Predictive factors for pregnancy after intrauterine insemination (IUI): An analysis of 1038 cycles and a review of the literature

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Objective: To determine the predictive factors for pregnancy after IUI.
Design: Retrospective study.
Setting: A single university medical center.
Patient(s): One thousand thirty-eight IUI cycles in 353 couples were studied between 2002 and 2005.
Intervention(s): Ovarian stimulation via SC injection of FSH or hMG was performed daily; IUI was then performed 36 hours after triggering ovulation if at least one follicle measuring >16 mm and an endometrial thickness of >7 mm (with triple-line development) were obtained.
Main Outcome Measure(s): Clinical pregnancy rates were analyzed according to the woman’s age, the type of infertility, the spermogram characteristics, the total motile spermatozoa (TMS) count, the E2 level before hCG injection, and the number of mature follicles.
Result(s): The couple with the best chance of pregnancy can be described as follows: an under 30 woman with cervical or anovulatory infertility and a man with a TMS ≥ 5 million spermatozoa. The “ideal” stimulation cycle enables the recruitment of two follicles measuring >16 mm with an E2 concentration >500 pg/mL on the day of hCG administration. The best results are obtained when IUI is performed using a soft catheter.
Conclusion(s): This study enabled the characterization of many prognostic factors for pregnancy and particularly those for women at risk of multiple pregnancies after IUI. (Fertil Steril® 2010;93:79–88. ©2010 by American Society for Reproductive Medicine.)
Key Words: Intrauterine insemination, ovarian stimulation, spermogram, clinical pregnancy rate, twin pregnancy

At present, 16% of prospective parents seek medical advice for infertility. Some of these couples will need to undergo IUI using the prospective father’s fresh sperm. This method of assisted reproductive technology is indicated in cases of cervical infertility, relative male factor infertility, anovulation, endometriosis with a healthy fallopian tube, and, lastly, unexplained infertility.

In the literature, many factors have been reported as influencing pregnancy rates after IUI: the woman’s age, the length of infertility, indications (type of infertility), the sperm count in the initial analysis or in the catheter, the number of mature follicles, the E2 concentration on the day of hCG administration, and the type of catheter used. However, the various investigators have not agreed on the nature and ranking of these criteria.

In France, the clinical pregnancy rate per IUI cycle is only 11.8%, and the rate of childbirth per cycle is below 9% (1).

The aim of this retrospective study was to report on 4 years of IUI practice (1038 cycles) at Amiens University Medical Center and determine the predictive factors for successful pregnancy and birth.

MATERIALS AND METHODS
Before each course of treatment, the following tests were performed: hysterosalpingography, serum hormone assays on the third day of the menstrual cycle (estradiol-17β, FSH, LH, and PRL), semen analysis (notably the total motile spermatozoa [TMS] count), and a postcoital test (Hüllner’s test).

After centrifugation of a semen sample in a discontinuous density gradient column (Puresperm, Nidacon, Mölndal, Sweden), the TMS count was obtained by multiplying the total sperm count by the prewash percentage of mobility. Sperm morphology was rated according to the World Health Organization (WHO) criteria (2). IUls with donor sperm were excluded from the present study.

The postcoital test was positive when more than 10 motile spermatozoa were observed in the endocervical sample with an Insler score >10. If the postcoital test remained negative despite the administration of additional vaginal estrogens or ovarian stimulation (i.e., cervical infertility), then IUI was considered to be appropriate.
Anovulatory infertility corresponded to polycystic ovary syndrome (diagnosed according to the Rotterdam criteria), and ovarian insufficiency was defined as a serum FSH level >9.5 IU/L at the beginning of the menstrual cycle.

A laparoscopy with tubal permeability evaluation was performed when the salpingography suggested fallopian tube infertility or when a combination of dysmenorrhea and dyspareunia suggested endometriosis as a cause of infertility. Only American Fertility Society (AFS) stage I or II pelvic endometriosis was considered to be an indication for IUI.

After this assessment, IUI was effectively indicated if all the following conditions were met: at least one permeable fallopian tube, an FSH level below 12 IU/L, and more than 500,000 motile, normal spermatozoa.

Ovarian Stimulation
All the IUI cycles were combined with gonadotropic ovarian stimulation. The treatment was initiated on the second day of the cycle and was continued until ovulation or observation of an LH initiating rise. We used urinary FSH (Febremon; Gynecorier, Sophia-Antipolis, France), recombinant FSH (Gonal-F; Ares-Serono, Geneva, Switzerland; or Puregon, Organon International Inc, Roseland, NJ), or hMG (Menopur, Ferring SAS, Ares-Serono, Geneva, Switzerland; or Puregon, Organon International Inc, Roseland, NJ), or hMG (Menopur, Ferring SAS, St. Prex, Switzerland). The administration of GnRH agonist was not required. The initial dose of gonadotropin prescribed (37.5–100 IU/day) depended on the woman’s hormonal profile and age and the duration of infertility. The initial dose was maintained until the first sixth day of stimulation and thereafter adapted as a function of the ovarian response.

The evaluation combined serum hormone assays (estradiol-17β and LH) and a vaginal ultrasound examination evaluating follicle number and size and endometrial maturation.

E2 and LH were measured using time-resolved immunoluminescence assays with an ACS:180 Plus analyser and E2-6II and LH2 kits (Bayer Corporation, Tarrytown, NY). The detection limits of the E2 and LH assays were 10 pg/mL and 0.07 IU/L, respectively. This evaluation was begun on the seventh day of treatment and repeated after 2 or 3 days, depending on the follicular growth. Ovulation triggering was achieved by SC injection of 250 μg of recombinant hCG (Ovitrelle, Ares-Serono). Insemination was performed 2 days later (i.e., 36 hours after the hCG injection). The criteria used for triggering ovulation were as follows: at least one follicle measuring >16 mm and triple-line preovulatory, endometrial maturation, with a thickness over 7 mm. If an LH initiating rise was observed (i.e., serum LH elevated by around 180% compared with the previous level), the insemination was delayed until the following day.

IUI and Luteal Support
Two hours before the insemination and after 48–72 hours of abstinence, semen was collected at the laboratory. After a motility determination, the spermatozoa were washed free from seminal liquid and prepared for insemination (postwash TMS = number of spermatozoa inseminated). Abnormal spermatozoa were rated according to the WHO criteria. Teratospermia was defined as an abnormal sperm rate of over 70%.

A soft catheter (the Frydman series from CCD, Paris, France) was used for the insemination process. The end of the catheter was placed in the center of the uterine cavity, and the sperm preparation (0.2–0.4 mL) was injected slowly (over 15 seconds). If the soft catheter was unable to pass the cervix, a hard catheter was used (the TDT series from CCD). A 2-week course of daily treatment with 400 mg of micronized P (Utrogestan, Cassene-Aventis, Paris, France) was prescribed. After this time, the woman was allowed to perform a pregnancy test (a serum β-hCG assay). If the test was positive, it was repeated 7 days later to check the β-hCG time course (micronized P was withdrawn at the same time). Clinical pregnancies were defined as those with a fetal heart beat on ultrasound. The pregnancy was qualified as ongoing when it reached 12 weeks of amenorrhea.

Statistical Methods
Results were expressed as means ± SD. Categorical variables were compared using a χ²-test, and continuous variables were analyzed using Student’s t-test. P < .05 was considered statistically significant. Multivariate logistic regression analysis was used to test for correlations between clinical/biological variables and the occurrence of pregnancy. To determine informative covariates, we performed backward variable selection by evaluation of the multivariate normality of estimates. The variables were normally distributed, and some were collinear, such as [1] the woman’s age and cycle number and [2] spermatozoa mobility and the number of inseminated spermatozoa. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated separately for each factor. CIs exclusive of unity were considered to be statistically significant. The study protocol was approved by the local independent ethics committee.

RESULTS
We studied a total of 1038 IUI cycles in 353 couples between 2002 and 2005. On average, each couple underwent 2.6 ± 1.6 IUI cycles (range, 1–9). The infertility had a female cause in 24.3% of cases, a male cause in 32.6% of cases, and combined male and female causes in 32.6% of cases. In 10.5% of cases, no cause could be found (i.e., unexplained infertility). The female causes could be broken down as follows, in order of prevalence: cervical infertility (31.5%), anovulation (22.2%), ovarian insufficiency (15.1%), AFS stage I and II pelvic endometriosis (8.1%), and fallopian tube anomalies (2.3%). Two causes were present in 20.9% of cases.

At the time of the first IUI cycle, the woman’s mean age was 31.5 ± 4.4 years, and the mean body mass index (BMI) was 23.6 ± 14.4 kg/m². More than a third of the women (33.9%) had achieved a prior, spontaneous pregnancy (and with their current partner in two-thirds of these cases). The precycle hormonal evaluation gave the following mean
values: FSH, 6.9 ± 2.4 IU/L; LH, 5.65 ± 4.5 IU/L; E2, 51.9 ± 45 pg/mL.

The average number of spermatozoa determined in the semen analysis was 60.5 ± 56.7 million/mL, with a progressive motile proportion (type a) of 32.8% ± 15% and a progressive, linear proportion (type a + b) of 42.9% ± 14.5%. The mean teratospermia rate was 37.2% ± 17%. The TMS count was 23.4 ± 14 million.

Recombinant or urinary FSH was administered in the majority of cycles (82.6%). The total dose of gonadotropin used was 585 ± 368 IU, and the length of stimulation was 8.5 ± 3.5 days. On the day of hCG injection or during a spontaneous LH peak, we observed 1.4 ± 0.6 follicles measuring >16 mm, with a concomitant mean E2 concentration of 291 ± 153 pg/mL and an endometrial thickness of 9.4 ± 1.8 mm.

IUI was performed with an average of 12.5 ± 4.6 million motile spermatozoa. One hundred thirty-six patients underwent insemination the day after observation of a spontaneous LH peak and achieved a clinical pregnancy rate of 14%; this value was not significantly different from the rate (13.6%) when the IUI was carried out 36 hours after triggering ovulation with hCG. Conversely, a significant difference (P < 0.01) in the clinical pregnancy rate was noted when IUI was carried out with a soft catheter (15.3%) rather than a hard one (7%).

The 1038 IUI cycles gave rise to 153 pregnancies (i.e., 14.7% per cycle). The pregnancies were divided into categories according to their subsequent outcome: eight biochemical pregnancies (5.2% of all pregnancies), four ectopic pregnancies (2.6%), 19 miscarriages during the first trimester (13.5%), and 122 ongoing pregnancies (79.7%). This corresponded to an ongoing pregnancy rate of 11.7% per IUI cycle. Of the 141 clinical pregnancies (ongoing pregnancies and early pregnancy loss), 19 were twin pregnancies (13.5%), but there were no triplet or other multiple pregnancies. At the end of the third cycle, 113 clinical pregnancies had been achieved (80%). A slight increase in the pregnancy rate was noticed during the sixth cycle, probably because of more intense stimulation (Table 1). Only 16 cycles were performed after more than six attempts, but no pregnancies occurred in these cases. The clinical pregnancy rate per couple was 39.9%, with an ongoing pregnancy rate per couple of 34.5%.

Focusing on the first IUI cycle (n = 353), the clinical pregnancy rate per cycle was 16.4%. The pregnant and nonpregnant groups did not significantly differ in terms of the woman’s age and the infertility type. The only significant parameter was the number of inseminated spermatozoa: 15.6 ± 14.7 million in the pregnant group versus 10.7 ± 10.3 million in the nonpregnant group (P < 0.02).

### Predictive Factors for Pregnancy: Characteristics of the Prospective Mother

The woman’s age was the strongest predictor of success in all indications, with an ongoing pregnancy rate per couple of 38.5% for the under 30s and 12.5% for the over 40s (P < 0.000001). The proportion of twin pregnancies decreased with age, with a significant difference between the under or over 30s (20% vs. 8.6%; P < 0.05; Table 2). Smoking addiction did not have a significant influence on IUI outcome.

Ovarian function was estimated in terms of the serum concentrations of FSH and E2 before the beginning of the cycle. The generally accepted thresholds are 9.4 IU/L and 80 pg/mL, respectively (3). In our study, the ongoing pregnancy rate per couple was 35.7%, with an FSH level below 9.4 IU/L and 28.9% with an FSH level below 9.4 IU/L (no significant difference); in terms of the E2 concentration, the ongoing pregnancy rate per couple was 36.2% (for <80 pg/mL) versus 18.7% (for >80 pg/mL; P = 0.05).

Couples treated for cervical or anovulatory indications achieved an ongoing pregnancy in 52.4% of cases. The

<table>
<thead>
<tr>
<th>Cycle</th>
<th>No. of cycles</th>
<th>Clinical pregnancy %/cycle (n)</th>
<th>Ongoing pregnancy %/cycle (n)</th>
<th>Cumulative cancellation rate % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>353</td>
<td>16.4 (58)</td>
<td>15.0 (53)</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>245</td>
<td>12.2 (30)</td>
<td>10.6 (26)</td>
<td>18.3 (55)</td>
</tr>
<tr>
<td>3</td>
<td>156</td>
<td>16.0 (25)</td>
<td>13.4 (21)</td>
<td>43.0 (118)</td>
</tr>
<tr>
<td>4</td>
<td>121</td>
<td>10.7 (13)</td>
<td>7.4 (9)</td>
<td>52.1 (132)</td>
</tr>
<tr>
<td>5</td>
<td>86</td>
<td>9.3 (8)</td>
<td>7.0 (6)</td>
<td>64.7 (158)</td>
</tr>
<tr>
<td>6</td>
<td>61</td>
<td>11.5 (7)</td>
<td>11.5 (7)</td>
<td>74.3 (177)</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>96.5 (223)</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>97.8 (226)</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>98.7 (228)</td>
</tr>
<tr>
<td>Total</td>
<td>1038</td>
<td>13.5 (141)</td>
<td>11.7 (122)</td>
<td></td>
</tr>
</tbody>
</table>

Note: After the sixth cycle (n = 16; 1.5% of all cycles), no pregnancies were observed. For clinical pregnancy rates, statistical differences were not significant for the first six cycles.

average ongoing pregnancy rate for other female causes was only 15% per couple ($P<.01$). The likelihood of a twin pregnancy was also higher with cervical and anovulatory indications (21% and 22%, respectively). No twin pregnancies were observed in cases of endometriosis, ovarian insufficiency, or unexplained infertility. Of the 28 patients with endometriosis, three achieved an ongoing pregnancy, and all belonged to the group in which endometriosis and male indications were combined.

More than seven patients out of 10 underwent less than 10 days of treatment, with a clinical pregnancy rate per cycle of 13.5%; this value did not significantly differ from that for patients who were stimulated for more than 10 days (13.6%). Forty cycles required more than 15 days of injection, with a clinical pregnancy rate per cycle of 17.5%.

The mean $E_2$ concentration on the day of hCG administration was 285 pg/mL in the no-pregnancy group and 329 pg/mL in the group with clinical pregnancy ($P<.05$). To further analyze these criteria, we selected an $E_2$ cutoff concentration of 500 pg/mL (which generally corresponds to two mature follicles) and also considered the number of follicles measuring $>16$ mm (one, two, or three or more) that were present on the day of hCG administration. In Table 3, we present only the cases for these data that were available on the day of hCG administration. We found that the clinical pregnancy rate per cycle was 12.9% versus 23.3%, depending on whether the $E_2$ concentration on the day of hCG administration was below or above 500 pg/mL ($P<.02$), respectively. The difference was also significant ($P<.02$) if the proportion of twin pregnancies was studied (9.2% ongoing pregnancies below 500 pg/mL vs. 35% above 500 pg/mL). Regarding the number of follicles $>16$ mm, the clinical pregnancy rate per cycle increased from 11.2% with one follicle to 23.2% with three or more ($P<.01$). Only 5.5% of the inseminations were carried out when three or more follicles $>16$ mm were observed on the day of hCG administration.

In contrast, the total number of FSH units administered (<500 IU, between 500 and 1000 IU, and $>1000$ IU), the size of the largest follicle (above or below 18 mm), and the endometrial thickness (above or below 8 mm) on the day of hCG administration had no influence on the clinical pregnancy rate per cycle (12.5%, 14%, and 16.4% for the three FSH classes; 12.9% and 13.6% for the two follicle size classes; 11.9% and 14.2% for the two endometrial thickness classes).

### Predictive Factors for Pregnancy: Characteristics of the Prospective Father

The clinical pregnancy rate per couple was 28.5% when the TMS was lower than 5 million and was significantly higher (44.3%) when the TMS was above 5 million ($P<.05$). This difference was particularly clear when the number of inseminated spermatozoa was higher or lower than 1 million, respectively (14% vs. 6.4% per cycle; $P=.10$). The smallest number of inseminated spermatozoa that led to a pregnancy was 45,000.

The clinical pregnancy rate per couple decreased from 40.7% to 21.4% if teratospermia was higher than the abnormal form threshold (70%; $P<.05$). Our center usually offers an intracytoplasmic sperm injection (ICSI) procedure if the percentage of abnormal forms exceeds 70%. Of 14 cases in which this was true, 10 men had $<50\%$ sperm mobility (progressive and linear) but a sperm count over 50 million/mL (two pregnancies, one spontaneous miscarriage, and one ectopic pregnancy). This suggests that the high sperm count compensated (at least in part) for the poor sperm quality.

Table 4 summarizes the predictive factors associated with the occurrence of pregnancy in a multivariate analysis.

### DISCUSSION

IUI is often suggested to infertile couples in which the woman has at least one permeable fallopian tube and the man has partially modified sperm. The pregnancy rate depends on sperm parameters, female factors, and the ovarian stimulation methods. We therefore decided to evaluate our results and search for factors that were predictive of pregnancy after IUI.

### Pretherapeutic Factors

In our study, the woman’s age significantly influenced the ongoing pregnancy rate, at 38.5% for the under 30s versus

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**TABLE 2**

Clinical and ongoing pregnancy rates per couple and the frequency of twin pregnancies for woman in different age groups.

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of couples (%)</th>
<th>Clinical pregnancy/couple % (n)</th>
<th>Ongoing pregnancy/couple % (n)</th>
<th>Twin pregnancy/clinical pregnancy % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤30</td>
<td>135 (38.2)</td>
<td>44.4 (60)</td>
<td>38.5 (59)</td>
<td>20 (12)$^a$</td>
</tr>
<tr>
<td>31–35</td>
<td>145 (41.2)</td>
<td>40 (58)</td>
<td>31.7 (46)</td>
<td>10.3 (6)$^b$</td>
</tr>
<tr>
<td>36–40</td>
<td>57 (16.1)</td>
<td>33.3 (19)</td>
<td>26.3 (15)$^a$</td>
<td>5.2 (1)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>16 (4.5)</td>
<td>25 (4)</td>
<td>12.5 (2)$^b$</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>353</td>
<td>39.9 (141)</td>
<td>34.5 (122)</td>
<td>13.5 (19)</td>
</tr>
</tbody>
</table>

$^{a,b}$Indicates significant difference at $P<.05$.

_Merviel. Pregnancy and IUI. Fertil Steril 2010._
12.5% for the over 40s. Nuojua-Huttunen et al. (4) found a 13.7% pregnancy rate per cycle among 811 IUI cycles in women younger than 40, 4.1% for those over 40, and no successful births after 42 years of age. Surprisingly, in Brzechffa et al.’s study (5), the age of women under 40 had no influence on the pregnancy rate after stimulation with clomiphene citrate and hMG. In contrast, Bronte et al. (6) examined 9963 cycles and reported an age-related difference in the pregnancy rate: 18.9% until age 26, 13.9% between 26 and 30, 12.4% between 31 and 35, 11.1% between 36 and 40, 4.7% between 41 and 45, and 0.5% over age 45 ($P < .001$). Lastly, Goverde et al. (7) stated that the woman’s age is the most important factor influencing the likelihood of pregnancy, whatever treatment is chosen (IUI or IVF) and that male factor or unexplained infertilities had no impact at all.

The performance of hormone assays (estradiol-17β and FSH) on the second or third day of the cycle is one way of evaluating ovarian reserves. In our study, we did not find any significant difference in pregnancies according to whether the FSH concentration was above or below 9.4 IU/L or whether the $E_2$ concentration was above or below 80 pg/mL. Mullin et al. (8) also evaluated these parameters with FSH and $E_2$ thresholds of 15 IU/l and 80 pg/mL, respectively. They also came to the conclusion that there were no significant differences in the per-cycle pregnancy rates: 15.4% versus 23% when FSH level was the criterion and 14.6% versus 21.7% for the $E_2$ baseline level.

Another success factor for post-IUI pregnancy is the length of infertility. Indeed, it has often been noted that the shorter the infertility duration, the lower the likelihood of pregnancy (9, 10). Nuojua-Huttunen et al. (4) reported significantly different pregnancy rates according to whether the length of infertility was below or above 6 years (14.2% vs. 6.1%). However, our study (like that of Goverde et al. [7]) does not show this difference. However, it should be emphasized that IVF is generally preferred when the infertility period is longer than 4 years.

### TABLE 3

Clinical and ongoing pregnancy rates per cycle and the frequency of twin pregnancies for the groups classified according to the $E_2$ concentration and the number of follicles $>16$ mm on the day of triggering.

<table>
<thead>
<tr>
<th>$E_2$ concentration on the day of triggering or the LH peak:</th>
<th>No. of cycles (%)</th>
<th>Clinical pregnancy %/cycle (n)</th>
<th>Ongoing pregnancy %/cycle (n)</th>
<th>Twin pregnancies/clinical pregnancies % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt;500$ pg/mL</td>
<td>845 (90.3)</td>
<td>12.9 (109)</td>
<td>11 (93)$^a$</td>
<td>9.2 (10)$^a$</td>
</tr>
<tr>
<td>$\geq 500$ pg/mL</td>
<td>90 (9.7)</td>
<td>23.3 (20)</td>
<td>20 (18)$^b$</td>
<td>35 (7)$^b$</td>
</tr>
<tr>
<td>Total</td>
<td>935</td>
<td>13.8 (129)</td>
<td>11.1 (111)</td>
<td>13.2 (17)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of follicles $&gt;16$ mm on the day of triggering or the LH peak:</th>
<th>No. of cycles (%)</th>
<th>Clinical pregnancy %/cycle (n)</th>
<th>Ongoing pregnancy %/cycle (n)</th>
<th>Twin pregnancies/clinical pregnancies % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>641 (63.7)</td>
<td>11.2 (72)</td>
<td>9.8 (63)$^c$</td>
<td>5.5 (4)</td>
</tr>
<tr>
<td>2</td>
<td>309 (30.7)</td>
<td>17.5 (54)</td>
<td>14.5 (45)$^d$</td>
<td>16.7 (9)</td>
</tr>
<tr>
<td>3</td>
<td>56 (5.6)</td>
<td>23.2 (13)</td>
<td>21.4 (12)</td>
<td>38.4 (6)</td>
</tr>
<tr>
<td>Total</td>
<td>1006</td>
<td>13.8 (139)</td>
<td>11.9 (120)</td>
<td>12.9 (18)</td>
</tr>
</tbody>
</table>

$^a,b$ Indicates significant difference at $P < .02$.

$^c,d$ Indicates significant difference at $P < .01$.


### TABLE 4

Factors associated with the occurrence of ongoing pregnancy (multivariate analysis).

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical or anovulatory infertility</td>
<td>3.49</td>
<td>2.53–4.61</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Woman’s age $&lt;40$</td>
<td>2.84</td>
<td>1.75–4.34</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Soft catheter</td>
<td>2.18</td>
<td>1.62–3.01</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Teratospermia $\leq 70%$</td>
<td>1.90</td>
<td>1.42–2.74</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>$E_2 \geq 500$ pg/mL at hCG administration</td>
<td>1.81</td>
<td>1.11–2.59</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>$&gt;1$ follicle $&gt;16$ mm at hCG administration</td>
<td>1.56</td>
<td>1.21–1.98</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>TMS $\geq 5$ million</td>
<td>1.55</td>
<td>1.12–2.69</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Note: TMS count is prewash; teratospermia means abnormal forms of spermatozoa according to the WHO criteria.

In this study, BMI and smoking status did not appear to affect pregnancy rates. Concerning the BMI, Dodson and Legros (11) did not find any difference, although they observed that the dose of gonadotropin had to be increased to stimulate obese women. A recent study (12) reported an observed that the dose of gonadotropin had to be increased.

Gros (11) did not find any difference, although they considered the pregnancy rates. Concerning the BMI, Dodson and Lehammond (20) showed that in IUI with donor sperm, the pregnancy rates per cycle were lower for patients with AFS stage I or II endometriosis (2% and 6.5%) than for control groups (11% and 14%). According to Nuojua-Huttunen et al. (4), endometriosis is also harmful, with a pregnancy rate per cycle of 15.3% in unexplained infertility versus 6.5% for endometriosis (P < .05). Prado-Perez et al. (21) compared three groups of women treated with IVF: one group without endometriosis, one with stage I or II endometriosis, and one with stage III or IV endometriosis. The pregnancy rates per cycle were 25.7%, 22.7%, and 5.6%, respectively. There was no significant difference between the first two groups, but in stage III or IV endometriosis, the difference becomes significant (P = .006). It has been suggested that cytokines and growth factors secreted by the ectopic endometrial tissue could interfere with ovulation, fertilization, implantation, and embryonic development (22). Shapiro et al. (23) studied the endometrial thickness in 207 IUI cycles after hMG stimulation. In the endometriosis group, the endometrium is often thinner than in the cases of the other indications (male factor infertility or anovulation), with an OR of 8.3 (95% CI, 2.4–37.4). Those results raise the question of whether patients presenting with endometriosis should be treated with IVF directly. Indeed, Dmowski et al. (24) published a study that aimed to compare pregnancy rates for couples treated with IUI and those treated directly with IVF. Each patient underwent laparoscopy to evaluate the pathology and surgically treat the endometriosis before stimulation. Although comparisons were drawn between the groups, the latter differed significantly (P < .05) in terms of the endometriosis stage, with more stage II cases in the IUI group and more stage IV cases in the IVF group. The pregnancy rate after the first IVF cycle was 47%, with a cumulative rate of 41% after six IUI cycles (P < .05). The conclusion was that IVF should be recommended to women over 38 if the endometriosis is stage III or IV or if a male or tubal factor coexists. If IUI is carried out anyway, Dmowski et al. advise limiting it to three or four cycles. Again, with respect to endometriosis, two prospective, randomized studies compared IUI in natural or stimulated cycles (25, 26). If we pool the results of both reports, the pregnancy rates are 2% for 280 natural cycles and 11% for 254 hMG-stimulated cycles.

Indications for Treatment: Female Factor Infertility

The best results were obtained in cervical indications, with a clinical pregnancy rate per couple of 55.6% (not linked to the woman’s age). In various studies focusing on this indication, Gallot-Lavallée et al. (13) reported that the mean pregnancy rate after insemination in a natural cycle is lower when stimulated by gonadotropin. However, other studies show that the cumulative pregnancy rate goes up to 43% (14) even when IUI is not preceded by induction of ovulation. Massin et al. (15) suggested performing IUI in spontaneous cycles in cervical indications when the women is younger than 35 and no male factors coexist. In our center, we are understandably interested in this approach because 21% of the pregnancies obtained in cervical indications were twin pregnancies.

In our study, a pregnancy rate per couple of 47.4% was obtained for an IUI carried out in cases of anovulation. A comparable result is found in the study by Vlahos et al. (16), with 19.1% of pregnancies per cycle for anovulation versus 9.1% in cases of endometriosis, 11% for male factor infertility, and 10% in cases of unexplained infertility. The same result appears in the article by Dickey et al. (17), who reported pregnancy rates of 46% for anovulation, 38% for cervical, male factor, or unexplained infertility; 34% for endometriosis; and 26% in cases related to the fallopian tubes. Our study also highlights the high clinical pregnancy rate when stimulation lasts more than 15 days (17.5% per cycle). The same results also come out of the Belaisch-Allart et al. (18) study, with a clinical pregnancy rate of 31.4% per cycle in the event of stimulation sustained for more than 15 days. However, the ongoing pregnancy rates per cycle are only 12.5% and 20%, respectively.

