Unexplained Infertility

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Introduction

Infertility is generally defined as the inability to conceive following one year of unprotected intercourse. This definition is often modified in couples where the female partner is 35 years of age or older, such that an infertility evaluation may be encouraged following only 6 months of unsuccessful attempted conception. Up to 30% of couples presenting with this chief complaint are eventually diagnosed as having unexplained infertility.[1] Couples with unexplained infertility are thought to represent either a subpopulation of patients in the lower extreme end of the normal distribution of fertility, or a group of patients with a defect in fecundity not detected by the routine infertility evaluation.[2] When compared to "normal, fertile" patients, couples with unexplained infertility demonstrate both diminished and delayed fecundity. Untreated, their pregnancy rates have been reported to be 34% within 6 months, 76% within 2 years, and 87% within 5 years.[3] In a review of previously published prospective, randomized trials, Guzick et al determined the cycle fecundity rate with expectant management in couples with unexplained infertility to be 1.3-4.1% - compared to the generally accepted cycle fecundity of 20% in proven fertile couples. [4]

This chapter will provide a critical, evidence based review of both the diagnosis and treatment of unexplained infertility.

Diagnosis

Traditionally, a diagnosis of unexplained infertility is made only when the basic infertility evaluation fails to reveal an obvious abnormality. This diagnosis therefore implies that a couple has evidence of normal, timely ovulation, adequate sperm production, fallopian tube patency, normal integrity of the endometrial cavity, adequate cervical mucus production, timely development of endometrial secretory change, and no evidence of pelvic endometriosis. Until recently, the basic infertility work-up included basal body temperature charting, a semen analysis, a hysterosalpingogram (HSG), a post-coital test (PCT), an endometrial biopsy (EMB), and a diagnostic laparoscopy.

Over the past several years, both the PCT and the EMB have fallen into disfavor. Two studies in particular helped diminish the importance of the PCT. In the early 1980s, a group of investigators performed mid-cycle intracervical insemination in a group of infertile women, followed a few hours later by laparoscopy.[5] During the surgical procedure, samples of cervical mucous and fluid surrounding the distal fallopian tubes were collected and analyzed for the presence of motile and non-motile sperm. The investigators were unable to correlate the findings in the cervical mucous with the findings in the peritoneal fluid surrounding the tubes and ovaries. In 1984, Collins, et al. followed a large group of patients who had discontinued their infertility treatment.[6] Pregnancy rates observed over a subsequent two-year period of time were correlated with results obtained from post-coital tests performed during their evaluations. No statistically

significant differences in pregnancy rates were observed in these couples, despite PCT results varying from more than 11 motile sperm per high power microscope field to no sperm seen at all. Based primarily on these studies, the PCT is no longer an integral part of the contemporary evaluation of infertility. While some physicians may still use it in isolated instances, such as assessing cervical mucous production in women treated with clomiphene citrate in order to determine whether or not to recommend intrauterine insemination (IUI), many others have eliminated it from their evaluation algorithm altogether.

The routine endometrial biopsy is also no longer a universally accepted part of the contemporary infertility evaluation. Initially proposed as the optimal way to assess the synchrony between the development of the endometrium and the embryo, the EMB was plagued by differences in interpretation as well as the fact that up to 30% of normal ovulatory women can have an occasional out of phase biopsy. [7] It may, therefore, be both reasonable and cost-effective to actually perform a biopsy only after a luteal phase length of fewer than 11 days has been detected in a preceding cycle. This approach will minimize patient discomfort and cost, while possibly reducing the incidence of a false positive diagnosis as well. Although still thought to be a cause of recurrent miscarriage, more recent data suggest that luteal phase defect is not a prevalent cause of infertility.[8]

The role of routine laparoscopy continues to be a source of much controversy, just like the association between endometriosis and infertility. Although most investigators recognize a strong correlation between infertility and stage III and IV endometriosis, no such consensus is present for stage I and II disease. A recent prospective, randomized,

multicenter Canadian trial ("EndoCAN") was the first well-designed study to demonstrate such an association.[9] In this trial, women diagnosed intraoperatively with Stage I or II disease were randomized to intraoperative resection or ablation of their disease or diagnosis alone. All patients were then followed expectantly for a minimum of 36 weeks. At the end of the study period, 31% of the patients in the laparoscopic surgery group had conceived, compared to 18% in the diagnostic group ($p<0.05$). Although interesting, these findings have not been universally accepted. A subsequent prospective, randomized Italian trial, similarly designed, has shown no difference in the one-year postoperative birth rate in 96 women undergoing resection/ablation or diagnosis alone at the time of laparoscopy.[10]

In the patient with a normal HSG and pelvic examination, who has no history of prior IUD usage, PID, or previous abdominal or pelvic surgery, the likelihood of finding significant pelvic adhesions is remote. In addition, an early or mid-follicular transvaginal sonogram appears to be a reasonable screening test for the presence of an ovarian endometrioma. In the absence of such a lesion, one can rule out the presence of Stage III or IV endometriosis with a high degree of certainty. Recent data suggest that a good history, an HSG, and a single transvaginal ultrasound may well eliminate a needless laparoscopy in up to 40% of patients. This number may even be higher if one includes patients who are found to have only stage I or II endometriosis at laparoscopy.[11]

Just as some tests appear to be losing their place in the diagnostic algorithm for infertility, others appear to be gaining inclusion. Recently, many specialists have added an early or mid-cycle pelvic sonogram to the basic infertility evaluation. This

examination facilitates the detection of uterine leiomyomata, endometrial polyps, and ovarian pathology, while also affording a timely assessment of maximal endometrial thickness and pattern.

As no universal algorithm exists for the diagnosis of infertility, it should not be surprising that there appears to be a lack of consistency among even Board Certified Reproductive Endocrinologists (REs). Glatstein et al., recently published a nationwide survey assessing the tests employed by such specialists as part of their routine infertility evaluation. Of the 473 Board Certified REs surveyed, 397 responded, representing a response rate of 83.9%.[12] Of the respondents, 54.7% were university hospital affiliated, while 45.3% were in private practice. Results from the survey (Table 1) indicate that at least 89% of REs perform a basic evaluation that includes a semen analysis, at least one method of ovulation assessment, an HSG, and a laparoscopy. Seventy-nine percent still perform post-coital testing, while 62.5% routinely perform an endometrial biopsy.

Treatment

Some data suggest that approximately 60% of couples with unexplained infertility of less than three years' duration will become pregnant with three years of expectant therapy.[14,15] Although these data may be somewhat promising, it is frequently difficult to ask a patient, even if she is young, to "keep trying for a few more years". In addition, following three years of infertility, the prospect of future fertility decreases by 24% each

year.[16] Therefore it is reasonable to initiate therapy once the couple is concerned enough to have made the decision to consult a physician.

The average normal fecundity for fertile couples in which the female partner is 35 years of age or younger is 20-25%, however the monthly pregnancy rate for couples with unexplained infertility is only 1.3-4.1%.[4] A laudable goal for the physician is therefore to increase the pregnancy rate for these couples to the normal monthly fecundity for fertile couples.

In the absence of a single correctable abnormality, the therapy for unexplained infertility has, by default, been empiric. Several different treatment regimens have been proposed, including the use of intrauterine insemination (IUI) with or without superovulation with either oral or injectable medications and the assisted reproductive technologies (ARTs). As these patients may truly be subfertile, rather than infertile, the need for appropriately designed controlled trials evaluating these empiric therapies is profound. Unfortunately, there has been a relative paucity of such studies.

Intrauterine Insemination

The use of IUI appears to improve cycle fecundity when combined with either clomiphene citrate (CC) or gonadotropins (see below), but its use alone in couples with purely unexplained infertility has only been evaluated in one prospective, randomized trial.[4,17,18] Kirby et al compared IUI to intercourse, each performed 40 hours following the detection of a serum LH rise, in 73 couples with unexplained infertility. Pregnancies

resulted in 3 of 123 (2.4%) intercourse cycles compared to 6 of 145 IUI cycles (4.1%,p=NS). Recently, Guzick and colleagues published a prospective, randomized trial comparing IUI to intracervical insemination (ICI).[17] In this study, they reported significantly greater cycle fecundity with IUI (18%) than ICI (10%), which was chosen as their "control" treatment.

Clomiphene Citrate Therapy

Although it has been suggested that the empiric use of CC in ovulatory women can cause alterations in the normal endocrinology of ovulation, its use has been championed by numerous investigators.[19] Superovulation with CC combined with intercourse has been evaluated in a prospective, randomized double blind placebo-controlled 4 month trial in 148 patients (564 cycles). Patients receiving 100 mg of CC from days 5-9 exhibited significantly higher fecundity (0.051) and cumulative pregnancy rates (19%) than did patients receiving placebo (0.0, 0%).[20] These results were confirmed in a subsequent prospective, randomized crossover trial of 118 couples with unexplained infertility.[21] In this study, the treated patients exhibited a significantly greater cumulative pregnancy rate over 3 cycles than did the placebo treated patients (22.3% vs. 14.6%, $p<0.05$). The empiric use of CC combined with IUI has been evaluated in a prospective, randomized study of 298 treatment cycles involving 67 couples.[22] In this trial, 14 pregnancies resulted from 148 treatment cycles (fecundity 0.095) compared to 5 pregnancies from 150 cycles involving timed intercourse (fecundity

0.033). A retrospective literature review involving 932 cycles suggested that the addition of IUI increased cycle fecundity rates with CC from 5.6% to 8.3%.[4] A subsequent prospective, randomized, crossover trial suggested superiority of CC/IUI when compared to IUI alone, as cycle fecundity rose from 5% to 26.1% when CC was added.[23]

In contrast, there is one recent prospective, randomized trial which suggests that clomiphene may not be efficacious in the treatment of unexplained infertility.[24] Fujii, et al compared the use of CC 50 mg in 18 women to 15 control patients. Cycle fecundity was significantly greater in the control patients (11/51, 0.21) than in the treated patients (4/66, 0.06, $p<0.005$), leading the authors to conclude that not only was clomiphene not beneficial, but rather it was detrimental.

Gonadotropin Therapy

Empiric gonadotropin therapy has been demonstrated to be an effective therapy for unexplained infertility, especially when combined with IUI. [4] Welner, et al treated 97 couples awaiting IVF with gonadotropins and IUI, and noted an improved fecundity compared to 48 control couples. [25] In a more recent study of 492 couples, both cycle fecundity and pregnancy rate per patient were superior when gonadotropin therapy plus IUI was compared to expectant management. [26]

A few trials comparing various stimulation regimens have been reported. In a prospective, randomized comparative trial, gonadotropin/IUI was found to be superior to

CC/IUI (cycle fecundity 0.19 vs. 0.04, $p<0.05$). [27] The addition of GnRH to gonadotropins, however, does not appear to improve fecundity rates. [28]

To the contrary, however, the addition of IUI to empiric gonadotropin therapy does appear to significantly improve fertility rates. This has been reported in patients stimulated with CC combined with gonadotropins as well as in patients stimulated with gonadotropins alone. [29,30] A literature review of 27 studies involving over 2900 patients suggested a significant improvement in fecundity when IUI was added to gonadotropin stimulation.[4] Similarly, Guzick's recent prospective, randomized, multicenter trial demonstrated that patients treated with gonadotropins (specifically FSH alone) combined with IUI had higher cumulative pregnancy rates (33%) than those treated with gonadotropins alone (19%), IUI alone (18%), or ICI (10%).[17]

Assisted Reproductive Technology

In vitro fertilization (IVF) frequently provides insight into the possible causes of the couple's infertility, as the procedure itself eliminates many "unknown" variables from consideration as possible etiologies for the infertility. For example, in the IVF procedure, both oocyte release and fertilization are clearly documented. In addition, uterine transfer lends relative comfort that the embryos have been placed into the correct anatomic location, bypassing potentially damaged fallopian tubes. While to the lay person, the only remaining variables are implantation and chromosomal normalcy, in fact

a litany of other biochemical, anatomic, and functional issues contributing to a successful pregnancy remain unaddressed.

Although advocated by many clinicians and supported by retrospective and/or uncontrolled trials, there are no well-designed studies evaluating the use of ART for purely unexplained infertility. The available literature, consisting of 18 studies involving in vitro fertilization (IVF) or gamete intrafallopian transfer (GIFT), suggests that pregnancy rates for these patients average approximately 20.7% (range 12.2%-31.4%) for treatment with IVF and 27% (range 19-28.6%) with GIFT.[4]

Other Therapies

In addition to the treatment regimens discussed above, a variety of other therapies have been proposed in the infertility literature. Specifically, the use of either bromocriptine or danazol has been studied in limited detail. Neither preparation has been demonstrated to be effective in pooled analyses of published studies.[31,32]

Conclusion

Despite the fact that most published studies evaluating empiric therapy for unexplained infertility include a heterogeneous patient population, type I evidence supporting the use of CC or gonadotropins combined with IUI does exist. Type II evidence supporting a recommendation for ART also exists. When appropriately monitored, these therapies appear to be both safe and effective.

When counseling patients about therapeutic options, it is important to include a discussion of both cost and efficacy. The literature suggests cycle fecundity rates of 4-18% for IUI alone, compared to 5-9% for CC without and 5-26% for CC with IUI. Published fecundity rates observed with gonadotropin therapy combined with IUI vary from 13-33%, and rates achieved with ART may even be higher.

Fortunately, as a result of these available therapies, many patients will be able to conceive. As there is more progress in scientific endeavors in this area, new diagnoses will be uncovered, new diagnostic tests will be developed, and new therapies will emerge.

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TABLE 1: Components of the Basic Infertility Evaluation Employed by Board Certified Reproductive Endocrinologists [7,13]

Test	Inclusion (%)
Semen analysis	99.9
Ovulation assessment (1 method)	98.0

Hysterosalpingogram (HSG)	96.0
Laparoscopy	89.1
Post-coital test	79.0
Prolactin level	66.4
Endometrial Biopsy	62.5
Luteal Progesterone Level	60.4
Thyroid Stimulating Hormone	58.9
Basal Body Temperature Charting	55.3
Ultrasound	54.5
FSH level	54.3
Hysteroscopy	53.2
Chlamydia cultures	54.3
Antisperm antibody testing	23.9