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Safety of Canephron® N for the treatment of urinary tract infections in the first trimester of pregnancy

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Abstract

Background: Urinary tract infections (UTIs) are among the most commonly occurring bacterial infections, particularly in pregnant women. Canephron® N (Bionorica, Germany) is a phytotherapeutic medicinal product that has pleiotrophic effects on the urinary system, including diuretic, spasmolytic, anti-inflammatory, antimicrobial and nephroprotective effects. The purpose of this retrospective study was to assess the safety of Canephron® N when used in the first trimester of pregnancy for the treatment of UTIs.

Methods: This was a retrospective, multi-center study that evaluated the effects of Canephron® N in 384 women who had used the herbal drug during the first trimester of pregnancy (between 2004 and 2009), and whose pregnancies ended in live births. The endpoints assessed in this study were the presence of congenital defects in the newborn.

Results: There were no significant differences in the incidence of congenital malformations in newborns whose mothers had taken Canephron® N in the first trimester of pregnancy, compared to the national statistical data for the Kiev population during the same period. The majority of newborns (>65 %) whose mothers had received Canephron® N during the first trimester of pregnancy had Apgar scores of 8 or above, indicating an excellent safety status.

Conclusions: The results from our study indicate that the use of Canephron® N during the first trimester of pregnancy was not associated with any teratogenic, embryotoxic or fetotoxic effects on the fetus.

Keywords: Canephron® N; Cystitis; Urinary tract infection; Pregnancy; First trimester; Safety; Prevention

Background

Urinary tract infections (UTIs) are among the most commonly occurring bacterial infections, particularly in pregnant women. Pregnancy is associated with specific physiological, structural and functional alterations in the urinary tract which facilitate bacterial growth and ascending infections [1]. Between 5 and 10 % of women experience a UTI during pregnancy, usually asymptomatic bacteriuria, acute cystitis and pyelonephritis [2]. The majority of UTIs are caused by bacterial species of enteric origin, namely *Escherichia coli*, which accounts for 70–85 % of cases [3], as well as *Klebsiella pneumoniae*, *Staphylococcus aureus* and the Group B streptococci [4–6]. If not properly treated, these infections can have serious consequences for the mother and fetus increasing the risk of pre-eclampsia, premature birth and low neonatal birth weight [1].

Antibiotics are frequently prescribed for the treatment of UTIs in pregnant women. Because of altered drug pharmacokinetics during pregnancy and the possibility of drug transfer across the placental barrier, the use of antibiotics during pregnancy should be approached with caution [7, 8]. Due to their potential teratogenic effects, certain antibiotics are unsuitable for use in pregnant women [9]. Antimicrobial agents considered safe in pregnancy are of the β lactam class including the penicillins, cephalosporins and fosfomycin trometamol [6, 10].

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Nevertheless, the use of antibiotics in general is associated with adverse events, including allergic reactions, gastrointestinal side-effects, and cardiac arrhythmia [11, 12], and these should be administered with utmost caution during pregnancy. In addition, the number of antimicrobial agents safe for use during pregnancy is further limited by the emergence of drug resistance amongst various bacterial species [6, 13]. Thus, there is a need for alternative treatment modalities for addressing UTIs that occur during pregnancy.

Canephron® N (Bionorica, Germany) is a phytotherapeutic medicinal product that consists of a fixed combination of centaury herb (*Centaurium* sp.), lovage root (*Levisticum officinale* Koch) and rosemary leaves (*Rosmarinus officinalis* L.). The plant components present in the drug has been shown to have pleiotrophic effects on the urinary system, including diuretic [14, 15], spasmolytic [16, 17], anti-inflammatory [18–20], antimicrobial [21–24] and nephroprotective effects [25]. Clinical data has revealed a therapeutic benefit in patients with UTIs, nephrolithiasis or urolithiasis [26, 27]. Canephron® N has been available on the European market for over 40 years and is registered as a traditional herbal medicine but is currently not licensed for use during pregnancy and lactation. Outside of the European Union (EU), however, it is one of the most frequently-prescribed phytotherapeutic medicines in pregnant women for the treatment of upper and lower UTIs. Although clinical studies in pregnant women have demonstrated Canephron® N to be safe and well tolerated, thus far no studies have focused specifically on its safety aspects when used during the first trimester of pregnancy.

The purpose of this retrospective study was to assess the safety of Canephron® N when used in the first trimester of pregnancy for the treatment of UTIs. The main endpoint of this study was the presence of congenital defects in the newborn.

