Polycystic ovary syndrome. A therapeutic challenge
Bayram, N.

Citation for published version (APA):

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CHAPTER 5

Laparoscopic electrocautery of the ovaries versus recombinant FSH in clomiphene citrate resistant polycystic ovary syndrome. Impact on women's health related quality of life.

Madelon van Wely, Neriman Bayram, Patrick M.M. Bossuyt, Fulco van der Veen

Human Reproduction. In press
Abstract

Background
Ovulation induction with gonadotrophins is the standard treatment strategy for women with clomiphene citrate (CC) resistant polycystic ovary syndrome. Laparoscopic electrocautery of the ovaries is an alternative treatment modality, leading to a comparable cumulative pregnancy rate. In deciding which treatment to opt for, women's health related quality of life should be taken into account.

Methods
A total of 168 CC resistant women with polycystic ovary syndrome were randomly assigned to receive either the electrocautery strategy, entailing laparoscopic electrocautery of the ovaries followed by CC and rFSH if anovulation persisted or ovulation induction with rFSH. We assessed health related quality of life (HRQoL) with the standard questionnaires Short Form 36, Rotterdam Symptom Checklist and Center for Epidemiological Studies Depression Scale, administered before randomisation and 2 weeks, 12 weeks and 24 weeks thereafter.

Results
The intention to treat analysis revealed no significant differences between the treatment groups on any of the scales at any point during follow-up. In women without an ongoing pregnancy, those treated with rFSH showed significantly more depressive symptoms than women allocated to electrocautery strategy, with or without CC, although differences were small. The intention to treat analysis revealed no significant differences between the treatment groups on any of the scales at any point during follow-up. In women without an ongoing pregnancy, those treated with rFSH showed significantly more depressive symptoms than women allocated to electrocautery strategy, with or without CC, although differences were small.

Conclusions
Overall, HRQoL was not affected in both groups. In women still under treatment, rFSH was slightly more burdensome for women's HRQoL than electrocautery with or without CC.

Key Words: ovulation induction, PCOS, clomiphene citrate resistant, health related quality of life, laparoscopic electrocautery, gonadotrophin, randomised controlled trial
Introduction

Polycystic ovary syndrome (PCOS) is a endocrine disorder with a great variety of presentations of the following symptoms and signs; menstrual disturbance, infertility, obesity, hirsutism, acne and endocrine abnormalities - including elevated LH/FSH ratio, hyperandrogenaemia and hyperinsulinaemia - and the appearance of polycystic ovaries on ultrasonography (Balen and Michelmore, 2002). Infertility due to chronic anovulation is the common reason for women with PCOS to seek treatment. The drug of first choice for ovulation induction is clomiphene citrate (CC), administered orally. However, about 20% of women with PCOS fail to ovulate on CC (Imani et al., 1998) and commonly ovulation induction with gonadotrophins will be the next treatment option for this women.

Laparoscopic electrocauter y of the ovaries is an alternative treatment modality for women with clomiphene citrate resistant PCOS. Electrocauter y of the ovaries has been shown to result in resumption of regular ovulatory cycles (Gjonnaess, 1984; Farquhar et al. 2004). Subsequently, after electrocauter y of the ovaries, women with persistent anovulation or recurrence of anovulation may respond to clomiphene citrate (Gjonnaess, 1984; Greenblatt and Casper, 1987).

We recently performed a randomised controlled trial comparing the electrocauter y strategy entailing laparoscopic electrocauter y of the ovaries followed by clomiphene citrate and recombinant FSH (rFSH) if anovulation persisted with ovulation induction with rFSH (Bayram et al., 2004). No difference could be proven in ongoing pregnancy rate in both study groups.

It is generally assumed that ovulation induction with gonadotrophins is burdensome due to the necessity of daily injections and because of the risk of multiple follicular development and multiple pregnancy (van Wel y et al., 2003; Bayram et al., 2004a). Therefore ovulation induction with FSH requires extensive monitoring. Electrocauter y of the ovaries is supposed to be a less burdensome treatment option, as it essentially involves a single procedure with minimal morbidity, eliminates the need for cycle monitoring and can lead to consecutive ovulations with minimal risks of multiple follicular development and multiple pregnancies (Donesky and Adashi 1996). Disadvantages are the surgical procedure itself, the unknown long term effect on ovarian function and possible adhesion formation.

