BACTERIAL EXTRACT FOR THE PREVENTION OF RECURRENT URINARY TRACT INFECTIONS IN PREGNANT WOMEN: A PILOT STUDY

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Summary: *Recurrent urinary tract infections (UTIs) are a frequent cause of concern during pregnancy, and there is a limited choice of appropriate antibiotic treatments. An alternative approach may be their prevention by an immunoactive bacterial extract that has already been shown to be safe and effective in children and adults. Preclinical investigations have demonstrated the absence of embryotoxic or teratogenic effects. The aim of this open multicenter pilot study was to investigate the efficacy and safety of the bacterial extract OM-8930 in pregnant women with recurrent UTIs. Sixty-two patients presenting with an acute UTI in weeks 16 to 28 of pregnancy were treated with one capsule daily of OM-8930 until delivery. Antibiotics were given concomitantly for acute infection at entry and when necessary. After entry, clinical checks were conducted 1 week after the end of initial antibiotic therapy and then every month until 6 weeks after delivery. The results show that the incidence of UTI recurrences was significantly reduced, with only 12 patients (19.4%) experiencing a recurrence during the study in comparison with 32 patients (52.5%) during the 6 months prior to the study (p = 0.002). The need for antibiotic therapy was also markedly reduced, with 34 patients (55.7%) requiring antibiotics before the study compared with eight (12.9%) during the study (p = 0.0002). Slight adverse events were observed in only two patients (nausea and heartburn). All newborns were healthy with normal Apgar scores. This pilot study shows that OM-8930 reduces the incidence of UTI recurrences during pregnancy and is well tolerated. No negative effects in the newborns were observed.*

Introduction

Urinary tract infections (UTIs) are common in women and are among the most frequent infections seen in general practice. Data from the USA indicate that UTIs lead to approximately 8 million consultations per year resulting in 100,000 hospitalizations and a global annual cost of $1.6 billion (1).

It is estimated that 20–30% of all women have one or more episodes of bacteriuria per year, of which 6%

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lead to a UTI. Evidence in the literature suggests that 50% of young women experience a recurrence after 12 months, depending on the immunocompetence of the urogenital system (2).

Around 80–85% of these UTIs are caused by *Escherichia coli* (3). UTIs are also the most frequent infections during pregnancy, with a prevalence of 5–10%. Preexisting asymptomatic bacteriuria, which outside of pregnancy requires no treatment in the majority of cases, is often the trigger for a symptomatic UTI, which is also favored by the changes in the urinary tract that occur during pregnancy. Several studies indicate that during pregnancy untreated asymptomatic bacteriuria more frequently leads to acute pyelonephritis. Preterm birth, adverse effects on intrauterine growth, preeclampsia, hypertension and anemia may follow (4, 5).

Early diagnosis and prompt treatment of UTIs are important to prevent complications in the mother or fetus during pregnancy. For this reason, all pregnant women should undergo a routine urine test at the first consultation. To avoid risk to the fetus, the choice of antibiotic should be appropriate for the week of pregnancy and is therefore rather limited: ampicillins and cephalosporins remain in the front line and can be prescribed with little risk to the fetus.

Considerable disagreement surrounds the duration of antibiotic treatment: studies with cephalexin (6) and amoxicillin (7) have shown that a single dose given daily over 3–7 days is sufficient and is as good as conventional therapy, although definitive resolution of the UTI is achieved in only 70% of cases. An advantage of short-course therapy, however, is that it causes little or no effect on the vaginal flora. Even when there are no symptoms or complaints, a urine test, including culture, should be conducted 7–14 days after the antibiotic treatment at the latest and, if infection persists, further differential and urological diagnosis should be undertaken to exclude other causes such as urinary obstruction or urolithiasis. If necessary, nitrofurantoin, *e.g.* 50 mg at night for 3–4 weeks should be prescribed as long-term prophylaxis. However, this preparation is contraindicated in the first 3 months of pregnancy and in the last 4 weeks before delivery as it can cause hemolytic anemia in the fetus (8-11).

It is now possible to use immunostimulation with the bacterial extract OM-8930 to avoid unnecessary treatment with antibiotics and to improve prevention against recurrence. *In vitro* and *in vivo* studies in animals and humans have shown that this preparation triggers a series of immunopharmacological effects (12–17). In particular, it increases the metabolic and functional activities of lymphocytes and macrophages, the levels of urinary and intestinal secretory IgA (sIgA) and serum IgA and IgG, which are specific for *E. coli* and other urinary pathogens.

