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CHAPTER 7

**Treatment preferences and trade-offs
for ovulation induction
in clomiphene citrate resistant patients
with polycystic ovary syndrome**

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Submitted

Abstract

Objective

To investigate patient preferences and trade-offs for laparoscopic electrocautery of the ovaries relative to ovulation induction with recombinant FSH (rFSH) in patients with clomiphene citrate resistant polycystic ovary syndrome.

Design

Assessment of preferences and trade-offs in a randomized controlled trial.

Setting

Academic Hospital.

Patients

Thirty-two clomiphene citrate resistant patients with polycystic ovary syndrome who had been randomly assigned to either laparoscopic electrocautery of the ovaries or ovulation induction with rFSH and 32 control patients with polycystic ovary syndrome under treatment with clomiphene citrate.

Interventions

Preference for laparoscopic electrocautery relative to rFSH was established during an interview. Trade-offs between treatment burden and effectiveness were evaluated by varying hypothetical pregnancy rates after laparoscopic electrocautery until patients switched in their initial preference.

Main Outcome Measures

Preference for laparoscopic electrocautery of the ovaries; trade-off between burden and effectiveness of treatment.

Results

The majority of the patients would prefer electrocautery of the ovaries over ovulation induction with rFSH if both treatment strategies resulted in similar pregnancy rates. However, most patients were willing to trade off their preference for increased effectiveness: the percentage of patients who preferred electrocautery over rFSH sharply declined when the difference in hypothetical pregnancy rates was more than 5% in favor of rFSH.

Conclusions

Patients with polycystic ovary syndrome are well able to express an informed preference for laparoscopic electrocautery of the ovaries or ovulation induction with rFHS. Preferences are guided by features of the respective treatments but seem to be dominated by their effectiveness as well as by their safety.

Key Words: Polycystic ovary syndrome, clomiphene citrate, laparoscopy, electrocautery, rFSH, pregnancy, patient preferences

Introduction

Polycystic ovary syndrome is a common endocrine disorder characterized by two out of the following three criteria; oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries (The Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group, 2004; The Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group, 2004a). Infertility due to chronic anovulation is the most common reason to seek treatment.

About 20% of women fail to ovulate on clomiphene citrate, the drug of first choice (Imani et al., 1998). For those who fail to ovulate with clomiphene citrate, the principal options include ovulation induction with gonadotrophins or laparoscopic electrocautery of the ovaries.

It is generally assumed that ovulation induction with gonadotrophins is a cumbersome treatment for patients due to the need for daily injections and intensive monitoring. Furthermore, ovulation induction with gonadotrophins bears the risk of multiple follicle development leading to termination of the cycle or multiple pregnancy (Bayram et al., 2004; Nugent et al., 2004). In contrast, electrocautery of the ovaries involves a single procedure with limited monitoring while potential complications inherent to ovulation induction with gonadotrophins are absent (Donesky and Adashi, 1995). Yet, as a surgical intervention, electrocautery carries a risk of complications, such as thermal damage of the intestines, bleeding from the ovary and adhesion formation (Greenblatt and Casper, 1993; Naether and Fischer, 1993; Saravelos and Li, 1996; Cohen, 1996; Tulandi and al Took, 1998).

Both treatment options clearly differ in terms of the invasiveness of the intervention, the intensity of monitoring and possible complications.

Because of the limited monitoring and absence of complications such as multiple follicle development and multiple pregnancies after electrocautery, we anticipated that most patients would express a preference for this strategy if effectiveness would be equal.

The primary aim of this study was to investigate patients' preferences for electrocautery of the ovaries compared to gonadotrophins. We studied treatment preferences in women who participated in a randomized controlled trial and in a control group of women with polycystic ovary syndrome treated with clomiphene citrate. In this trial the electrocautery strategy was found to be equivalent to ovulation induction with rFSH alone with ongoing pregnancy rates of 67% for both strategies (Bayram et al., 2004a). The major difference however was a lower number of multiple pregnancies in the group first treated with electrocautery and clomiphene citrate.

Materials and Methods

Patients

Patients included in a multicenter randomized controlled trial were invited to this treatment preference study. Eligible patients were those with chronic anovulation WHO type II (WHO, 1993) and polycystic ovaries not responding to clomiphene citrate.