In deciding which treatment to opt for, women's health related quality of life (HRQoL) should also be taken into account. In our multicenter trial therefore we compared health related quality of life in women after laparoscopic electrocauter y followed by clomiphene citrate when anovulation persisted and after ovulation induction with rFSH.

Methods

The study was part of a randomised controlled trial that is reported in detail elsewhere (Bayram et al., 2004).

Patients

Women who participated in our randomised controlled trial with sufficient Dutch or English language skills to complete questionnaires were eligible for measurement of
health-related quality of life. Consenting women with clomiphene citrate resistant polycystic ovary syndrome were included in the trial. All included women underwent a diagnostic laparoscopy. Women with bilateral tubal obstruction, extensive adhesions of ovaries and/or tubes and severe endometriosis were excluded from the trial. Immediately following the laparoscopy, women were randomly assigned to receive either the electrocautery strategy entailing laparoscopic electrocautery of the ovaries followed by clomiphene citrate and rFSH if anovulation persisted or ovulation induction with rFSH. Allocation was performed by using a computer program with block randomisation, stratified for centre. Participating centres called the Centre for Reproductive Medicine in the Academic Medical Centre, which acted as the trial co-ordination centre. The trial took place between February 1998 to October 2001 in 29 Dutch hospitals (Bayram et al., 2004). Electrocautery of the ovaries was immediately performed after randomisation using an Erbotom ICC 350 Unit (Erbe BV, Zaltbommel, The Netherlands) and was done with a bipolar insulated needle-electrode. Depending on the size of the ovary, 5-10 punctures were created on each ovary, distributed randomly over the surface. If anovulation persisted for eight weeks after the procedure or if the woman became anovulatory again during follow up, treatment with clomiphene citrate was re-introduced. If ovulation occurred, this dose was maintained for a maximum of six ovulatory cycles. If no ovulation occurred the dose was increased to a maximum of 150 mg. If women remained anovulatory despite clomiphene citrate ovulation induction with rFSH was started as described below.

Women allocated to rFSH, received progesterone, immediately after randomisation. Ovulation induction with rFSH (folitropin alpha, Gonal-F; Serono Benelux BV, The Hague, The Netherlands) started on cycle day (CD) 3, according to the chronic low-dose step-up protocol (Christin-Maitre et al., 2003; Bayram et al., 2004).

**Instruments**

The objective of this sub-study was to compare health-related quality of life in women after electrocautery strategy and ovulation induction with rFSH. Health related quality of life (HRQoL) was defined as having a physical, psychological, and social dimension. As the study population included essentially healthy women who are medically treated for their infertility we expected that this population would in general have normal quality of life scores. However the stress that comes with their infertility status and child wish may influence women's HRQoL. We therefore assessed HRQoL with three standard self-administered questionnaires with established validity and reliability as we expected that together they would cover most of the relevant HRQoL related effects. The Standard Form 36 (SF-36) is a generic instrument composed of 36 questions organised into eight sub-scales: physical functioning, role limitations due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems, and general mental health (Brazier et al., 1992; Ware et al., 1993; Aaronson et al., 1998). The subscale scores were transformed to a 0 to 100 scale, with higher scores indicating better quality of life.

The Rotterdam Symptom Checklist (RSCL) comprises four sub-scales: physical symptoms, psychological distress, activity level, and a single item measuring overall quality of life (De Haes et al., 1996). The RSCL was originally developed to evaluate HRQoL in cancer patients. The subscale scores were transformed to a 0 to 100 scale, with higher scores indicating more symptoms and a lower quality of life.
The Center for Epidemiological Studies Depression scale (CES-D) measures the subjective experience of depression as characterised by affective, cognitive, behavioural and psychological symptoms (Bouma et al., 1995). It produces scores between 0 and 60, with higher scores indicating more feelings of depression. A CES-D score of 16 or greater is considered to be a rough indicator for presence of clinical depression.