The aim of treatment is to improve the immune defenses in the urogenital tract mucosa, *i.e.* to prevent bacterial adherence and thus colonization in the region of the vagina and urethra. A particularly important role is played by sIgA, which is produced by plasma cells and bound *via* a glycoprotein to the cells of the epithelium (18). It is now known that a reduced sIgA titer is a predisposing factor for recurrent UTIs (2, 19, 20).

Several double-blind and open clinical studies have shown that OM-8930 significantly reduces the risk of UTI recurrence, especially that of cystitis, and improves laboratory parameters (bacteriuria, leukocyturia) as well as clinical symptoms (dysuria) (21–28), as confirmed in a recent metaanalysis (29).

Because all the preclinical toxicological and teratogenic studies performed in embryos to date have shown no negative effects of OM-8930 and the clinical trials have revealed a high therapeutic effect with a very low incidence of mild and reversible adverse effects, the aim of the present trial was to investigate the efficacy and safety of this extract in preventing recurrent UTIs in pregnant women.

Materials and methods

This open clinical pilot study on the efficacy and safety of OM-8930 was conducted at six gynecological practices in Switzerland. The test preparation OM-8930 is a lyophilized bacterial extract containing immunoactive detoxified fractions of selected *E. coli* strains (Uro-Vaxom®, OM PHARMA, Meyrin/Geneva, Switzerland). A total of 77 women with asymptomatic or acute symptomatic UTIs in weeks 16–28 of pregnancy were enrolled in the study. All the women were informed of the aims and objectives of the study and gave their consent. Treatment with OM-8930, at the recommended dosage of one capsule every morning on an empty stomach, commenced concomitantly with antibiotic therapy and continued until the end of pregnancy. Antibiotics were prescribed if necessary. Clinical checks were conducted 1 week after the end of the initial antibiotic therapy and then monthly until 6 weeks after delivery.

Criteria for inclusion in the study were a bacteriuria of $\geq 10^5$/ml in midstream urine or $\geq 10^4$/ml in urine collected by catheter. Bacteriuria was demonstrated by using the following culture media: cystine-lactose-electrolyte-deficient medium for the determination of total germ count (Gram-positive and Gram-negative) and McConkey medium for the selective count of Gram-negative microorganisms.

Exclusion criteria included preexisting urological diseases such as urolithiasis or urinary obstruction, reduced renal function (serum creatinine > 1.8 mg%), allergic predisposition, treatment with other immunogenic preparations, known fetal anomalies and known familial congenital malformations, among other criteria.

Efficacy was assessed on the basis of the number of UTI recurrences, short- and long-term efficacy and antibiotic use compared with the 6 months prior to the start of the study. Further parameters for efficacy included dysuria, bacteriuria, the number of leukocytes and erythrocytes in the urine sediment and demonstration of the presence of albumin and nitrite.

The short- and long-term effects of OM-8930 were assessed subjectively by the investigating physician on a 4-point scale (from 0 = no effect to 3 = certain effect).

The safety of the product was determined on the basis of the number, type, duration and severity of the adverse effects occurring in the pregnant women and the condition of the newborns (Apgar score).

In the absence of an untreated control group, the study data were compared with those from the 6-month period prior to the start of the study. Statistical comparison of the various parameters was achieved using a time-adjusted coefficient to account for the fact that the two phases were not identical in duration. The data from the 6-month reference period were multiplied by the time-adjusted coefficient, which was derived by dividing the duration of OM-8930 therapy in days by 180 days (6 months).

Statistical analysis was performed by Biometrix SA (Gland, Switzerland) using the statistical software SPSS+ release 5.0 (SPSS, Chicago, IL, USA), NCSS release 7.0 (Number Cruncher Statistical System, Kaysville, UT, USA) and Testimate release 5.1 (*Internationale Datenanalyse und Versuchsplanung*, Gauting/Munich, Germany). The time-adjusted data for the study period and the prior reference period were compared using the Wilcoxon rank test for paired data. The evolution of the data between the start and the end of the study was also analyzed using the Wilcoxon rank test for paired data or the McNemar test for dichotomic paired data.