Methods

Study design

This was a retrospective, multi-center study that evaluated the effects of Canephron® N in 384 women who had used the herbal drug during the first trimester of pregnancy, and whose pregnancies ended in live births. All the women were monitored up to the end of pregnancy at the Isida Obstetrics and Gynecology Clinic, Institute of Pediatrics, Obstetrics and Gynecology of the Ukrainian Academy of Medical Sciences, from 2004 to 2009. All patients provided written informed consent regarding the use of their data for study purposes. The data in national registry is only provided as frequency (in % of malformation) in working papers. Therefore exact number of control patients cannot be provided. Nonethless, the data is verified and reported in national registry.

Study population and Canephron® N treatment

Since an individual's parity status is known to have a substantial impact on the outcome of a pregnancy [28], and the number of multiparous cases was not sufficient for a separate study, we included the primiparous (singleton) and multiparous cases in our evaluation. All participants had to have taken Canephron® N for at least 14 days during the first trimester of pregnancy, for the treatment of UTIs. The Canephron® N daily dosage used was 6 tablets or 150 drops. In the majority of cases, the women took Canephron® N before becoming aware of their pregnancies. The main exclusion criteria were the presence of hereditary diseases, multiple pregnancies, and chronic exposure to known toxic or genotoxic substances.

Endpoints

The main endpoint of this study was the presence of congenital defects in the newborn. Furthermore, intrauterine developmental defects were assessed according to the World Health Organization (WHO) International Classification of Diseases (ICD)-10 classification [29]. Specifically, the presence of congenital malformations of the genital organs, congenital malformations of the urinary system, congenital malformations and deformities of the musculoskeletal system and other congenital malformations were evaluated [29]. The results obtained were compared against the national statistical data for Kiev during the same 5-year period from primiparous pregnancies in women who had not used Canephron® N. The status of the newborn infant was evaluated using the 10-point Apgar scoring system one minute after birth [30].

In case there was a pathological pregnancy and/or developmental disorder in the newborn, further evaluations were performed in order to assess the relationship between the malformations and Canephron N® intake (including the duration of drug administration, administration of other medications, the mother's age, presence of defects in the family, laboratory data, exposure to other known risk factors such as smoking or some professional hazards). The presence of congenital malformations in the infant was evaluated alongside the timing of when the mother took Canephron® N (using the first day of the last menstrual period as a point of reference).

Statistical analysis

Statistical analysis of the results was performed using Statistics for Windows® (version 5.3, Statsoft, USA).

The relative risk (RR) ratios were calculated according to the following formulas:

$$\mathrm{RR} = p_1/p_2$$

Where RR = relative risk, p_1 = frequency of the event in the experimental group, and p_2 = frequency of the event in the control group.

$$\mathrm{SE}\left(from\ \mathrm{Log_e\,RP}\right) = \sqrt{\frac{1}{r_1}+\frac{1}{r_2}-\frac{1}{n_1}-\frac{1}{n_2}}$$

where SE = standarderror 0.05,
r_1 and r_2 = number of events in the experimental and control groups,
n_1 and n_2 = number of patients in the experimental and control groups,
95 % CI confidence interval = $\log_e$ RR ± 1.96 × SM.

Results

The age of the participants ranged from 17 to 39 years (average 21 ± 2.2 years). A total of 170 (44.3 %) of the women were primiparous and 214 (55.7 %) were multiparous. Of the 384 women, 361 took Canephron® N tablets (6 tablets daily), and 23 received Canephron® N drops (150 drops daily). The average duration of the treatment was 23 ± 1.25 days. In 196 cases (51.05 %), Canephron® N was used as a monotherapy and in 188 cases (48.95 %) it was used as part of combination therapy (alongside the antibacterial agents phosphomycin, aminopenicillins, and cephalosporins). The indications for treatment with Canephron® N in the study population are summarized in Table 1.

There were no significant differences in the incidence of malformations in newborns whose mothers had taken Canephron® N in the first trimester of pregnancy, compared to the national statistical data for the Kiev population during the same period 2004–2010 (Table 2). Out of the 384 women who took Canephron® N during the first trimester of pregnancy, a total of 14 (3.65 %) gave birth to infants with congenital malformations. This percentage is similar to that for the general Kiev population during this period (3.71 % In according to report of State Institution "Center for Health Statistics of the Ministry of Health of Ukraine".

