The type of catheter has no impact on the pregnancy rate after intrauterine insemination: a randomized study

A.-M.Vermeylen¹, T.D’Hooghe, S.Debrock, L.Meeuwis, C.Meuleman and C.Spiessens

Department of Obstetrics and Gynecology, University Hospital Leuven, Leuven, Belgium

¹To whom correspondence should be addressed at: Department of Obstetrics and Gynecology, University Hospital Leuven, Herestraat 49, 3000 Leuven, Belgium. E-mail: amvermeylen@hotmail.com

BACKGROUND: This study was done to test the hypothesis that intrauterine insemination (IUI) using a soft-tip catheter results in a higher live birth rate than IUI using a hard-tip catheter. METHODS: Five hundred and forty patients were randomized into those inseminated with a soft-tip catheter (group 1, n = 267) and those inseminated with a hard-tip catheter (group 2, n = 269). Four patients were excluded. Main outcome measures included pregnancy rate and live birth rate per cycle. RESULTS: Both groups were similar with regard to female age, duration of infertility, ovarian stimulation and sperm quality. No significant differences were observed between group 1 and group 2 regarding clinical pregnancy rate per cycle (20 versus 19%), live birth rate per cycle (15 versus 14%), multiple live birth rate per cycle (4 versus 6%) and multiple live birth per total of live births (5 versus 8%, overall 6%), respectively. CONCLUSION: Our hypothesis that IUI using a soft tip catheter results in a higher live birth rate per cycle than IUI using a hard-tip catheter was not confirmed in this study. Multiple live birth rate after treatment with low-dose gonadotrophins and IUI can be kept low (6%).

Key words: catheter/hard tip/infertility/intrauterine insemination/soft tip

Introduction

Various types of catheters are commercially available for intrauterine insemination (IUI) and embryo transfer. They differ according to diameter, distal opening and consistency (hard tip or soft tip). The impact of the consistency of the catheter has been investigated based on the hypothesis that a soft-tip catheter would be less damaging for the endometrial lining and would limit uterine contractions that could expel embryos after embryo transfer or sperm suspensions after IUI. The pregnancy rate per cycle is increased after embryo transfer with a soft catheter when compared to embryo transfer with a hard-tip catheter according to several randomized studies (McDonald and Norman, 2002; van Weering et al., 2002). However, not much information is available regarding the impact of catheter consistency on pregnancy rates after IUI.

So far, the impact of two catheter types, that is, the soft-tip Wallace catheter (Marlow, Willoughby, OH, USA) and the hard-tip Tom Cat catheter (Tom Cat catheter, Sherwood Medical, St. Louis, MI, USA) on the pregnancy rate in IUI cycles has been assessed in two studies (Lavie et al., 1997; Smith et al., 2002). A third study used other catheters, that is, the soft-tip Soft-Pass catheter (Cook, Spencer, IN, USA) and the hard-tip Tom Cat catheter (Kendall Sovereign, Mansfield, MA, USA) (Miller et al., 2005). The first study (Lavie et al., 1997) was prospective but not randomized and assessed the effect of the type of catheter on the endometrial three-layer pattern and on the pregnancy rate in 102 IUI cycles. Although the total destruction of the endometrial three-layer pattern was lower in the soft catheter group [12.5% (4/32)] than in the firm catheter group [50% (40/80)], the pregnancy rate was similar in both groups. In the second study, with larger sample size (n = 747 IUI cycles) and randomized design (Smith et al., 2002), the pregnancy rate was similar in the soft catheter group (16%) and the firm catheter group (18%). In the third study (Miller et al., 2005), a prospective, randomized, controlled study, 100 patients were enrolled. No statistically significant difference in pregnancy rates was observed between rigid and flexible catheter groups. However, the Golden standards for outcome after assisted reproduction treatment, that is, live birth rate per cycle and the multiple live birth per cycle or per total number of live births, were not reported in these studies (Lavie et al., 1997; Smith et al., 2002). Nevertheless, it has to be admitted that it is unlikely that the catheter type will influence the spontaneous abortion rate by causing a long-term effect on uterine contractility.

