RCT to evaluate the influence of adjuvant medical treatment of peritoneal endometriosis on the outcome of IVF

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STUDY QUESTION: Does a 3-month adjuvant hormonal treatment of mild peritoneal endometriosis after laparoscopic surgery influence the outcome of IVF stimulation in terms of number of mature oocytes obtained per cycle?

SUMMARY ANSWER: Complementary medical treatment of mild peritoneal endometriosis does not influence the number of oocytes per treatment cycle.

WHAT IS KNOWN ALREADY: Endometriosis is a disease known to be related to infertility. However, the influence of superficial endometriosis—and its treatment—is still a matter of debate.

STUDY DESIGN, SIZE, DURATION: A prospective controlled, randomized, open label trial was performed between February 2012 and March 2014 and embryological and clinical outcomes were measured. Patients with laparoscopically diagnosed peritoneal endometriosis (n = 120) were treated by laser surgery after which they were sequentially randomized by computer-generated allocation to one of the two groups. The primary outcome of the trial was the number of Metaphase II (MII) oocytes. Sample size was chosen to detect a difference of two MII oocytes with a power of 80%. The control group (Group B) received the classical long protocol IVF stimulation, whereas the research group (Group A) had an additional pituitary suppression, of 3 months using a long-acting GnRH agonist, prior to IVF.

PARTICIPANTS/ MATERIALS, SETTING, METHODS: A total of 120 patients were included in the study, 61 of them in the study group and 59 patients in the control group. One patient of the control group was lost to follow up leading to 58 evaluable patients.

MAIN RESULTS AND THE ROLE OF CHANCE: There was no difference in terms of the number of MII oocytes obtained per cycle: 8.2 in both groups (difference in MII between A and B: 0.07 [−1.89; 2.04] 95% confidence interval (CI)). Pregnancy rate did not differ, being 39.3% for Group A (24 out of 61 patients) versus 39.7% for Group B (23 out of 58 patients) (95% CI around difference in pregnancy rate between A and B: −0.31% [−17.96%; 17.86%]). However, a significantly (P = 0.025) lower dose of FSH (2561 IU for Group A and 2303 IU for Group B, 95% CI around difference in FSH between A and B: −258.6 IU [−483.4 IU; −33.8 IU]) and a significantly (P = 0.004) shorter stimulation period (Group A 12.3 days and Group B 11.3 days, 95% CI around difference in stimulation period between A and B: −1.03 days [−1.73 days; −0.33 days]) were needed to reach adequate follicle maturation in the control group.

LIMITATIONS, REASON FOR CAUTION: The validity of this study is limited to mild peritoneal endometriosis, and does not apply to ovarian endometriosis, which is also commonly seen in infertility patients.

WIDER IMPLICATIONS OF THE FINDINGS: There is no indication for complementary medical treatment of peritoneal endometriosis in terms of IVF outcome. On the contrary, stimulation takes longer and requires a higher amount of medication.

STUDY FUNDING/COMPETING INTEREST(S): There was no external funding for this clinical trial in the IVF Center, AZ Jan Palfijn, Ghent. There are no competing interests to declare.
Introduction

Endometriosis is a well-known cause of infertility (Vercellini et al., 2014). The pathophysiological mechanisms by which endometriosis induces infertility remain controversial (Gupta et al., 2008; Carvalho et al., 2013). In the frozen pelvis patient, with Fallopian tubes fixed in adhesions, endometriosis obliterates tubal patency (Molloy et al., 1987). In patients with endometriotic ovarian cysts, hormonal response to stimulation is negatively influenced, and oocyte quality seems to be reduced (Suziki et al., 2005). An unfavorable effect of endometriosis on fertility has also been described in patients without obvious problems at the Fallopian tubes or the ovaries (Grzechocinska and Wielgos, 2012). Peritoneal endometriosis, even with small implants, causes inflammation and the accumulation of activated macrophages (Defrère et al., 2011; Capobianco and Rovere-Querini, 2013), expressing high levels of cyclo-oxygenase (Kim et al., 2011), with increased secretion of prostaglandin (PG) F2 α and PGE2 (Sharma et al., 2010; Wang et al., 2012). These are likely to play a pivotal role in disease pathophysiology as well as in the clinical sequelae, such as pain and infertility (Wu et al., 2002). Also, the peritoneal immune surveillance systems are impaired in endometriosis patients (Itoh et al., 2011) with a decrease of natural killer cell activity in peritoneal fluid, disturbed T-lymphocyte function (Belléis et al., 2013), and infiltration of macrophages. In addition, the inflammatory reaction and the generation of free oxygen radicals causes an increased production of cytokines, such as interleukin 6 and 8, and nuclear factor kappa B, which interfere with cell quality leading to poor oocyte quality and impaired fertilization (Gupta et al., 2008, 2014).