From February 1998 to October 2001 consenting patients had been randomly assigned either to a treatment strategy entailing laparoscopic electrocautery of the ovaries followed by clomiphene citrate and rFSH when anovulation persisted or to ovulation induction

with recombinant FSH (rFSH), (follitropin alpha, Gonal-F; Serono Benelux BV, The Hague, The Netherlands). For this study, we only invited patients who were treated at the Academic Medical Center (the trial co-ordination center).

Electrocautery was performed using an Erbotom ICC 350 Unit (Erbe BV, Zaltbommel, The Netherlands) and done with a bipolar insulated needle-electrode. Clomiphene citrate was reintroduced when anovulation persisted or if the patient became anovulatory again. If patients remained anovulatory despite the maximum dose of 150 mg clomiphene citrate, ovulation induction with rFSH was started. Further details of the design and results of this randomized controlled trial have been reported elsewhere (Bayram et al., 2004a).

A control group of consecutive patients with chronic anovulation and polycystic ovaries undergoing ovulation induction with clomiphene citrate were also invited to the study. The rationale for choosing these patients as controls was that they were informed about their condition and that they were potential candidates for treatment with either electrocautery of the ovaries or ovulation induction with rFSH if they became resistant to clomiphene citrate.

Methods

Preferences for electrocautery relative to rFSH were studied in an interview. All interviews were conducted by the first author.

Participating patients were first informed about the purpose of the study. The descriptions of both treatments were in accordance with the information that they had received during the initial informed consent procedure. Participants received written information on the possible advantages and disadvantages of both treatments. Potential advantages of laparoscopic electrocautery of the ovaries compared to rFSH are no need of daily injections, less need for intensive monitoring and minimal chance for complications such as multiple follicle development and multiple pregnancies. Disadvantages are the need for surgery and therefore possible complications as thermal damage of the intestines, bleeding from the ovary and adhesion formation can occur.

The chances of a pregnancy were set at 40% after electrocautery and 35% after ovulation induction with rFSH, based on data available in the literature at the time the study was initiated. After reading the treatment descriptions the women were asked which treatment they would prefer. We asked them for the reason for their treatment preference. We then investigated if patients were willing to trade-off their preference for a difference in effectiveness by systematically varying pregnancy rates after electrocautery. If electrocautery was the initially preferred option, the pregnancy rate after electrocautery was systematically decreased with 5% steps, until the patient's preference switched to rFSH. If rFSH was the initially preferred option, the pregnancy rate after electrocautery was set at 50%. When the patient's treatment preference switched to electrocautery the pregnancy rate after electrocautery was systematically decreased with 5% steps until her treatment preference switched back to rFSH. The pregnancy rate threshold at which the women would prefer electrocautery over rFSH was registered.

In our randomized controlled trial all women underwent a diagnostic laparoscopy to exclude women without patent tubes or with severe endometriosis and/or adhesions from

the trial. It is possible that the perceived burden of rFSH is lower in a strategy not including this diagnostic laparoscopy. Therefore, the preference assessment procedure was repeated in a scenario without a laparoscopy preceding ovulation induction with rFSH. The pregnancy rate was varied in the same way as described above. We registered the rate at which participating women would prefer electrocautery over rFSH without diagnostic laparoscopy.

After completion of the trial, the actual pregnancy rates after electrocautery strategy and rFSH were found to differ substantially from those initially used in the preference assessment. In trial patients, the ongoing pregnancy rate after ovulation induction with rFSH was 67% after 12 months versus 34% six months after electrocautery only. Administration of clomiphene citrate further increased the pregnancy rate in the electrocautery group to 49% and subsequent administration of rFSH in that group raised the pregnancy rate to 67% at 12 months (Bayram et al., 2004a). All patients who had participated in our randomized controlled trial were approached again after the trial to be interviewed. In this second interview patients were asked for their preference for the electrocautery strategy relative to rFSH using the pregnancy rates as estimated in the trial. Two scenarios were offered: a scenario with and a scenario without a diagnostic laparoscopy.

In a previous study we had found that patients' treatment preferences were guided by the difference in effectiveness between two treatment alternatives rather than by the absolute percentages (Nieuwkerk et al., 1998). Therefore, we present our findings as the difference in pregnancy rates of which patients would prefer the electrocautery strategy relative to rFSH. We investigated the agreement in treatment preference between the first and the second interview using kappa statistics.

Results

Thirty-two consecutive trial patients in the Academic Medical Center were invited to this study. All patients agreed to be interviewed. Forty-eight control patients were also asked to participate, of which 32 (67 %) agreed to be interviewed.

