LECTURE NOTES

Course: Advanced Course in Reproductive Medicine

Module - 12: Management of Early Pregnancy

➢ LEARNING OUTCOMES

- Identify methods for monitoring first trimester pregnancies conceived after infertility treatment.
- Describe the basic physiologic changes in first trimester embryo and fetal development.
- Describe essential elements of patient education, counseling and anticipatory guidance in early pregnancy.
- Identify the psychological adjustments to pregnancy after infertility treatment.
- Explain the impact of infertility treatment on the risk of multiple gestations and describe consequences related to high-order multiples.
- Describe the diagnosis and management of ectopic pregnancy.
- Describe techniques available for prenatal aneuploidy screening and diagnosis.
- List methods of identifying early pregnancy loss with effective interventions and counseling.
- Identify appropriate patient resources and referrals.

1. INTRODUCTION:

Early pregnancy is often an exciting yet anxiety-provoking time for couples, particularly for those who have invested time, emotion and money in infertility treatment. Early diagnosis, and appropriate assessment and management of the pregnancy are important in identifying potential difficulties, such as a multiple gestation or pregnancy loss, and in promoting a healthy pregnancy. A multidisciplinary team of healthcare providers plays an important role in providing optimal care and patient education.

2. GESTATIONAL CALENDAR:

The gestational calendar begins on the first day of the menstrual period of the conception cycle. Ovulation generally occurs at the end of gestational week 2, followed by conception and implantation. The first missed menses is at the end of gestational week 4. A woman who has a positive pregnancy test with a missed period is in her 4^{th} gestational week, although the actual pregnancy is only 2 weeks into development.

It should be noted that this may not be applicable for cycles with long follicular phases, and thus gestational dating may be more accurately based on the date of ovulation or embryo transfer. The pregnancy "due date" is typically calculated using a gestation of 280 days from the last menstrual period (LMP).

.

3. PREGNANCY HORMONES:

With fertilization and implantation, trophoblast cells of the blastocyst secrete human chorionic gonadotropin (hCG), which is responsible for supporting the corpus luteum. The corpus luteum produces steroids, primarily progesterone, required for pregnancy growth until the seventh to about the tenth week of pregnancy, when it is gradually replaced by the functioning placenta. Estrogen is produced by the placenta converting fetal androgens through the process of aromatization.

4. PREGNANCY MONITORING:

In vitro fertilization and embryo transfer is an assisted reproductive technology in which sperm and eggs are retrieved and combined outside of the body in a laboratory dish where fertilization occurs. The fertilized eggs or embryos are then transferred to the woman's uterus with the hope one will implant and develop into a viable fetus.

- **SERUM HCG:**

  Pregnancy is detected by measurement of serum hCG, which reflects circulating levels of the hCG produced by the syncytiotrophoblast cells of the developing embryo. The hormone is detected using antibodies to the hCG subunit; this is commonly referred to as a "beta hCG." By the time of the expected but missed menses, serum beta-hCG levels are approximately 100 IU/L. This level is variable and may be influenced by many factors, including multiple gestation. Maximum levels of 100,000 IU/L are reached at 8 to 10 weeks' gestation. Levels decrease and remain steady at 10,000 – 20,000 IU/L around 18-20 weeks. Various methods are used to measure serum hCG levels, and these tests may detect levels as low as 25 IU/L

- **URINARY HCG:**

  Home urinary hCG tests are variable and detect hCG levels of 25-100 IU/L, and thus may be falsely negative when used in the fourth and fifth gestational weeks when levels may be below the detectable range.

5. MATERNAL SERUM HCG LEVELS:

To evaluate early pregnancy, the first hCG level is commonly drawn at the time of an expected but missed menses, at about 4 to 5 weeks' gestation. Although a higher initial level may predict a better outcome, higher levels produced by a multiple gestation can affect the interpretation of the initial result. A second measurement should be performed 48 hours later. Failure to rise at least 66% may prompt further evaluation to rule out an ectopic or nonviable pregnancy. The timing of the first hCG measurement may be modified based on the mode of conception, such as spontaneous, intrauterine insemination (IUI) or IVF. In addition to initial and percent rise in hCG, oocyte age is an important variable and should be considered in conjunction with hCG results.

6. PREGNANCY MONITORING ULTRASOUND FINDINGS:

Gestational Age	β-hCG level	US Finding
4 weeks	1,000-1,200 IU/L	Gestational sac
5 weeks	7,200 IU/L	Yolk sac
5 – 6 weeks		Fetal pole
6 weeks	10,800 IU/L	Fetal pole with cardiac activity
7 weeks		Fetal movement
8 weeks		Head, limb buds
9 weeks		Choroid plexus development, normal midgut herniation is prominent
12 weeks		Hands, fingers; midgut seen in abdomen

This chart provides landmarks seen by transvaginal ultrasound and typical correlations with gestational age and beta hCG levels. Transvaginal ultrasonography is preferred in early pregnancy as the higher frequency (5-8 MHz) allows for better resolution of the image than transabdominal ultrasound. Also, a full bladder is not required and body habitus does not interfere as significantly with penetration as with transabdominal ultrasonography.

Signs of pregnancy can be seen with transvaginal ultrasound as early as 4 weeks after the last menstrual period. An early gestational sac at this time may measure 4 to 5 mm and is surrounded by a hyperechogenic (bright white) ring representing decidual tissue. Typical growth of the gestational sac is 1 mm in mean diameter per day. Note that a gestational sac may be confused with a fluid collection or pseudosac associated with an ectopic pregnancy.

The presence of a yolk sac, typically seen at 5 weeks' gestation, confirms an intrauterine pregnancy. The yolk sac will increase in size from 7 to 13 weeks to a maximal diameter of 6 mm. A yolk sac that is greater than 7 mm in size without an associated fetal pole correlates with a higher likelihood of abnormal pregnancy

An early fetal pole can begin to be seen prior to 5 completed weeks' gestation and typically grows at a rate of 1 mm/day.

Early cardiac activity may be detected at 5 weeks' 5/7 days' to 5 weeks' 6/7 days' gestation. Fetal cardiac motion should be detected by the time the embryo is 5 mm in diameter. Absence of cardiac activity at this size is indicative of early failed pregnancy. The fetal heart rate is relatively slow when seen prior to 6 weeks' gestation, typically between 110 and 115 beats per minute (bpm), and quickly increases to approximately 140 bpm by 9 weeks' gestation. In general, varying with maternal age, the risk of miscarriage after appropriate cardiac activity is seen at 8 weeks' gestation is significantly reduced. By 9 weeks' gestation, the choroid plexus, the part of the brain where cerebrospinal fluid is produced, can be visualized on ultrasound, along with a prominent midgut. At 12 weeks' gestation, hands and fingers are visible.

