of peptidoglycan synthesis [21]. This bactericidal activity occurs at an earlier step than the action of β -lactams or glycopeptides [22]. The lack of structural relationship to other known antibiotics and the peculiar mechanism of action make cross-resistance to fosfomycin uncommon. In addition, fosfomycin decreases bacterial adhesion to uroepithelial cells, contributing to its effectiveness in the treatment of UTIs [23].

Safety profile of fosfomycin is characterized by good tolerability in women for the treatment of UTIs.

Analysis of our data, collected by a large sample of Italian pregnant women in a multicenter study, shows that no outcome of pregnancies is negatively affected by intake of fosfomycin, thus indicating that this antibiotic can be safely used also when UTIs are occurring during pregnancy.

Disclosure of interest.

The authors report no conflicts of interest.

Founding

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Table 1. Sociodemographic features of total sample and women assuming fosftomycin during pregnancy.

	Pregnant women treated with fosfomycin (n=187)	Total sample of pregnant women (n=5362)
Age	33.7 ± 5	34.0 ± 5
Parity		
Nulliparous	73 (39.1%)	2140 (39.9%)
Multiparous	114 (60.9%)	3222 (60.1%)
Education		
Less than High School	36 (19.25%)	1072 (19.9%)
High School	75 (40.1%)	2252 (42%)
Graduate/post graduate	76 (40.64%)	2038 (38%)
Smoking habits		
Non Smokers	150 (80.2%)	4343 (81%)
Smokers	37 (19.8%)	1019 (19%)
Smokers keeping smoking behaviour during pregnancy	12 (32.43%)	347 (34.1%)

Table 2. Pregnancy outcomes of total sample and women assuming fosfomycin during pregnancy.

Outcomes of pregnancy	Pregnant women treated with fosfomycin (n=187)	Total sample of pregnant women (n=5362)
Average neonatal birth weight (kg)	3.208±562	3.200±609
Average gestational age (days)	276±13	272.2±21
Threatened miscarriage	18 (11.25%)	678 (12.6%)
Spontaneous delivery (%)	164 (87.7%)	4698 (87.6%)
Urgent cesarean sections (%)	23 (12.3)%	664 (12.4%)