

Georgia Reproductive Specialists

A cost efficient approach to infertility diagnosis and Treatment for the OBGYN generalist

Introduction

The purpose of this proposal is to outline suggested clinical pathways for the management of infertility and common reproductive endocrinology problems. The goal is to create an approach that provides the greatest success while using limited resources in the most cost-effective fashion.

A traditional approach to the management of Reproductive Endocrinology & Infertility problems can be found in any traditional text. However, most texts do not take into account the limited availability of resources within a managed care environment, and do not address the issue of stratification of care into that provided by an OB/GYN generalist and that provided by the reproductive endocrinology subspecialist. To that end, this outline will attempt to focus on what care is best provided by which practitioner. To design a cost-effective, medically appropriate evaluation and treatment plan, we must take the patient's age into consideration. While there is little necessity to initiate aggressive therapy for the 20 year old with unexplained infertility, those over 35 deserve a more aggressive approach.

Initial Infertility Evaluation

- **Complete history and physical examination:** Obtain all previous medical records for treatment related to infertility, hormonal or menstrual disturbances, anovulation, gynecologic surgery, or pelvic infection. Appropriate medical information should be gathered on the husband. Particular attention needs to be directed toward a review of medications that may interfere with fertility (*i.e. Calcium channel blockers or Lipitor in males*) or those that might be teratogenic.
- **Initial Medical Laboratory Evaluation:** TSH, Prolactin, CF screen, CBC, ABO, RH-Type and antibody screen, HIV, HBSag, HCab, VDRL, Chlamydia/GC DNA probe, PAP smear, midluteal am progesterone above 10 ng/ml suggests normal ovulation. (*Progesterone levels may drop up to 50% by the afternoon and after a meal.*)
- **Evaluation of Ovulation:** BBT charts from up to 3 months may be reviewed. While patients may be encouraged to initially record BBTs, these charts are only of value retrospectively determining that the patient has in fact ovulated and are of little value predicting when ovulation will occur.
- **Individualized Laboratory Testing:**

African American: Sickle screen and thalasmeia as appropriate.

Over 30: FSH and estradiol may be obtained on cycle day 3 along with an antral follicle count. Antimullerian Hormone, AMH testing can be done on any cycle day.

FSH values above 10 miu/ml or an LH:FSH ratio above 3:1 or AMH <0.4 should result in REI review.

Ultrasound screening for ovarian volume and antral follicle count on cycle day 3 may enhance the sensitivity of ovarian reserve monitoring.

Irregular Menses: DHEAS values above 250 ug/dl, although still in the normal range, may be seen in patients with polycystic ovary syndrome. These patients usually benefit from metformin therapy before ovulation induction with letrozole. For those above 600 ug/dl, consultation should be considered.

Irregular Menses with Hirsutism, Acne or Obesity: Many of these patients benefit from metformin (Glucophage), combined metformin & pioglitazone Actoplusmet, or pioglitazone (Actos) therapy whether or not they meet the diagnostic criteria for PCOS. A 2-hour insulin glucose tolerance test is likely to be the earliest test to indicate insulin resistance. A simple glucose tolerance test without insulin levels would not be adequate to predict who might benefit from therapy with an insulin lowering medication. Obese patients with markedly increased insulin levels may benefit from treatment with exenatide (Byetta) or liraglutide (Victoza) injections with weight loss and improved lipid status.

The free testosterone panel may be helpful to monitor the effectiveness of metformin therapy. Fasting am 17 hydroxyprogesterone is ordered during the follicular phase if adult onset congenital adrenal hyperplasia is suspected. Values above 150 deserve referral for cortrosyn stimulation testing. If the patient appears Cushingoid, decadron 1mg is administered at midnight and an 8am fasting cortisol level is obtained the next morning. If PCOS is suspected, cardio C-reactive protein, homocysteine and a lipid panel should be ordered.