Pregnancy status may be described as pregnancy of unknown location, blighted ovum/anembryonic, clinical, or ongoing.

- **With a pregnancy of unknown location**, a pregnancy is detected by presence of serum or urinary hCG, but is not yet seen with ultrasound. Beta-specific hCG levels may be normal or lower than normal, and may rise, not rise, or decrease.

- **A blighted ovum or anembryonic gestation** is a gestational sac with no embryonic presence identified on ultrasound examination. The sac may not be totally anechoic on ultrasound. Typically, Hcg levels decrease.

- **A clinical pregnancy** is diagnosed once a pregnancy is confirmed by ultrasound; hCG levels rise appropriately as noted in the previous chart.

- **An ongoing pregnancy** is a current, viable intrauterine pregnancy that has been confirmed by ultrasound, but definitions specifying gestational age vary between 12 and 20 weeks.

7. BASIC EMBRYO DEVELOPMENT:

The zygote is kept in the fallopian tube for about three days by the spastic contractions of the estrogen-dominated isthmus. As progesterone increases, muscle tone decreases. In the fallopian tube, the zygote undergoes cleavage division (1-cell to 8-cell), compaction and blastocyst formation. The inner cell

mass becomes the fetus and the outer cells become the placenta and fetal membranes. Approximately seven days after fertilization, the blastocyst bursts from the zona pellucida, which is called hatching, and implants in the wall of the uterus, which is called nidation. Implantation requires prior conditioning of the endometrium by progesterone, which causes the stromal cells to swell and accumulate glycogen, lipids and protein. The presence of hCG from the blastocyst stimulates the corpus luteum of the maternal ovary to secrete progesterone. Anti-progestins such as RU486 can block implantation. The blastocyst attaches to the wall of the uterine fundus at the embryonic pole. Trophoblast cells then invade through the endometrial epithelium into the endometrial stroma aided by proteases. Stromal cells decidualize, a process by which they enlarge and become transcriptionally active, and surround the blastocyst.

Within 11 days of fertilization, the trophoblast forms two layers, the cytotrophoblast and the syncytiotrophoblast, containing lacunae. The placenta forms a barrier to permit exchange of nutrients, gases and wastes with only slight mixing of fetal blood with maternal blood. Fetal blood cells can normally be found in the maternal circulation in all cases. As the lacunae enlarge, the trophoblast forms villi, which consist of a vascularized core of cytotrophoblast covered by syncytiotrophoblast. The trophoblast erodes the maternal spiral arteries, which then flow directly into the intervillous spaces. The fully developed placenta consists of the following three layers of membranes: 1) amnion (inner), which is a single layer of ectodermal epithelium completely enclosing the embryo; 2) chorion (outer), which surrounds the amniotic sac and includes the villi and trophoblast; and 3) the decidua of the maternal endometrium.

The uterofetoplacental circulation is established by about 6 gestational weeks and is completed by 10 weeks, connecting the maternal decidua through the chorionic villi to the fetus via the umbilical vessels.

• DEVELOPMENTAL WEEKS:

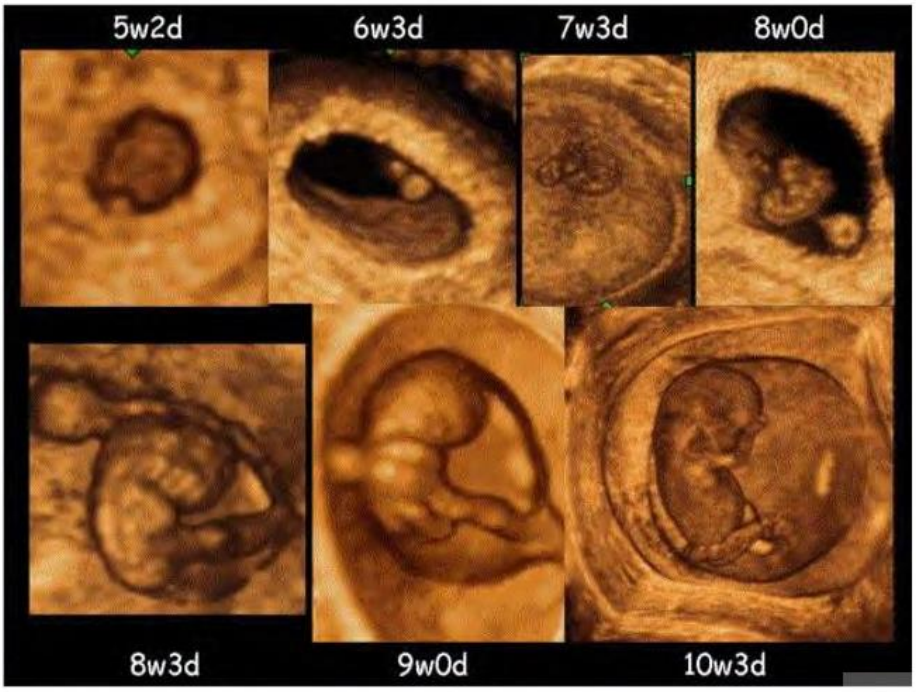
In the following discussion of embryonic and fetal development, the time line indicates developmental week and does not refer to gestational age. To correlate with gestational age, adjust by adding 2 weeks to account for time from the last menstrual period to fertilization. Some of the major hallmarks of embryologic development are noted here. Developmental weeks 3 through 8 represent the period of organogenesis, which is critical for normal development and is the time when most structural birth defects occur. The neural tube closes during developmental week 4, and at week 5, limb and facial development begin and the embryo appears tightly C-shaped.

• FIRST TRIMESTER:

In developmental week 6, there is early formation of fingers and toes; brain vesicles are prominent; the external ear forms; and umbilical herniation begins. Umbilical herniation is caused by swelling from intestinal loops in the umbilical cord and is a normal embryologic event. Midgut herniation at this gestational age should not be confused with an omphalocele, which is the abnormal herniation of abdominal organs through an enlarged umbilical ring. **In the 7th developmental week**, pigmentation of the retina is seen; fingers and toes separate; and the upper lip and nipples form.

In the 8th developmental week, limbs are long and bent at the elbows and knees; the face is more human-like; and the tail disappears. **In weeks 11 to 13**, the bowel returns to the abdominal cavity, and the long bones and skull ossify. The embryo is called a fetus at the 8th gestational/10th developmental week.

8. NORMAL EMBRYOLOGIC DEVELOPMENT:



Shown here is the normal morphological development of an embryo from 5 to 10 weeks of gestation using 3D ultrasound.

9. PATIENT EDUCATION AND COUNSELING:

Patients who become pregnant following infertility treatment typically have many questions about their care and concerns about the well-being of their pregnancy. Accurate information and anticipatory guidance about their activity, diet and safety, as well as support of their psychological needs, are important in the early weeks before being referred for obstetrical care.

- **LUTEAL SUPPORT:**

Many women will require luteal phase support for an infertility treatment-conceived pregnancy.
Recall that the corpus luteum is the primary source of progesterone until approximately 10 weeks' gestation. The placenta begins to produce steroids between 7 and 9 weeks' gestation until it takes over completely.
Corpus luteal cells are disrupted during oocyte retrieval in women who use IVF to conceive. In addition, co-treatment with gonadotropin-releasing hormone (GnRH) analogs to prevent a premature luteinizing hormone (LH) surge and ovulation continues to suppress endogenous LH production after discontinuation of medicine. These low levels of LH may not be sufficient to stimulate the corpus luteum. Thus, pregnancies conceived with ART require exogenous support with daily progesterone until 7-10 weeks' gestation. Progesterone supplementation has only been shown to be beneficial in randomized controlled trials after downregulation with GnRH agonists. Progesterone levels can be followed on a periodic basis or supplementation continued until placental production is expected. Because recipients of oocyte donation do not have a corpus luteum, they require exogenous supplementation of both progesterone and estrogen until the placenta is fully competent. Progesterone

and estrogen supplementation is also needed in unstimulated frozen embryo transfer cycles.

- **DIETARY GUIDANCE:**

Dietary recommendations for pregnancy include the following:

- An additional 300 calories over a woman's current intake is usually recommended for pregnant women with normal prepregnancy body mass index (BMI), and more for women with a multiple gestation.
- Women should take a daily multivitamin with at least 30 mg ferrous iron and 0.4 mg/day of folic acid.
- Daily vitamin and mineral intake more than twice the recommended daily dietary allowance should be avoided, as it could be toxic.
- If a woman has a history of having a child affected by a neural tube defect or if the male partner has a neural tube defect (NTD), the woman should take 4 mg folic acid daily for at least one month prior to conception and during early pregnancy.
- Seven or more servings per day of fruits and vegetables, and 6 to 9 servings of whole grains per day are recommended.
- At least 4 servings per day of dairy products provide calcium, protein, and vitamin D.
- The recommended intake of calcium is 1,000 mg/day, the same as for nonpregnant women.
- Sixty grams per day (2-3 servings) of protein are recommended.
- Fats should make up about 20-35% of the daily caloric intake, with limited saturated and trans fats.

There are certain dietary restrictions in pregnancy that can minimize risks to the developing fetus. Fish is an excellent source of protein and healthy fats, but because most fish and shellfish do contain trace methylmercury, which is neurotoxic to the fetus, the U.S. Environmental Protection Agency and Food and Drug Administration recommend consumption of no more than 12 ounces of fish and shellfish that are lower in methylmercury.

Pregnant women should consume no more than two servings of canned tuna per week and no more than 6 ounces of albacore "white" tuna. Fish and seafood with low levels of mercury include shrimp, salmon, pollock, and catfish. Fish with high levels of mercury, which should be avoided, include swordfish, shark, tile fish and king mackerel. Because of their suppressed immune systems, pregnant women are at increased risk for infection with Listeria monocytogenes, a bacterium found in certain foods.

Infection can result in miscarriage and a wide range of fetal and infant health problems. Listeria is killed by pasteurization and cooking; however, in certain ready-to-eat foods, such as hot dogs and deli meats, contamination may occur after cooking but before packaging. The Centers for Disease Control and Prevention and the Food and Drug Administration recommend that pregnant women avoid the following foods: hot dogs and luncheon meats, unless reheated until steaming hot; soft cheeses such as feta, brie, and camembert, "blue-veined cheeses," and Mexican soft cheeses such as "queso blanco," "queso fresco," or panela, unless made with pasteurized milk; refrigerated pâtés or meat spreads, and

refrigerated smoked seafood, such as "nova-style," unless in a cooked dish, such as a casserole. Hispanic pregnant women are at even greater risk of listeriosis because of traditional dietary habits.

Women should be encouraged to drink at least eight 8-ounce glasses of water or other fluids each day and to avoid caffeinated beverages and all forms of alcohol.

10. WEIGHT GAIN GUIDELINES (IOM) GUIDELINES:

According to the guidelines issued in 2009 by the Institute of Medicine (IOM), healthy American women at a normal weight for their height (BMI of 18.5 to 24.9) should gain 25 to 35 pounds during a singleton pregnancy. Underweight women (BMI less than 18.5) should gain more, 28 to 40 pounds, and overweight women (BMI of 25 to 29.9) should gain less, 15 to 25 pounds. Obese women (BMI greater than 30) should limit gain to 11 to 20 pounds. Calculations for rate assume a weight gain of 0.5–2.0 kg (1.1–4.4 lb) during the first trimester. Women pregnant with twins in the normal BMI category should aim to gain 37-54 pounds; overweight women, 31-50 pounds; and obese women, 25-42 pounds. Women carrying high- order multiples likely will need even more weight gain, with appropriate nutritional interventions.

11. NAUSEA AND VOMITING OF PREGNANCY (NVP):

Early pregnancy nutrition may be hampered by nausea and vomiting of pregnancy (NVP), which is frequently referred to as morning sickness. However, symptoms may occur at any time of the day or night. It is experienced by a majority of women by 9 weeks' gestation. Frequent small carbohydrate meals may help, along with avoidance of greasy or spicy foods. Use of fresh ginger root, vitamin B6 and motion sickness bands appear to be effective in relieving symptoms. Other treatments, such as acupuncture, have not been shown to be more effective than placebo.

- **Management:**

Most cases of nausea and vomiting of pregnancy can be managed without medications and resolve by the end of the first trimester. In some women, the severe vomiting of hyperemesis gravidarum can cause dehydration and electrolyte imbalance and become serious, requiring close medical attention. Hyperemesis gravidarum tends to be more common in younger women and in multiple gestations.

