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

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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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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).

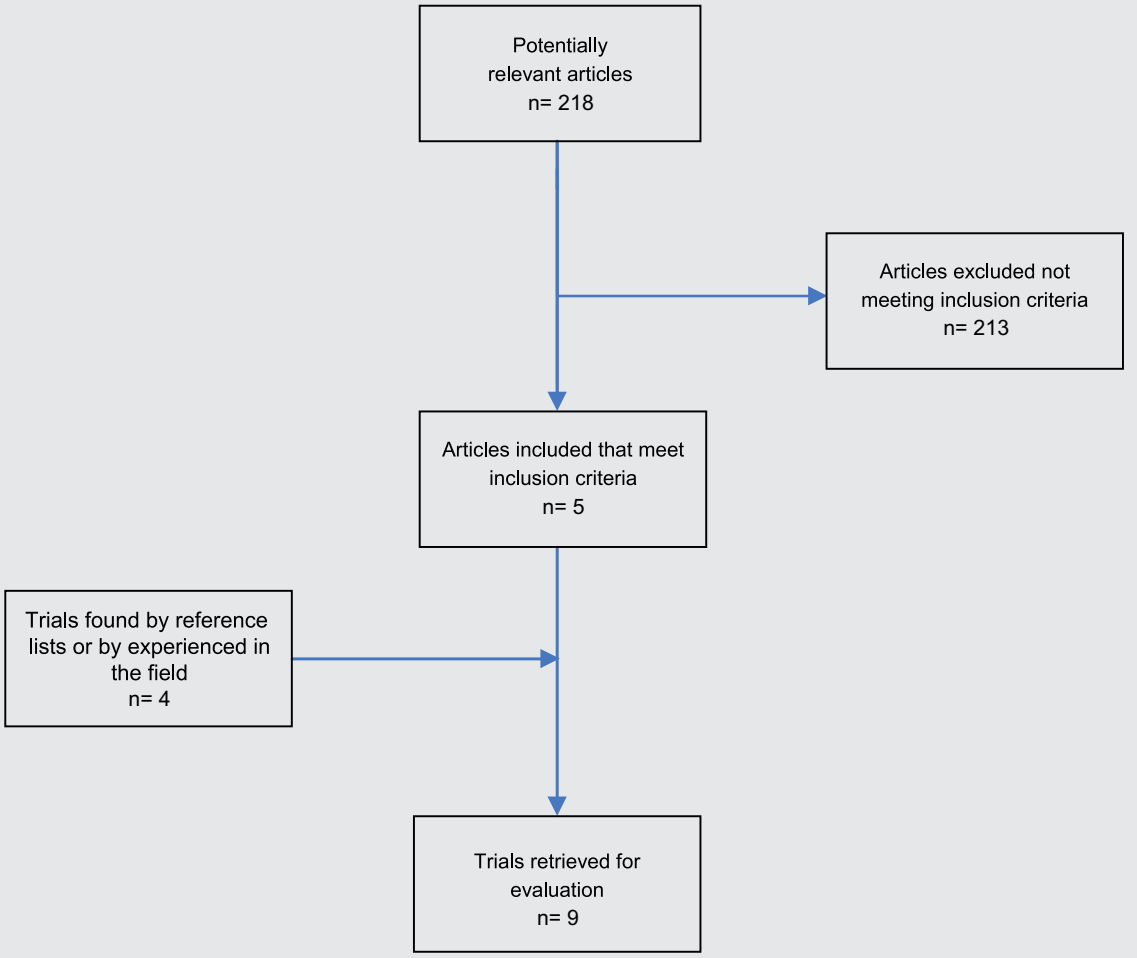
Women Starting with CC as First Line of Treatment

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).

FIGURE 1



Trial flow.

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Another prospective study evaluated the value of *Chlamydia* antibody titer in the routine performance of a fertility workup in women starting with CC as first-line treatment (7). The *Chlamydia* antibody titer was positive in 33 of 711 women (5%). Only 190 women were tested with HSG or diagnostic laparoscopy, and 10 women (5%) had evidence for bilateral tubal pathology. Another 197 women did not have tubal patency testing, but were pregnant during follow-up, therefore bilateral tubal blockage is impossible. In a total of 387 women the tubal status was known and 10 women (3%) had evidence for bilateral tubal blockage.