Low risk for tubal disease: For patients without a history of pelvic pain, surgery, dysmenorrhea or dyspareunia, a serum chlamydia IgG antibody panel should be obtained. As tubal disease or peritubal adhesions are the frequent sequelae of asymptomatic chlamydia infection, more aggressive evaluation of the fallopian tubes and pelvis are required if an elevation is noted. Alternatively, IVF may be a more cost effective approach if the risk of significant tubal disease is high.

Semen Analysis: Testing should be obtained before any invasive procedure such as HSG, laparoscopy, or ovulation induction is considered. A semen analysis is considered current if it has been obtained within the last 12-18 months. If the male has had a recent febrile illness, testing should be postponed 2-3 months. Abnormal values should be rechecked no sooner than 4-8 weeks. If on repeat, the total motile count per sample is greater than 5 million, ovulation induction and intrauterine insemination may be of benefit. Isolated motility defects may benefit from treatment with proXeedtm (*acetyl L-carnitine and L-carnitine*). Smokers should be placed on antioxidant supplementation (*Vitamin C 1gm/day and Vitamin E 400u/day or Juice Plus Antioxidants*). REI and urologic consultation is indicated. Varicocele repair is controversial and should only be considered if the varicocele is rather large. If WBC's are present, prolonged antibiotic therapy may be considered. A serum prolactin, FSH, testosterone and sperm antibody testing should follow abnormal semen analysis. A Sperm Chromatin Structure Assay (SCSA) measures sperm DNA fragmentation and identifies men with low fertility potential. An SCSA test should be considered for men with a history of varicocele, cryptorchid testes, chemotherapy, testicular cancer, radiation exposure, pesticide exposure, long distance bike riding or unexplained infertility.

For those with azoospermia, FSH, free testosterone panel, estradiol, chromosomal analysis and Y microdeletion tests are indicated.

- **Tubal Factor Infertility:**

- Assessment of Risk Factors:**

1. **Dysmenorrhea**, if associated with pelvic tenderness, uterosacral nodularity or perimenstrual diarrhea, should be considered evidence of endometriosis.

2. **Dyspareunia**
3. **Previous pelvic surgery**
4. **IUD complications** such as removal for pain, bleeding or infection
5. **History of PID**
6. **Elevated chlamydia IgG titers**

Evaluation of Tubal Factors:

1. **Over 35, > 3 years infertility & risk factors:** Tubal patency should be determined preoperatively to rule-out proximal tubal obstruction that can be treated during an initial laparoscopic procedure. Laparoscopy or IVF should be considered early in the evaluation.
 2. **Low risk factors, anovulatory infertility or AID candidates:** HSG may be delayed if no risk factors are present. Ovulation induction or AID (donor insemination) may be considered for 3-4 cycles before considering HSG. A recent study has shown that one additional pregnancy will occur for every 60 diagnostic laparoscopies performed in women with low risk of tubal disease resulting in a cost of ~\$600,000 per additional pregnancy. IVF is far more cost effective than diagnostic laparoscopy in women without significant risk factors.
- **Post-coital Testing** has not been shown to correlate well with fertility and therefore is rarely indicated.
 - **Endometrial Biopsy:** The routine use of endometrial biopsy to confirm the adequacy of luteal phase has poor predictive value for the management of infertility. It is only indicated for those patients with regular cycles and recurrent pregnancy loss. Endometrial biopsy, therefore, is not indicated in the diagnosis of infertility.

Initial Treatment for Infertility

- **Empirical Treatment:** Female patients are treated with prenatal vitamins. Both male and female partners may be treated empirically with doxycycline 100 mg BID for presumed ureaplasma infection. Prevalence of this infection is > 35% and treatment costs roughly one-tenth the cost of culture evaluation. Males are started on Vitamin C 1,000 mg daily or Juice Plus antioxidants.
- **Preconception Counseling:** The risks of genetic abnormalities are discussed for those with a family history or age > 35. Smoking cessation, alcohol reduction, weight loss and marital counseling are recommended as indicated. Males are encouraged to avoid hot tubs, saunas, steam baths and hot baths.