One of the major advantages of IVF in endometriosis patients is the mere fact that both oocytes and sperm are removed from this unfavorable environment with free oxygen radicals. Nonetheless, fertilization rates of oocytes obtained from endometriosis patients seemed less favorable than in other fertility patients (Harb et al., 2013). GnRH agonists are widely used in endometriosis therapy, mainly for pain reduction (Ruhland et al., 2011). Continuous exposure of the pituitary to these drugs leads to down-regulation of the GnRH receptor and desensitization of the pituitary gland, inducing a hypo gonadotrophic—hypo gonadal situation which deprives the existing endometriosis lesions of endocrinological stimulation, and thereby diminishes the occurrence of new endometriotic seedlings (Sampson, 1927). Also, a significant reduction of the inflammatory reaction has been reported (Orvieto et al., 2006). A 3-month hormonal therapy might therefore create a more favorable environment for oocyte maturation, with better oocyte quality and better fertilization rates as well as embryo quality. The present trial aims at empirically testing this hypothesis in a prospective randomized setting. In order to avoid bias from interfering pathophysiological mechanisms, indication was limited to peritoneal endometriosis. Ovarian endometriosis, with its possible influence on ovarian function, and severe endometriosis with massive fibrosis and/or adhesions (mechanical factors) were excluded from the study.

Materials and Methods

In our routine clinical set-up, the combination of hysteroscopy and laparoscopy is used as a diagnostic tool in all patients with unexplained infertility and in all couples with a minor male factor. During this procedure therapeutic measures are taken, such as adhesiolyis or coagulation of endometriotic lesions, whereby all visible lesions are destroyed by bipolar or laser coagulation.

In the period between February 2012 and March 2014, 377 patients from a total of 732 patients presenting for advanced fertility treatment were admitted to the surgery program for endoscopic evaluation of tubal and peritoneal factors. Patients undergoing hysteroscopy and laparoscopy (n = 28) showed normal gynecological anatomy. A total of 52 patients presented with severe endometriosis or ovarian endometriotic cysts. Peritubal adhesions, tubal fibrosis and tubal block were diagnosed as the main infertility factor in the largest group of patients undergoing endoscopic intervention. Only patients with mild peritoneal endometriosis were consecutively admitted to the study population.

Patients with ovarian endometriosis were excluded from enrollment since the possible effect on ovarian function could bias the analysis of the results (Coccia et al., 2014). A prospective RCT was performed at the IVF center of the hospital Jan Palfijn Ghent. Institutional Review Board approval was obtained (O.L.V. hospital Aalst, 2012/015). Written informed consent was obtained from all participants.

Inclusion criteria were: patients younger than 38 years with indication for IVF treatment (e.g. fallopian tube blockage, post infectious fibrosis of the lamina muscularis of the salpinx, peritubal adhesions and/or andrological factors). Exclusion criteria were: patients older than 38 years, severe male problems, e.g. indication for testicular sperm extraction, severe endometriosis, ovarian endometriotic cysts, deep fibrosing endometriosis of the recto-vaginal septum and uterine pathology such as congenital malformation of the uterine cavity or fibroids. Also patients with major endocrine problems were excluded.