There were no studies on the association between tubal pathology and pregnancy chance.

Women Starting Second-Line Treatment if CC Failed to Result in Pregnancy

Semen analysis. We found no studies on the prevalence of semen abnormalities in women who ovulate but fail to get pregnant. One prospective study reported on the association between semen parameters and live birth in 160 women with PCOS (8). Only couples with a TMSC of more than 1 million were included. The odds ratio of live birth rate for semen analysis was 1.0 (95% CI 0.81–1.23), indicating that semen parameters in the range used in this particular study were not able to predict the chances on a live birth.

Tubal patency testing. We found three prospective studies in which the prevalence of tubal pathology was evaluated. A HSG or diagnostic laparoscopy was performed in 120 women in whom one-sided tubal occlusion was present in 16 women (13%), and bilateral tubal occlusion was present in 10 women (8%) (5). In the other two studies, pelvic disease was present in 24%–37% of women (3, 6). Pelvic disease was not defined as tubal blockage or endometriosis. We found no studies on the capacity of tubal patency testing to predict pregnancy in women who ovulate but fail to get pregnant with CC.

CC-Resistant Women

Semen analysis. We found no studies on the prevalence of semen abnormalities in women who did not ovulate with CC. We detected one randomized controlled trial in which

TABLE 1

Characteristics of included studies.

Study	Women	Interventions	Outcomes
McGovern et al., 2007 (4)	Prospective cohort study of 1,313 women starting with CC selected for a randomized controlled trial. All women attending the fertility clinic with 8 or fewer menstrual cycles per year. Period of inclusion was not defined.	Semen analysis in all women, with normospermia defined as a concentration >20 million/mL in at least one sample. Assessment of tubal patency at HSG or laparoscopy.	Incidence of oligospermia in women starting with CC. Incidence of bilateral tubal blockage in women starting with CC.
Gysler et al., 1982 (3)	Prospective cohort study of 753 women starting ovulation induction with CC and a child wish attending a fertility clinic between 1970 and 1980.	A semen analysis in women starting with CC, with oligospermia defined as a sperm density <20 million, volume <2 mL, and/or motility <50%. Unknown amount of performed semen analysis. Assessment of tubal patency in 182 women who fail to get pregnant with CC, an HSG or laparoscopy was performed.	Incidence of azoospermia and oligospermia in women starting with CC. Tubal pathology at HSG or DLS in women ovulatory with CC, without pregnancy.
Hammond et al., 1983 (6)	Prospective cohort study of 159 women with oligomenorrhea or amenorrhea treated with CC for induction of ovulation between 1977 and 1981.	A semen analysis in all women who ovulated with CC but did not get pregnant, with oligospermia defined as a TMSC between 10 and 60 million. Assessment of tubal patency at HSG or diagnostic laparoscopy.	Monthly fecundability ratios.
Van Tetering et al., 2007 (7)	Prospective cohort study of 711 WHO class II anovulatory women starting CC, between January 2002 and December 2004.	*Chlamydia* antibody titer determined before start of treatment. When positive, tubal patency testing was performed at HSG or laparoscopy; when negative, treatment was started with CC. In 169 women with a negative CAT an HSG or laparoscopy was performed.	Incidence of a positive CAT in women starting CC. Incidence of bilateral and unilateral tubal obstruction.
Imani et al., 1999 (9)	Prospective cohort study of 160 couples with WHO class II anovulation and a TMSC >1 million ovulatory after CC, between January 1993 and January 1998.	A semen analysis was performed conform with the WHO class II guidelines.	Mean (SD) TMSC and OR (95% CI) for women who conceived compared with women who ovulated but did not conceive.
Kotarski et al., 1993 (5)	Prospective cohort study of 120 women starting with CC.	HSG.	Incidence of unilateral and bilateral tubal obstruction in women starting with CC.

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TABLE 1

Continued.

