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Does the postcoital test predict pregnancy in WHO II anovulatory women? A prospective cohort study

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ABSTRACT

Objective: To assess the capacity of the postcoital test (PCT) to predict pregnancy in WHO II anovulatory women who are ovulatory on clomiphene citrate (CC). In these women, an abnormal PCT result could be associated with lower pregnancy chances, but this has never been proven or refuted.
Study design: Prospective cohort study was performed between December 2009 and September 2012 for all women who started ovulation induction with CC in one university clinic and two teaching hospitals in the Netherlands. A PCT was performed in one of the first three ovulatory cycles. Ovulation induction with CC was continued for at least six cycles. The PCT was judged to be positive if at least one progressive motile spermatozo was seen in one of five high power fields at 400× magnification. The primary outcome was time to ongoing pregnancy, within six ovulatory cycles.
Results: In 152 women the PCT was performed. 135 women had a reliable, well-timed PCT. The ongoing pregnancy rate was 44/107 (41%) for a positive and 10/28 (36%) for a negative PCT. The hazard rate for ongoing pregnancy was 1.3 (95% CI 0.64–2.5) for a positive versus a negative PCT.

Thirty five of 77 (46%) women with clear mucus had an ongoing pregnancy versus 12 of 45 (27%) women in whom the mucus was not clear (HR 2.0; 95% CI 1.02–3.84, $p = 0.04$).
Conclusion: The present study suggests that the outcome of the postcoital test in women with WHO-II anovulation that undergo ovulation induction with CC does not have a large effect on ongoing pregnancy chances over time.

Introduction

Anovulation and oligo-ovulation are important causes of subfertility and are estimated to contribute to 20% of all cases of female subfertility [1,2]. The recommended first-line treatment for ovulation induction is the anti-oestrogen clomiphene citrate (CC) according to the ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group [3]. CC will restore ovulation in almost 80% and will result in pregnancy in 50% of all women.

Though CC results in high pregnancy rates, several studies have shown that CC has a negative effect on the cervical mucus [4–6]. The Dutch guidelines and the National Institute for Health and Clinical Excellence guidelines are not specific on the necessity to perform a PCT to exclude or demonstrate a cervical factor in women ovulating after induction as evidence on the relation between cervical factor and pregnancy chances does not exist.

The studies on the negative effect of CC on the cervical mucus did not evaluate whether abnormal cervical mucus was associated with lower pregnancy chances and the only prospective follow-up

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study on the relation between the result of the PCT and pregnancy rates describes the PCT outcome in some women, while the pregnancy rates are described in other women [4–7]. Therefore the association between outcome of the PCT and pregnancy chances cannot be determined from this study.

In view of this lack of knowledge we initiated a prospective cohort study to evaluate the relationship between the result of the postcoital test and time to ongoing pregnancy after ovulation induction with CC in women with WHO II anovulation.

Material and methods

Between December 2009 and September 2012, we performed a multicenter prospective cohort study in one university clinic and two teaching hospitals in the Netherlands. All women with WHO II anovulation attending these clinics were asked to participate in this study. The study protocol was approved by the Institutional Review Board of the Medical Spectrum Twente of Enschede (registration number: P08-37), and had local approval from the board of the other participating hospitals.

Participants

We studied women with WHO class II anovulation who started ovulation induction with CC. Women needed to have oligo- or anovulation, combined with signs of hyperandrogenism or polycystic ovaries on ultrasound. Women younger than 18 years and women with other causes of anovulation, like thyroid disease or hyperprolactinaemia were not eligible for the study. The total motile sperm count had to be above 1 million in at least one semen analysis before starting ovulation induction. The cut-off point of 1 million was chosen to exclude severe male factor. Tubal patency tests before start of treatment were not mandatory, as the incidence of bilateral tubal obstruction is low within this group of women and tubal patency testing is not without risks [8], but women with already known bilateral tubal obstruction were excluded. Women could enter the study only once.

Study design and treatment regimen

Ovulation induction with CC was started after a spontaneous or progesterone induced menstrual bleed. From the third or fifth day until the seventh or ninth day after menstruation women took CC with a minimum of 50 mg to a maximum of 150 mg a day. If ovulation did not occur with the lowest dose of 50 mg/day, it was increased with steps of 50 mg to a maximum of 150 mg a day in the next cycles. Ovulation was established according to local protocol. Centres used a biphasic temperature curve, a follicle with a diameter $\geq$18 mm on transvaginal ultrasonography, progesterone $\geq$16 nmol/l in the second half of the cycle or a cycle length $\leq$35 days to define ovulation. The menstrual cycle was considered regular if the duration of the cycle was between 23 and 35 days.