Therefore, the aim of this study was to test the hypothesis that IUI with a soft-tip catheter results in a higher pregnancy rate and a higher live birth rate per cycle than IUI with a hard-tip catheter.

Materials and methods

Patient groups

The study was performed in a total of 540 IUI cycles that were carried out in 418 patients (Cook group: n = 204; Frydman group n = 214) during the period 2001–2002. There was no selection according to...
Female characteristics and semen values (mean +/- SD) of patients

All patients had undergone a full infertility investigation including hormonal evaluation between day 2 and day 5 of the cycle, confirmation of ovulation by luteal progesterone determination or endometrial biopsy dating, two sperm examinations according to the most recent WHO criteria (World Health Organization, 1999), hysteroscopy and laparoscopy. The major indications for IUI included unexplained infertility (subfertility of at least 1 year duration in the presence of normal sperm examinations, regular menstrual cycle, normal hormonal values, open Fallopian tubes and normal uterine cavity), mild male infertility (an average of more than 5 x 10^6 motile sperm after preparation in two diagnostic samples, before the treatment, regardless of sperm morphology) and cervical factor infertility (negative post-coital test with or without previous cervical surgery).

The randomization was performed on the cycle level. After the informed consent form was signed, the study nurse drew a sealed envelope, which contained a form indicating which catheter should be used for the IUI procedure: a Soft-pass insemination catheter (Cook, J-SPI-068015, Indiana, USA) or a Frydman classical catheter (CCD, Paris, France).

Sperm analysis and preparation

Semen was collected by masturbation after 3–5 days of sexual abstinence. A semen analysis was performed following the WHO guidelines (World Health Organization, 1999). Sperm morphology was evaluated after Papanicolaou staining using strict criteria (Menkveld et al., 1990).

After liquefaction, the sperm sample was centrifuged over a discontinuous three-layer (50/70/100%) density gradient (Isolate Sperm Preparation Medium, Irvine Scientific, Santa Ana, CA, USA or Pure-Sperm, Nidacon International AB, Göteborg, Sweden) followed by one wash with HEPES-buffered Earle’s balanced salt solution supplemented with 0.3% human serum albumin (Sigma Chemical, St. Louis, MO, USA) and a second wash using IVF medium (MediCult, Copenhagen, Denmark) or fertilization medium (Cook, Sydney, Australia). The sample was then resuspended in 750 μl of IVF medium and subsequently incubated in a volume of 1–1.25 ml at 37°C and 5% CO₂. Immediately before the insemination, the sperm sample was concentrated by centrifugation to a volume of 250 μl.

Ovarian stimulation

In 97 cycles, ovarian stimulation was performed with Clomiphene citrate, in a dose of 50–100 mg from days 3–7, and in 443 cycles, ovarian stimulation was performed with non-recombinant FSH/LH (Menopur, Ferring, Suffern, NY, USA) in a low-dose step up stimulation protocol starting with 75 IU on day 2 of the cycle, as described before (Cohen, 2005). Ovarian response was monitored by ultrasound measurement of follicular size and by determination of serum estradiol (E₂) using a competitive electrochemiluminescence immunoassay (Roche Modular E170, Roche Diagnostics, Basel, Switzerland). In the clomiphene citrate group, ultrasound monitoring began on days 10 or 11 of the cycle. In the FSH/LH group, ultrasound monitoring began on day 6 of the cycle, and the average duration of ovarian stimulation was 10–12 days. A dose of 10 000 IU hCG (Pregnyl, Organon, Oss, Netherlands) was injected subcutaneously when one or two mature follicles were seen on ultrasound (≥16 mm). When women had three or more mature follicles (≥14 mm) at the time of hCG injection, selective follicle aspiration was performed before IUI, and usually one or two mature follicles were left intact after this procedure. The IUI was performed about 38–40 h after hCG injection. All patients were asked to abstain from intercourse for at least 3 days (maximum 5 days) before the day of IUI.

Statistical analysis

The endpoints were the pregnancy rate per cycle, (defined as positive hCG per IUI cycle) and the live birth rate per cycle (defined as the live birth of at least one child per IUI cycle). A power calculation estimated that a sample size of 270 patients per group was needed to show a 10% difference in pregnancy rate. Differences in pregnancy rate and live birth rate between groups were statistically evaluated by the χ² test and the Fisher’s exact test.

