

Infertility Management

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Initial Work-up For Mary

Infertility affects approximately 15% of reproductive-age couples in the U.S and is defined as “the failure of a couple to conceive after 12 months of frequent, unprotected intercourse (Beckman et al., 2010, p. 337). If a couple does not conceive within this time frame, medical intervention is recommended. Using the given scenario of John and Mary, and the initial appearance that she is ovulating based on her regular cycles and Basal Body temperature (BBT’s), this paper will cover the workup for both the male and female and explain the reasons behind some of the abnormal results that may be encountered.

The following tables include the labs and procedures to be performed on Mary as part of the initial infertility workup. Whereas an infertility specialist will do most of the procedures, the blood work can be done ahead of time to provide as much information as possible.

Lab	What	When
HCG (Beta or urine)	Determines if currently pregnant	Beta can be drawn anytime, urine should be done with first urine of the morning ~1 wk after the first day of a missed period
LH, FSH, Estradiol (E2)	To obtain baseline levels	Draw on day 3 of menstrual cycle
Progesterone	To confirm ovulation and the presence of a corpus luteum. Is an accurate indicator of ovulation	Draw mid-luteal phase, approximately day 21 of cycle
Thyroid Panel	To rule out causes of ovulatory dysfunction	Anytime
Prolactin	Inhibits FSH and GnRH and therefore suppresses ovulation	During the menstrual cycle
STIs	To rule out infections	Anytime
Mid cycle LH (urine)	To assess the presence and timing of ovulation	Monitored at home by the patient in anticipation of the pre-ovulatory LH surge. Done every day ~ day 11-14

		of cycle. Easy to miss d/t pulsatile nature of LH.
Mid-cycle E2 & U/S	Measures the amount of estradiol that the granulosa cells in the egg are producing. The U/S is to determine if the uterine lining is developing adequately to support the egg on implantation.	Done between days 10-12

Procedure	What	When
Post-coital	To evaluate sperm concentration and their interaction with the cervical mucus	Obtained 2-12 hrs after intercourse, 1-3 days prior to ovulation
HSG	Performed to view the uterus and fallopian tubes	Anytime other than menstrual cycle. Preferably 2-5 days after menstrual cycle
Trans-vaginal U/S	To look for structural abnormalities / anomalies	Anytime
Endometrial Biopsy	Small sample taken of the endometrium to reveal how it has responded to hormonal signals during the cycle	Done just before the end of the menstrual cycle
Vaginal & cervical viral and bacterial cultures	To detect any adverse infections interfering with conception	Anytime; preferably other than during the menstrual cycle

Note. All testing information was obtained from Beckman et al., 2012; DeMasters, 2012; and The Fertility Institutes, 2012.

Abnormal Semen Analysis

Though statistics vary, the male factor accounts for 25-40% of the issues in infertile couples (Ghadir, Ambartsumyan & DeCherney, 2013, p. 879). Some conditions are identifiable and reversible, where others are not (American Urological Association [AUA] and American Society for Reproductive Medicine [ASRM], 2006, p. S202). Should a semen analysis for John

return abnormal results, a second analysis is indicated 4 weeks later for comparison and to rule out improper “catch” technique or failure to abstain from sex or masturbation for 2-5 days prior to collection. Additionally, the sample should be collected in the lab to ensure that it is processed within one hour of collection. Low-volume or absent ejaculate suggests retrograde ejaculation, lack of emission, ejaculatory duct obstruction, hypogonadism, or congenital bilateral absence of the vas deferens (CBAVD) (AUA & ASRM, 2006, p. S205).