- **Medication:**

Nearly all drugs, including over-the-counter medications, cross the placenta and have the potential to affect the developing fetus. It is best to verify the safety of all medications used, including over-the-counter and prescription drugs, in the first trimester when organogenesis is occurring. Examples of known teratogens are retinoids, phenytoin, and warfarin. Generally, acetaminophen may be used for pain relief, but nonsteroidal anti-inflammatory drugs such as ibuprofen and aspirin should be avoided, especially in the third trimester, because of constriction of the fetal ductus arteriosus and risk for persistent pulmonary hypertension in the newborn. For constipation, dietary fibers such as psyllium or surface-active agents such as docusate can be used. Calcium carbonate may be used as an antacid. Pregnant women should not smoke and should also avoid second-hand smoke. Smoking in pregnancy is associated with premature rupture of membranes, placental abruption, and placenta previa, as well as preterm birth, and low-birthweight infants. There are several sources of information about teratogens.

Certain medications for chronic conditions, such as epilepsy, depression, bipolar disorder, or antiphospholipid syndrome, should not be abruptly discontinued. If a safer alternative is available, the

medication should be changed. Multidisciplinary care is needed to manage medications for these women.

Metformin often is used to treat obese anovulatory women with polycystic ovary syndrome (PCOS) and insulin resistance. It is not clear if the risk of first-trimester miscarriage for these women is decreased with the continued use of metformin during pregnancy. Although there does not appear to be an increased rate of birth defects or complications at birth with metformin use in pregnancy, each case should be individually reviewed.

- **Physical Activity:**

In the absence of medical or obstetrical complications, the American College of Obstetricians and Gynecologists recommends thirty minutes of daily moderate-intensity exercise, such as swimming, brisk walking or prenatal exercise classes. Activities that carry a high risk of falling or trauma should be avoided, as well as heavy lifting. Scuba diving is not safe in pregnancy, as the fetus is at increased risk for decompression sickness. Women with ovarian hyperstimulation syndrome may need restricted activity until it resolves. Both the lap and shoulder belt should be used in car travel, with the lap belt placed low across the hip bones. Occasional air travel is considered safe in pregnancy up until 36 weeks' gestation. Women should be advised to use a seatbelt while seated (fastened at the hip bones) and periodically move lower extremities and ambulate. Hydration and support stockings may also be used to minimize any risk of venous thrombosis.

Cramping is commonly experienced with intercourse. If the woman has a history of preterm labor and symptoms occur, intercourse may be discouraged because of the risk that prostaglandins in semen and with climax may initiate uterine contractions.

12. PREGNANCY AFTER INFERTILITY:

Some studies have shown that singleton conceptions with assisted reproductive technology (ART) treatments, such as IVF and intracytoplasmic sperm injection (ICSI), have slightly higher rates of adverse pregnancy outcomes. A 2007 report from the National Institute of Child Health and Human Development noted that, although the vast majority of singleton ART pregnancies are uncomplicated, the rates for nearly all perinatal and maternal complications and certain genetic risks are higher than for spontaneously conceived singleton gestations. It is not clear whether these risks are related to the treatment or to an underlying reproductive pathology. The report noted that ART patients tend to be older than average, and age is an independent, contributory risk factor for many complications. This was also observed in another report from the National Center for Chronic Disease Prevention and Health Promotion of the Centers for.
Disease Control, which noted that women who conceive with ART are more likely than women who do not to enter pregnancy with a chronic condition and develop complications during pregnancy and labor and delivery. The report also observed that infants born after ART are at increased risk for adverse health outcomes.
Maternal, perinatal and neonatal complications are common with multiple births, but ART treatment itself was not found to be a risk factor for adverse perinatal outcome in twin deliveries, according to a population-based study. The study found that risks for several outcomes, such as very low birthweight and infant death, were somewhat lower among ART twin deliveries. However, it is important to remember that the risk of adverse outcomes among twin births is substantially higher than those of singleton births. First-trimester bleeding is more common with ART pregnancies, and while bleeding does not necessarily indicate a miscarriage, an association has been shown with obstetrical and perinatal problems.

13. MULTIPLE GESTATIONS:

The incidence of twin and high-order (triplet or greater) multiple gestations has increased over the past 20 years, primarily due to the increased use of drugs for ovulation induction and the frequent transfer of multiple embryos in ART procedures. Several issues in infertility care contribute to the increased incidence of high-order multiple pregnancies. An infertile couple's sense of urgency may lead to a preference for more aggressive treatments involving gonadotropin use or more embryos transferred in IVF cycles. Clinicians may feel competitive pressure to achieve higher pregnancy rates by transferring a greater number of embryos in IVF cycles. Inadequate or absent health care insurance coverage may cause couples to pursue an option less costly than IVF or to limit the number of IVF cycles and request that more embryos be transferred at each attempt.

- **INFERTILITY TREATMENT AND MULTIPLE GESTATION RATES:**

Multiple birth rates vary according to mode of conception. While multiples comprise only about 3% of all live births, approximately half are conceived with infertility therapies and ART treatments. The rate of twins with spontaneous conception is 1.25%; with clomiphene citrate, 5-8%; and with gonadotropin stimulation, 15-20%. With IVF, the twinning rate is 15 to 33% and varies inversely with maternal age, and directly with the number of embryos transferred. High- order multiples (triplets or more) make up less than 5% of all multiple births, but the vast majority are a result of infertility therapies, with only 7 to 18% occurring spontaneously. Less than 2% of IVF cycles result in high-order multiples. In turn, approximately 40% of high-order multiples are related to ovulation-inducing drugs without ART (mostly gonadotropins), and about 40% result from ART.

- **VANISHING TWIN:**

The vanishing twin phenomenon, in which one multiple spontaneously disappears, is a common occurrence, particularly in IVF cycles with transfer of more than one embryo. In up to 36% of twin gestations from infertility therapy, one twin vanishes before 12 weeks. This type of loss occurs at even higher rates in high-order multiples. Spontaneous reduction of one or more gestational sacs before the 12th week has been found in 53% of triplets and 65% of quadruplets. Spontaneous loss is more likely with higher initial numbers of gestational sacs and with older maternal age. Accompanying vaginal bleeding is not unusual, and the surviving fetus is usually not affected.

- **MONOZYGOTIC TWINNING:**

Monozygotic twins, also considered "identical twins," develop from the same fertilized ovum, and thus have the same genetic material. About two thirds of monozygotic twins are monochorionic, that is, they share a single placenta. Rarely, monozygotic twins share a single amnion. The image shown here is of monochorionic, monoamniotic twins at 8 weeks' gestation. In spontaneous conceptions, monozygotic twinning is a random event occurring at a rate of about 1 in 250 live births. However, the incidence of monozygotic twinning is increased in pregnancies resulting from ART treatment, compared to spontaneous conceptions.