Study	Women	Interventions	Outcomes
Eijkemans et al., 2003 (8)	Prospective cohort study of 240 WHO class II women. All women started ovulation induction with CC. Women who did not conceive in 6 ovulatory cycles with CC or did not ovulate on doses up to 150 mg for 5 consecutive days underwent gonadotropin induction of ovulation based on a lowdose step-up protocol.	Semen analysis at start of treatment.	Male partner's median (range) TMSC for women who conceived of a pregnancy resulting in a live birth and for women who did not get pregnant (*P* value).
Van Wely et al., 2005 (10)	Randomized controlled trial including 168 CC-resistant women with PCOS between February 1998 and October 2001. A prognostic study was performed of 85 women allocated to receive recombinant FSH.	All male partners had two semen analyses after a minimal sexual abstinence of 2 days and analysis of semen was performed within 1 hour after ejaculation. After liquefaction, volume, concentration, and motility were defined.	Univariate ORs for ongoing pregnancy rate, 95% CI and *P* values were calculated for TMSC as a predicator for pregnancy.
Van Wely et al., 2005 (11)	Randomized controlled trial including 168 CC-resistant women with PCOS between February 1998 and October 2001. A prognostic study was performed of 83 women allocated to receive laparoscopic electrocautery of the ovaries followed by CC and recombinant FSH when anovulation persisted as part of a randomized controlled trial.	All male partners had two semen analyses after a minimal sexual abstinence of 2 days and analysis of semen was performed within 1 hour after ejaculation. After liquefaction, volume, concentration, and motility were defined.	Univariate ORs for ongoing pregnancy, 95% CI and *P* values were calculated for TMSC as a predicator for pregnancy.

Note: 95% CI = 95% confidence interval; CAT = computed axial tomography; CC = clomiphene citrate; DLS = diagnostic laparoscopy; HSG = hysterosalpingography; PCOS = polycystic ovary syndrome; OR = odds ratio; TMSC = total motile sperm count.

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TABLE 2

Summary of search results.

Fertility workup	First line: starting with CC	Second line: ovulatory with CC, not pregnant	Second line: anovulatory with CC	Subfertile ovulatory
Semen analysis				
Prevalence of oligospermia	4%–10% (3, 4)	X	X	59% (15)
Prevalence of azoospermia/TMSC $<1 \times 10^6$	0.3% (3)	X	X	8%–17% (12, 14)
Predictive value, OR (95% CI)	*P*=.9 (8)	1.00 (0.81–1.23) (9)	1.00 (0.99–1.00) (10, 11)	0.59 (0.44–0.78) (18)
Tubal pathology				
Prevalance of bilateral obstruction	3%–4% (4, 7)	8% (3, 5, 6)	X	6%–8% (12, 14)
Predictive value, OR (95% CI)	X	X	X	0.13 (0.05–0.30) (18)

Note: 95% CI = 95% confidence interval; CC = clomiphene citrate; OR = odds ratio; TMSC = total motile sperm count.

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168 CC-resistant women were allocated to ovulation induction with laparoscopic electrocautery or with recombinant FSH (10, 11). Partners of women allocated to laparoscopic electrocautery had a median TMSC of 66×10^6 (range, $5–641 \times 10^6$). The TMSC was not able to predict the chances on an ongoing pregnancy after electrocautery (OR 1.0; 95% CI 0.99–1.00) (10). Partners of women allocated to recombinant FSH had a median TMSC of 98×10^6 (range, $5–641 \times 10^6$) and also in these women TMSC was not able to predict the chances on an ongoing pregnancy (OR 1.0; 95% CI 0.99–1.00) (11).

Tubal patency testing. We found no studies on the prevalence of test abnormalities and the capacity of the tests to predict pregnancy in CC-resistant women.

DISCUSSION

In this systematic review, we evaluated the prevalence of male factor infertility and tubal pathology and their association with pregnancy chances in subfertile women with ovulation problems. Evidence was limited as only nine studies could be included.

In women starting with CC as first-line treatment the prevalence of a male factor infertility was 10% and in 0.3% of couples azoospermia was found. Bilateral tubal disease was observed in 3%–4% of women. One study found that semen parameters were not associated with pregnancy chance. There were no studies on the association between tubal pathology and pregnancy chance.