Women were asked by their physicians to fill out the questionnaires at home. To compare short and long-term treatment effects, we assessed the HRQoL at four time points. The first set of questionnaires was completed one to two weeks before randomisation. Women subsequently completed the questionnaires at two weeks, 12 weeks and 24 weeks after randomisation.

Analysis
Baseline values from women with clomiphene citrate resistant PCOS were tabulated and compared with reference values from the general population, where available. Health related quality of life was first compared between treatment groups studied on an intention-to-treat (ITT) basis. A mixed-model analysis of variance was used to detect changes in health related quality of life over time (time effect), to compare HRQoL between treatment groups (treatment effect), and to examine any interactions between changes in over time and treatment group (time by treatment effect).

Baseline values were included in the analysis as covariables. Women with missing measurements were included in the analysis whenever data were available at baseline and for at least one time point during the trial (Zwinderman, 1992). Mean effects with their 95% confidence intervals (95% CI) were calculated.

An ongoing pregnancy was expected to have a large effect on the HRQoL. Although the cumulative pregnancy rates were equivalent at 12 months, the time to pregnancy differed between groups. Therefore, a second analysis was performed, limited to the measurements of women without an ongoing pregnancy.

Descriptive data analysis was conducted with the use of the SPSS for Windows 11.0 statistical software (SPSS Inc.; Chicago, IL, USA). Fixed model repeated measurement analysis of variance was performed using the mixed procedure for serial measurements of SAS for Windows 6.12 statistical software (SAS Institute Inc., Cary, NC, USA). Adjustments were made for multiple comparisons.

The power calculation for the randomised trial was based on excluding a difference in the ongoing pregnancy rate at 12 months after treatment (Bayram et al., 2004). Our hypothesis for the HRQoL study was that laparoscopic electrocautery of the ovaries would be less burdensome to women than ovulation induction with rFSH. Using a two-sided significance level of 0.05, including 168 participants would allow us to detect an effect size of 0.44 with a power of at least 80% in an unconditional analysis of variance. This amounts to changes in effect size of 6 to 11 on the different items of the SF-36 scale.

Results

Patients
One hundred sixty-eight women were included in the study, of which 83 were allocated to the electrocautery strategy and 85 to rFSH. Three women in the electrocautery strategy group and eight women in the rFSH group had insufficient Dutch- or English-language
skills to complete the questionnaires. Two eligible women in the electrocautery strategy group and three women in the rFSH group did not return a baseline and follow-up questionnaire. In total, health related quality of life data of 152 women were available: 78 allocated to the electrocautery strategy and 74 allocated to rFSH. Baseline characteristics of all women are listed in Table 1.

Within 24 weeks 26 of the 78 women (38%) in the electrocautery strategy group had reached an ongoing pregnancy and 34 of 74 women (46%) had reached an ongoing pregnancy after ovulation induction with rFSH.

The patient flow during the trial is presented in Figure 1. In the electrocautery strategy group 22 and 39 women were being treated with clomiphene citrate at week 12 and 24, respectively. At week 24 seven of the 39 women subsequently started with rFSH.

**Health related quality of life**

We compared health-related quality of life (HRQoL) after electrocautery of the ovaries followed by clomiphene citrate when anovulation persisted versus rFSH. Results of the comparisons are presented in Table 2a and 2b. As administration of clomiphene citrate after electrocautery of the ovaries did not have a significant effect on any of the scales of the HRQoL, we analysed women that had received electrocautery of the ovaries, with or without clomiphene citrate, as a single group: the electrocautery strategy group.

**Short-form 36**

Baseline values were comparable to the values from the reference population, reflecting the relative healthy status of the participating women. The ITT analysis comparing electrocautery strategy and rFSH showed no statistically significant treatment effect on any of the SF-36 sub-scales (Table 2a). Two weeks after laparoscopy, women in both groups reported significantly more limitations in: physical functioning, social functioning, role limitations due to physical problems, vitality and pain. At 12 and 24 weeks these limitations had disappeared. The occurrence of an ongoing pregnancy resulted in significantly more role limitations due to physical problems, fewer role limitations due to emotional problems and a better mental health. Limiting the analysis to women without an ongoing pregnancy revealed no significant differences in treatment or time-effect.