In endometriosis, the pregnancy rate per couple was close to 10.7% in our study. This situation is one of the most difficult to treat successfully. Indeed, Jansen (19) and Toma and Hammond (20) showed that in IUI with donor sperm, the pregnancy rates per cycle were lower for patients with AFS stage I or II endometriosis (2% and 6.5%) than for control groups (11% and 14%). According to Nuojua-Huttunen et al. (4), endometriosis is also harmful, with a pregnancy rate per cycle of 15.3% in unexplained infertility versus 6.5% for endometriosis (P < .05). Prado-Perez et al. (21) compared three groups of women treated with IVF: one group without endometriosis, one with stage I or II endometriosis, and one with stage III or IV endometriosis. The pregnancy rates per cycle were 25.7%, 22.7%, and 5.6%, respectively. There was no significant difference between the first two groups, but in stage III or IV endometriosis, the difference becomes significant (P = .006). It has been suggested that cytokines and growth factors secreted by the ectopic endometrial tissue could interfere with ovulation, fertilization, implantation, and embryonic development (22). Shapiro et al. (23) studied the endometrial thickness in 207 IUI cycles after hMG stimulation. In the endometriosis group, the endometrium is often thinner than in the cases of the other indications (male factor infertility or anovulation), with an OR of 8.3 (95% CI, 2.4–37.4). Those results raise the question of whether patients presenting with endometriosis should be treated with IVF directly. Indeed, Dmowski et al. (24) published a study that aimed to compare pregnancy rates for couples treated with IUI and those treated directly with IVF. Each patient underwent laparoscopy to evaluate the pathology and surgically treat the endometriosis before stimulation. Although comparisons were drawn between the groups, the latter differed significantly (P < .05) in terms of the endometriosis stage, with more stage II cases in the IUI group and more stage IV cases in the IVF group. The pregnancy rate after the first IVF cycle was 47%, with a cumulative rate of 41% after six IUI cycles (P < .05). The conclusion was that IVF should be recommended to women over 38 if the endometriosis is stage III or IV or if a male or tubal factor coexists. If IUI is carried out anyway, Dmowski et al. advise limiting it to three or four cycles. Again, with respect to endometriosis, two prospective, randomized studies compared IUI in natural or stimulated cycles (25, 26). If we pool the results of both reports, the pregnancy rates are 2% for 280 natural cycles and 11% for 254 hMG-stimulated cycles.

Indications for Treatment: Male Factor Infertility

In cases of male factor infertility, we obtained a clinical pregnancy rate of 41.7% per couple. If we only consider the number of spermatozoa, their mobility, and the abnormal forms, our study does not show any significant difference according to these parameters, as long as they are normal. In contrast, if we combine oligospermia (<20 million/mL) and asthenospermia (mobility at <25%), the rate of clinical pregnancy per couple decreases from 37.6% to 13.4% (P < .05). With respect to the sperm count, Sakhel et al. (27) obtained (for 1662 IUI cycles) a pregnancy rate per cycle of 30.3% with more than 5 million spermatozoa/mL versus 18.8% with less than 5 million (P = .10). Belaisch-Allart et al. (18) obtains a pregnancy rate per cycle of 12.5% with less than 10 million spermatozoa/mL and of 17% with more than 20 million. Although these differences are not statistically significant, those two studies illustrate a direct relationship between the number of spermatozoa (in the initial analysis or in the catheter) and the pregnancy rate.
Focusing now on mobility, Belaisch-Allart et al. (18) did not find any link between the percentage of motile spermatozoa (< or \( \geq 40\% \)) and the pregnancy rate. In contrast, Sakhel et al. (27) described an increase in the pregnancy rate from 17.1% to 30.4% if the mobility exceeded 20% \((P=0.06)\). In our study, only initial (d-type) immotility proved to be a significantly predictive parameter: the pregnancy rate per couple decreased from 40.9% to 19.3% if 70% of the spermatozoa were immobile. To the best of our knowledge, there are no studies focusing solely on this parameter.

With respect to spermatozoid morphology, Burr et al. (28) noted a drop in the pregnancy rate from 18.2% to 4.3% per cycle when teratospermia reaches 90%. According to Belaisch-Allart et al. (18), a teratospermia rate over 80% argues against IUI. Furthermore, Karabinus (29) did not report any difference in the pregnancy rate under this threshold. Wainer et al. (30) analyzed 2564 IUIs and reported that the pregnancy rates were not significantly influenced by teratospermia as long as more than 5 million motile spermatozoa were available for insemination. However, our present study shows a pregnancy rate per couple that decreases from 40.7% to 21.4% if the degree of teratospermia is greater than 70% \((P<.05)\). In our center, we perform a spermogram during each IUI cycle if the baseline teratospermia value is around 70%. If the teratospermia worsens, we suggest an ICSI procedure.

Miller et al. (31) reported a pregnancy rate per cycle of 12.4% when the total number of collected motile spermatozoa (TMS) is over 20 million, compared with 7.4% when it is between 10 and 20 million. For a value under 10 million, he suggests steering the couple towards IVF. In the same sense, Dickey et al. (32), Horvath et al. (33), and Van Voorhis et al. (34) reported the best pregnancy rates when more than 10 million motile spermatozoa were selected. According to other investigators, the threshold is lower: Huang and Lai (35), for example, consider that it could be around 5 million. We found the same result in our study, with a pregnancy rate per couple of 44.3% for over 5 million versus 28.5% for under 5 million \((P<.05)\).

