Purpose: To provide a consistent process for determining the optimal course of evaluation of couples with a reduced capacity to conceive compared to the fertility rates of the general population.

Goal: To assist staff in understanding the clinical signs and impact of infertility, and provide a clinical rationale and approach to diagnosing the causes of infertility before referring the infertile couple for more advanced diagnostic and treatment modalities provided by reproductive endocrinologists and infertility specialists.

### Detailed Steps/Screen Shots

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| 1. Background Information | - Definition: the inability to conceive following 1 year of unprotected intercourse in cases where the female is ≤35 years of age or following 6 months of unprotected intercourse for women > 35 years of age.  
- The causes of infertility may be attributable to the female in 40% of cases, to the male in 20% of case and to a combination of both male and female factors in 20% if cases.  
- The cause of infertility cannot be determined in up to 20% of couples.  
- Female factors can further be divided into tubal (40%), ovulatory (40%), uterine (10%) and cervical (10%).  
- Cigarette smoking adversely affects fertility  
- Endometriosis is associated with infertility; however, the mechanism of impaired fertility in the presence of minimal disease has not been clearly elucidated  
- If a HSG is performed for diagnostic evaluation of infertility, there is an increased chance of fertility (10% over the ensuing 6 months) as thin, filmy adhesions may be lysed by the dye injected into the tubes, which will allow them to become patent.  
- Luteal phase deficiency has never been established as a cause of infertility.  
- It has never been demonstrated that antibodies against sperm in either the male or female partner is a cause of infertility.  
- It has never been demonstrated that asymptomatic infection of the male or female genital tract can cause infertility.  
- The spontaneous conception rate for the “normal” couple is 25% per ovulatory cycle  
- Fecundity declines gradually after age 32 and more precipitously after age 37. National data from the SART registry 2009 demonstrates that the percentage of embryo transfers resulting in live births decreased progressively from 47.5% in women younger than 35 years to 38.2% for women aged 35–37 years, 28.3% for women aged 38–40 years, 17% for women aged 41–42, and 6.2% for women over the age of 42. The age-related decline in fertility is accompanied by a significant increase in the rates of aneuploidy and spontaneous abortion  
- The post-coital test has never been demonstrated to correlate with pregnancy outcome and should only be used in cases where the outcome will significantly affect treatment strategy. The test may be considered useful in cases of suspected sexual dysfunction or to assess the need for IUI when clomiphene citrate is being utilized to induce ovulation or treat unexplained infertility (10% of women treated with clomiphene may exhibit a significant reduction in cervical mucus). |
| 2. Client/Target Population | - This guideline applies to all couples exhibiting a decreased capacity to conceive as compared to the fertility rates present in the general population. |
3. **Diagnosis**

Initial consultation with the infertile couple should include a complete medical and menstrual history and physical examination, preconceptional counseling, and instruction on the optimization of coital timing. Preliminary diagnostic testing should be initiated. This may be performed by the general obstetrician/gynecologist or by the reproductive endocrinologist and would include:

- In a healthy asymptomatic woman, labs should be drawn for CBC, blood type, Rh and rubella status in addition to a pap smear within 12 months of the previous test. Additionally, cystic fibrosis screening and infectious disease screening (Chlamydia and GC) should also be done. Further genetic screening for populations at risk for specific inheritable diseases should be performed.
- ACOG, CDC and FDA recommended bloodwork to be drawn
- In women over 35, FSH and Estradiol should be measured on day 1, 2 or 3 of the menstrual cycle with normal values FSH < 15 mIU/mL and estradiol <80 pg/ml. FSH levels over 10mIU/ml may be considered as suspect for diminished ovarian reserve
- Assessment of ovulatory function may be based upon a proper menstrual history, use of basal body temperature charting, or a mid-luteal (day 21 of a 28 day cycle) progesterone assay. Progesterone levels >3 ng/ml are indicative of ovulation. The adequacy of ovulation cannot be ascertained through serum progesterone measurements as progesterone is secreted in episodic pulses (consequently, a progesterone <3ng/ml does not necessarily indicate anovulation).
- A semen sample should be collected for evaluation of sperm count, motility, morphology, viscosity, volume and density after abstinence from ejaculation for 2 to 3 days. Analysis should be performed according to W.H.O. criteria and may include assessment of strict morphology. This examination should occur within 60 minutes after ejaculation.
- Collection should ideally be performed onsite at the laboratory location. If specimen transport is required, the specimen should be collected in a clean glass jar and maintained at body temperature in colder climates. Water-based lubricants may be utilized to assist in the collection process. Coitus interrupts is not an appropriate collection methodology. Specialized collection condoms may be utilized in certain circumstances.
- A test of tubal patency may be accomplished via a HSG. When performing a HSG, prophylactic antibiotic coverage (usually with doxycycline) should be utilized in the presence of positive STD history and/or when tubal blockage is identified. The procedure should be performed in the follicular phase of the cycle, once all menstrual bleeding has ceased. The reproductive endocrinologist should review the HSG films directly.
- Evaluation of the uterus may be accomplished via a HSG, sono-hysterogram or by direct visualization via office-based hysteroscopy.

More advanced testing and treatment, if needed, should come under the auspices of a board certified/eligible reproductive endocrinologist. This more sophisticated evaluation and treatment includes, but is not limited to: hysterosalpingogram, sono-hysterogram, diagnostic hysteroscopy; ovulation induction with agents other than clomiphene citrate (gonadotropins) IUI, IVF, and any infertility-related surgery in cases where IVF is not an option due to religious, financial or other concerns.

- Ovarian reserve testing may consist of baseline FSH and estradiol levels, and measurement of anti-mullerian hormone and antral follicle counts.
- A cervical factor may be suspected in cases of prior cervical surgery (cauterization, laser ablation, cone biopsy) or where a congenital anomaly is identified and may be assessed via a post-coital test primarily to evaluate adequacy of cervical mucus production. The presence or absence of sperm may also be evaluated by this methodology when sexual dysfunction is a consideration.
### 4. Medical Treatment and Surgery

- Anovulatory women or those with oligomenorrhea or amenorrhea who wish to conceive should be treated with agents that induce ovulation once specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated. Clomiphene citrate is the initial agent of choice. Dosage adjustments should be based exclusively upon ovulatory response, and not be based upon failure to conceive. If a woman has not conceived within 6 ovulatory cycles, a move to gonadotropins or preferably IVF would be the next treatment option. Gonadotropin treatment regimes should employ optimal stimulation regimens that ideally yield no more than 2 mature follicles. Women who do not conceive within 6 ovulatory cycles, are poor or hyper-responders to gonadotropin therapy should be directed to IVF
- Diagnostic laparoscopy should only be performed if there is a significant history of pelvic pain or a persistent pelvic mass has been identified (see infertility surgery guidelines).
- Male factor infertility may be treated with limited IUI cycles (no more than 4), sperm donation, or ideally IVF.
- Tubal factor infertility should be treated with IVF
- Uterine factor infertility may be addressed surgically in cases of sub-mucous myomas, polyps, or congenital anomalies
- Cervical factor infertility may be subject to a trial of IUI, but should move to treatment with IVF if IUI is not successful within 4 cycles.
- Unexplained infertility in women under the age of 35 may initially be addressed with a limited ($\leq$3) number of clomiphene IUI cycles but should progress rapidly to IVF. Women age 35 and older should be advised to move directly to IVF.

### 5. Best Practices and Medical Director Escalation

- Each couple should be instructed about the optimal time to conceive and should be encouraged to have frequent intercourse within the 7 day period surrounding the day of presumptive ovulation (days 11 – 17 of a 28 day cycle). There is no ideal regimen of coital frequency and the timing thereof may be left to individual discretion and desires.
- HSG should be avoided if pelvic tenderness is present or there is a history of salpingitis or any STD. If a hydrosalpinx is discovered, antibiotics should continue for one week.
- More than 3 cycles of clomiphene with or without IUI for unexplained infertility as well as any move to gonadotropin/IUI should be reviewed by the medical director.
- All infertility-related surgery, with the exception of hysteroscopic procedures, should be reviewed by the medical director.

### 6. Case Example

| Case Example | N/A |
7. Bibliography

- The Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists and The Practice Committee of the American Society for Reproductive Medicine: Age-related fertility decline: a committee opinion. American Society for Reproductive Medicine 2008
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<th>7. Bibliography (continued)</th>
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