INTERIM FIRST YEAR PERFORMANCE OF THE IUB™ SCu300A IN COMPARISON WITH THE IUD TCu380A INTRAUTERINE DEVICE

April, 2016

Summary

Background: The IUB™ SCu300A ("IUB™") is a novel, intrauterine, non-hormonal contraceptive device. The current study summarizes the twelve-month follow-up data regarding IUB™ efficacy, safety, and quality of life (QoL) in comparison to the TCu380A. The two year follow-up study was initiated in June 2014 and is conducted in Romania and Bulgaria.

Study Design: A total of 367 women were recruited and randomized into two study arms: 245 were assigned the IUB™ device and 122 the IUD comparator. Patients were asked to describe four QoL parameters: bleeding duration, bleeding intensity, degree of pain and cramps, and general description of the menstruation, all at four different time points (1, 4, 8, and 12 months) following device insertion.

Results: Dysmenorrhea and particularly pain and cramps were reduced in the IUB™ group with a marked trend of improvement in all measured quality of life parameters. Efficacy and safety measures were comparable. Following investigator training on proper insertion of the IUB™ device, expulsion rates decreased significantly. No perforations were reported.

Conclusion: Twelve-month follow-up data demonstrates improved overall quality of life with the IUB™ SCu300A compared to the TCu380A, while maintaining comparable efficacy and safety. Proper IUB™ insertion has been shown to significantly reduce risk of expulsion.

Introduction

The IUB™ SCu300A ("IUB™", OCON Medical Ltd., Modi'in, Israel) is a novel, intrauterine, non-hormonal contraceptive device. Its mechanism of action is similar to other copper intrauterine devices (IUDs), utilizing copper for preventing pregnancy locally within the uterus. It is comprised of several pure copper beads with a total 300mm² surface area strung on a uterus-adapted spherical frame, creating a ball-shaped structure (figure 1, left). The frame is pre-loaded in linear form into a tube for easy insertion, but once released in the uterus it remembers its 'programmed' shape and coils into a round and smooth form, with no sharp edges. The purpose of this unique three dimensional design is to fill the uterine cavity (figure 1, right), and by that minimize the risks for uterine perforation, device mal-positioning and expulsion. A preliminary proof-of-concept trial was published in 2014.

In June 2014 a post marketing study was initiated to obtain clinical performance data of the IUB™ with regards to its efficacy, safety and quality of life (QoL) aspects. The long-standing, T-shaped TCu380A copper intrauterine device was selected as a comparator. This report
summarizes the twelve-months follow-up interim results of the study, which is planned to continue for a total of 24 months.

**Materials and Methods**

The study is a prospective, single (subject) blind, two-arms controlled study. A total of 367 subjects aged 18-45 (mean=33) were enrolled in twelve centers throughout Romania and Bulgaria, randomized and underwent insertion of the study and control devices at the time of the database lock. No major protocol deviation was recorded. Of the total number of subjects enrolled, n=245 (66.3%) were assigned the IUB™ SCu300A and n=122 (33.7%) were assigned the comparator IUD. Recruitment was initiated in June 2014 but was halted after the enrollment of the first n=88 subjects; following a 45-day pause, recruitment was resumed and an additional n=279 subjects joined the study. No statistically significant differences were observed between the study arms regarding age, height, weight, BMI, marital status, uterus and ovaries measurements, parity and prior contraceptive use.

Study endpoints were as follows:
- **Efficacy**: pregnancy rate.
- **Safety**: expulsion, mal-position and perforation rates.
- **Quality of life (QoL)**:
  - Menorrhagia: bleeding period measured in days, and bleeding intensity measured by number of tampons/pads used per day.
  - Dysmenorrhea: pain and cramps measured on a 1-10 scale (10 being most painful), and general description of menstruation measured on a 1-10 scale (10 indicating highest discomfort).

Each subject was asked to scale QoL parameters prior to device insertion and at 1, 4, 8, and 12 months. Subjects were also physically examined after 1, 4 and 12 months in order to monitor the safety parameters.

All statistical analyses were performed using SAS® version 9.4 software.

**Results**

**Efficacy**: A total of four pregnancies in the IUB™ arm and one in the IUD arm were recorded; time to pregnancy was not statistically different between study arms. Table 1 shows the calculated pregnancy rates and the Pearl Index for each study arm. Published Pearl index range for copper intrauterine devices is 0.7 – 1.5, it is thus clear that both devices not only exhibit comparable efficacy, but meet the standards regarding pregnancy prevention.