It has been suggested that the number of motile spermatozoa inseminated is a potential predictive factor. In our study, the pregnancy rate per cycle was around 6.4% when the number of inseminated motile spermatozoa was below 1 million and 14% when the number was over 1 million (not significant). For the 9963 cycles studied by Bronte et al. (6), the pregnancy rate was about 11% per cycle when between 4 and 6 million motile spermatozoa were inseminated. An additional increase in the number did not improve the rate, but the value significantly falls if the count goes below 2 million (5%). Campan et al. (36) did not obtain any pregnancies when the number of inseminated motile spermatozoa was below 1 million. According to Sakhel et al. (27), the inseminated motile spermatozoa count is the most significant parameter \((P=0.009)\), with an 8% pregnancy rate per cycle with less than 500,000 inseminated spermatozoa versus 30.6% for a count over 5 million. Lastly, Belaisch-Allart et al. (18) noted a 2.9% pregnancy rate per cycle (for 880 inseminations) when fewer than 1 million spermatozoa were inseminated but a 15%–18% pregnancy rate per cycle with between 1 and 10 million \((P<.05)\).

**Indications for Treatment: Unexplained Infertility**

In cases of unexplained infertility, we obtained a clinical pregnancy rate per couple of 35.1%. Dickey et al. (17) and Aboulghar et al. (37) reported values of 38% and 29.8% per couple, depending on whether six or more IUI cycles were performed or whether a cutoff at three cycles was preferred. Hughes analyzed the data from 22 studies and a total of 5214 cycles (38). The pregnancy rate per cycle for this indication is 15% for stimulation with gonadotropin, 6% in natural cycles, and 7% for stimulation with clomiphene citrate. This metaanalysis prompted the publication of guidelines by the Royal College of Obstetricians and Gynaecologists (RCOG) in 1998: RCOG advises ovarian stimulation followed by IUI as an effective treatment for couples in which infertility is unexplained. Guzyck et al. (39) published a meta-analysis of 45 studies and 1806 IUI cycles. The pregnancy rates in natural cycles and those stimulated with clomiphene citrate or hMG were 3.8% \((n=378)\), 7.7% \((n=315)\), and 17.1% \((n=1113)\), respectively. On the basis of Guzyck et al.’s article, Colhen et al. (40) provided a summary of 17 randomized studies representing 3662 cycles. In practice, IUI was seen to be generally superior to intercourse planned in stimulated cycles \((OR, 2.1; 95\% CI, 1.3–5.5)\) in seven randomized studies. In contrast, the difference between IUI in stimulated cycles and natural cycles was not significant \((OR, 1.7; 95\% CI, 0.9–3.2)\).

The choice between IUI and IVF in cases of unexplained infertility was the major theme of a debate in 2003 between Collins (41) (who judged that the cost/efficacy balance in this situation was in favor of IVF) and Hughes (42) (who was convinced of the superiority of IUI as the first-line treatment for couples, when the woman’s age and the duration of infertility were appropriate). A study of the Cochrane Database led by Pandian et al. (43) selected five randomized studies, with the birth rate as the only treatment outcome. This study again emphasized the efficacy of IUI after stimulation, when compared with IVF. Aboulghar et al. (37) has proposed the following compromise: start with three IUI cycles, and in the event of failure, perform ICSI. They obtained a pregnancy rate of 29.8% using IUI and 36.7% using ICSI.

**Technical Aspects of IUI**

Several investigators have demonstrated the superiority of FSH or hMG over clomiphene citrate alone (38, 39, 44, 45). A combination of clomiphene citrate with hMG or FSH (with equivalent results to the use of gonadotropin alone) results in a lower total dose of gonadotropins (44).

Use of GnRH antagonists sometimes enables inhibition of the spontaneous LH peak and the avoidance of inseminations on the weekend. These compounds are probably destined to
play a greater role in IUI. In a prospective study, Stan et al. (46) compared 62 cycles using antagonists with 43 cycles without them and did not find any significant difference in terms of either the number of follicles measuring over 16 mm on the day of hCG administration or endometrial thickness. The pregnancy rate per cycle was 12% in the antagonist group versus 7% in the control group (nonsignificant difference). Checa et al. (47) also performed a prospective study comparing cycles with or without antagonist use and reported a significant difference in the length of the treatment (10.3 days in the antagonist group vs. 8.4 in the control group), the E2 concentration on the day of hCG administration (733 pg/mL vs. 521 pg/mL), and endometrial thickness (9.9 vs. 8.6 mm). The pregnancy rate was 20% per cycle in the antagonist group versus 12.5% in the control group, but this difference was not significant.

In the present study, we identified two significant factors: the number of follicles >16 mm and the E2 concentration on the day of hCG administration. We also found a strong link between these two parameters and the rate of multiple pregnancies. Plosker and Amato (48) showed that the recruitment of at least two follicles increases the likelihood of success in cases of ovarian stimulation combined with IUI (2% for one follicle versus 15% for at least two follicles; \( P < .006 \)). Based on an analysis of 9963 cycles, Bronte et al. (6) found similar results, with pregnancy rates of 7.6% for one follicle, 10.1% for two follicles, 8.6% for three follicles, and 14% for four follicles (\( P < .001 \)). They also identified significant differences in the multiple pregnancy rate when comparing one and two or more follicles (2.9% vs. 16%). Belaisch-Allart et al. (18) (with 880 cycles) confirmed these results, with a clinical pregnancy rate per cycle of 13.8% with one or two follicles and 19.6% with at least three follicles. In the same study, the pregnancy rate per cycle varied according to the E2 concentration: 14.2% per cycle for <500 pg/mL on the day of hCG administration, 16.2% for between 500 and 1000 pg/mL, 16.5% for between 1000 and 1500 pg/mL, and, lastly, 22.1% for over 1500 pg/mL. The multiple pregnancy rate was 10% for one or two follicles and 22% for at least three follicles. Finally, Nuoja-Huttunen et al. (4) noted a rate of 5.7% with a single follicle >16 mm versus 16.3% with three follicles but did not find any link between the number of follicles and the multiple pregnancy rate.