- **DIZYGOTIC TWINNING:**

Dizygotic twins share a common uterine environment, but develop from different ova. Each develops with a separate chorion and amnion. Spontaneous dizygotic twinning is more common in African-American women, older women, those with higher parity and those with a maternal family history of twinning. However, the highest rates of twinning are seen in white women, especially those over age

35 years; this is probably due to a greater access to and use of infertility services by this population.

- ## ULTRASOUND DIAGNOSIS:

Ultrasound examination is the only safe and reliable method for a definitive diagnosis of multiple gestation. First-trimester ultrasound is highly accurate in diagnosing multiple gestations and in determining chorionicity, especially between 10 and 14 weeks' gestation. Monochorionicity appears on ultrasound as a T-shaped junction. Early gestational diagnosis is also possible. In the image on the left, vaginal ultrasound demonstrates two live embryos and two yolk sacs surrounded by a single chorion. In the image on the right are dichorionic/diamniotic twins at 8 weeks' 3 days gestation.

- ## MULTIPLE GESTATION – RISKS:

All multiple gestations, including twins, have increased maternal, fetal and neonatal morbidity and mortality. Generally, risks increase as the number of fetuses increases. Note the comparisons between births at less than 32 and less than 37 completed weeks of gestation for singletons, twins, triplets, and high-order multiples. Conceptions with multiple embryos are at increased risk for ovarian hyperstimulation syndrome as well.

- ## MULTIPLE GESTATION – COMPLICATIONS:

The major source of perinatal morbidity and mortality in twin gestations is spontaneous preterm birth. **The rate of preterm twin** delivery is 60% before 37 weeks, and 22% before 33 weeks. Over 93% of triplets and other high-order multiples are born preterm. Though neonatal outcome is similar for singletons, twins, and triplets matched for gestational age, actual outcomes are not equivalent because the average length of gestation for singletons, twins, and triplets is about 39, 35, and 32 weeks of gestation, respectively. There is good evidence that practices such as cervical cerclage and bed rest do not prevent preterm birth; moreover, there is no effective therapy for preventing preterm birth.

Studies have found that rates of **gestational hypertension and preeclampsia** are twice as high in twin compared with singleton pregnancies (13 percent in twins versus 5 to 6 percent in singletons for both disorders). Early severe preeclampsia and HELLP syndrome, which is characterized by hemolysis, elevated liver enzyme levels and a low platelet count, also tend to occur more frequently in multiple gestations.

Monozygotic multiples, particularly those sharing a placenta, are at higher risk for complications compared to dizygotic twins. In addition to twin-to-twin transfusion syndrome, monozygotic multiples have a higher incidence of congenital anomalies.

Infant mortality in twins is five-fold higher than that of singletons (37 versus 7 per 1000 live births), and twins account for 12 to 15 percent of neonatal deaths.

Because of the risk of complications, consideration of **referral of high-order multiple gestations to a maternal-fetal** medicine specialist may be in order.

- ## MULTIPLE GESTATION – PREVENTION:

Historically, strategies for preventing high-order multiple gestations in ovarian stimulation cycles have included careful monitoring of estradiol levels and follicle development, with cycle cancellation or conversion to an IVF cycle with cryopreservation of excess embryos. Recently, studies have shown that for unexplained infertility, a fast-track plan that moves directly from treatment with oral ovulation

induction agents and intrauterine insemination to use of in vitro fertilization has the shortest time to pregnancy, is more cost-effective, and avoids the risk of high-order multiples with gonadotropin ovulation induction.

ASRM has established guidelines for embryo transfer. In appropriately selected patients, single embryo transfer appears to be superior to double embryo transfer when taking into account the number of deliveries with at least one live-born child, incremental cost-effectiveness ratio, and maternal and pediatric complications.

- **MULTIFETAL REDUCTION:**

Multifetal reduction is the termination of one or more fetuses in a multiple gestation. Since the risk of complications is proportional to the number of fetuses in utero, the goal of multifetal pregnancy reduction is to reduce the risk of adverse outcomes in survivors of high-order pregnancies by decreasing the number of fetuses. Multifetal reduction is typically performed from 10 to 13 weeks' gestation. Under ultrasound guidance, potassium chloride is injected into the fetal thorax. Asystole is confirmed by ultrasound. A reduction is considered selective when a specific fetus or fetuses are selected because of prior prenatal diagnosis indicating an anomaly or genetic defect.

- **MULTIFETAL REDUCTION OUTCOMES:**

Benefits of multifetal reduction include a reduced risk of preterm labor and perinatal mortality, reduced risk of long-term neurodevelopmental morbidity of offspring, and reduced maternal risk of pregnancy complications. It may also alleviate the economic and psychological impact of a multiple birth on families. This graph shows fetal outcomes for preterm delivery of triplets reduced to twins compared to triplets managed conservatively; the rate of preterm delivery at less than 32 weeks was decreased by half for reduced triplets. Reduction to twins also has been shown to reduce mortality: perinatal mortality for reduced twins (from triplets) was 26.6/1000 versus 92/1000 (triplets managed conservatively).

- **MULTIPLE GESTATION – REDUCTION:**

There are, however, risks involved in the procedure, including a 6% chance that all fetuses may be lost. The procedure also does not completely eliminate the risks associated with multiple pregnancy. Generally, higher starting numbers before reduction are associated with poorer perinatal and infant outcomes in the remaining fetuses. Reduction may also present an ethical dilemma for some clinicians and patients and may have adverse psychological consequences. Multifetal reduction should not be included as a routine part of ART treatment cycles in which excessive numbers of embryos have been transferred.

14. SPONTANEOUS MISCARRIAGE:

The rate of spontaneous **miscarriage in the general population is 15.8%** according to data from the Centers for Disease Control and Prevention (CDC) reported in 2006. Patients undergoing a fresh cycle of IVF do not appear to have a higher rate of miscarriage compared to age-matched women in the general population. Cycles with cryopreserved and thawed embryos possibly have a slightly higher rate of miscarriage than the general population.

Age is the single most important factor for predicting the likelihood of miscarriage. In the case of IVF, the maternal genetic age is the most important determinant of miscarriage rate.