Results

The female age, duration of infertility and ovarian stimulation parameters were comparable between the Soft-pass catheter group and the Frydman catheter group (Table I). The sperm parameters (percentage of progressive motile sperm, number of sperm, normal forms and number of motile sperm used for insemination) were also comparable between the two groups (Table I).

In the Soft-pass catheter group three IUI cycles were excluded for analysis and patients were switched to IUI with the Frydman catheter, because insemination was impossible with the Soft-pass catheter. In the Frydman catheter group, one IUI procedure was impossible due to cervical resistance, and the patient was inseminated using an embryo transfer catheter (Cook, K-SOFT-5100, Eight Mile Plains, Queensland, Australia) and subsequently excluded for analysis. Therefore, 267 IUI cycles and 269 IUI cycles were available for analysis in the Soft-pass catheter group and the Frydman catheter group, respectively.

As summarized in Table II, there was no significant difference in pregnancy rate per cycle between the Soft-pass catheter group and the Frydman catheter group [20.2% (54/267) and 18.6% (50/269), respectively]. Both the live birth rate per cycle [14.6% (39/267)] and the multiple live birth rate per cycle [4% (2/54)] in the Soft-pass catheter group were comparable to the live birth rate per cycle [14.5% (39/269)] and the multiple live birth rate per cycle [6% (3/50)] in the Frydman catheter group. The results according to the type of ovarian stimulation are also summarized in Table II. After ovarian stimulation with

| Table I. Female characteristics and semen values (mean +/- SD) of patients treated with IUI using a Soft-pass catheter (n = 267) or a Frydman catheter (n = 269) |
|---------------------------------|------------------|------------------|
|                                | Soft pass        | Frydman          |
| **Female characteristics**     |                  |                  |
| Age female (years)             | 31.3 ± 4.3       | 31.8 ± 3.9       |
| Duration infertility (years)   | 3 ± 1.6          | 3.1 ± 1.5        |
| Primary infertility            | 72% (192)        | 72% (193)        |
| FSH/LH stimulation             | 83% (221)        | 81% (217)        |
| Number of follicles ≥14 mm at time of hCG injection | 1.7 ± 1 | 1.6 ± 0.9 |
| Estradiol (pg/ml) at time of hCG injection | 325 ± 239 | 320 ± 223 |
| Number of cycles               | 2.1 ± 1.3        | 2.1 ± 1.5        |
| **Semen characteristics (pre-processing)** |                  |                  |
| Progressive motile sperm (%)   | 54 ± 15          | 54 ± 15          |
| Number of sperm (million/ml)   | 68 ± 63          | 72 ± 57          |
| Normal forms                   | 16.5 ± 7.5       | 18.6 ± 9.3       |
| Number of motile sperm for insemination (millions) | 32.9 ± 29.8 | 33.6 ± 32 |

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gonadotrophins, the number of multiple live births per number of pregnancies was 6%. There was no significant difference in pregnancy rate when the following groups were compared: Soft-pass with FSH stimulation versus Soft-pass with CC stimulation, Frydman with FSH stimulation versus Frydman with CC stimulation, Frydman with FSH stimulation versus Soft-pass with FSH stimulation and Frydman with CC stimulation versus Soft-pass with CC stimulation.

Discussion

Intrauterine insemination and embryo transfers after IVF are a common practice in the treatment of infertility and can be performed using soft-tip catheters or hard-tip catheters. To the best of our knowledge, our study is the third randomized trial so far to investigate the effect of catheter consistency on the pregnancy rate after IUI, using other catheter types than those used in other randomized studies (Smith et al., 2002; Miller et al., 2005) or in the non-randomized prospective controlled study (Lavie et al., 1997), as discussed in the introduction section. In our study, the pregnancy (live birth) rate per cycle was comparable in the two groups. These data confirm the results from the published randomized studies (Smith et al., 2002; Miller et al., 2005) and suggest that the consistency of the catheter is not a major determining factor in clinical outcome after IUI.