Table 1 Indications for treatment with Canephron® N in the study population

Indication	n (%)
Chronic lower urinary tract infection (non-acute)	79 (20.6)
Acute cystitis or exacerbation of chronic cystitis	21 (5.5)
Prophylaxis for chronic pyelonephritis (non-acute)	203 (52.9)
Acute pyelonephritis or exacerbation of chronic pyelonephritis	34 (8.8)
Urolithiasis	18 (4.7)
Chronic glomerulonephritis	29 (7.5)

Table 2 Incidence of developmental defects in newborns of the study population, compared to national statistical data of the general Kiev population during the same period

	Total developmental defects in the study population (N = 384)		Total developmental defects in the general Kiev population 3.71 %
Organ system	n	% of total developmental defects	% of total developmental defects
Urinary tract	4	28.6	34.7
Heart	3	21.4	22.5
Central nervous system	3	21.4	18.2
Gastrointestinal tract	2	14.3	10.2
Musculoskeletal system	2	14.3	12.5
Multiple organ systems	-	-	1.9
Total	14 (3,65 % from 384)	100	100

There were two cases of malformations of the urinary system in the Canephron® N population (both renal agenesis). There was one case of duplication of the pelvicalyceal system and one case of ectopic pelvic kidney. Cardiac malformations included transposition of the great arteries, atrial septal defect and Ebstein's anomaly. Nervous system malformations included agenesis of the corpus callosum, brain cyst, and congenital hydrocephalus with ventriculomegaly. Digestive system malformations consisted of anal atresia and pylorostenosis. Malformations of the musculoskeletal system comprised absence of the distal phalanx of the finger and syndactyly of the foot.

Next, we examined the relationship between the timing of Canephron® N administration in the first trimester of pregnancy and the presence of any congenital malformations in the newborn (Table 3). The timing of Canephron® N intake was assessed relative to the first day of the last menstrual period.

Out of the 4 women who took Canephron® N at the earliest and most vulnerable period of pregnancy (Day 29–50), none of their infants had congenital malformations. Of the 106 women who took Canephron® N between Day 51–70, 4 gave birth to infants with congenital malformations, and 10 of the 274 women who took Canephron® N between Day 71–84 gave birth to infants with congenital malformations. The incidence of these malformations is similar to that of the general Kiev population.

Table 3 Timing of Canephron® N administration in the first trimester of pregnancy and the presence of congenital malformations in the newborn

Timing (number of days from the 1st day of the last menstruation)	Congenital malformations	
	Present	Absent
	N = 14 (100 %)	*N* = 370 (100 %)
29–50 (*n* = 4)	-	4 (1.08)
51–70 (*n* = 106)	4 (28.6)	102 (27.6)
71–84 (*n* = 274)	10 (71.4)	264 (71.3)
Total	14 (100)	370 (100)

We calculated the RR and the 95 % confidence interval (CI) of developing congenital birth defects in newborns whose mothers were taking Canephron® N in the first trimester of pregnancy. The RR was 0.941 (95 % CI: 0.526–1.68), indicating the absence of any effects of Canephron® N on the incidence of congenital birth defects in our study. Finally, the status of the newborns was evaluated one minute after birth using the Apgar scoring system (Fig. 1). Using the Apgar scoring system, each of five main characteristics (heart rate, respiratory effort, muscle tone, reflex irritability, and color) is assigned a value of 0 to 2. The total score is the sum of the five sub-scores, with a score of 7 or more indicating that the new-born baby's condition is good to excellent [30]. The majority of newborns had scores of 8–10 points on the Apgar scale, indicating that their condition was excellent, and suggesting that the use of Canephron® N during the first trimester of pregnancy did not affect the general status of the newborns.

Discussion

Inflammatory diseases of the urinary system are among the most commonly-occurring diseases in pregnant women [31]. Due to hormone-related dilation of the renal pelvis and ureters, pregnant women have increased risk of bacterial invasion of the kidneys and pyelonephritis [31]. During pregnancy, bacteriuria that progresses to pyelonephritis has been associated with poor outcomes for the mother and child. UTIs during pregnancy increase the risk of maternal hypertension, anemia, and pre-term labor, as well as low-birth weight [32, 33]. Therefore, addressing UTIs that occur during pregnancy is an important means for preventing pregnancy complications.

In the Ukraine, Canephron® N is a frequently-used phytotherapeutic medicine for the treatment of UTIs in pregnant women. The drug has been shown to have pleiotrophic effects on the urinary system, including diuretic, spasmolytic, anti-inflammatory, antimicrobial and nephroprotective effects [14]. Our study was conducted in order to establish the safety and teratogenic potential of Canephron® N when used during this critical period. The first trimester of pregnancy marks a period of crucial morphogenetic events, when the fetus is particularly susceptible to morphologic alterations due to adverse environmental exposures [34]. Since no data is currently available on the safety of Canephron® N during this