A cohort of 120 consecutive patients (16.4% of all patients presenting for advanced fertility treatment) with mild peritoneal endometriosis, and without ovarian endometriosis factor, Stage I or II, according to the American Fertility Society classification, were randomized into 2 groups. To significantly detect a difference of 2 Metaphase II (MII) oocytes between groups with a SD in each group equal to 4, 120 subjects in total are needed (80% power, 2-sided t-test, 5% significance level). The randomization was carried out through a computer program by the study coordinator, who did not come in contact with the individual patients. The patients in Group A were started on a 3-month pituitary suppression with a long-acting GnRH agonist (Zoladex® 3.6 mg, AstraZeneca, Cheshire, UK), using one ampule in the abdominal subcutaneous fat tissue on a monthly basis. Ten days after the last dose of Zoladex® was administered, the ovarian stimulation was initiated with Menopur® giving three ampules of 75 IU s.c. daily.

**TRIAL REGISTRATION NUMBER:** EudraCT nr: 2012-000784-25.

**TRIAL REGISTRATION DATE:** First registration on 29 February 2012 and re-entered on 23 August 2012, NCT01682642 (due to a change of staff).

**DATE OF FIRST PATIENT’S ENROLLMENT:** 8 March 2012.

**Key words:** IVF / endometriosis / peritoneal implants / embryo quality / Metaphase II oocytes
The second group (Group B) was referred to IVF straight away, without hormonal treatment. To avoid possible bias from comparing long protocol stimulation with short protocol stimulation, the patients in Group B were given a long protocol schedule, using buserelin nasal spray (3 × 3 puffs/day) (Suprefact®, Sanofi-Aventis, Frankfurt-am-Main, Germany) from Day 20 of the pretreatment cycle. They were started on Day 3 after initiation of menstruation, with progesterone level lower than 1.5 ng/ml, using three ampules of Menopur® 75 IU (Ferring, Aalst, Belgium) s.c. on a daily basis. The so-called pretreatment cycle (down-regulation) was the first cycle after the endoscopic coagulation of endometriosis lesions.

In both groups, an ultrasound evaluation of the size and number of the follicles, as well as the endometrial thickness was performed on Day 7, starting from the first administration of Menopur®. Levels of estrogen, progesterone, LH and FSH were measured at the start of the stimulation (baseline), on Day 7, the day of triggering and the day after triggering, as in routine IVF monitoring (Unicell DXI 800 Beckman Coulter, USA). After exactly 36 h, a vaginal ultrasound guided oocyte retrieval took place. Embryo transfer was performed on Day 3 after egg retrieval, using a soft tip catheter (Wallace®, Smiths Medical International, Kent, UK). One or two embryos were transferred according to the Belgian legislation (one embryo at first attempt in women < 36 years old, one or two embryos depending on embryo quality in the second attempt, two embryos transferred from the third attempt onwards; for women over 36 years, two embryos per transfer). The luteal phase was supported by the vaginal application of 200 mg micronized progesterone (Utrogestan®, Besins, Brussels, Belgium: vaginal tablets, three times a day), as well as s.c. hCG (Pregnyl®, MSD, Brussels, Belgium) 1500 IU on Days 1 and 5 after transfer (van der Linden et al., 2015).

hCG and progesterone were measured 13 days after transfer, and in case of positive results a first ultrasound examination was performed 10—14 days later to confirm pregnancy, to exclude ectopic implantation, and to count the number of gestational sacs. Two weeks later assessment of heart activity was performed using a vaginal ultrasound probe, in which case ongoing pregnancy was diagnosed.

The primary end-point of the trial was the number of MII oocytes. Secondary end-points studied were: pregnancy rate, number of cumulus oocyte complexes, number of fertilized oocytes at two pronuclei (2PN) stage, number of embryos transferred, total FSH used, number of days of stimulation and embryo quality (assessed by analyzing the number of blastomeres, the homogeneity of the embryo, the fragmentation rate and an evaluation over time from fertilization day until Day 5) and (number of) cryopreserved embryos (Baczkowski et al., 2004). The following analyses were performed: univariate analysis of the different primary and secondary end-points to check if there was a difference between both treatment groups, verification of distribution of the different covariates between both arms, analysis of pregnancy rate stratified by embryo quality and a longitudinal analysis of the different hormone profiles. For continuous variables, a parametric t-test (allowing for a different variance in both groups if necessary) was used to compare treatment groups. If the underlying distribution deviated from normality, a non-parametric Wilcoxon test (t-approximation) was performed instead. Summary measures comprised mean, median, SD, range and 95% confidence interval (CI) around the difference between both study arms. Binary variables (e.g. pregnancy rate 0/1, embryo quality A/B) are compared using a chi² test or the Fisher exact test. 95% CIs for the difference in proportions are 95% binomial exact confidence limits. For the primary end-point (number of MII oocytes) and the most important secondary one, namely, pregnancy rate, a multivariate regression model was also applied adjusting for baseline covariates age, duration of infertility, BMI, basal progesterone level and basal FSH level, to test the difference between both treatment groups. Non-significant

Figure 1 Comparison of stimulation cycles in a RCT to evaluate the influence of adjuvant medical treatment of peritoneal endometriosis on the outcome of IVF.
covariates are removed from the model. A value of $P < 0.05$ was considered significant.

All statistical analyses are performed by means of SAS® (Cary, NC, USA).

Results

Between March 2012 and February 2014, 152 patients were screened for the study and 120 were enrolled and treated according to the study protocol. One patient was lost to follow up, therefore results for 119 patients could be analyzed (Fig. 2). The average (mean ± SD) patient age was 31 years (± 4.0), with a range of −38 years. The mean BMI was 23 kg/m² (± 4.4). The mean duration of infertility was 2.7 years (± 1.87). All patients suffered from primary infertility.

The baseline covariates age, BMI, duration of infertility, basal progesterone and basal FSH levels were fairly normally distributed and thus compared by means of Student’s $t$-test to check for proper randomization. Analysis of covariates for comparison of baseline covariates between both groups disclosed that the duration of infertility, BMI, basal progesterone level and basal FSH level were not significantly different between two groups, but patients of Group B tended to be slightly older than those of Group A ($P = 0.060$) (Table I).

The distribution of all continuous end-points studied was normal (with the exception of number of frozen embryos); therefore comparisons between both groups were carried out by means of $t$-tests. Multiple comparisons are performed without any adjustment for multiple testing. Hence all $P$-values apart from the $P$-value corresponding to the primary hypothesis testing should be interpreted with care in an exploratory manner. The primary end-point number of MII oocytes did not differ between both groups ($P = 0.941$). A regression model applied to MII as response and adjusted for the above baseline covariates, did not change the results: the effect of group on mean MII response remains insignificant ($P = 0.788$) and age is the only covariate that can be significantly retained in the model indicating that with increasing age the mean number of MII oocytes decreases. The total amount of FSH administered and the number of stimulation days were significantly higher in Group A ($P = 0.025$ and 0.004, respectively, versus Group B). There was no difference in terms of number of cumulus oocyte complexes and number of fertilized oocytes at 2PN stage. Also the number of transferred embryos, being limited by Belgian law, was equal in both groups (Table II). The distribution of number of cryopreserved embryos deviated from normality and was compared by means of non-parametric Wilcoxon test and not found to differ between study groups ($P = 0.144$).
The pregnancy rate was similar in the two groups ($P = 0.972$): Group A 39.3%, Group B 39.7%. A logistic regression model of pregnancy rate adjusted for the baseline covariates revealed no significant difference between groups ($P = 0.693$). Also here age is the only covariate that could be significantly retained in the model with older patients resulting in lower pregnancy rate. The proportion of patients with supernumerary embryos that could be frozen was slightly, although not significantly, lower in Group A (37.7%) (23/61 patients) than in Group B (44.8%) (26/58 patients) ($P = 0.430$). In terms of embryo quality there was no significant difference between Groups A and B, after stratification for embryo quality, is maintained peritoneal inflammation. The difference we intended to test was the possible effect of adjuvant medical therapy, trying to prevent small or still invisible lesions (at the time of laparoscopy) from developing, since these may maintain peritoneal inflammation.

The covariates for both groups were similar, including age. Age is an important factor in fertility and it could have been expected that the slightly younger patients from Group A (although not statistically significant) would respond better to Zoladex treatment. However, no differences were found in the embryological evaluations (between the two groups, suggesting that there was no effect of the complementary medical endometriosis therapy on oocyte quality). An identical number of embryos were transferred at Day 3 after oocyte retrieval, leading to identical pregnancy rates and freezing rates of supernumerary good quality embryos. The only significant difference between groups was the duration of stimulation and the amount of medication needed to achieve MII oocytes. In Group A, with long lasting suppression, a significantly higher amount of hPROM (Menopur®) was needed. Accordingly, the average duration of stimulation was longer. These findings agree with the Cochrane Review of Albuquerque et al. (2013). Since the longer duration of stimulation and the higher amount of medication needed resulted in a higher medical cost but were not compensated by better clinical outcome features, it is concluded that there is no benefit of a long hormonal suppression in endometriosis patients. Nonetheless, the possible effect of hormonal suppression in endometriosis patients

### Discussion

In endometriosis patients, we aimed to reduce the inflammation of the peritoneum and the resulting `defense' reaction of the body using a double approach. First, laparoscopic destruction of all visible endometriotic lesions was performed in both study groups: it was considered unethical not to treat pathological lesions. Indeed, for general health reasons, and to prevent future development of new endometriosis, all patients were adequately treated for their disease. We admit that there is still controversy about the usefulness of diagnostic laparoscopy and treatment of peritoneal endometriosis in patients referred for IVF (Child, 2013). On the other hand, at the time of this diagnostic endoscopy, other, easily correctable causes of infertility, such as peritoneal adhesions, can be cured, restoring natural fertility with a number needed to treat $= 9$ (for every nine laparoscopies one additional spontaneous pregnancy occurs, thus avoiding the need for IVF) (Musich and Behrman, 1982). The difference we intended to test was the possible effect of adjuvant medical therapy, trying to prevent small or still invisible lesions (at the time of laparoscopy) from developing, since these may maintain peritoneal inflammation.

The covariates for both groups were similar, including age. Age is an important factor in fertility and it could have been expected that the slightly younger patients from Group A (although not statistically significant) would respond better to Zoladex treatments. However, no differences were found in the embryological evaluations (between the two groups, suggesting that there was no effect of the complementary medical endometriosis therapy on oocyte quality). An identical number of embryos were transferred at Day 3 after oocyte retrieval, leading to identical pregnancy rates and freezing rates of supernumerary good quality embryos. The only significant difference between groups was the duration of stimulation and the amount of medication needed to achieve MII oocytes. In Group A, with long lasting suppression, a significantly higher amount of hPROM (Menopur®) was needed. Accordingly, the average duration of stimulation was longer. These findings agree with the Cochrane Review of Albuquerque et al. (2013). Since the longer duration of stimulation and the higher amount of medication needed resulted in a higher medical cost but were not compensated by better clinical outcome features, it is concluded that there is no benefit of a long hormonal suppression in endometriosis patients. Nonetheless, the possible effect of hormonal suppression in endometriosis patients

### Table I Analysis of the covariates used in the RCT on the influence of adjuvant medical treatment of peritoneal endometriosis on IVF outcome.

