Pregnancy complications and metabolic disease in women with clomiphene citrate-resistant anovulation randomized to receive laparoscopic electrocautery of the ovaries or ovulation induction with gonadotropins: a 10-year follow-up

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Objective: To assess long-term effects of laparoscopic electrocautery of the ovaries compared with ovulation induction with gonadotropins in women with clomiphene citrate (CC)-resistant polycystic ovary syndrome (PCOS) on the incidence of pregnancy complications like gestational diabetes, hypertensive disorders, and metabolic or cardiovascular disease.
Design: Long-term follow-up study.
Setting: Twenty-eight hospitals within the Netherlands.
Patient(s): One hundred sixty-eight CC-resistant women who had participated in a randomized controlled trial between 1998 and 2001 comparing electrocautery and gonadotropins.
Intervention(s): Postal questionnaire, search in medical files.
Main Outcome Measure(s): Pregnancy complications, metabolic or cardiovascular disease.
Result(s): Eighty-two percent of follow-up data were obtained. Thirteen of 68 women (19%) allocated to electrocautery, and 14 of 63 women (22%) allocated to gonadotropins had evidence for pregnancy complications (relative risk 0.86; 95% confidence interval 0.43–1.7). At follow-up, 12 of 69 (17%) women allocated to electrocautery, and 13 of 69 (19%) women allocated to gonadotropins had evidence for metabolic or cardiovascular disease (relative risk 0.90; 95% confidence interval 0.39–2.1). The risk of these was modified by body mass index (BMI), but not by female age or treatment allocation. This study is based on questionnaires and data from medical files. In the absence of routine screening, under-reporting in our follow-up study is likely.
Conclusion(s): Electrocautery in women with CC-resistant PCOS does not affect pregnancy complications or metabolic or cardiovascular disease later in life compared with ovulation induction with gonadotropins. (Fertil Steril® 2014;101: 270–4. ©2014 by American Society for Reproductive Medicine.)
Key Words: Metabolic syndrome, polycystic ovary syndrome, long-term follow-up, surgery, ovulation induction

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Polycystic ovary syndrome (PCOS) is the most common form of anovulatory infertility (1). According to the revised diagnostic criteria established in 2003 the disease is characterized by oligo-ovulation and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and/or polycystic ovaries (PCO) by ultrasound, and two of these three categories should be present for the diagnosis of PCOS (2).

Women with PCOS have a higher risk for development of gestational diabetes (odds ratio [OR] 2.9; 95% confidence interval [CI] 1.7–5.1), pregnancy-induced hypertension (OR 3.7; 95% CI 2.0–6.8), or preeclampsia (OR 3.5; 95% CI 1.95–6.2). These data are based on a meta-analysis reporting data on 5,293 pregnant women (721 with PCOS and 4,572 controls) (3). However, with significant between-study heterogeneity in studies exploring the risk for gestational diabetes, the effect of PCOS per se is unclear. All studies in which preeclampsia was an end point reported a lower parity, higher body mass index (BMI), or more multiple pregnancies among women with PCOS vs. controls. Subgroup analyses correcting for BMI were not possible and therefore the effect of PCOS itself on the development of preeclampsia is also unknown (3, 4).

Later in life women with PCOS have a significant risk of impaired glucose tolerance or diabetes. Risks are highest in women who have both oligo-ovulation and hyperandrogenism and the risks are further amplified by obesity (5, 6). Many studies report that women with PCOS, whether lean or obese, have an increased cardiovascular risk profile with a higher blood pressure and abnormal lipid profile with higher low-density lipoprotein (LDL), but lower high-density lipoprotein (HDL) cholesterol and advanced arterial intima media thickness and coronary artery calcification compared with control subjects (7–12). Direct evidence for increased morbidity and mortality with cardiovascular disease is suggestive but inconclusive (13).

The etiology of PCOS remains unclear, but it is most likely a primary disorder of ovarian and/or adrenal steroidogenesis. Polycystic ovary syndrome is often accompanied by selective insulin resistance, in which muscle is insulin resistant, whereas the ovaries, adrenals, and adipose tissue remain relatively sensitive to the effects of insulin, thereby promoting androgen production and obesity (14). Familial factors related to metabolic syndrome seem to be fundamental to the pathogenesis of PCOS. Up to 70% of women with PCOS had at least one parent with the metabolic syndrome (15, 16). Because of this multifactorial origin with a genetic predisposition, women with PCOS have an increased risk for metabolic and cardiovascular disease.

Laparoscopic electrocautery of the ovaries is an established treatment for women with clomiphene citrate (CC)-resistant PCOS, with at least comparable pregnancy rates (PR) and lower costs compared with immediate ovulation induction with gonadotropins (17, 18). Whether laparoscopic electrocautery has an effect on gestational diabetes, hypertensive disorders during pregnancy, or the metabolic or cardiovascular disease has never been evaluated. We set out to assess these end points in a long-term follow-up study in women with PCOS who had originally participated in a multicenter randomized controlled trial comparing laparoscopic electrocautery of the ovaries or ovulation induction with gonadotropins (19).

MATERIALS AND METHODS

Study Design

We performed a follow-up study of all 168 women with CC-resistant PCOS who had been included in the multicenter randomized controlled trial, which had been performed between February 1998 and October 2001. In this trial, all women had chronic anovulation and PCOs as diagnosed by transvaginal ultrasound. Women had been resistant to CC, which was defined as a persistent anovulation after taking 150 mg/d CC for 5 days. For women allocated to ovulation induction with gonadotropins, treatment was started on day 3 by a daily SC injection of 75 IU recombinant gonadotropins, according to the low-dose step-up protocol. The ovaries from women allocated to the electrocautery strategy were cauterized with a bipolar insulated needle electrode and each ovary was punctured 5–10 times, depending on its size. 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 gonadotropins according to the low-dose step-up regime, if anovulation persisted with 150 mg/d CC for 5 days. From 12 months after randomization treatment was continued according to local protocol (19). The Institutional Review Board approval of the original protocol allowed contacting the women in the future. All women in the study had given informed consent for contacting them in the future.

In January 2009, all 168 women were asked to participate in the follow-up study. Data were obtained by a postal questionnaire and, when the information was not sufficient or consistent, by telephone interviews. In the questionnaire we asked for occurrence of pregnancy, possible complications like gestational diabetes or hypertensive disorders, and the occurrence of type 2 diabetes, hypertension, or cardiovascular disease at the time of the questionnaire. To obtain additional information on pregnancy complications we searched the medical files of all women who became pregnant to be informed on the course of the pregnancy, laboratory results for glucose levels, and blood pressure during pregnancy; hypertension laboratory results including proteinuria, term of delivery, and neonatal outcome and weight. We did a chart review of all women for the period during which they were still undergoing fertility treatment. When the women were no longer under treatment the only way to obtain data was by asking them. We were not able to assess all diagnostic criteria at long term, specifically blood pressure measurement for all women.

Gestational diabetes was defined as a fasting glucose level of $\geq$7 mmol/L, or a glucose level of $\geq$7.8 mmol/L 2 hours after a glucose tolerance test (GTT) with 75 g of glucose (20). Pregnancy-induced hypertension was defined as hypertension with a diastolic blood pressure $\geq$90 mm Hg, without proteinuria developing after 20 weeks of gestation. Preeclampsia was defined as hypertension, as mentioned previously, complicated by proteinuria, which implies $\geq$0.3 g of protein