**Rotterdam symptom checklist**

The ITT analysis found no significant treatment or time effect for physical symptoms, psychological distress and overall quality of life on the RSCL (Table 2b). For activity level, a statistically significant interaction between changes in health related quality of life over time and treatment group was observed. At two weeks the activity level was significantly impaired in women allocated to electrocautery strategy. Activity level was restored to baseline values at 12 and 24 weeks after diagnostic laparoscopy. In the rFSH group, no such changes from baseline in activity level were seen. The occurrence of an ongoing pregnancy resulted in a lower psychological distress score. A sub-analysis limited to women without an ongoing pregnancy revealed no significant differences in treatment or time-effect.

**CES-D**

The ITT analysis of the depression scale scores did not reveal any significant time or
treatment effect (table 2b). The occurrence of an ongoing pregnancy resulted in a lower CES-D score, indicating it to be less likely for these women to have depressive symptoms. Limiting the analysis to women without an ongoing pregnancy revealed no changes from baseline in depression score in women treated with the electrocautery strategy. In the rFSH group however, more depressive symptoms were reported at two weeks as compared to their baseline values. The mean difference between electrocautery strategy and rFSH was 4.8 points (95% CI: 0.3 to 9.3, p=0.04). These differences persisted during rFSH treatment, as could be observed at 12 and 24 weeks after diagnostic laparoscopy (Figure 2).

The observed increase in CES-D scores does not automatically imply that these subjects had a clinical depression. A CES-D score of 16 and greater is taken to signify that a person shows depressive symptoms. Of the 24 non-pregnant women in the rFSH group, seven (29%) had a score of 16 or greater before diagnostic laparoscopy and nine (38%) at 24 weeks after diagnostic laparoscopy. For the 41 non-pregnant women in the electrocautery strategy group these numbers were 22 (53%) and 14 (34%) respectively (Figure 3).

Discussion

This study compared the health related quality of life in women with clomiphene citrate resistant PCOS, after laparoscopic electrocautery of the ovaries followed by clomiphene citrate when anovulation persisted, versus ovulation induction with rFSH. The intention to treat analysis showed no overall differences between both study groups on any of the scales at any point of follow-up. Two weeks after laparoscopy, women in both groups reported significantly more limitations in physical functioning, social functioning, vitality and pain as compared to baseline but these limitations had disappeared at 12 weeks, suggesting that these effects were entirely due to the diagnostic laparoscopy. The burden of laparoscopy would not have been present if women in the rFSH group had not received a diagnostic laparoscopy.

All SF-36 scores and the RSCL scores for psychological distress and overall quality of life were comparable to a normal healthy reference population of women. The RSCL scores for physical symptoms, however, were somewhat higher than determined for a healthy reference population. Indeed headaches and abdominal aches were more often noticed in both treatment groups possibly due to the stress accompanying infertility treatment (Abbey et al. 1992). There was no reference value available for the RSCL activity item. As the mean activity scores were all between 1 and 8 on a scale of 0 to 100 (good to bad), these women appeared to have a healthy activity level.

Child wish was the reason why the participating women sought help. Therefore, pregnancy was expected to have an effect on the HRQoL. In our analysis we controlled for ongoing pregnancy rather than clinical pregnancy. This was done because the occurrence of an ongoing pregnancy was the endpoint of our randomised controlled trial. Hence, women with a miscarriage until gestational age of 12 weeks would remain in the trial.

As expected, an ongoing pregnancy had a significant effect on health related quality of life, as could be observed on the mean scores for role limitations due to physical problems and mental health of the SF-36 questionnaire, the psychological distress score of the RSCL questionnaire, and the depression score of the CES-D questionnaire.
Limiting the analysis to women without an ongoing pregnancy for these sub-scales revealed that women in the rFSH group had significantly more depressive symptoms than women that received electrocautery of the ovaries with or without clomiphene citrate, although the absolute difference was small.