<table>
<thead>
<tr>
<th>Baseline covariate</th>
<th>Summary measure</th>
<th>Group A</th>
<th>Group B</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration infertility (years)</td>
<td>Mean (SD)</td>
<td>2.9 (1.64)</td>
<td>2.5 (2.07)</td>
<td>T-Test</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>2.7</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.9–8</td>
<td>0.75–13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>2.47–3.41</td>
<td>1.89–3.11</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>30.3 (3.63)</td>
<td>31.7 (4.28)</td>
<td>T-Test</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>30</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>22–38</td>
<td>22–38</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>29.40–31.26</td>
<td>30.58–32.83</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Mean (SD)</td>
<td>23.4 (4.20)</td>
<td>23.1 (4.58)</td>
<td>T-Test</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>23.4</td>
<td>22.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>16.7–33.5</td>
<td>17.6–42.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>22.31–24.58</td>
<td>21.88–24.33</td>
<td></td>
</tr>
<tr>
<td>Basal progesterone level (µg/l)</td>
<td>Mean (SD)</td>
<td>0.74 (1.45)</td>
<td>0.64 (0.36)</td>
<td>T-Test</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0.1–11.4</td>
<td>0.1–1.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>0.36–1.12</td>
<td>0.54–0.74</td>
<td></td>
</tr>
<tr>
<td>Basal FSH level (IU/l)</td>
<td>Mean (SD)</td>
<td>5.3 (3.83)</td>
<td>5.1 (2.30)</td>
<td>T-Test</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>4.5</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>1.4–26.3</td>
<td>1.5–17.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>4.25–6.27</td>
<td>4.52–5.77</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval.
is not fully excluded, since patients in both groups were treated by a
down-regulation protocol of which the duration was however, different.
Also, a possible negative effect on the number of MII oocytes could be
explained by the fact that stimulation was started 10 days after the last
application of long-acting GnRH agonist, whereas other investigators
have reported a better ovarian response if a recovery period of 2
weeks is introduced between the administration of the long-acting
GnRH agonist and the initiation of the controlled ovarian stimulation
(Surrey et al., 2002). Therefore, it is suggested that a 2-week recovery
period should be respected after pre-IVF suppression of ovarian function
with GnRH agonists, in order not to depress the ovarian responsiveness
to stimulation. Comparing a group of patients on a long-term down-
regulation protocol with a group without down-regulation would not
have been an option, since this would have blurred the comparison
between the two groups (bias of comparing long protocol with short
protocol stimulations) and would have rendered any conclusion regard-
ing complementary hormonal suppression therapy impossible. The
external validity of this study is limited to mild peritoneal endometriosis
only, and does not apply to ovarian endometriosis, which is one of the
most frequent forms of endometriosis seen in infertility patients.

### Conclusion

The present RCT did not reveal any differences in terms of number of MII
oocytes obtained in a group of patients suffering from mild peritoneal
endometriosis with a post-surgical 3-month period of down-regulation,
in comparison with patients treated immediately after laparoscopy with a
long protocol stimulation for IVF. In addition, no difference was detected
in either the embryological or clinical results between two groups.
However, the study was not powered to make final conclusions on
these particular topics, only for the analysis of the number of MII
oocytes (primary objective). The longer duration of stimulation and
the higher amount of medication needed argue against a 3-month dur-
ation of complementary hormonal adjuvant therapy for endometriosis
in IVF patients.

### Acknowledgements

A special contribution was made by Mrs Lieve Declercq and Mrs Caroline
Van de Steene, study coordinators, who performed the randomization and