In our center, we saw no difference between insemination after a spontaneous LH peak or after an ovulation triggered by hCG. Jakus et al. (49) compared 261 hCG-triggered patients with 166 who were inseminated after a spontaneous LH peak. He noted a significant difference in the duration of stimulation, with 14 days for the first group versus 15 days for the second. The pregnancy rate per cycle was similar, with, respectively, 8% and 5.9%. In contrast, Plosker and Amato (48) showed a significant effect (\( P = .05 \)), with a pregnancy rate of 13% when ovulation is triggered or maintained by hCG versus 3% when the LH peak is spontaneous.

If we now focus on endometrial thickness, the literature is full of studies concerning the impact of this parameter on the successful pregnancy rate after ET, but the results are very disparate. Noyes et al. (50), Kovacs et al. (51), and Weissman and Casper (52) found a link between endometrial thickness and the pregnancy rate, whereas De Geyter et al. (53), Puerto et al. (54), and Yuval et al. (55) stated the contrary. Many studies have sought to identify a threshold thickness needed to obtain a successful pregnancy. According to Coulon et al. (56), Schild et al. (57), and Kupesic (58), the optimal thickness is between 8 and 15 mm. Kolibianas et al. (59) evaluated the impact of endometrial thickness on the pregnancy rate obtained by IUI after treatment with clomiphene citrate and found that it was not a predictive factor, with a mean thickness of 7.7 ± 0.3 mm in cases of successful pregnancy versus 8.1 ± 0.4 mm in cases of failure. Our results do not allow us to classify endometrial thickness as a predictive factor of pregnancy. It should be noted that two pregnancies were achieved with a thickness below 7 mm, and no pregnancies were obtained with a thickness greater than 13 mm.

In our study, the mean number of IUIs per couple was 2.6. More than 80% of clinical pregnancies were obtained during the first three cycles. Plosker and Amato (48) advise considering IVF after three unsuccessful IUI. Likewise, Nuoja-Huttunen et al. (4) noted that the highest pregnancy rate in 811 cycles (18%) was seen during the first cycle and that 97% of all pregnancies result from the first four cycles. In cases of unexplained infertility, Aboughar et al. (37) found a cumulative pregnancy rate (in a study of 1112 cycles) of 39.2% after three cycles (16.4% per cycle) and 48.5% after six cycles. They underlined the fact that the pregnancy rate per cycle was 9.3% after the third IUI cycle versus 36.6% when ICSI was preferred and concluded that the best balance between cost and efficacy is found in the first three IUI cycles (\( P < .01 \)). At present, it is generally admitted that IUI should be limited to four or six cycles and that IVF should be performed in the event of failure.

In the present study, the type of catheter used was correlated with differing pregnancy rates, 15.3% per cycle for a soft catheter versus 7% for a hard catheter (\( P < .02 \)). In IVF, in has also been reported that the type of catheter has an impact on the likelihood of pregnancy after ET. Wood et al. (60) found an advantage of soft over rigid catheters for ET, with pregnancy rates of 36% versus 17%, respectively. In IUI, Smith et al. (61) and Spiessens et al. (62) did not observe a difference, whereas in an ultrasound evaluation, Lavie et al. (63) found that a soft catheter is significantly less damaging for the endometrium than a hard one. Miller et al. (64) performed a prospective study on this subject and noted pregnancy rates per cycle of 16% and 22% with rigid and soft catheters, respectively, although this difference was not statistically significant.

In the present study, we also sought to establish predictive factors for twin pregnancy: the women’s age, the cause of infertility, the number of follicles >16 mm, and the E2 concentration on the day of hCG administration. In this respect, Tur et al. (65) performed a retrospective multivariate analysis of 1878 pregnancies after ovulation stimulation. Of these, 294
were twin pregnancies and 107 were triplet pregnancies or higher. The following risk factors were identified (listed here in order of importance): more than three follicles measuring 10 mm or an E₂ concentration >862 pg/mL on the day of hCG administration and age under 32. These results highlight two important elements that should be determined when evaluating the risk of multiple pregnancies. First, all the follicles must be taken into account before triggering ovulation and particularly those of intermediate size (between 11 and 15 mm). Second, combining the E₂ level and an ultrasound examination enabled better estimation of the risk. Third and finally, analysis of the population is as important as the intensity of the ovarian response when evaluating the twin pregnancy risk. To limit our twin pregnancy rate after IUI (13.5%) or even to decrease it while maintaining a satisfactory rate of single pregnancies, we could apply Massin et al.’s proposals (15). They determined “stimulation objectives” that take in account the woman’s age, ovarian status, duration of infertility, and indications (type of infertility):

1. Recruitment of a single follicle: Massin et al. suggest performing insufflations during natural cycles in cases of strictly cervical or male indications, when the patients are young and the ovarian status is normal. If stimulation is undertaken despite this favorable context, they specify that it has to be performed carefully and with a monofollicular objective.

2. Recruitment of two follicles: in other situations, Massin et al. recommend increasing the number of preovulatory follicles. This may generally double the pregnancy rate and maintain an acceptable level of risk of multiple pregnancies. In contrast, they indicate that there is no advantage in increasing the number of follicles to three for young patients because the risk of multiple pregnancies would be multiplied 10-fold.

3. Recruitment of three follicles: in the case of older patients, Massin et al. indicate that an increase in the number of follicles is beneficial for the pregnancy rate and that the risk of multiple pregnancies (although not evaluated precisely) does not seem to be high.

Conclusions

This study was carried out to establish the strongest predictive factors for post-IUI pregnancy and to determine cases most at risk of multiple pregnancies. In summary, we can say that couples with the best probability of pregnancy are those in which [1] the woman is under 30 and suffers from cervical infertility or anovulation and [2] her partner has a TMS of ≥ 5 million. The “ideal” stimulation cycle allows for the recruitment of at least two follicles measuring >16 mm, with an E₂ concentration >500 pg/mL on the day of hCG administration. The IUI procedure itself should be carried out slowly with a soft catheter holding at least 1 million motile spermatozoa.

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