A PCT was performed during the basic fertility work-up in one of the first three ovulatory cycles. The test was planned based on cycle history or the basal body temperature (BBT) curve in the preceding cycle or ultrasound findings in the present or preceding cycle. In couples in whom the timing depended on the BBT and cycle length, the PCT was scheduled the day before the expected ovulation. In couples where the timing depended on ultrasound findings, the PCT was performed once the dominant follicle was $\geq$18 mm. The couple was asked to have intercourse four to sixteen hours before the appointment. The PCT was carried out by cleaning the cervix, followed by aspiration of endocervical mucus using a 1 ml disposable syringe or forceps. Clarity (clear or not clear) and spinnbarkeit were assessed and recorded. Mean number of progressive motile spermatozoa in a high power field at 400× magnification were determined. The PCT was judged to be positive if at least one progressive motile spermatozo was seen in one of five high power fields at 400× magnification. All other PCT results were considered to be negative. In case of a normal, positive test, only one PCT had to be performed. If progressive motile spermatozoa were absent, the test was scheduled again two days later or following the confirmation of a dominant follicle on ultrasound. In case the timing of the PCT was not optimal the test was planned again next month, based on ultrasound measuring of the follicle or LH tests. In case the test was negative again, and timing was appropriate the PCT test was considered to be negative. Follow-up started immediately after starting ovulation induction and ended at six ovulatory cycles. CC was continued for at least six cycles for both a positive and negative result of the PCT within a time horizon of 12 months.

Outcome measures

The primary endpoint of this study was time to an ongoing, viable intrauterine pregnancy, confirmed by ultrasonography, defined as a fetal heart beat seen by vaginal ultrasonography at 12 weeks' gestation. The first day of the last menstrual period was considered to mark the end of time until natural conception. Time to pregnancy was censored at the day of start of any other treatment within six months after the start of ovulation induction with CC or at the day of the last contact during follow up, if the couple had no ongoing pregnancy.

Secondary outcomes were ovulation, clinical pregnancy, defined as any registered heart beat at sonography, ectopic pregnancy and miscarriage, defined as loss of an intra uterine pregnancy (confirmed by ultrasound or histological examination) before the 12th week of pregnancy and multiple gestation, defined as a registered heartbeat of at least two fetuses at 12 weeks of gestation.

Power calculation and statistical analysis

We planned a comparison between women with a positive and women with a negative result of the PCT. We anticipated that 50% of women would have an ongoing pregnancy within six ovulatory cycles, and that the ratio of a positive versus a negative PCT was 1.5:1. This ratio was based on data reported in the literature and a retrospective search in the clinics where women would be included. To prove that a negative PCT indicates a decrease of 20% chance for an ongoing pregnancy within six months compared to a standard of 50%, with a power of 80% and an alpha of 5%, 234 women needed to be included. To account for drop out, which we estimated not to be substantial, we aimed to include 250 women.

We compared time to ongoing pregnancy by constructing Kaplan Meier curves for women with a positive and negative result of the PCT. We performed Cox proportional hazard analyses to assess the association between the outcome of the PCT with time to ongoing pregnancy as a dependent variable adjusted for female age, total motile sperm count and duration of subfertility. Associations were expressed as hazard rate ratios (HR). We performed two sensitivity analyses. In the first we assumed that all the unrepeated negative PCTs would have been negative, in the second we assumed that all the unrepeated negative PCTs would have been positive.

We performed a separate analysis based on number of progressive motile spermatozoa per high power field and mucus quality. We classified the findings at PCT into four groups and compared pregnancy rates for women without progressive motile spermatozoa, for those with 1 progressive motile spermatozo, for those with 1–5 progressive motile spermatozoa and for women with more than five progressive motile spermatozoa per high power field at 400× magnification. Log rank test was used to test whether time to ongoing pregnancy differed significantly between groups. We classified the cervical mucus as clear or not clear. The effect of CC dose was not be taken into account since no evidence exists that the