The **diagnosis** of miscarriage can be made in several ways. A patient may experience symptoms

suggestive of a miscarriage, including bleeding, spotting and cramping, or may pass gestational tissue vaginally. Declining levels of hCG in the first trimester are also suggestive of a miscarriage. Finally, an ultrasound that shows no evidence of a fetal heartbeat after 6-7 weeks' gestation strongly suggests a miscarriage.

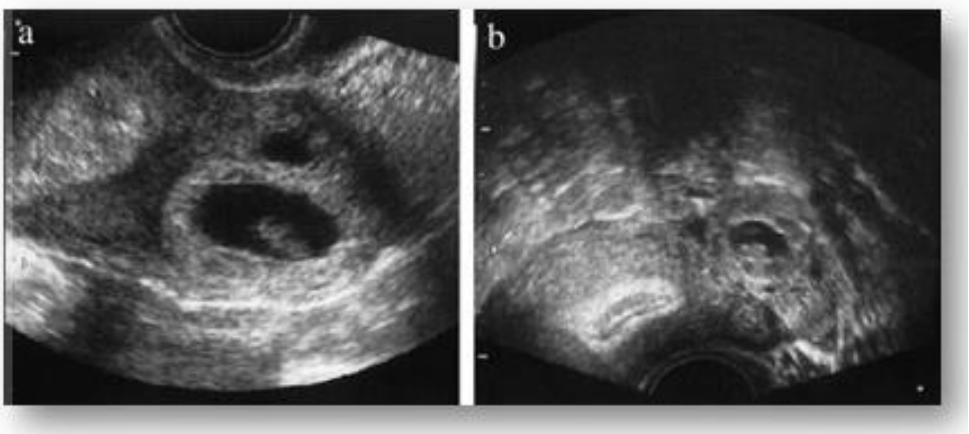
15. ECTOPIC/ HETEROTOPIC PREGNANCY:

Infertility treatment is also associated with an increased risk of ectopic and heterotopic pregnancies. Ectopic implantations typically occur in the fallopian tube but may be in any extrauterine location. Heterotopic pregnancy refers to a multiple gestation with both an intrauterine implantation and an abnormal implantation. IVF is associated with a 2.2% rate of ectopic pregnancy, compared with about 2% in the general population. The incidence of heterotopic pregnancy with infertility treatment is approximately 1 in 3900 pregnancies.

- **ECTOPIC PREGNANCY – DIAGNOSIS:**

Diagnosis of an ectopic pregnancy requires consideration of a patient's history (including her gestational age), findings on pelvic ultrasound, and trends in hCG levels. As noted earlier, abnormal hCG levels can indicate an ectopic or abnormal intrauterine pregnancy and should be followed approximately every 48 hours to assist in clinical diagnosis.

A pelvic ultrasound is an integral part of the ectopic pregnancy evaluation. Due to the detection thresholds of an ultrasound, a normal singleton intrauterine pregnancy may not be confirmed until hCG levels are >2000 IU/L. However, it is crucial to consider the possibility of multiple gestation, particularly in patients undergoing infertility treatment. In this circumstance, hCG values may be higher than otherwise expected, and still reflect a normal pregnancy. For this reason, it is always critical to factor gestational age into decisions involving evaluation of an early pregnancy. For instance, a normal twin pregnancy may not be visible in the uterus despite the fact that hCG levels exceed 2000 IU/L. Shown here is a transvaginal ultrasound scan of a left tubal ectopic triplet pregnancy. The interstitial gestational sac with live embryo and a blighted twin is seen in the left image and an additional ampullary gestational sac with a live embryo in the right hand image.



*Transvaginal ultrasound scan of left tubal ectopic triplet pregnancy. Interstitial gestational sac with live embryo and a blighted twin (**a**) and an additional ampullary gestational sac with a live embryo (**b**).*

As a final part of the ectopic pregnancy, any patient with a suggestive history should be evaluated promptly. A suggestive history would include symptoms of significant (particularly sharp) pelvic pain, with or without vaginal bleeding. This applies to infertility patients who have a normal hCG trend, but

have not had an ultrasound confirming an intrauterine pregnancy, though as stated above, gestational age is an important part of the consideration. Management options depend on how these diagnostic puzzle pieces fit together and patient stability.

- ## ECTOPIC PREGNANCY – MANAGEMENT:

  - **MANAGEMENT OF SUSPECTED ECTOPIC:**

When an ectopic pregnancy is suspected but not confirmed, management is largely driven by clinical symptoms. In select circumstances, a stable patient can be followed closely to determine more accurately whether an ectopic pregnancy is present. If the hCG trend is markedly abnormal, but there is suspicion this reflects a miscarriage rather than an ectopic pregnancy, consideration of endometrial sampling can allow the clinician to differentiate between a failing intrauterine pregnancy (miscarriage) versus whether an ectopic pregnancy is more likely; that is, no gestational tissue is present when the endometrium is sampled.

  - **MANAGEMENT OF CONFIRMED ECTOPIC PREGNANCY:**

Methotrexate treatment and surgery generally are reserved for circumstances in which an ectopic pregnancy can be definitively diagnosed or is suspected with high probability.
Methotrexate, a chemotherapeutic agent when used at high doses, is injected at very low doses. It acts by impairing the rapid cell division seen in tissues like a developing embryo. In certain circumstances, repeated doses of methotrexate are required to adequately treat an ectopic pregnancy, as determined by the trend in hCG levels. Methotrexate will fail in some circumstances though, especially when hCG levels are particularly high or the ectopic mass is particularly large. Certain patients are not candidates for methotrexate therapy, including those with hepatic, hematologic or renal insufficiency, or with a co-existing intrauterine pregnancy. Surgery can be avoided in most cases, but is always indicated in the circumstance of an acutely unstable patient with a high likelihood of (or confirmed) ectopic pregnancy.

Patients who have failed to respond to methotrexate may also require surgery. Laparoscopy is nearly always used to perform a salpingectomy or salpingostomy for removal of the ectopic pregnancy.

16. PRENATAL SCREENING AND DIAGNOSIS:

Techniques and indications for prenatal screening and diagnostic testing are addressed in the following section.

- **SCREENING AND DIAGNOSIS: WHO SHOULD BE OFFERED WHAT?**

The American College of Obstetricians and Gynecologists recommends that all women should be offered aneuploidy screening or diagnostic testing along with counseling, to understand the benefits and limitations of their choices. Maternal age should not be used as the sole determinant to offer screening or testing.