Ovulation Induction

- **Anovulation (non PCOS, < 36 years old, FSH<10 miu/ml):** Letrozole 5 mg (*or less often clomiphene 50mg*) is administered from cycle day 3 through 7. A baseline ultrasound, informed consent and urine pregnancy test are obtained each cycle to reduce the risk of exposing an early pregnancy to these medications. Recent abstracts suggest that early pregnancy exposure may increase the risk of fetal anomalies. On the first cycle, an LH & FSH level may be obtained on cycle day 9, 10 or 11. If the LH:FSH ratio is > 3:1, or the FSH or LH are above 10 miu/ml, then referral is indicated as viable pregnancy is not likely with clomiphene or letrozole therapy. The patient begins urinary LH monitoring no sooner than cycle day 12. (*Some women demonstrate a false positive LH surge if less than 4 days from the last dose. In fact, the presence of an early false positive surge indicates an abnormal LH response to clomiphene or letrozole and indicates that pregnancy is unlikely with oral therapy*). The patient is instructed that the LH surge may not be as dark as in a non-treatment cycle. A color change that is almost as dark as the reference strip should be considered a positive indication.

If no positive indication is seen by cycle day 16, an ultrasound is obtained to evaluate:

1. Was ovulation missed?
2. Is there adequate follicular development (follicle size > 20 mm)?
3. Is the endometrium adequate (>6 mm with mature 20 mm follicle)?

If adequate follicle and endometrium are present, then ovulation can be triggered with hCG 10,000 units, thereby avoiding the anti-estrogen effects of higher clomiphene doses in subsequent cycles. If, however, follicular development is inadequate, the dose is increased and the cycle is repeated at 100 mg of clomiphene the next month. If inadequate follicular development is seen with 100 mg, successful treatment with clomiphene is unlikely. When letrozole is utilized the endometrium and mucus are not adversely affected and higher doses do not seem to improve the follicular response. Therefore, injectable therapy would be needed.

For those patients who undergo ultrasound with discrepant results, the following options should be considered. For those with follicular size of 20 mm and endometrium of 6mm or less, an estradiol value is obtained. If a 14-18 mm follicle is seen with an endometrium of 6mm or more, you can assume follicular growth of 2-3 mm/day and administer hCG 10,000 units IM in 1-2 days.

Satisfactory ovulation can be confirmed with a midluteal am progesterone above 10 ng/ml. This is carried out for no more than three additional cycles before referral is indicated. If the patient does not conceive, intrauterine insemination (IUI) is added 24 hours after the LH surge is detected, or 36-42 hours after hCG is administered.

- **Anovulation (PCOS):** Women who have evidence of PCOS are best managed with metformin, pioglitazone, or ActoplusMet (*a combination of metformin and pioglitazone*) therapy combined with a low-processed carbohydrate diet (*such as "South Beach"*) and exercise. If metformin is not tolerated, patient refuses, or regulation of the menses does not occur after three to six months on metformin therapy, then ovulation induction with clomiphene, letrozole or low dose injectable gonadotropins should be considered. See <http://www.ivf.com/pcostreat.html>

Patients may be candidates for metformin, a glitazone or combination therapy if she has 8 or fewer menses per year and any of the following:

1. Failure to respond to clomiphene or letrozole
2. Fasting insulin above 10miu/ml
3. Elevated androgens
4. Acanthosis nigricans
5. Family history of diabetes
6. Polycystic appearing ovaries on transvaginal ultrasound.
7. Abnormal lipid levels or other signs of metabolic syndrome

Metformin is started at 500 mg daily with a meal and increased to 500 mg twice daily after the first week, then increased to three times per day the following week. One week later, if the previous dose levels are tolerated, the dose is increased to 850 mg bid. Patients should be pre-screened with a serum BUN, creatinine, and ALT level. They should discontinue the medication approximately 48 hours prior to surgery or an IVP dye X-ray and resumed three days later. BBT charts are maintained and reviewed after a three month interval. If a 16 day temperature elevation is noted, an EPT (*home pregnancy test*) is performed. Metformin is continued until 12 weeks. Patients on Actos or Actoplusmet should discontinue these medications when pregnant

and may be switched to metformin, as tolerated. The continuation of metformin through 12 weeks gestation may reduce the risk of first trimester miscarriage.

If the patient fails to regulate cycles after three months of therapy, consideration is given to continuing an additional three months, adding/switching to rosiglitazone or pioglitazone, ovarian drilling, letrozole or low dose injectable gonadotropin therapy.

Avandamet 2/500 mg bid, Actoplusmet 15/500 mg bid or Avandia 4-8 mg/day or Actos 15-20 mg/day therapy may be initiated after a normal baseline ALT.

- **Hyperandrogenic PCOS Patient Scheduled for Laparoscopy:** Ovarian drilling may be performed at the time of laparoscopy. Small follicular cysts should be punctured and drained at the time of laparoscopic surgery with up to 10-12 punctures per ovary. A monopolar needle may be used with a cutting current of 15-20 watts. To avoid problems with hemostasis, care should be taken to avoid puncturing a corpus luteum. Ovulation occurs in 50-60% with pregnancies reported in up to 50%. The beneficial effect may be short lived. After ~6 months, the abnormal ovarian androgen milieu usually returns. Adhesions may complicate this surgery. Care should be taken to insure hemostasis and consideration be given to using adhesions barriers or hydro flotation. This treatment appears to be less effective in smokers.
- **Anovulation (> 36 years old, FSH <10 mIU/ml)** Injectable gonadotropins may be more appropriate in this patient and consultation should be considered.
- **Hypothalamic Hypogonadotropic Amenorrhea:** For patients with hypothalamic, hypogonadotropic amenorrhea (*failure to withdraw to progesterone, absent cervical mucus, weight < 100lbs., exercise > 30 miles/week or >3 hours of aerobic exercise/week*) clomiphene/letrozole therapy is usually not successful. Alternative methods of ovulation induction include naltrexone 50 mg/day, GnRH pump, or low dose injectable gonadotropins.
- **Hyperprolactinemia:** MRI is usually reserved for those with symptoms, those with non-suppressible prolactin, or those with prolactin above 40 ng/ml. Suppression of prolactin level is initiated with Parlodel therapy at 1.25 mg(1/2 tablet) h.s. for one week. This is increased to BID during the second week. During the third week, 2.5mg is taken h.s. and 1.25 mg in the am and finally during the fourth week, 2.5 mg is taken BID. A repeat prolactin level is obtained, fasting am, 1 week after the full dose is reached. If the level is not suppressed, the dose may be increased to 2.5 mg TID as the patient is able to tolerate. Patients frequently experience postural hypotension, dizziness, and GI distress. Decreasing the dose temporarily or administering the tablets vaginally can reduce this. (*Double the dose for vaginal administration*). Alternatively, Dostinex 0.5 mg 1/2 tablet can be administered twice weekly, and increased after two or three weeks to 1 tablet twice weekly. If regulation of the menstrual cycle and ovulatory BBT's are not present after 2-3 months of normal prolactin levels, letrozole therapy may be initiated.

Surgical Management of Infertility

Surgical caveats:

- No patient should be taken to surgery without a current semen analysis or recent day 3 FSH and estradiol if over 35.
- Patients with bipolar disease (*both proximal obstruction and distal peritubal disease*) are unlikely surgical candidates with pregnancy rates lower than 5%.
- Repeat fimbrioplasties or distal salpingostomies are rarely successful and should be avoided. Surgery should be avoided in patients with hydrosalpinx greater than 2-3 cm or those with thickened walls. If a large hydrosalpinx or a markedly thickened fallopian tube is seen at diagnostic laparoscopy, salpingectomy should be performed. Pregnancy rates are low after surgical correction and IVF pregnancy rates are decreased and miscarriage increased in the presence of a hydrosalpinx.

- Photo documentation of intraoperative findings both prior to and after surgical correction to assist if subsequent REI consultation becomes necessary.
- Preoperative REI consultation should be considered for those over 37. Although IVF may not be a covered benefit, it may be in the patient's best interest to avoid delay and consider this option. A surgical trial of 1-2 years may delay the application of assisted reproductive techniques beyond an age where a reasonable likelihood of success is to be expected.

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