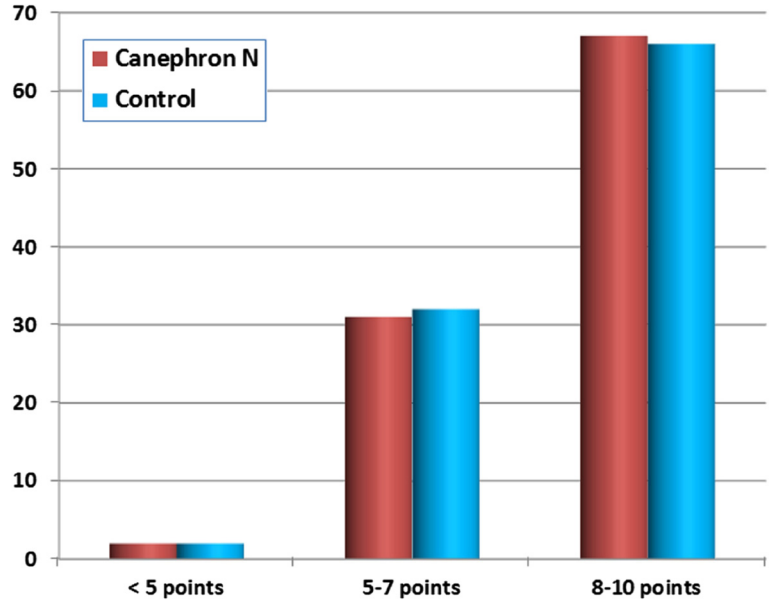

Fig. 1 Apgar scores of newborns whose mothers used Canephron® N during the first trimester of pregnancy. *Red*: Newborns of patients treated with Canephron® N in the first trimester of pregnancy. *Blue*: Statistical data of newborns from the same clinics whose mothers did not take Canephron® N

critical period of pregnancy, we conducted a retrospective analysis of a systematically selected study population. As a comparator group, the national statistical data of the general Kiev population during the same period was used. The main findings from our study indicated no increased incidence of congenital birth defects in the study population, which consisted of women who had used Canephron® N during the first trimester of pregnancy. Further analysis of the RR supported these findings, indicating the absence of any effects of Canephron® N on the risk of congenital birth defects. Finally, the majority of newborns whose mothers had received Canephron® N treatment during the first trimester of pregnancy had an excellent general status immediately after birth, as assessed using the Apgar scoring system.

The safety findings from our study support the previously-published findings on Canephron® N in the prevention and treatment of UTIs and related diseases in pregnant women. Three studies have investigated the effects of Canephron® N in pregnant women, focusing primarily on efficacy [35–37]. The study by Ordzhonikidze et al. included 300 pregnant women with a range of urinary pathologies including asymptomatic bacteriuria, gestational, exacerbation of chronic pyelonephritis, or chronic urinary disease without exacerbations [36]. An independent study by Medved et al. included 30 pregnant women with type I diabetes mellitus who had gestational pyelonephritis or exacerbations of chronic pyelonephritis [35]. The third study was a prospective, randomized study that included 85 pregnant women with a range of renal pathologies [38]. In all three studies, Canephron® N was administered alongside standard therapy and had beneficial effects in pregnant women suffering from various renal pathologies. Although no detailed safety analyses were performed in these studies, Canephron® N showed a good safety and tolerability profile across all the study populations [27]. It should be noted that the drug was not administered in the first trimester of pregnancy in all three studies.

Two additional studies investigated the potential effects of Canephron® N on the rates of congenital malformations [38, 39]. Repina et al. followed up 115 children (aged 5 months–3.5 years) born to women who were treated with Canephron® N during the second or third trimester of pregnancy. The study reported no adverse effects on the fetus during pregnancy and no postpartum effects on the children born to mothers who had been treated with the drug while pregnant [39]. A large prospective-retrospective study evaluating the teratogenic, embryotoxic and fetotoxic effects of Canephron® N in 1647 women indicated no evidence of any developmental or congenital effects [38]. Our data builds on the findings from these studies, suggesting that the use of Canephron® N during the first trimester of pregnancy is not associated with teratogenic effects in the fetus.

The limitations of our study are related to its retrospective design, and the resulting lack of data on potential confounding factors that may have affected the incidence of congenital birth defects in our study population. Furthermore, the number of individuals included in the study population was relatively small (a total of 384) and in (48.95 %) cases, Canephron N was used as part of combination therapy (alongside with the antibacterial agents phosphomycin, aminopenicillins, and cephalosporins). It is also worth mentioning that some of the users might have experienced miscarriage due to the "all or nothing" rule early in pregnancy and such cases are not reported in the present study.

Conclusions

The results from our study indicate that the use of Canephron® N during the first trimester of pregnancy was not associated with any teratogenic effects on the fetus, and had no effects on the general condition of the newborn infants.

Abbreviations

CI: Confidence interval; ICD: International classification of diseases; EU: European union; RR: Relative risk; UTI: Urinary tract infection; WHO: World Health Organization.

Competing interests

Vlodimir Medved declares that he has no competing interest.

Authors' contributions

VM conceptualized the project and wrote and read the final manuscript.

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