For a low volume sample, it is important to remind the male to collect the entire sample as the first part contains the greatest density of sperm (Beckman et al., 2010, p. 342). If it is a true low-volume sample, retrograde ejaculation is considered. This is an ejaculate volume of less than 1.0ml and is another reason to verify that the small sample wasn't attributed to an abstinence period of less than 1 day or failure to catch the entire sample. A post-ejaculatory urinalysis is performed and the presence of sperm in the patient with low volume, azoospermia, or aspermia is suggestive of a retrograde ejaculation diagnosis (AUA & ASRM, 2006, p. S205). Patients with complete ejaculatory duct obstruction produce low-volume, fructose negative, acidic, azoospermic ejaculates. This is also the finding with CBAVD. Elevated white blood cells in the semen also affect sperm function and motility (AUA & ASRM, 2006, p. S205).

An endocrine evaluation is also warranted, so reproductive hormones must also be assessed. In a male, FSH, LH, inhibin, and testosterone levels need to be drawn. FSH is necessary for sperm production, LH stimulates testosterone production, which is needed for sperm production and is responsible for male sex characteristic development, and decreased inhibin production is associated with low sperm production and a rise in FSH (DeMasters, 2012).

The health history also provides important information to determine the cause for an abnormal semen analysis. History of an undescended testicle can impact sperm production, as

does delayed puberty or Klinefelter's syndrome. Mumps after puberty may result in testicular atrophy and early puberty may indicate adrenal issues. All of these problems may affect adult male fertility (DeMasters, 2012). Occasionally, male infertility may be the indicator of a more serious condition, such as testicular cancer or a pituitary tumor (Beckman et al., 2010, p. 342). Headaches and visual disturbances may point to pituitary issues and male breast enlargement may indicate hormonal imbalances (DeMasters, 2012). A history of prostatitis, genital infections to include STIs, and genital trauma must also be obtained, in addition to pelvic surgeries that may have damaged the urethra or vas deferens.

Systemic illness such as kidney disease, diabetes, thyroid disease, seizure disorder or sickle cell may negatively impact fertility, and cystic fibrosis may affect the epididymis or vas deferens, which will be discussed under the heading "Congenital Absence of the Vas Deferens". Frequent respiratory infections have also been implicated in altering the structure of sperm and creating motility issues (DeMasters, 2012).

Exposure to high temperatures, such as long periods of sitting in a hot tub or sauna may also reduce sperm count, as does tight fitting biker shorts. Finally, alcohol, smoking, cancer therapy, radiation and chemical exposure, and recreational or illicit drugs may all have an impact on male fertility (DeMasters, 2012).

Abnormal Hysterosalpingogram (HSG)

A hysterosalpingogram (HSG) is a specialized radiological procedure to evaluate the structure and function of the fallopian tubes and pelvis. Radiocontrast dye is injected into the uterus through the cervix, and as the uterus fills with dye, it will spill into the abdominal cavity through the fallopian tubes if they are open (Advanced Fertility Center of Chicago, 2012). Multiple x-rays are taken during the procedure to capture the flow of the dye and record the

results. The results provide a wealth of information to assist in evaluating for uterine anomalies. These include leiomyomas, hydrosalpinx, endometrial polyps, intrauterine adhesions, or congenital anomalies such as septate, bicornuate, unicornuate, or didelphic uterus (Beckman et al., 2010, p. 340).

The normal uterine cavity should be smooth and symmetrical, the proximal two-thirds of the fallopian tubes should be thin, and the distal one-third will be dilated in comparison as it consists of the ampulla (Beckman et al., 2010, p. 341). An abnormal HSG is indicated by failure of the dye to flow freely through the fallopian tubes or if there is an abnormal shape to the uterus, indicating the possibility of congenital anomalies or pelvic adhesions which may have been caused by previous pelvic infections, endometriosis, or abdominal or pelvic surgery (Beckman et al., 2010, p. 341).

Chlamydia and Gonorrhea are usual causes of pelvic infections and salpingitis. Hydrosalpinx is a fluid filled blockage of the fallopian tube caused by a previous infection that also prevents communication between the uterus and ovaries, indicated by failure of the contrast dye to flow through the fallopian tube (ASRM, 2012). Endometriosis causes scarring and distortion of the fallopian tubes (Beckman et al., 2010, p. 342) and leiomyomas, also known as uterine fibroid, are benign smooth muscle tumors in the myometrium (Latendresse, McCance & Morgan, 2010, p. 837-838). Leiomyomas tend to increase the size of the uterine cavity and increase endometrial surface area.