<table>
<thead>
<tr>
<th>Device used</th>
<th>no._of_pregnancies / total no._of_women (%)</th>
<th>95% CI</th>
<th>Pearl Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUB</td>
<td>4/245 (1.63 %)</td>
<td>0.45 % ; 4.13 %</td>
<td>1.1</td>
</tr>
<tr>
<td>IUD</td>
<td>1/122 (0.82 %)</td>
<td>0.02 % ; 4.48 %</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Table 1: Pregnancy rates, their respective two-sided 95% exact binomial confidence interval (CI), and Pearl Index calculations for each device. IUD=TCu380A.*

**Safety**: No perforations or mal-positions were reported in either group. Expulsion rates were relatively high for IUB™ in the first group of 86 participants (two upper rows in Table 2). Recruitment was paused for 45 days and investigators were further trained regarding the insertion technique. The remaining 281 participants were then recruited (two lower rows in table...
2). Data demonstrates that following proper insertion of the IUB™ device, expulsion rates decreased significantly. Importantly, the difference in expulsion rates between the two devices during the second period was found to be insignificant (p=0.41).

<table>
<thead>
<tr>
<th>Recruitment Period</th>
<th>Treatment group</th>
<th>% expulsions / # of women</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>IUB</td>
<td>13.79% (8/58)</td>
<td>6.15% ; 25.38%</td>
</tr>
<tr>
<td></td>
<td>IUD</td>
<td>3.57% (1/28)</td>
<td>0.09% ; 18.35%</td>
</tr>
<tr>
<td>2nd</td>
<td>IUB</td>
<td>4.81% (9/187)</td>
<td>2.22% ; 8.94%</td>
</tr>
<tr>
<td></td>
<td>IUD</td>
<td>0.00% (0/94)</td>
<td>0.00% ; 3.85%</td>
</tr>
</tbody>
</table>

Table 2: Expulsion rates and their respective two-sided 95% exact binomial confidence interval (CI) are shown for both study arms. IUD=TCu380A.

**Quality of life (QoL):** Figure 2 displays the average scores for QoL parameters for each study arm. Results indicate a definite advantage for the IUB™ with regards to pain and cramps experienced by the patients (Figure 2, lower left panel). Bleeding intensity also drops more significantly for the IUB™ arm as shown by the decrease in number of sanitary aids used per day (Figure 2, upper right panel). Bleeding period and description of menstruation both show an overall superiority of IUB™ over the TCu380A, these results are statistically insignificant (Figure 2, upper left and lower right panels, respectively).

![Graphs showing QoL parameters](image)

**Figure 2:** QoL parameters as reported by each woman at baseline and at 1, 4, 8, and 12 months following device insertion. Scores are shown in blue for IUB™ and in red for the IUD (TCu380A) comparator. All figures are mean and the vertical bars indicate the standard error.
In order to further evaluate the advantages of the IUB™ device, additional data analysis was conducted on women who reported of improvement with regards to each QoL parameter. 'Improvement' was defined if evaluation of the patient was equal or improved compared to baseline at any follow-up point during the study. Importantly, patients who reported the highest possible level at baseline (scoring '1' for pain and cramps for example) were excluded from this analysis.

Similar analysis was performed on the proportion of decrease in QoL. 'Decrease' was assigned to women who had at least one point in which the status was worse than the reported baseline. Results of both analyses are presented in figure 3.

In the case of pain and cramps it is evident that the proportion of women who felt an improvement is significantly higher for IUB™ compared to the TCu380A IUD (Figure 3, upper panel). This is further strengthened by data presented (Figure 3 bottom panel) demonstrating that the proportion of patients who reported of deterioration in pain status throughout the treatment is lower in the IUB™ arm. As for the other QoL parameters, there is a statistically insignificant though clear trend favoring the IUB™ device for both the 'Improvement' and 'Decrease' analyses.

**Discussion**

This study is the first large scale comparative study of the IUB™ SCu300A. The IUB™ was found to have equivalent efficacy in preventing pregnancy to the long-standing TCu380A IUD, while maintaining all safety parameters. Expulsion rate was relatively high in the first recruitment group, but became comparable to that in published literature after training of practitioners on insertion technique. It was demonstrated that avoiding withdrawal of the insertion tube before IUB™ deployment reduces expulsion rate dramatically.
In parallel with the recruitment period of this study a second, larger and stiffer IUB™ variant was developed - the IUB™ SCu300B (15 mm vs. 12 mm in diameter). Post marketing data for the second variant (not shown in this report) shows a significant decrease in expulsion rate to 1.4% during the first year of use, which is considerably lower than current published rates for any device.

Regarding quality of life, a statistically significant advantage for the IUB™ treatment vs. TCu380A IUD in the pain and cramps parameter was demonstrated under different approaches and definitions (some shown in this report) while the bleeding period, bleeding intensity and description of menstruation are similar for both devices with a statistically insignificant advantage for the IUB™.

To conclude, results obtained so far indicate that the IUB™ performance is as efficient and as safe as other intrauterine, non-hormonal devices represented by the TCu380A and is particularly beneficial at least with regards to pain and cramps which are a major source of dissatisfaction for IUD users. The planned additional one-year follow-up will allow a longer term analysis with observed trends expected to become more definitive at that time. Further studies are planned of the IUB™ variants including an ongoing study in Austria which is planned to be completed by the end of 2016.

References: