Published in final edited form as:

Fertil Steril. 2007 February ; 87(2): 442–444.

Utility of Screening for Other Causes of Infertility in Women with “Known” Polycystic Ovary Syndrome

Peter G. McGovern, MD^a, Richard S. Legro, MD^b, Evan R. Myers, MD, MPH^{c,d}, Huiman X. Barnhart, PhD^d, Sandra A. Carson, MD^e, Michael P. Diamond, MD^f, Bruce R. Carr, MD^g, William D. Schlaff, MD^h, Christos Coutifaris, MD, PhDⁱ, Michael P. Steinkampf, MD^j, John E. Nestler, MD^k, Gabey Gosman, MD^l, Phyllis C. Leppert, MD, PhD^m, and Linda C. Giudice, MD, PhD, MScⁿ for the NICHD-Reproductive Medicine Network

a Department of Obstetrics, Gynecology and Women’s Health, UMDNJ-New Jersey Medical School, Newark, NJ

b Department of Obstetrics and Gynecology, Pennsylvania State University, Hershey, PA

c Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, NC

d Duke Clinical Research Institute, Duke University Medical Center, Durham, NC

e Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX

f Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI

g Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, TX

h Department of Obstetrics and Gynecology, University of Colorado, Denver, CO

i Department of Obstetrics and Gynecology, University of Pennsylvania School of Medicine, Philadelphia, PA

j Department of Obstetrics and Gynecology, University of Alabama, Birmingham, AL

k Department of Medicine, Virginia Commonwealth University School of Medicine

l Department of Obstetrics and Gynecology, University of Pittsburgh, Pittsburgh, PA

m Reproductive Sciences Branch, National Institute of Child Health and Human Development, Bethesda, MD

n Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, CA

Abstract

We investigated the prevalence of abnormal screening results (questionnaire and testing for other causes of oligo-ovulation, male or tubal factor infertility) in a group of 1,313 oligo-ovulatory women (included and excluded subjects) screened for inclusion in the PPCOS Trial, a multicenter clinical

Reprint requests: Peter G. McGovern, M.D. UMDNJ-New Jersey Medical School, Department of Obstetrics, Gynecology and Women’s Health, 185 South Orange Avenue, MSB-E506, PO Box 1709, Newark, NJ 07101-1709, Email: mcgovepg@umdnj.edu, Phone: 973-972-2235, FAX: 973-972-4574.

Supported by NIH/NICHD grants U10 HD27049 (CC), U01 HD38997 (EM), U10 HD39005 (MD), U10 HD27011 (SC), U10 HD33172 (MS), U10 HD38988 (BC), U10 HD38992 (RL), U10 HD38998 (WS), U10 HD38999 (PM), U54-HD29834 University of Virginia Center for Research in Reproduction Ligand Assay and Analysis Core, GCRC grant MO1RR00056 to the University of Pittsburgh, and a GCRC grant MO1 RR 10732 and construction grant C06 RR016499 to Pennsylvania State University

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

trial conducted at 13 sites in the USA. Other than failure to demonstrate laboratory evidence of hyperandrogenemia, the most common reasons for subject exclusion were persistent oligospermia and tubal factor infertility.

Keywords

PCOS; infertility testing; male factor; tubal factor

The best initial medical management of normogonadotropic anovulatory infertility associated with the Polycystic Ovary Syndrome (PCOS) is currently the subject of great interest and a number of large well-designed clinical trials. The current ongoing NICHD-sponsored multicenter trial of the Reproductive Medicine Network (Pregnancy in Polycystic Ovary Syndrome or PPCOS) is specifically designed to determine whether clomiphene citrate alone, metformin XR (Glucophage XR®) alone, or the combination is the safest and most efficient way to achieve livebirth in these women. With very different presumed mechanisms of action, it is entirely possible that the two agents will have synergistic effect upon the incidence of ovulation, but the combination may also exacerbate the known side effects of each drug individually.

By initial design, the pre-entry screening criteria for the PPCOS Trial included assessment of the male partner and tubal and uterine anatomy, along with exclusion of other causes of anovulation (congenital adrenal hyperplasia, hypothyroidism, premature ovarian failure, etc). As PPCOS was designed to use livebirth pregnancy as the outcome measure, the power analysis demanded a very large number of subjects (over 600). This gave us a unique opportunity to examine the prevalence of various other causes of infertility in women with infertility “obviously” related to their anovulation and the PCOS. We could find no previous publications which evaluated the prevalence of male factor or tubal factor infertility in women with PCOS, nor could we find studies which described the relative prevalence of other causes of anovulation (such as hypothyroidism, premature menopause, etc.) which may masquerade as PCOS. The purpose of this study was to examine the prevalence of other infertility problems in couples presenting for inclusion in the PPCOS Trial.

Subjects for the PPCOS Trial were recruited from the practices of REI physicians at the Reproductive Medicine Network’s Clinical sites, along with 5 other NIH-funded locations. They were also solicited through advertisements using a pre-approved text asking for “women with 8 or fewer menstrual cycles per year who desired pregnancy”. IRB approval was obtained at each site prior to study initiation and written informed consent was obtained from each potential participant.

Screening tests for inclusion/exclusion criteria included semen analysis (concentration > 20 million/ml on at least one sample), assessment of tubal patency (at least one open tube at hysterosalpingogram, saline hysterosonogram, or laparoscopy), and laboratory testing to detect uncorrected thyroid disease, hyperprolactinemia, 21 hydroxylase deficiency, premature menopause, diabetes, or chronic liver or renal disease (normal values for the individual sites’ laboratories for TSH, prolactin, FSH, 17 hydroxyprogesterone, fasting glucose, electrolytes/AST/ALT, BUN, and creatinine). Evaluations for androgen-secreting tumors and Cushing’s syndrome were not performed routinely, but rather only when they were clinically suspected by the enrolling physician. Hyperandrogenemia was a required inclusion criterion, as this study was designed and initiated prior to the 2003 Rotterdam conference. Each site defined hyperandrogenemia prior to study initiation using their local laboratory values.

Screening results are listed in Table 1. Other than failure to demonstrate laboratory evidence of hyperandrogenemia (249/1280 or 19.5%), the most common medical reason for subject exclusion was oligospermia, seen in 10.1% of couples. The next most common abnormality was tubal factor, seen in 4.2%. Although infrequent, congenital adrenal hyperplasia was diagnosed just as often as thyroid disease and hyperprolactinemia and more commonly than premature menopause. Cushing's syndrome and androgen-secreting tumors were rare. 1.6% (14/902) of subjects were excluded due to a diagnosis of Type I or II diabetes, while 1.0% (8/822) were excluded due to elevated liver enzymes. No subjects were found to have renal disease, known heart disease, or a history of deep vein thrombosis, pulmonary embolus or cerebrovascular accident preventing study participation.

Limitations of this analysis are that: 1) not all couples completed all screening tests, as once they had an abnormality preventing enrollment they may have not completed all of their testing; and 2) there was heterogeneity in the recruitment of subjects, in that some investigators clinically pre-screened women and referred into the study only women without clinically apparent cause for infertility, whereas other investigators did not pre-screen. Therefore, application of the results to all women with PCOS may underestimate the true prevalence of other causes of infertility in the PCOS population, whereas it may overestimate the prevalence of other causes in women with PCOS whose initial clinical evaluation was normal. Nevertheless this study provides a unique opportunity to evaluate data from a large multicenter trial studying many women with oligovulatory infertility in all ethnic groups from around the country.

There exists very little data on the prevalence of other infertility factors in women with PCOS. Induction of ovulation will usually succeed in cases with normal female anatomy and good male reproductive function, but less likely to result in healthy pregnancy in cases of tubal occlusion or severe male factor infertility. MEDLINE search (1966–2005) using the terms polycystic ovary syndrome, male infertility and tubal infertility uncovered no references in which the probability of finding poor quality sperm or abnormal anatomy in women with PCOS was investigated. For many couples with PCOS, a full infertility evaluation is pursued only after failure to conceive with oral agents. Standard texts support treatment without further evaluation (1): "...women with ovulatory dysfunction are obvious candidates for ovulation induction. In general, only limited additional evaluation is needed...In the majority of cases, it is entirely appropriate to begin treatment immediately, even before other potential causes of infertility have been investigated."

This is interesting, given the acknowledged discrepancy between ovulation and pregnancy rates in PCOS patients treated with clomiphene citrate. It may be due to pressure from the couple to start therapy without delay, or because the couple (or practitioner) feel confident that the major infertility factor is anovulation.

Unfortunately, the screening process only required a sperm concentration to meet entry criteria, and no information was obtained regarding other semen parameters. Classic studies from MacLeod and Gold demonstrated that only 1/3 of men with poor motility (2) had oligospermia (defined as a concentration under 20 million/ml) and only 1/3 of men with poor morphology had oligospermia (3). Therefore the actual prevalence of poor quality sperm, including those men with low motility or low morphology, is likely to be significantly greater than 10%.

More recent data confirm this: the Andrology Laboratory at New Jersey Medical School (D. McCulloh, personal communication) reports that 747/1513 (49.4%) semen analyses were abnormal (concentration < 20 million/ml, or motility < 50%, or Kruger morphology < 4%), and that 381/747 (51.0%) of abnormal samples were oligospermic. Thus the incidence of male factor infertility is approximately double the incidence of oligospermia, and we can estimate

that as many as 20% of PCOS couples would have been diagnosed with a male factor if all 3 parameters had been recorded.

Tubal/peritoneal factors are also likely to be more prevalent than demonstrated using the mainly non-invasive methods employed in this study. After a “normal” HSG, Mol et al. (4) report bilateral tubal occlusion at laparoscopy in 5% of women, while other authors report a 15% incidence of moderate-severe endometriosis, pelvic adhesions or tubal occlusion.

Presumably detection of these significant other infertility factors will help improve success with ovulation induction. We conclude that testing for other causes of infertility or oligo-ovulation is clinically useful in women presenting with “known” PCOS-related infertility.

References

1. Speroff, L.; Fritz, M., editors. Clinical Gynecology Endocrinology and Infertility. 7. Lippincott, Williams and Wilkins; Philadelphia, PA: 2005.
2. MacLeod J, Gold RZ. The male factor in fertility and infertility III. An analysis of motile activity in the spermatozoa of 1000 fertile men and 1000 in infertile marriage. *Fertil Steril* 1951;2:187–204. [PubMed: 14831643]
3. MacLeod J, Gold RZ. The male factor in fertility and infertility IV. Sperm morphology in fertile and infertile marriage. *Fertil Steril* 1951;2:394–414. [PubMed: 14879850]
4. Mol BWJ, Collins JA, Burrows EA, Van Der Veen F, Bossuyt PMM. Comparison of hysterosalpingography and laparoscopy in predicting fertility outcome. *Hum Reprod* 1999;14:1237–42. [PubMed: 10325270]
5. Al-Badawi IA, Fluker MR, Bebbington MW. Diagnostic laparoscopy in infertile women with normal hysterosalpingograms. *J Reprod Med* 1999;44:953–7. [PubMed: 10589406]

Table 1

Screening test results in potential PPCOS subjects (n=1313)

Criteria for exclusion	Abnormal test/total subjects tested	Prevalence
Normal serum androgen level	249/1280	19.5%
Oligospermia	95/881	10.1%
Bilateral tubal blockage	35/839	4.2%
Currently pregnant	20/968	2.0%
Diabetes	14/902	1.5%
Congenital adrenal hyperplasia	10/937	1.1%
Hyperprolactinemia	10/993	1.0%
Liver disease	8/822	0.9%
Uncontrolled thyroid disease	9/985	0.9%
Premature menopause	5/985	0.5%
Androgen-secreting tumors	1/1038	0.1%
Cushing's syndrome	1/1032	0.1%