In this first interview we asked patients for their preference for treatment with electrocautery or treatment with rFSH. The results are reported separately for the group of patients who were treated with laparoscopic electrocautery of the ovaries (n=17), rFSH (n = 15) and control patients (n=32).

Figure 1 shows the cumulative percentages of patients who preferred electrocautery over rFSH at specified differences in pregnancy rates after electrocautery compared to rFSH in a scenario *with* a diagnostic laparoscopy. Sixteen of the 17 patients treated with electrocautery (94%), 13 of the 15 patients treated with rFSH (87%), and 28 of the 32 (86%) control patients would prefer electrocautery if electrocautery and rFSH resulted in equal pregnancy rates. The main reason for choosing electrocautery was the absence of daily hormonal injections (67%) and the lower chance of multiple follicular development and multiple pregnancies after electrocautery (20%). One patient treated with electrocautery, two treated with rFSH and three control patients did not opt for electrocautery because of fear of the cauterization procedure.

The percentage of patients that preferred electrocautery over rFSH sharply declined when the difference in hypothetical pregnancy rates exceeded 5% in favor of rFSH, indicating

that most patients were willing to trade-off their initial treatment preference for increased effectiveness.

Figure 2 shows the cumulative percentages of patients who preferred electrocautery over rFSH at specified differences in pregnancy rates after electrocautery compared to rFSH in a scenario *without* a diagnostic laparoscopy. Most patients would still prefer electrocautery over rFSH if the latter strategy did not require a diagnostic laparoscopy. Fourteen of the 17 patients treated with electrocautery (82%) 10 of the 15 patients treated with rFSH (67%), and 24 of the 32 (78%) control patients would prefer electrocautery if electrocautery and rFSH resulted in equal pregnancy rates. Most patients (53%) who preferred electrocautery explained that they did so in order to be informed about tubal patency. A further 22% said to prefer electrocautery because of the eliminated need of daily hormonal injections. Three patients treated with electrocautery, five treated with rFSH and eight control patients would never opt for electrocautery because of fear of the surgical procedure. The percentage of patients that preferred electrocautery over FSH sharply declined when the difference in hypothetical pregnancy rates exceeded 5% in favor of rFSH. With this alternative scenario most patients were also willing to trade-off their preference for increased effectiveness.

The 32 trial patients that had been treated with either electrocautery or rFSH also participated in the second interview. In contrast with the first interview, patients were now asked for their preference for treatment with an electrocautery strategy entailing electrocautery followed by treatment with clomiphene citrate and rFSH when anovulation persisted or ovulation induction with rFSH. Patients were also informed that both the electrocautery strategy and ovulation induction with rFSH resulted in an ongoing pregnancy rate of 67% at 12 months.

In a scenario *with* a diagnostic laparoscopy 15 patients treated with electrocautery strategy (88%) and 8 patients treated with rFSH (53%) preferred the electrocautery strategy. The main reason for choosing the electrocautery strategy was the reduced likelihood of requiring daily hormonal injections (59%) and the observation that electrocautery leads to less multiple follicular development and fewer multiple pregnancies (13%). Nine patients (28%) preferred rFSH because of fear of the electrocautery procedure and three (9%) because of the reduced time to pregnancies the mean time to pregnancy was one month longer when treating women with electrocautery strategy in comparison to ovulation induction with rFSH.

Most women treated with the electrocautery strategy who had opted for electrocautery in the first interview made a similar choice in the second interview (kappa 0.64, $p=0.005$). There was less agreement in the women treated with rFSH (kappa 0.30, $p=0.1$).

In a scenario *without* a diagnostic laparoscopy 11 patients treated with the electrocautery strategy (65%) and 9 patients treated with rFSH (60%) preferred the electrocautery strategy. The main reason for choosing the electrocautery strategy was the reduced need for daily hormonal injections (41%). A further 22% said to prefer the electrocautery strategy because of the diagnostic value of the laparoscopy in this strategy. Twelve patients (38%) preferred rFSH due to fear of an operation and three (9%) because of the reduced time to pregnancy following rFSH treatment.

Most women treated with the electrocautery strategy who had opted for electrocautery in the first interview made a similar choice in the second interview (kappa 0.57, $p=0.025$). This was also the case for most women treated with rFSH (kappa 0.57, $p=0.01$).

Discussion

In this study, the majority of patients preferred electrocautery under the assumption that both treatment modalities result in similar pregnancy rates. Yet, these patients were prepared to trade off this initial preference and to choose rFSH when that treatment would be more likely to lead to an ongoing pregnancy. We found this preference pattern both in patients who actually had been treated with electrocautery or rFSH in a randomized controlled trial as well as among patients currently treated with clomiphene citrate.

Our results demonstrate that pregnancy rates are the decisive factor in decision making among most infertility patients. Yet we observed a marked inter-individual variability in preferences. In the most realistic scenario – no diagnostic laparoscopy before rFSH – about one third of patients expressed a marked preference for one of the treatment options. Some patients never chose for rFSH as they did not want to receive hormonal injections while others never opted for electrocautery as they did not want to undergo a surgical procedure. The prospect of a potential multiple pregnancy was never mentioned as a reason not to opt for rFSH.

When asking patients for their preference, we had initially set the pregnancy rate after laparoscopic electrocautery of the ovaries at 40%. That percentage was based on the pregnancy rates reported in studies published at that time. The pregnancy rates actually observed in our randomized controlled trial comparing electrocautery followed by clomiphene citrate and rFSH when anovulation persisted with rFSH were markedly higher. In both groups 67% of women became pregnant, the only difference being the absence of multiple pregnancy after electrocautery and clomiphene citrate. We believe that participants are guided by differences in pregnancy rates between both treatments rather than by absolute percentages. We therefore trust that our results can safely be extrapolated. To test this assumption, we planned a second series of interviews in our trial patients, using the pregnancy rates as obtained in the trial. Although fewer patients opted for the electrocautery strategy in the second interview, there was substantial agreement between the treatment choices in the two interviews.

Other studies on treatment preference have shown that patients who actually have experienced a certain treatment express a preference for that particular treatment (Birnie et al., 2000). In our study patients in both treatment groups were more inclined to prefer electrocautery over rFSH, as were patients in the control group.

In all, our results show that patients with polycystic ovary syndrome are very well able to express an informed preference for one of two treatment strategies. This preference is guided by the features of the respective treatments but it seems to be dominated by their effectiveness as well as by their safety. Is this result important? We feel it is. It is nowadays generally acknowledged that patient preferences should be incorporated into medical decision making (Kassirer, 1994). Several studies have shown that patient's perspectives on the burden and benefits of therapy can differ from those of health professionals (Devereaux et al., 2001) This implies that physicians should explicitly and actively seek patients' views when making decisions about treatment that can affect these patients' well being (Montgomery and Fahey, 2001) Increased access to information for patients and an emphasis on patient autonomy make it likely that the dynamics of decision making between patients and physicians will increasingly move toward shared decision making in the near future. This will be supported by the development of decision aids which allow

patients to explore and express their preferences for available treatment options (Devereaux et al., 2001; Holmes-Rovner et al., 2001).

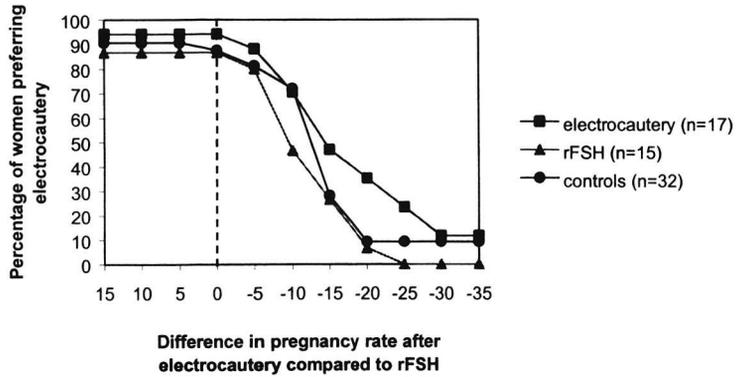


Figure 1. Patient preferences for laparoscopic electrocautery relative to ovulation induction with recombinant FSH in a scenario with a diagnostic laparoscopy.

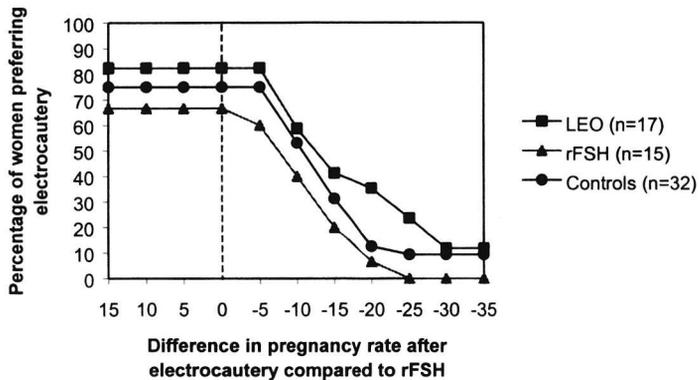


Figure 2. Patient preferences for laparoscopic electrocautery relative to ovulation induction with recombinant FSH in a scenario without a diagnostic laparoscopy.