In women starting with second-line treatment if CC failed to result in pregnancy there were no studies on the prevalence of male factor infertility. One study found that semen parameters were not associated with pregnancy chance. Of the women, 8%–9% had evidence for bilateral tubal obstruction. There were no studies on the association between tubal pathology and pregnancy chance.

In CC-resistant women there were no studies on the prevalence of male factor infertility. Two studies found that TMSC did not predict live birth rate. There were no studies on prevalence of tubal pathology or on its association with pregnancy chance.

Although all studies had a prospective design, many were flawed. First, in most studies only a part of the basic fertility workup was performed in consecutive couples. For example, once a TMSC less than 1 million was detected, tubal patency testing was not performed. This may have underestimated the true prevalence of tubal pathology in women starting with CC as first-line treatment (3, 4). Second, definitions of abnormalities varied. For example, in one trial oligospermia was defined as a concentration at less than 20 million/mL in at least one sample (4), whereas another trial defined oligospermia as a volume of less than 2 mL, concentration less than 20 million/mL, and more than 50% low motility or a combination of these abnormalities (3). Third, the definition of women who ovulate but fail to get pregnant varied with the number of ovulatory cycles ranging from 1–12. Women with just one ovulatory cycle may have different fertility prospects from women with 12 ovulatory cycles. We found no studies on the prevalence of semen abnormalities in these women. Fourth, for every subgroup of women with PCOS and for every test only at maximum one study was available on both the prevalence of other causes of subfertility, and the predictive value of those tests. Consequently, pooling was not possible and firm recommendations are thus impossible to make.

Subfertile ovulatory women clearly have to undergo an extensive fertility workup (12–15). Based on the available evidence there is no rationale for such a workup in anovulatory women. Arguments for testing should be based on the prevalence of a test abnormality in combination with the costs and risk of the test.

The number of studies included in this review is small. Many studies have been performed for the ovulatory subfertile population, but this was not the population of interest of our review. It is interesting to notice that the results of this review are comparable with the results of the first study exploring this field (3). One might postulate that the probability of other fertility limiting factors in women with PCOS is very low. Therefore, it is likely that there is a selection against other subfertility factors in anovulatory women (16). The prevalence of azoospermia was estimated to be 0.3% (3), whereas in the ovulatory subfertile population 8% has been found (12, 14). This implies that one would have to test 12 subfertile ovulatory couples versus 330 anovulatory couples to detect one man with azoospermia. For the clarity of this review we chose an undisputable outcome for tubal

blockage. Bilateral tubal blockage narrows down the treatment options, whereas others might not.

Based on the scarce evidence collected in this review it is impossible to make firm recommendations for the performance and timing of a basic fertility workup in anovulatory women. Thus, the clinical problem of what fertility testing to do in women with PCOS remains and needs to be dealt with. We did not investigate at which time a basic fertility workup is performed in daily practice.

It is our personal view that the basic fertility workup in women starting with CC as first-line treatment should be limited to a semen analysis. Compared to subfertile ovulatory women, in these women 25 times as many semen analyses and two times as many tubal patency tests should be performed to detect one abnormality. Still, we do suggest this, because a semen analysis is an inexpensive test without any risk, whereas tubal patency tests are expensive and have a higher risk of complications. In case of azoospermia further investigations should be done. For all other outcomes ovulation induction CC should be started, because this is a cheap treatment, with a lower burden and lower chance for multiple pregnancies compared with ovulation induction with gonadotropins.

In women who need to start second-line treatment if CC failed to result in pregnancy or women with CC resistance we suggest to perform a semen analysis and a tubal patency test. In women with CC resistance, laparoscopic electrocautery is superior to ovulation induction with FSH (17) and tubal assessment can easily be performed during the laparoscopic electrocautery procedure. Bilateral tubal disease was observed in 4% of women starting with first-line treatment, whereas 8%–9% of women starting second-line treatment showed evidence for bilateral tubal obstruction (12, 14). This is comparable to women with other causes of subfertility, which may validate assessment of patency of the tubes. Earlier testing means more frequent unnecessary testing, generating costs, and carrying additional risks.

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