The subanalysis was performed in women that did not become pregnant. If these women would be more inclined to leave the study the resulting selective drop-out may have affected the course of the HRQoL values. As the cumulative pregnancy rates were comparable in both study arms such a selective drop-out would likely have affected the HRQoL values in a similar way in both groups. Furthermore, we cannot exclude that in the electrocautery group expectations regarding treatment outcome at the moment of a change in treatment from wait into CC and from CC into rFSH may have been of influence on the emotional well being. This effect could explain the observed difference in CES-D score in non-pregnant women.

To our surprise, all HRQoL measurements taken before diagnostic laparoscopy and randomisation were worse in the group that was to receive electrocautery of the ovaries with or without clomiphene citrate than in women that were to be treated with rFSH. This difference was not reflected in the baseline characteristics of the participants. For this reason, we took the baseline measurements into account in our analysis.

Ovulation induction with rFSH requires daily injections and intensive monitoring and bears the risk of multiple follicular development and multiple pregnancy (Bayram et al., 2004). Laparoscopic electrocautery of the ovaries on the other hand, essentially requires a single procedure only. Therefore we had expected that ovulation induction with rFSH would be more burdensome to women. This assumption has not been confirmed, a small difference was seen in the CES-D scale in the sub-analysis only. We cannot exclude that differences also exist in other HRQoL items, however, as the study was powered to exclude a difference in pregnancy rates, the sample size was probably not sufficient to detect small changes in HRQoL.

In our randomised controlled trial the ongoing pregnancy rate was comparable in both study groups (Bayram et al., 2004). After electrocautery of the ovaries and additional treatment with clomiphene citrate an ongoing pregnancy rate of almost 50% was seen, eliminating the need for ovulation induction with rFSH in half of the clomiphene resistant women with PCOS. The cumulative ongoing pregnancy rate per woman of electrocautery of the ovaries, followed by clomiphene citrate and rFSH when anovulation persisted was equivalent to that of ovulation induction with rFSH alone in a time span of 12 months (67% in both treatment groups: rate ratio 1.01; 95% confidence interval 0.81 to 1.24). However, the major difference between the two treatment arms was the occurrence of multiple pregnancies. All multiple pregnancies occurred after ovulation induction with rFSH (rate ratio 0.11; 95% confidence interval 0.01 to 0.86). Multiple pregnancies are a major obstetric, psychological and economic problem (Ozturk and Templeton, 2002). Reduction or prevention of the occurrence of multiple pregnancies should be the major goal of treatment in clomiphene citrate resistant women with PCOS. Our findings on HRQoL do not supply any additional data for the recommendation that electrocautery strategy should be the treatment of choice in this patient group.

This study was supported in part by grant OG 93/007 from the Health Insurance Funds Council, Amstelveen, The Netherlands. Financial support for rFSH treatment (Gonal-F) was obtained from Serono, The Netherlands.
### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Electrocautery strategy N=83</th>
<th>rFSH N=85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (SD)</td>
<td>28.5 (3.7)</td>
<td>28.7 (4.1)</td>
</tr>
<tr>
<td>Mean body mass index (SD)</td>
<td>27.9 (6.3)</td>
<td>27.3 (8.8)</td>
</tr>
<tr>
<td>Mean waist hip ratio (SD)</td>
<td>0.83 (0.09)</td>
<td>0.84 (0.08)</td>
</tr>
<tr>
<td>Mean duration of infertility (years) (SD)</td>
<td>2.8 (2.2)</td>
<td>2.8 (2.1)</td>
</tr>
<tr>
<td>Type of infertility N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>63 (76)</td>
<td>64 (75)</td>
</tr>
<tr>
<td>Secondary</td>
<td>20 (24)</td>
<td>21 (25)</td>
</tr>
<tr>
<td>Parity N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>64 (77)</td>
<td>66 (78)</td>
</tr>
<tr>
<td>Multiparous</td>
<td>19 (23)</td>
<td>19 (22)</td>
</tr>
<tr>
<td>Education N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only primary school</td>
<td>21 (25)</td>
<td>24 (29)</td>
</tr>
<tr>
<td>Secondary school</td>
<td>52 (63)</td>
<td>46 (54)</td>
</tr>
<tr>
<td>University</td>
<td>10 (12)</td>
<td>15 (18)</td>
</tr>
</tbody>
</table>

SD = standard deviation

---

**Figure 1. Flow diagram**

Randomized (n=168)

Allocation

- Electrocautery strategy (n=83)
  - Received electrocautery (n=83)
  - HRQoL measurement (n=78)##

- Recombinant FSH (n=85)
  - Received rFSH (n=85)
  - HRQoL measurement (n=74)##

Completed questionnaires

- Electrocautery week 2 (n=72)
  - Electrocautery + CC week 2 (n=0)
  - week 12 (n=47)
  - week 24 (n=21)
  - week 24 (n=39)

- rFSH week 2 (n=69)
  - week 12 (n=66)
  - week 24 (n=58)

Analysis

- Available for analysis (n=75)
  - Excluded from analysis (n=3): baseline but no follow-up measurement

- Available for analysis (n=73)
  - Excluded from analysis (n=1): baseline but no follow-up measurement

# Baseline HRQoL measurement completed before randomisation
Table 2a. - Specification of the SF-36 questionnaire

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment</th>
<th>Baseline</th>
<th>Time after laparoscopy</th>
<th>Reference</th>
<th>Analysis with baseline value as covariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 weeks</td>
<td>12 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>electrocautery</td>
<td>89 (18)</td>
<td>83 (23)</td>
<td>89 (17)</td>
<td>81 (16)</td>
</tr>
<tr>
<td></td>
<td>rFSH</td>
<td>93 (15)</td>
<td>90 (14)</td>
<td>93 (10)</td>
<td>88 (16)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>electrocautery</td>
<td>84 (18)</td>
<td>76 (19)</td>
<td>79 (19)</td>
<td>78 (20)</td>
</tr>
<tr>
<td></td>
<td>rFSH</td>
<td>85 (15)</td>
<td>78 (20)</td>
<td>81 (19)</td>
<td>81 (23)</td>
</tr>
<tr>
<td>Role limitations - physical</td>
<td>electrocautery</td>
<td>86 (29)</td>
<td>60 (42)</td>
<td>77 (37)</td>
<td>68 (39)</td>
</tr>
<tr>
<td></td>
<td>rFSH</td>
<td>91 (24)</td>
<td>67 (36)</td>
<td>85 (26)</td>
<td>75 (37)</td>
</tr>
<tr>
<td>Role limitations - emotional</td>
<td>electrocautery</td>
<td>75 (35)</td>
<td>78 (35)</td>
<td>72 (41)</td>
<td>68 (42)</td>
</tr>
<tr>
<td></td>
<td>rFSH</td>
<td>86 (26)</td>
<td>76 (36)</td>
<td>77 (34)</td>
<td>78 (38)</td>
</tr>
<tr>
<td>Mental health</td>
<td>electrocautery</td>
<td>71 (16)</td>
<td>73 (17)</td>
<td>71 (17)</td>
<td>75 (17)</td>
</tr>
<tr>
<td></td>
<td>rFSH</td>
<td>78 (14)</td>
<td>75 (16)</td>
<td>76 (16)</td>
<td>75 (20)</td>
</tr>
<tr>
<td>Vitality</td>
<td>electrocautery</td>
<td>66 (18)</td>
<td>64 (19)</td>
<td>63 (20)</td>
<td>60 (17)</td>
</tr>
<tr>
<td></td>
<td>rFSH</td>
<td>72 (15)</td>
<td>68 (17)</td>
<td>67 (19)</td>
<td>63 (19)</td>
</tr>
<tr>
<td>Pain</td>
<td>electrocautery</td>
<td>86 (20)</td>
<td>69 (20)</td>
<td>83 (20)</td>
<td>83 (20)</td>
</tr>
<tr>
<td></td>
<td>rFSH</td>
<td>87 (18)</td>
<td>72 (20)</td>
<td>85 (17)</td>
<td>82 (22)</td>
</tr>
<tr>
<td>General health</td>
<td>electrocautery</td>
<td>74 (19)</td>
<td>76 (18)</td>
<td>74 (19)</td>
<td>77 (19)</td>
</tr>
<tr>
<td></td>
<td>rFSH</td>
<td>83 (15)</td>
<td>81 (14)</td>
<td>81 (15)</td>
<td>75 (20)</td>
</tr>
</tbody>
</table>

Results are expressed as mean (SD)
1 The subscale scores were transformed to a 0 to 100 scale, with higher scores indicating better quality of life.
2 Interaction between changes in health related quality of life over time and treatment group
3 Number of women that completed the questionnaire: in the electrocautery group | in the rFSH group

Note: Baseline values were taken as covariable in the repeated measurement model. No significant treatment effect was found for any of the subscales.
Table 2b. - Specification of the RSCL and CES-D questionnaires

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Baseline</th>
<th>2 weeks</th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>Reference</th>
<th>Analysis with baseline value as covariable</th>
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<td>Time after laparoscopy</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2 weeks</td>
<td>12 weeks</td>
<td>24 weeks</td>
<td></td>
<td>Time-effect p-value</td>
</tr>
<tr>
<td><strong>RSCL^2:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Time-effect p-value</td>
</tr>
<tr>
<td>Physical symptoms</td>
<td>electrocautery</td>
<td>22 (17)</td>
<td>25 (19)</td>
<td>24 (16)</td>
<td>29 (16)</td>
<td>10 (9)</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>rFSH</td>
<td>17 (16)</td>
<td>22 (18)</td>
<td>22 (15)</td>
<td>24 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological distress</td>
<td>electrocautery</td>
<td>26 (19)</td>
<td>22 (21)</td>
<td>26 (20)</td>
<td>25 (21)</td>
<td>17 (18)</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>rFSH</td>
<td>21 (16)</td>
<td>18 (16)</td>
<td>18 (17)</td>
<td>19 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity level</td>
<td>electrocautery</td>
<td>2 (6)</td>
<td>6 (10)</td>
<td>2 (9)</td>
<td>4 (10)</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>rFSH</td>
<td>1 (4)</td>
<td>2 (6)</td>
<td>2 (6)</td>
<td>3 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall quality of life</td>
<td>electrocautery</td>
<td>27 (19)</td>
<td>27 (16)</td>
<td>29 (20)</td>
<td>31 (19)</td>
<td>21 (84)</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>rFSH</td>
<td>22 (16)</td>
<td>29 (20)</td>
<td>24 (16)</td>
<td>24 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CES-D^3:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Time-effect p-value</td>
</tr>
<tr>
<td>Depression</td>
<td>electrocautery</td>
<td>11 (8)</td>
<td>10 (8)</td>
<td>12 (10)</td>
<td>12 (11)</td>
<td>&lt; 16</td>
<td>0.36</td>
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<tr>
<td></td>
<td>rFSH</td>
<td>7 (7)</td>
<td>10 (10)</td>
<td>8 (9)</td>
<td>9 (10)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results are expressed as mean (SD); NS = not significant

\^1 Interaction between changes in health related quality of life over time and treatment group

\^2 The RSCL subscale scores were transformed to a 0 to 100 scale, with higher scores indicating lower quality of life.

\^3 The CES-D produces scores between 0 to 60, a score of 16 or greater is considered to be a rough indicator for presence of clinical depression

Note: Baseline values were taken as covariable in the repeated measurement model. No significant treatment effect was found for any of the subscales.
Figure 2. Changes in CES-D score compared to baseline values in non-pregnant women (means ± standard errors). Closed circles = electrocautery strategy; open circles = rFSH.

Figure 3. Histogram expressing the proportion of non-pregnant women with a CES-D score of 16 or larger for both treatment strategies before and at 2, 12 and 24 weeks after laparoscopy.
References