- **MATERNAL GENETIC SCREENING DURING PREGNANCY:**

There are several options currently available for genetic screening during pregnancy. These options are continuously changing and often will depend upon factors such as the local availability of screening options, insurance coverage and patient preference. All of the screening options are very similar in many respects: they take a woman's baseline risk for having a child with a particular birth defect, and

then assess factors that are specific to her pregnancy to provide a residual risk estimate. This risk assessment can then be utilized to assist a woman in the optional decision to proceed with a diagnostic test.

Screening tests for aneuploidy are available in all trimesters. Triple, quad, and penta screens, cell-free DNA, and ultrasound can be performed in the first trimester. Integrated, sequential, and contingent screening are performed in the first and second trimesters.

- **MATERNAL SCREENING: FACTORS THAT EFFECT LEVELS:**

- **MATERNAL AND FETAL FACTORS:**

  Certain maternal factors can impact biochemical markers. For example, increased maternal body weight is associated with decreased biochemical levels. Race of the mother and fetus can also impact levels. For example, alpha fetoprotein (AFP) levels, which are associated with open neural tube defects, are increased in Asian and African American populations. Human chorionic gonadotropin (hCG) and unconjugated estriol levels are highest in Asians and increased in African Americans. In women with preexisting diabetes, maternal serum AFP is decreased, but there is a higher incidence of neural tube defects. Women with a previous child with Down syndrome or an open neural tube defect are also at increased risk. Multiple gestation can impact all levels, as more than one fetus is producing the protein, which can alter results. Gestational age also is a factor, as levels change with increasing gestation. All of these factors must be accurately reported to the laboratory providing the risk assessment, as they can substantially change the results.

- **FIRST-TRIMESTER SCREENING:**

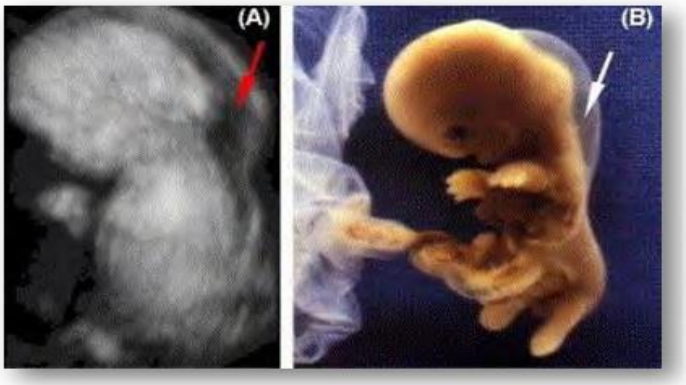
First-trimester maternal screening is usually performed between 10 and 14 weeks' gestation. The screen involves a blood test for serum free β-hCG, or total human chorionic gonadotropin (hCG) along with pregnancy-associated plasma protein A analyte levels and ultrasound for nuchal translucency measurement.

- **FIRST-TRIMESTER SCREENING RESULTS:**

  In pregnancies with Down syndrome, the hCG level is generally higher than average and the PAPP-A level is lower than average. In pregnancies with trisomy 18, both biochemical markers can be reduced.

- **FIRST-TRIMESTER ULTRASOUND SCREENING NUCHAL TRANSLUCENCY (NT):**

  First-trimester screening ultrasound measures the nuchal translucency or the thickness at the back of the neck of the fetus. As the nuchal measurement increases, so does the risk for fetal anomalies, including Down syndrome. Some centers may use fetal nasal bone measurement; a shortened length or absence may also be associated with aneuploidy. Nuchal thickening in an 11-week fetus is shown in the two images; in panel A by 3D ultrasound and in panel B by pathology.



(A) A 3D view of an 11-week-old fetus with thickened nuchal translucency (red arrows). (B) An 11-week-old fetus with thickened nuchal translucency (white arrows).

Obtaining the ultrasound measurement for the fetal nuchal translucency can be difficult and should be performed at a center that has ultrasonographers with additional training and who perform these measurements on a routine basis. The most accurate first-trimester screening Includes both biochemical markers combined with fetal nuchal translucency measurements. In some pregnancies, such as high-order multiples or demise of a twin, biochemical analysis during first trimester is not accurate and only nuchal translucency measurements can be performed.

- **POSITIVE FIRST-TRIMESTER SCREENING:**

If a first-trimester screen shows an increased risk for fetal aneuploidy (also called a "positive" Screening), prenatal diagnosis through chorionic villus sampling or amniocentesis is possible. Both procedures are described in detail later in this module. In addition to the risk for aneuploidy, there are other conditions associated with increased nuchal translucency measurement.

The risk for congenital cardiac defects is increased with measurements of greater than 3.0 mm in fetuses with a normal karyotype. Referral is recommended for a targeted ultrasound and a fetal echocardiogram at about 20 weeks' gestation. Over 200 reported mendelian disorders have been associated with nuchal thickening, including Noonan syndrome, 22q11.2 deletion syndrome (also called velocardiofacial syndrome or DiGeorge syndrome), and some skeletal dysplasias. Genetic testing for some of these conditions may also be available through chorionic villi sampling or amniocentesis.

- **SECOND – TRIMESTER MATERNAL SERUM SCREENING:**

Second-trimester maternal serum screening is performed typically between 15 and 22 weeks' gestation. Triple screen maternal serum analytes are alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and unconjugated estriol (uE3). The addition of dimeric inhibin A (DIA) for a quadruple screen improves the detection rate for Down syndrome. The penta screen is still being validated, but the additional test of invasive trophoblast antigen appears to be helpful. It is important to note that levels of these biochemical markers fluctuate over the course of gestation, but that specific deviations from the norm have been associated with fetal disorders.

Second-trimester maternal serum screening can provide a risk estimate for fetal Down Syndrome and trisomy 18, as well as open neural tube defects. Some centers also incorporate results of a second-trimester ultrasound into risk assessment.

- **NEURAL TUBE DEFECTS (NTDS):**

Neural tube defects (NTDs) are relatively common, with a population incidence of 1 to 2 per 1000 pregnancies. Ninety-five percent of NTDs occur in families with no family history of the condition. Open neural tube defects are a spectrum of birth defects caused by abnormal closure of the neural tube in early pregnancy, and range from spina bifida to anencephaly. The development and closure of the neural tube is normally completed within 28 days after conception, before many women are aware that they are pregnant. It is generally accepted that NTDs result from failure of the neural tube to close, but the embryologic basis of the clinical variation in neural tube defects is poorly understood. The genetic controls of the cellular mechanisms of closure have yet to be determined, although several possible associated genes have been identified in animal models. Neural tube defects may be open or occult (hidden) and maternal serum screening will only detect open neural tube defects. Those defects that are covered with skin will not be detected. These skin-covered lesions will vary in severity, though some may not cause serious clinical manifestations. For example, spina bifida occulta is associated with a defect in only the bony arch of the vertebra. It is usually asymptomatic and is not likely to be detected by maternal serum screening, as there is no

opening in the fetus that would result in an increase of AFP in the maternal serum.