### Table II Analysis of the embryological and clinical parameters (primary and secondary end-points).

<table>
<thead>
<tr>
<th>End-point</th>
<th>Summary measure</th>
<th>Group A</th>
<th>Group B</th>
<th>Difference A − B [95% CI]</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>#COC</td>
<td>Mean (SD)</td>
<td>11.2 (6.76)</td>
<td>11.1 (7.38)</td>
<td>0.13</td>
<td>0.922†</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>10</td>
<td>8.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0–29</td>
<td>1–35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#MII</td>
<td>Mean (SD)</td>
<td>8.2 (5.92)</td>
<td>8.2 (4.82)</td>
<td>0.07</td>
<td>0.941‡</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>7</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0–30</td>
<td>0–19</td>
<td></td>
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<tr>
<td>#2PN</td>
<td>Mean (SD)</td>
<td>5.4 (4.03)</td>
<td>5.6 (4.20)</td>
<td>−0.28</td>
<td>0.714‡</td>
</tr>
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<td></td>
<td>Median</td>
<td>4</td>
<td>4.5</td>
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<td></td>
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<tr>
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<td>Range</td>
<td>0–16</td>
<td>0–16</td>
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<tr>
<td>#embryo transfer</td>
<td>Mean (SD)</td>
<td>1.3 (0.51)</td>
<td>1.3 (0.63)</td>
<td>−0.05</td>
<td>0.648*</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>1</td>
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<td></td>
<td>Range</td>
<td>0–2</td>
<td>0–3</td>
<td></td>
<td></td>
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<tr>
<td>Total FSH dose (IU)</td>
<td>Mean (SD)</td>
<td>2561 (621.7)</td>
<td>2303 (604.8)</td>
<td>258.6</td>
<td>0.025‡</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>2513</td>
<td>2250</td>
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<td>1575–4050</td>
<td>1350–4050</td>
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<tr>
<td># days stimulation</td>
<td>Mean (SD)</td>
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<td>11.3 (1.98)</td>
<td>1.03</td>
<td>0.004‡</td>
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<td></td>
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<td>Range</td>
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<td>7–19</td>
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<td></td>
</tr>
<tr>
<td>#cryo</td>
<td>Mean (SD)</td>
<td>0.9 (1.40)</td>
<td>1.6 (2.31)</td>
<td>−0.77</td>
<td>0.144+++</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>0–6</td>
<td>0–8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryo (Y/N)</td>
<td>Yes (n/N)</td>
<td>37.7% (23/61)</td>
<td>44.8% (26/58)</td>
<td>−7.12</td>
<td>0.430+++</td>
</tr>
<tr>
<td></td>
<td>No (n/N)</td>
<td>62.3% (38/61)</td>
<td>55.2% (32/58)</td>
<td>−24.68%; 11.20%</td>
<td></td>
</tr>
<tr>
<td>Embryo quality</td>
<td>Quality B (n/N)</td>
<td>40.7% (24/59)</td>
<td>32.7% (18/55)</td>
<td>7.95%</td>
<td>0.379+++</td>
</tr>
<tr>
<td></td>
<td>Quality A (n/N)</td>
<td>59.3% (35/59)</td>
<td>67.3% (37/55)</td>
<td>−10.54%; 26.02%</td>
<td></td>
</tr>
<tr>
<td>Pregnancy rate</td>
<td>Yes (n/N)</td>
<td>39.3% (24/61)</td>
<td>39.7% (23/58)</td>
<td>−0.31%</td>
<td>0.972+++</td>
</tr>
<tr>
<td></td>
<td>No (n/N)</td>
<td>60.7% (37/61)</td>
<td>60.3% (35/58)</td>
<td>−17.96%; 17.86%</td>
<td></td>
</tr>
</tbody>
</table>

Five patients have no information on embryo quality.
#COC, number of cumulus oocytes complexes; #MII, number of Metaphase II oocytes; #2PN, number of two pronuclei; Cryo, cryopreserved embryo; Y/N, yes/no.
*CI, confidence interval around difference between Groups A and B.
†P-value of t-test (although not normally distributed) = 0.032.
‡T-Test.
+++Wilcoxon t-approximation.
+++x² test.
collected the hormonal and embryological data. We thank Mrs Katrien Verschueren, Ir., M.Sc., of Living Statistics, for the statistical analysis.

**Authors’ roles**

The primary author is W.D., he recruited most patients and performed the clinical follow up.

K.O. is heading the IVF laboratory and provided the embryological data.

I.K.V. was involved in the statistical analysis of all data measured.

F.C. is the inspiring man behind the hypothesis of inflammation caused by endometriosis and the possible influence on oocyte quality. He was the first reviewer of the original draft.

P.D. is the general coordinator of all studies in our center. He was committed in the study from the concept, over the study set-up, through the follow-up, till the final analysis of the results and the concept of the paper. He also made the final editing.

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**Conflict of interest**

None declared.

**References**


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