References

Bayram, N., van Wely, M., and van der Veen, F. (2004) Recombinant FSH versus urinary gonadotrophins or recombinant FSH for ovulation induction in subfertility associated with polycystic ovary syndrome. The Cochrane Library, Issue 2, 2004, Chichester, UK: John Wiley & Sons, Ltd.

Bayram, N., van Wely, M., Kaaijk, E. M., Bossuyt, P. M. M., and van der Veen, F. (2004a) Using an electrocautery strategy or recombinant follicle stimulating hormone to induce ovulation in polycystic ovary syndrome: randomised controlled trial. *BMJ* 328, 192-195.

Birnie, E., Moninckx, W. M., Zondervan, H. A., Bossuyt, P. M. M., and Bonsel, G. J. (2000) Comparing treatment valuations between and within subjects in clinical trials: does it make a difference? *J. Clin. Epidemiol.* 53, 39-45.

Cohen, J. (1996) Laparoscopic procedures for treatment of infertility related to polycystic ovarian syndrome. *Hum. Reprod. Update* 2, 337-344.

Devereaux, P. J., Anderson, D. R., Gardner, M. J., Putnam, W., Flowerdew, G. J., Brownell, B. F., Nagpal, S., and Cox, J. L. (2001) Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study. *BMJ* 323, 1218-1222.

Donesky, B. W. and Adashi, E. Y. (1995) Surgically induced ovulation in the polycystic ovary syndrome: wedge resection revisited in the age of laparoscopy. *Fertil. Steril.* 63, 439-463.

Greenblatt, E. M. and Casper, R. F. (1993) Adhesion formation after laparoscopic ovarian cautery for polycystic ovarian syndrome: lack of correlation with pregnancy rate. *Fertil. Steril.* 60, 766-770.

Holmes-Rovner, M., Llewellyn-Thomas, H., Entwistle, V., Coulter, A., O'Connor, A., and Rovner, D. R. (2001) Patient choice modules for summaries of clinical effectiveness: a proposal. *BMJ* 322, 664-667.

Imani, B., Eijkemans, M. J., te Velde ER, Habbema, J. D., and Fauser, B. C. (1998) Predictors of patients remaining anovulatory during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrhoeic infertility. *J. Clin. Endocrinol. Metab.* 83, 2361-2365.

Kassirer, J. P. (1994) Incorporating patients' preferences into medical decisions. *N. Engl. J. Med.* 330, 1895-1896.

Montgomery, A. A. and Fahey, T. (2001) How do patients' treatment preferences compare with those of clinicians? *Qual. Health Care* 10, 39-43.

Naether, O. G. and Fischer, R. (1993) Adhesion formation after laparoscopic electrocoagulation of the ovarian surface in polycystic ovary patients. *Fertil. Steril.* 60, 95-98.

Nieuwkerk, P. T., Hajenius, P. J., van der, V., Ankum, W. M., Wijker, W., and Bossuyt, P. M. M. (1998) Systemic methotrexate therapy versus laparoscopic salpingostomy in tubal pregnancy. Part II. Patient preferences for systemic methotrexate. *Fertil. Steril.* 70, 518-522.

Nugent, D., Vandekerckhove, P., Hughes, E., Arnot, M., and Lilford, R. (2004) Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. The Cochrane Library, Issue 2, 2004, Chichester, UK: John Wiley & Sons, Ltd.

Saravelos, H. and Li, T. C. (1996) Post-operative adhesions after laparoscopic electro-surgical treatment for polycystic ovarian syndrome with the application of Interceed to one ovary: a prospective randomized controlled study. *Hum. Reprod.* 11, 992-997.

The Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group (2004a) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil. Steril.* 81, 19-25.

The Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group (2004b) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum. Reprod.* 19, 41-47.

Tulandi, T. and al Took, S. (1998) Surgical management of polycystic ovarian syndrome. *Baillieres Clin. Obstet. Gynaecol.* 12, 541-553.

WHO, (1993) WHO manual for the standardized investigation and diagnosis of the infertile couple. Cambridge. Cambridge University Press 1993.

