The basic fertility workup in women with polycystic ovary syndrome: a systematic review

Marleen J. Nahuis, M.D.,[a,b,c] G. Jurjen E. Oosterhuis, M.D.,[b] Peter G. A. Hompes, M.D.,[c] Madelon van Wely, M.D.,[a] Ben Willem J. Mol, Ph.D.,[a] and Fulco van der Veen, Ph.D.[a]

[a] Center for Reproductive Medicine, Department of Obstetrics and Gynaecology, Academic Medical Center, Amsterdam; [b] Department of Obstetrics and Gynaecology, Medisch Spectrum Twente Hospital Group, Enschede; and [c] Center for Reproductive Medicine, Department of Obstetrics and Gynaecology, VU Medical Center, Amsterdam, the Netherlands

Objective: To summarize the evidence for the use of commonly accepted fertility tests in subfertile women with ovulation problems.
Design: Systematic review.
Setting: Not applicable.
Patient(s): The study population included women starting with clomiphene citrate (CC) as first-line treatment, women starting with second-line treatment if CC failed to result in pregnancy, and women starting with second-line treatment if CC failed to result in ovulation (CC resistant).
Intervention(s): Performance of a semen analysis or tubal patency test before or during treatment.
Main Outcome Measure(s): Prevalence of abnormal tests as well as the diagnostic and prognostic performance of these tests.
Result(s): Four studies reported on 3,017 women starting with CC as first-line treatment. The prevalence of male factor infertility was 10%, and in 0.3% of couples azoospermia was found (two studies). Semen parameters were not associated with pregnancy chance (one study). The prevalence of bilateral tubal disease was 4% (two studies). Three studies reported on 462 women starting with second-line treatment if CC failed to result in a pregnancy. Semen parameters were not predictive for pregnancy (one study). The prevalence of bilateral tubal disease in these women was 8% (three studies). Two studies reported on 168 CC-resistant women and total motile sperm count did not predict live birth (two studies). For all other outcomes, no studies were available.
Conclusion(s): Data on the basic fertility workup in subfertile women with anovulation are scarce. Based on the available data, the workup should contain a semen analysis, and, for women who need to start second-line treatment if CC failed to result in pregnancy or women with CC resistance, assessment of tubal patency. (Fertil Steril® 2013;100:219–25. ©2013 by American Society for Reproductive Medicine.)
Key Words: Anovulation, clomiphene citrate, *Chlamydia* antibody titer, tubal pathology, semen analysis

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Most cases of anovulatory subfertility are caused by polycystic ovary syndrome (PCOS). The first-line treatment in these women is ovulation induction with clomiphene citrate (CC), which will restore ovulation in almost 80% and will result in pregnancy in 50% of all women (1). Second-line intervention is either exogenous gonadotropins or laparoscopic electrocautery of the ovaries. The use of exogenous gonadotropins is associated with increased chances for multiple pregnancy and therefore intense monitoring of ovarian response is required. Recommended third-line treatment is IVF (2). Treatment strategies for ovulation induction are relatively well defined, but less is known on the optimal workup for other fertility reducing factors before starting ovulation induction.

The Dutch guidelines, the National Institute for Health and Clinical Excellence guidelines, and the American Society for Reproductive Medicine (ASRM) recommend a semen analysis for subfertile women with anovulation or oligo-ovulation. The ASRM also recommends a hysterosalpingography (HSG) before the start of treatment in

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Reprint requests: Marleen J. Nahuis, M.D., Center for Reproductive Medicine, Department of Obstetrics and Gynaecology (H4-205), Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands (E-mail: m.nahuis@vumc.nl).

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women more than 35 years of age when clinical history raises suspicion of tubal or uterine pathology and a HSG in all other women after three to six ovulatory cycles without conception. However, these guidelines are not based on solid evidence. A rational fertility workup in anovulatory women can only be developed when we know the prevalence of other causes of subfertility, such as male factor, cervical factor, or tubal pathology and the value of testing for these factors for pregnancy chances in these women.

The aim of this study was to perform a systematic review of the literature to identify data on the prevalence of abnormal fertility tests and the association of these test results and the chances to conceive in case ovulation occurs. We distinguished three groups of women: women starting with CC as first-line treatment, women starting with second-line treatment if CC failed to result in pregnancy, and CC-resistant women.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

To identify all relevant trials we searched the Embase from 1966 and Medline databases from 1988 to November 2011. The Cochrane Central Register and Web of Science were also searched. Search strategies were carried out based on the following terms: polycystic ovary syndrome, AND one of the following factors: oligospermia, azoospermia, tubal pathology, or hysterosalpingography. In addition, references from all relevant articles were checked and hand searches of the abstracts of annual meetings of the ASRM and the European Society for Human Reproduction and Embryology (ESHRE) were performed. No language restrictions were applied. The searches were conducted independently by M.N. and M.W.

Definition of Outcome Measures

Studies were selected if the target population were women with PCOS. The definition of PCOS had to follow the standards of the ESHRE/ASRM 2003 consensus or the criteria used in the article had to be, in retrospect, in consensus with the definition.

We extracted results from all studies found on basic fertility workup performed in subfertile women with PCOS. We distinguished three groups of women: women starting with CC as first-line treatment, women starting with second-line treatment if CC failed to result in pregnancy, and women starting with second-line treatment if CC failed to result in ovulation (CC-resistant women), defined as women who did not ovulate taking 150 mg of CC for 5 days at the beginning of the cycle.

We were interested in the following tests: semen analysis and tests for tubal pathology. In the detected studies, we searched for evidence on the prevalence of a male factor infertility, or tubal pathology. Finally, we explored the included studies for data on the association between semen parameters or presence of tubal pathology and chances to conceive.

Statistical Analysis

We reported prevalence of test abnormalities as well as the prevalence of disease for every study. To assess the association between pregnancy chance and outcome of a test, we report the association between parameters both for dichotomous and continuous tests. To do so, we present odds ratios (ORs) and 95% confidence intervals (CIs), as well as *P* values when appropriate.

RESULTS

The search strategy yielded 218 publications, of which 213 publications were excluded as they did not fulfill the selection criteria (Fig. 1). No studies were excluded due to language restrictions. Five articles were included (3–7). Two additional studies were found by searching the references of the detected articles (8, 9), and two studies were found by asking experts in the field (10, 11). Thus, a total of nine studies could be included in this article.

According to our inclusion criteria, studies should be based on the Rotterdam consensus meeting that was published in 2004. No articles were excluded due to failure to satisfy these criteria. Although five of the nine studies were published before 2004, these studies fulfill—in retrospect—the Rotterdam criteria and were therefore not excluded (3, 5, 6, 8, 9). Four studies reported on 3,017 women starting with CC as first-line treatment (3, 4, 7, 8), three studies reported on 462 women starting with second-line treatment if CC failed to result in a pregnancy (3, 5, 9), and two studies reported on 168 women with CC resistance (10, 11).

The main characteristics of the nine included studies are shown in Table 1. Seven prospective cohort studies (3–9) were included and two randomized controlled trials (10, 11).

Women Starting with CC as First Line of Treatment

Semen analysis. We found two prospective follow-up studies in which the prevalence of poor semen quality in women starting with CC as first-line treatment was evaluated (Table 2). The prevalence of azoospermia was 3 of 753 male partners (0.3%) (3). Prevalence of oligospermia varied from 4%–10% (2, 3). Oligospermia was defined as a sperm density of less than 20 million/mL in a volume of less than 2 mL, motility below 50%, or a combination in one study (3) and as a concentration below or less than 20 million/mL in the other study (4).

One study evaluated the predictive value of the total motile sperm count (TMSC) and found that the median TMSC in women starting with CC as first-line treatment with and without a live birth after treatment, were 52 and 80 million, respectively, with a range from 1–693 million ($P=.9$). The TMSC was not able to predict the chances on a live birth in these women (8). However, only TMSC above 1 was included and azoospermia was excluded.

Tubal patency testing. We found one study reporting on the test results of 1,313 women with anovulation in whom part of the fertility workup was performed before inclusion in a randomized controlled trial comparing CC alone, metformin alone, or a combination of both to determine the safest and most efficient way to achieve live birth. In 839 of 1,313 women a HSG or diagnostic laparoscopy was performed to evaluate the patency of the tubes before start of the allocated intervention. In these 839 women the prevalence of bilateral tubal blockage was 4% (4).