Long-term outcomes in women with polycystic ovary syndrome initially randomized to receive laparoscopic electrocautery of the ovaries or ovulation induction with gonadotrophins

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BACKGROUND: Long-term effects of laparoscopic electrocautery of the ovaries are unknown. To study the long-term effects of laparoscopic electrocautery of the ovaries and gonadotrophins, we followed women with clomiphene-resistant polycystic ovary syndrome (PCOS) randomly allocated to one of these treatments until 8–12 years after their initial treatment.

METHODS: Between February 1998 and October 2001 168 women with clomiphene citrate-resistant PCOS were included in a randomized controlled trial comparing an electrocautery strategy to a strategy starting with rFSH. In 2009 these women were contacted about their reproductive outcome and menstrual cycle regularity. Analysis was by intention-to-treat. We compared time to conception resulting in live birth, subsequent pregnancies, ectopic and multiple pregnancies, menopause, as well as minimal and maximal menstrual cycle length.

RESULTS: After 8–12 years, the cumulative proportion of women with a first child was 86% in women who had been allocated to electrocautery versus 81% in women who had been allocated to immediate rFSH [relative ratio (RR): 1.1; 95% confidence interval (CI): 0.92–1.2]. Treatment with electrocautery resulted in a significantly lower need for stimulated cycles to reach a live birth; 53% after electrocautery versus 76% after rFSH (RR: 0.69; 95% CI: 0.55–0.88). The cumulative proportion of women with a second child was 61% after electrocautery versus 46% after rFSH (RR: 1.4; 95% CI: 1.00–1.9). Overall, there were 7 twins out of 134 deliveries (5%) after electrocautery versus 10 twins out of 124 deliveries (8%) in the rFSH group (RR: 0.65; 95% CI: 0.25–1.6). Fifty-four per cent of the women allocated to electrocautery had a regular menstrual cycle 8–12 years after randomization versus 36% in those allocated to rFSH (RR: 1.5; 95% CI: 0.87–2.6).

CONCLUSION: In women with clomiphene-resistant PCOS, laparoscopic electrocautery of the ovaries is as effective as ovulation induction with FSH treatment in terms of live births, but reduces the need for ovulation induction or ART in a significantly higher proportion of women and increases the chance for a second child. Clinicians may use these data when informing clomiphene-resistant anovulatory women about treatment options.

Key words: clomiphene citrate / PCOS / electrocautery / ovulation induction / follicle-stimulating hormone
Introduction

In women with polycystic ovary syndrome (PCOS) who do not ovulate when treated with clomiphene citrate (CC), ovulation induction with gonadotrophins and laparoscopic electrocautery of the ovaries are established second line treatments with comparable success rates (Farquhar et al., 2007, Thessaloniki Group, 2008). Yet it has been suggested that electrocautery can lead to permanent ovarian damage and adhesion formation due to destruction of ovarian tissue (Greenblatt, 1993, Kaya et al., 2005; Api 2009; Hendriks et al., 2010). This in turn would lead to premature ovarian failure and secondary infertility.

Long-term data on the impact of laparoscopic electrocautery on pregnancy outcome and menstrual cycle regularity are limited. Two observational follow-up studies reported on pregnancy rates and menstrual cycle regularity after electrocautery of the ovaries in women with PCOS. One study included 212 women who underwent laparoscopic electrocautery between 1986 and 1993 and followed them for a maximum of 6 years (Naether et al., 1994). After 6 years only six women (3%) remained for evaluation. Another study included 194 women with PCOS, who underwent electrocautery between 1991 and 1999 and followed them for a maximum of 9 years after electrocautery, but only 85 (44%) women had a follow-up of more than 3 years (Amer et al., 2002b). The reported pregnancy rates were between 61 and 70% and the ectopic pregnancy rate ranged from 0 to 1.5% (Naether et al., 1994; Amer et al., 2002b). Regular menstrual cycles were reported in 55–92% of women (Naether et al., 1994; Amer et al., 2002b). Neither of these studies had included a comparison. A randomized controlled trial comparing laparoscopic electrocautery of the ovaries and gonadotrophin therapy in 50 women ran from 1996 to 1999. A long-term follow-up study, based on this trial included 33 women of whom 29 had undergone electrocautery and 4 gonadotrophins (Mohiuddin et al., 2007). In total 23 of 29 women (79%) had at least one live born child and the ectopic pregnancy rate was 3%. The menstrual cycle regularity was only known for 25 women allocated to electrocautery and 15 women (60%) had a regular menstrual cycle 6–10 years after electrocautery. The small study size and low response rate in the follow-up study jeopardize the validity of this comparison between electrocautery and gonadotrophins.