Congenital anomalies of the uterus are also known as mullerian duct anomalies. They are created due to defects in the mullerian duct system and they are often asymptomatic and therefore unrecognized (Iverson, DeCherney & Laufer, 2012). A septate uterus has a normal external surface, but two endometrial cavities divided by a midline septum, whereas a bicornuate

uterus has an indented fundus and two endometrial cavities (Iverson et al., 2012). A unicornuate uterus has a normal cavity with fallopian tube and cervix, but the failed mullerian duct may have many configurations, ranging from no development to partial development, and may even have a normal but non-functional endometrial lining (Iverson et al., 2012). A didelphyic uterus is a complete failure of the two mullerian ducts to fuse and it creates a double uterus, each with its own cervix.

Congenital Absence of the Vas Deferens

Congenital bilateral absence of the vas deferens (CBVAD) is suspected in males with azoospermia and a low volume of ejaculated semen (Correlagan, 2010, p. 1). It is established by physical examination and the detection of at least one pathogenic CFTR mutation (AUA & ASRM, 2006, p. S203). This mutation is a recessive inherited condition and is also linked to cystic fibrosis (Correlagan, 2010, p. 1). Since surgery is not an option to correct this defect, treatment options that the endocrinologist can offer include microsurgical epididymal sperm aspiration (MESA), percutaneous epididymal sperm aspiration (PESA), or testicular sperm extraction (TESE) to retrieve healthy, motile sperm.

MESA is done under general anesthesia to while PESA is performed with a local anesthetic. PESA is easier on the patient but retrieves fewer sperm (Filderman, 2007, p. 7). Both techniques are for the retrieval of sperm from the epididymis. TESE is performed under local or general anesthesia and is the biopsy of a portion of testicle to extract sperm from the seminiferous tubules. The retrieved sperm are then used for intracytoplasmic sperm injection (ICSI), in which a single sperm is injected into one egg and then implanted into the uterus.

Premature Menopause and Other Options

The average age for menopause in the United States is between 50 and 52 years of age and marks the end of a women's reproductive cycle (Beckman et al., 2010, p. 329).

Approximately 1% of women undergo menopause before the age of 40 and is referred to as premature ovarian failure. With advancing reproductive age, the remaining oocytes become increasingly resistant to FSH and so FSH levels begin to rise during the perimenopausal years, eventually reaching levels >30 IU/L once menopause is reached (Beckman et al., 2010, p. 329). This is due to the absence of the negative feedback that E2 provides to the anterior pituitary in normal follicle development, which would decrease FSH levels.

Without the release of E2 from a developing oocyte, there would not be an E2 positive feedback loop to create the surge of LH necessary to induce oocyte release as would normally be expected between days 10-14. However, if Mary was experiencing amenorrhea, determining when days 10-14 would not be possible. Additionally, without the release of progesterone from a corpus luteum, there would be no negative feedback to decrease both the FSH and LH levels. Therefore, FSH levels would continue to rise, as described above, and LH levels would most likely remain at a constant level, at approximately 8-12 IU/L, which is the level it is at in the first few days of the follicular phase while awaiting increases in E2 levels to provide the positive feedback needed for the LH surge (Beckman et al., 2010, p. 307).

If John and Mary still want children and are having difficulty conceiving, there are other options. Ovulation induction and in vitro fertilization are possible if viable oocytes can be retrieved from Mary, and there is also the possibility of using a surrogate. With a surrogate, Mary's fertilized eggs would be implanted in another female should Mary's uterus not be viable for pregnancy. Additionally, adoption would be available if there was no possibility of

conceiving with either Mary's eggs or John's sperm or if the couple were not interested in pursuing the other options.

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