Why does catheter consistency have a positive impact on clinical outcome after IVF with embryo transfer (reviewed in NICE guideline, 2004) but not after IUI? First, the effect of catheter tip on uterine contractility can be hypothesized to be more important at or around the time of implantation (embryo transfer) than at the time of ovulation (IUI). Indeed, after IUI, sperm is known to reach the peritoneal cavity very soon, but embryo implantation in the uterus occurs only about 7 days after fertilization. In contrast, after embryo transfer, the embryo will float around before implantation or will be apposed to endometrial cells without firm attachment for a few days (embryo transfer day 2 or day 3) or will implant within 1 day (embryo transfer day 5 or day 6). Therefore, the implantation rate per embryo may be reduced if the embryo transfer catheter causes direct damage to embryo(s) and/or endometrial lining or if the embryos are expelled through the cervix or via the Fallopian tubes. It has been recognized over the last years that the technique of embryo transfer is very important, and attention is needed for all details with respect to patient installation, preparation, catheter insertion under ultrasound guidance, etc (Schoolcraft et al., 2001). Second, any potential negative effect of a hard-tip catheter used for IUI may be overcome by the sheer volume of inseminated sperm (0.5 ml), at least 10 times higher than the suspension fluid for embryos (0.04 ml). In that context it is interesting to note that there is randomized evidence that IUI with a much higher volume (up to 4 ml) of inseminated sperm is more successful than classical IUI using 0.5 ml (Mamas, 1996; NICE guideline, 2004).

In our study, the total multiple live birth rate per cycle (5%) and the total multiple live birth per total number of live births (6%) were low, even lower than reported in previous publications from our centre (Spiessens et al., 2003), much lower than reported in the literature after ovarian stimulation with FSH.
(19%, Guzik et al., 1999; 27%, Goverde et al., 2005; 25%, Dickey et al., 2005) or with clomiphene citrate (10%) (reviewed in Cohlen et al., 2000, 2005), but higher than the 0% multiple pregnancy rate reported after ovarian stimulation with low-dose FSH in combination with GnRH antagonists (Ragni et al., 2004). In our study, the number of multiple live births per number of pregnancies was 6% after ovarian stimulation with gonadotrophins and 0% after ovarian stimulation with clomiphene citrate. The probability of achieving a multiple pregnancy after ovarian stimulation with IUI is correlated with the aggressiveness of the stimulation protocol and not with the catheter type. In our ovarian stimulation protocol, two drugs were used at low doses: clomiphene citrate (in a dose of 50–100 mg from days 3–7) or FSH/LH (75 IU in a low-dose step up system from day 2 of the cycle). Furthermore, only when one or two mature follicles were seen on ultrasound (≥16 mm), hCG was injected, and 38–40 h after hCG injection, the IUI was performed. If three or more follicles were observed, we performed selective follicular aspiration under ultrasound guidance 34 h after hCG injection till only one dominant follicle or two mature follicles were left, immediately followed by IUI. This technique seems to be efficient (De Geyter et al., 1996; Albano et al., 2001) to prevent multiple pregnancies after ovarian stimulation, but still needs to be confirmed in further studies.

We would like to point out three weaknesses in our study. First, bias may have been introduced by variability in outcome according to the rank order of the IUI cycles. Indeed, the study was done in all IUI cycles including the first cycle and subsequent cycles, and no selection was made according to cycle number. Second, bias may have been introduced by variability in skills between physicians performing the inseminations. However, in our study, it was impossible to assess whether the number of inseminations was equally distributed between inseminators, because the name of the inseminator was not written down systematically in the file of the patient. Third, the lack of information regarding sperm morphology at the time of IUI can be considered as another weakness. Indeed, sperm morphology can affect the monthly fecundity rate and the cumulative live birth rate after controlled ovarian stimulation and IUI, as published recently (Spiessens et al., 2003).

In conclusion, our randomized study has not confirmed our hypothesis that catheter consistency affects the pregnancy rate after IUI. Furthermore, our results indicate that low-dose FSH ovarian stimulation in combination with IUI leads to an acceptable pregnancy rate per cycle (18%) and an acceptable multiple live birth rate per total number of live births (7.7%).

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References


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