To add to the existing evidence, we set out to document the long-term effects of laparoscopic electrocautery of the ovaries in clomiphene-resistant PCOS women compared with gonadotrophins, with an emphasis on reproductive outcome and menstrual cycle regularity. This study is based on the largest randomized controlled trial performed so far (Bayram et al., 2004).

Materials and Methods

We studied 168 women with clomiphene-resistant PCOS who had participated in a multicentre randomized trial between February 1998 and October 2001. In this trial, all women had chronic anovulation and polycystic ovaries as diagnosed by transvaginal ultrasound, and had been resistant to clomiphene. Clomiphene resistance was defined as a persistent anovulation after taking 150 mg CC daily for 5 days. Of the 168 women included, 83 women had been allocated to an electrocautery strategy and 85 were allocated to initial recombinant follicle stimulating hormone (rFSH). Central computerised allocation had been performed with random blocks, stratified for centre.

The ovaries of women allocated to electrocautery were cauterized with an Erbotom ICC 350 Unit (Erbe; Zaltbommel, The Netherlands). A bipolar insulated needle electrode (length 345 mm, shaft diameter 5 mm) was pressed at right angles to the surface of a follicle and the needle (length 15 mm, shaft diameter 0.9 mm) was inserted in the follicle and surrounding tissue. Each ovary was punctured randomly 5–10 times, depending on its size. The automatic stop function guaranteed a reproducible coagulation. If women ovulated in six subsequent cycles, no further treatment was given. If anovulation persisted for 8 weeks, treatment was followed by CC. Treatment was followed by rFSH if anovulation persisted with CC 150 mg per day for 5 days. Women allocated to the rFSH strategy were treated with rFSH starting on Day 3 of the cycle according to the low-dose step-up regime (Hamilton-Fairley et al., 1991).

Follow-up

Follow-up ended 1 year after randomization. In January 2009 all 168 women were asked by mail to participate in the follow-up study. They were sent a postal questionnaire and, when the information was not sufficient or inconsistent, were contacted for telephone interviews. Non-responders were sent a second questionnaire, followed by telephone contact if necessary and possible. To add to these data, we searched the medical files of all women who participated in the trial.

Questionnaire

The questionnaire had items about current body mass index, anticonception use, menstrual pattern, child wish, past fertility treatments and reproductive outcome. We collected details on all desired pregnancies that occurred during the follow-up period, including live birth, multiple pregnancies, miscarriages and ectopic pregnancies. We also asked whether these pregnancies had occurred by natural conception, with or without ovulation induction or by a form of ART. Regular cycles were defined as cycles lasting <35 days.

Statistical analysis

The primary outcome in our analysis was conception resulting in live birth. Secondary outcomes were ectopic pregnancies, multiple pregnancies and miscarriages, as well as menstrual cycle regularity. Analysis was performed according to intention-to-treat principle: all conceptions leading to live birth during the follow-up period were analysed within the treatment group to which the women had originally been allocated. The effectiveness of primary electrocautery compared with ovulation induction with rFSH was expressed as a relative ratio (RR) for all outcomes, with corresponding 95% confidence intervals (CI).

Analysis of a second pregnancy after inclusion in the trial was performed for all women included. Kaplan–Meier curves were plotted to evaluate the difference in time to live birth between the two groups. Differences in time to first and second live birth were tested for statistical significance with the log-rank test statistic. We also compared the total number of live births (twin as a single count) in each group using a Mann–Whitney U-test. The original sample size for the trial had been based on a non-inferiority design, using a 5% margin, guided by an expected ongoing pregnancy rate of 38% within 12 months after treatment with gonadotrophins versus 52% in the electrocautery group. With a sample size of 84 women in each group, we would have a power of 80% to detect a relative risk of 1.27 or larger for the long-term effects, using a 5% significance level and two-sided testing, and assuming a live birth rate of 70% in the control group.
Results

In the randomized trial, 83 women had been assigned to an electrocautery strategy (electrocautery group) and 85 women to a strategy with ovulation induction with rFSH (rFSH group). Baseline characteristics were comparable between the two groups, and have been reported elsewhere (Bayram et al., 2004). Mean duration of subfertility was 2.8 years and 64% of the couples had primary subfertility.

We were able to obtain follow-up data for 159 of the 168 women (95%): 79 of 83 women from the electrocautery group (95%) and 80 of 85 women from the rFSH group (94%). We received complete and consistent questionnaires from 58 women. Information for an additional 21 women was found in their medical file. We contacted the remaining 80 women by telephone for further information.

The flow of women after inclusion in the trial is shown in Fig. 1. In the analysis we combined the outcome data that we published in our original report with the data obtained in the questionnaire. For the women who could not be reached in this follow-up, we used the data as known at 12 months after randomization.

Median follow-up time was 134 months in the electrocautery group and 133 months in the immediate rFSH group. The mean female age at follow-up for women allocated to electrocautery was 40.1 (SD 3.5) and 40.3 (SD 4.0) years, respectively. The average BMI was 28.2 (SD 6.3) and 27.0 (SD 6.5), respectively.

Reproductive outcome

In total, 71 of 83 couples (86%) had a conception leading to live birth in the electrocautery group versus 69 of the 85 couples (81%) in the rFSH group (RR: 1.1; 95% CI: 0.92–1.2, log-rank test: 0.24, P = 0.63) (Fig. 2).

Of the 83 women allocated to the electrocautery strategy, 27 women (33%) achieved a conception leading to a first live birth without additional treatment, whereas 44 women (53%) needed further medical treatment to do so: 14 needed CC, 22 needed FSH, 1 needed FSH and IUI, 3 needed IUI and 4 needed IVF treatment. Of the 85 women allocated to the rFSH strategy, 4 women (5%) had a spontaneous first live birth and 65 women (76%) needed treatment: 55 needed FSH, 2 needed FSH and IUI, 1 needed CC and 7 needed IVF treatment. Electrocautery thus resulted in a significantly lower need for stimulated cycles to reach a live birth: 44 of 71 live births versus 65 of 69 live births in the rFSH group (RR: 0.69; 95% CI: 0.55–0.88).

Second live birth

Of the 83 women allocated to the electrocautery strategy, 51 women (61%) had a second live birth. Of the 85 women allocated to rFSH treatment, 39 women (46%) had a second live birth (RR: 1.3; 95% CI: 1.01–1.8, log-rank test: 4.77, P = 0.03) (Fig. 3).

Of the 83 women in the electrocautery group, 29 women (35%) achieved a conception leading to a second live birth without additional treatment, whereas 22 women (24%) needed further medical treatment to do so: 5 needed CC, 1 needed IUI, 12 needed rFSH, 3 needed FSH plus IUI and 1 needed IVF treatment. Of the 85 women allocated to the rFSH strategy, 23 women (27%) had a spontaneous second live birth and 16 women (19%) needed further treatment to do so: 2 needed CC, 8 needed FSH, 3 needed FSH plus IUI and 3 needed IVF treatment. Thus, electrocautery resulted in a non-significant difference in need for stimulated cycles to reach a second live birth: 22 of 51 live births in the electrocautery group versus 16 of 39 live births in the rFSH group (RR: 1.4; 95% CI: 0.80–2.5).

A further 24 women delivered a third child, 11 women in the electrocautery group and 13 women in the rFSH group. One woman in the electrocautery group and three women in the rFSH group delivered also a fourth live born child. Overall, there were 134 live births in the electrocautery group and 124 live births in the immediate rFSH group (P = 0.09).

Of the 134 women who had a pregnancy leading to live birth in the electrocautery group, seven delivered a twin (5%). Of the 124 pregnancies leading to live births in the rFSH group, 10 (8%) were twin births (RR: 0.65; 95% CI: 0.25–1.6). All twin pregnancies occurred in stimulated cycles. Neonatal death occurred in one twin pregnancy at 26 weeks of gestation and in one triplet pregnancy at 22 weeks of gestation.

Of the 175 pregnancies after electrocautery, 5 were ectopic pregnancies. Of the 159 pregnancies after rFSH, 3 were ectopic pregnancies (RR: for ectopic pregnancy 1.5, 95% CI: 0.37–6.2). Of the pregnancies after electrocautery, 31 were miscarriages versus 23 after rFSH (RR for miscarriage 1.2, 95% CI: 0.75–2.0).

Menstrual pattern

Data on menstrual patterns were available for 138 women for whom follow-up data could be obtained by questionnaire. Oral contraceptives were used by 32 of 69 women in the electrocautery group and 31 of 69 women in the rFSH group. Two women were pregnant and one woman was being treated with rFSH for ovulation induction at the time of the questionnaire. Three women had a hysterectomy because of intractable hypermenorrhoea and dysmenorrhoea. The menstrual cycle remained unknown for one woman. Of the remaining women a regular menstrual cycle was reported by 19 of 35 women (54%) in the electrocautery group and 12 of 33 (36%) women in the rFSH group (RR: 1.5; 95% CI: 0.9–2.6). Sixteen of 35 women (46%) in the electrocautery group and 21 of 33 (64%) women in the rFSH group had an irregular cycle. None of the women had her last menstruation more than a year ago. Mean minimal and maximal cycle duration were 40 days and 106 days for women allocated to electrocautery strategy and 55 and 178 days for women allocated to the rFSH strategy.

Discussion

Although laparoscopic electrocautery of the ovaries has been shown to be more cost-effective than ovulation induction with gonadotrophins (Bayram et al., 2004; Farquhar et al., 2002; Van Wely et al., 2004a; Van Wely et al., 2004b), fear for possible long-term side effects have made many clinicians reluctant to offer this treatment.

In this long-term follow-up, we have shown that after 8–12 years of follow-up the cumulative chances of delivering at least one live born baby were not lower in the electrocautery strategy group than in the rFSH group, but 5% higher, though not significantly different. We also observed that electrocautery significantly increased the number of women with a second child. Electrocautery eliminated the need for ovulation induction or ART for the first child in a
Figure 1 Flow of women after inclusion in the trial.
significantly higher proportion of women and electrocautery resulted in a non-significant difference for stimulated cycles to reach a second live birth. The high intrauterine pregnancy rate and low ectopic pregnancy rate clearly demonstrate that post-operative adhesion formation, if at all present, is not an important clinical problem. None of the women in our study had peri-operative complications or an early menopause, which may indicate that electrocautery is a safe technique and that it is unlikely that menopause before 40 years should occur as a consequence of destroying ovarian tissue.

A strong point of this follow-up study is that our analyses are based on a balanced randomized controlled trial with a high follow-up rate and intention to treat analysis. For three women allocated to electrocautery and five women allocated to rFSH, it remained unknown if they had a live born child after inclusion in the trial. With the assumption that all remaining five women allocated to rFSH got pregnant and
none of the three women allocated to electrocautery got pregnant, 71 of 83 couples (86%) would have a conception leading to live birth in the electrocautery group versus 74 of the 85 couples (87%) allocated to rFSH (RR: 0.98; 95% CI: 0.87–1.1). Even this extreme scenario would not have changed our results significantly. Although we have no data on how long women remain with regular menses after electrocautery, we do know that women have more frequent regular menses 8–12 years after electrocautery compared with women initially treated with rFSH.

Notwithstanding the methodological shortcomings of previous studies, their reported results were comparable to our findings (Naether et al., 1994; Amer et al., 2002b; Mohiuddin et al., 2007). Although we did not measure ovarian reserve, endocrinological follow-up studies after electrocautery indicate that mean LH, FSH, LH:FSH ratio and/or androgen levels remain unchanged in 5–20 years of follow-up (Naether et al., 1994; Gjonnaess, 1998; Amer et al., 2002a; Mohiuddin et al., 2007), which underpins the safety of the procedure as found in this study.

Since the introduction of clomiphene citrate, gonadotrophins and GnRH, ovulation induction has always been a medical intervention, which is understandable given the endocrine basis of PCOS and the excellent results obtained. This historical background probably explains the resistance of many against the surgical approach. This resistance may have been reinforced by the very fact that surgery is invasive and aims to damage the ovaries. These considerations and emotions have probably overruled the available data demonstrating the cost-effectiveness of electrocautery of the ovaries. The importance of this study is that it provides solid evidence for its long-term safety and effectiveness and should thereby convince professionals caring for CC resistant women to offer laparoscopic electrocautery as a safe and effective second line treatment.

In summary, electrocautery of the ovaries is a safe treatment in clomiphene-resistant PCOS women that eliminates the need for ovulation induction or ART in a significant proportion of women and obviates cycle monitoring necessary with gonadotrophins. Moreover, it is at least as effective as immediate gonadotropin therapy for the first child and a randomized controlled trial of laparoscopic ovarian diathery versus gonadotropin therapy for women with clomiphene citrate-resistant polycystic ovary syndrome. Fertil Steril 2002;78:404–411.


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