Results

Of the 77 pregnant women enrolled in the study, 3 were excluded from the analysis because of failure to comply with the study protocol. Among the

remaining 74 patients, 12 did not meet the inclusion criteria: 10 because of bacteriuria of $< 10^4$/ml and 2 as they were enrolled after week 28 of pregnancy, leaving 62 assessable patients. The pregnant women were aged 19–38 years (mean 26.9 [± 4.6] years). The number of previous births varied from zero (n = 19) to five (n = 1) with a majority having had one birth (n = 29), followed by two (n = 9) and three (n = 4).

The main diagnoses at entry into the study are shown in Table I. Thirty-six patients (58.1%) had cystitis; 20 patients (32.2%) had a UTI without more precise indications, of whom only three (4.8%) were asymptomatic, and six patients (9.7%) had pyelitis.

As envisaged in the study protocol, treatment commenced between weeks 16 and 28 of pregnancy (mean: week 23). The mean treatment duration was 119 ± 29 days. Patient compliance was assessed at each visit on the basis of the remaining medication and was estimated, with one exception, as "good".

The efficacy of the bacterial extract was determined on the basis of the number of recurrences during the study period compared with that in the 6-month phase prior to the start of the study. During OM-8930 therapy there was a significant reduction (p = 0.002) in recurrences with only 12 patients (19.4%) suffering from UTI recurrences compared with 32 patients (52.5%, time-adjusted) in the previous 6 months (Fig. 1).

A second important criterion was the number and duration of antibiotic treatments, which were markedly reduced. Before the start of the study 34 patients (55.7%, time-adjusted) required additional antibiotic therapy compared with only 8 (12.9%) during OM-8930 therapy (Fig. 2). Again, the difference between the two phases was statistically significant (p = 0.0002). The duration of antibiotic treatment was also reduced from a mean of 3.2 to 2 days (p = 0.0016) (Table II).

In addition, dysuria, nitrituria, leukocyturia and erythrocyturia also showed significant improvement from entry into the study until 6 weeks after delivery ($p < 0.001$). The rate of dysuria fell from 87.1% to 1.7% (Table III).

Table I *Type and number of urinary tract infections (UTIs) prior to treatment*

Diagnosis	Number of patients (n = 62)	Percentage %
Acute cystitis	31	50.0
Recurrent cystitis	5	8.1
Acute pyelitis	4	6.5
Recurrent pyelitis	2	3.2
Acute UTI	15	24.2
Recurrent UTI	2	3.2
Asymptomatic UTI	3	4.8

The subjective assessment of efficacy by the investigating physicians was highly positive. They considered that the short- and long-term efficacy of OM-8930 was certain or possible in 59 patients (95.2%).

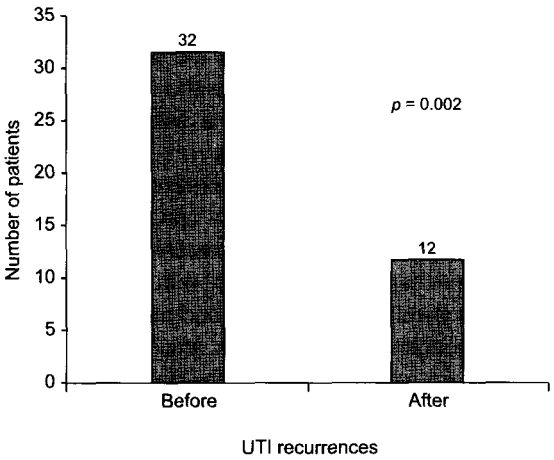

Fig. 1 The number of patients with urinary tract infection (UTI) recurrences (time-adjusted) before the start of the study and after OM-8930 therapy.

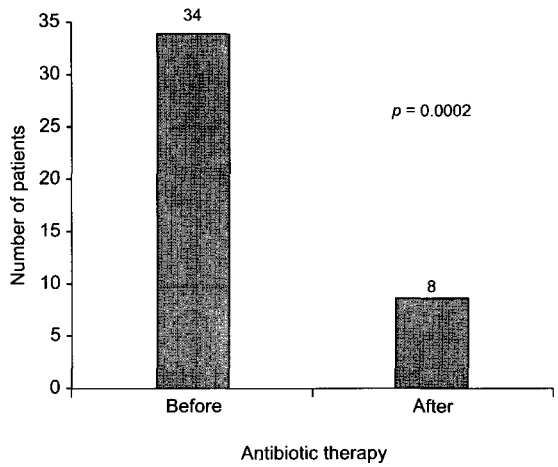

Fig. 2 The number of patients undergoing antibiotic therapy (time-adjusted) before the start of the study and after OM-8930 therapy.

Suspected adverse effects occurred only in 2 of the 74 patients (2.7%) of the safety population and took the form of transient slight nausea or mild heartburn. The patients were able to continue in the study despite these effects, which the physicians considered to be probably due to the pregnancy itself.

The condition of the newborns was examined using the Apgar score, among other measures. The mean Apgar score was 8.6/9.5/10.0. The mean birth weight was 3,321 g (± 427) and the mean length was 49.3 cm (± 2.03). Umbilical cord pH measurements indicated an arterial pH of 7.20 (± 0.13) and a venous pH of 7.36 (± 0.06). No malformations were found in the newborns.

Discussion

The efficacy and safety of OM-8930 have been demonstrated in various double blind and open clinical studies (21–28). More than 1,000 patients participated in these studies and were evaluated for both efficacy and tolerance, with the following conclusions: the bacterial extract significantly reduced the number of UTI recurrences and the need for antibiotic therapy, as well as bacteriuria, leukocyturia and dysuria. These findings have been confirmed by a recent metaanalysis (29).

In the present open pilot study, the effect of the bacterial extract was assessed in 62 patients in weeks 16–28 of pregnancy who presented with asymptomatic or acute symptomatic UTI. The number of recurrences was significantly reduced in comparison with the 6 months prior to the start of the study, *i.e.* only 12 (19.4%) rather than 32 (52.5%) of the pregnant women experienced UTI recurrences. Before treatment, 34 (55.7%) of the patients required antibiotics, while during treatment this number fell to 8 (12.9%). In addition, the mean duration of antibiotic administration fell from 3.2 to 2 days. Furthermore, only 1.7% of patients reported dysuria, compared with 87.1% before the start of OM-8930 treatment. These results confirm once again the findings of earlier studies.

Table II *Comparison of the average duration of antibiotic administration (in days, time-adjusted)*

Parameter	During the 6 months prior to the start of the study (in days)	During OM-8930 therapy (in days)	Comparison *p*-value
Duration of antibiotic administration	3.2	2.0	0.0016

Table III *Evolution of dysuria during OM-8930 therapy*

Consultation	Number of patients			*p*-value
	Number	Dysuria	%	
Entry	62	54	87.1	
1 week after the end of the initial antibiotic	57	13	22.8	< 0.001
1 month after the start of the study	59	3	5.1	< 0.001
3 months after the start of the study	52	4	7.7	< 0.001
6 weeks after delivery	58	1	1.7	< 0.001

Concerning safety, only two patients (2.7%) reported symptoms that could be regarded as adverse effects (slight nausea and mild heartburn) and no negative effects were observed in the newborns.

On the basis of the different studies performed to date, the tolerance of OM-8930 can be classified as good: only 4% of patients developed adverse effects, most of which were gastrointestinal symptoms and skin reactions. None of these events was considered serious. Interactions with other medications have not been observed to date. Furthermore, preclinical embryotoxicity and teratogenicity studies showed no risk to the fetus.

Clinical examination showed that the newborns in this study were without exception normal (size, birth weight, malformation). There were no problems with neonatal adaptation (umbilical pH values, Apgar score). No controlled studies with this bacterial extract in pregnant women are as yet available. However, on the basis of currently available data and knowledge, the use of OM-8930 after week 16 of pregnancy appears to present no risk to the fetus.

In conclusion, although these findings should be confirmed in large controlled trials, the present data indicate that the administration of OM-8930 for UTIs during pregnancy reduces the number of recurrences. This has the advantage of minimizing the use of antibiotics, which is often regarded as complicated during pregnancy because of the potential risk to the unborn child. With timely and adequate treatment of UTIs, pregnancy complications such as preterm birth, adverse effects on intrauterine growth, preeclampsia, hypertension and anemia can be reduced or prevented (4, 5). In the long term, prompt treatment and prevention could also reduce the risk of UTIs becoming chronic and of sequelae such as chronic pyelonephritis and renal insufficiency.

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