- **SECOND TRIMESTER SCREENING RESULTS:**

	DS	Tri 18	ONTD	SLO	Twins	IUFD
AFP	↓	↓	↑		↑	↓
uE3	↓	↓		↓	↑	↓
hCG	↑	↓			↑	
DIA	↑	↓			↑	

AFp – alpha fetoprotein
uE3 – unconjugated estriol
hCG – human chorionic gonadotropin
DIA – dimeric inhibin A

DS – Down syndrome
Tri 18 – trisomy 18
ONTD – open neural tube defect
SLO – Smith-Lemli-Opitz
IUFD – Intrauterine fetal demise

In this grid is a general guide to results of second-trimester screening. Important associations to remember are that AFP is elevated with fetal open neural tube defects. AFP and unconjugated estriol levels are low and hCG and dimeric inhibin A levels are high with Down syndrome. All levels are low with trisomy 18. With twins, all are typically high. However, a low level in one twin and a high level in the other may "average" out to a normal level, masking the abnormal level of the affected twin.

17. OTHER CAUSES* OF ABNORMAL SCREENING RESULTS:

There are many other causes for abnormal biochemical markers in maternal serum screening. For example, this is a partial list of differential diagnoses for elevated levels of maternal serum AFP and hCG, and decreased estriol levels. Additional prenatal screening and/or testing may detect some of these conditions.

18. ADDITIONAL APPROACHES TO SCREENING:

As discussed previously, there are many different approaches to combining first- and second-trimester screening. Integrated screening combines first- and second-trimester screening, but results are provided only in the second trimester. Sequential screening combines first- and second-trimester screening as well, but results are provided after each step. With contingent screening, first-trimester screening is done, and if there is increased risk, the woman is offered CVS. If she has decreased risk, no additional screening is done. For intermediate risk, second- trimester screening is performed.

Each approach has its benefits and limitations and should be discussed with the patient in detail prior to offering the screen. In addition, depending upon the resources that are locally available, all options may not be accessible.

19. EXPLAINING "POSITIVE" SCREENING RESULTS:

Reporting positive screening results to patients requires a careful and thoughtful explanation. Detailed pretest counseling should help avoid confusion and unnecessary anxiety, as the patients' understanding makes all the difference while waiting for their follow-up appointment.

It is important to choose words with caution and avoid phrases like "positive for Down syndrome." Rather, consider saying, "Increased risk compared to other women your age" and "Further testing is needed to know for sure." Alternatively, offer a risk estimate; convert to a percentage as people interpret risk estimates differently. Genetic counseling to discuss further pregnancy assessment through screening or diagnostic testing may be beneficial.

20. TARGETED (LEVEL II) ULTRASOUND:

A targeted, or level II, ultrasound is done in the mid-to-late second trimester (16-24 weeks) to look for fetal anatomic abnormalities. Although some are proposing earlier anatomic screening ultrasound, the data are not sufficient to confirm this approach. Ultrasound can be used to screen for fetal birth defects and chromosome abnormalities. For example, an atrioventricular canal defect increases the risk for fetal Down syndrome and omphalocele and/or diaphragmatic hernia increase the risk for fetal trisomy 18. Fetal "soft markers" or "soft signs" may also increase the risk for certain fetal conditions. These markers are not considered birth defects; however, some studies have shown that certain markers, such as echogenic bowel or shortened long bones, may be associated with an increased risk for Down syndrome, and choroid plexus cysts with trisomy 18.

21. DIAGNOSTIC TESTING:

When a patient decides to proceed with a diagnostic procedure, the two main options she has are CVS or amniocentesis. Both can be utilized to test for extra or missing fetal chromosomes, gross structural rearrangements (such as translocations), and additional or missing information.

Amniocentesis can also screen for open neural tube defects by analyzing the level of AFP in the amniotic fluid. Additional genetic testing may also be performed through very specific molecular or biochemical testing. Molecular and biochemical testing requires knowing what specific test needs to be ordered, which laboratories will do the testing, and what samples are needed. There is a small risk of pregnancy complications including miscarriage with both these procedures.

22. CHORIONIC VILLUS SAMPLING:

Chorionic villus sampling utilizes either a catheter or a needle to biopsy placental cells that are derived from the same fertilized egg as the fetus. The exact procedure used is dependent on location of the placenta. Ultrasound guidance is used with all CVS procedures. With a transcervical procedure, the catheter is inserted vaginally and passed through the cervix to the placenta and 15-30 mg of tissue are obtained via suction. In a transabdominal approach, a 20- gauge needle is used to pass through abdominal and uterine walls into the placenta. Sampled tissue is examined under the microscope to confirm fetal origin; a second pass may be necessary. Complication rates are based on the assumption of two passes. Women who are Rh negative should receive Rhogam due to the risk of isoimmunization.

23. POSSIBLE COMPLICATIONS OF CVS:

There are, of course, complications with the use of CVS, as with any invasive procedure.

Maternal complications include vaginal spotting or bleeding, uterine cramping, and infection. There is a less than 1% chance of miscarriage associated with the procedure. CVS-associated fetal limb defects were reported when the procedure was performed very early, at 8 to 9 weeks' gestation, but this risk is not increased over the general population risk when the procedure is performed after 10 weeks. There is a 1 to 2% risk of placental mosaicism with CVS procedures. Mosaicism is a discrepancy in the chromosomal makeup of a fetus compared with its placenta.

With **confined placental mosaicism**, the chromosome abnormality is only in the placenta and is not representative of the fetal chromosomal makeup. However, some cases of mosaicism are due to a fetal chromosome abnormality. Follow-up amniocentesis and counseling regarding a specific anomaly is strongly recommended.

24. AMNIOCENTESIS:

During amniocentesis, a small sample of the amniotic fluid that surrounds the fetus is removed. This fluid contains cells that are shed primarily from the fetal skin, bladder, gastrointestinal tract, and amnion. The procedure begins with cleansing of the maternal abdominal skin. Under ultrasound guidance, a 22-gauge needle passed through abdomen and uterine wall and into the amniotic sac. Approximately 15 to 20 mL of amniotic fluid is withdrawn into a syringe.
Additional fluid may be necessary if performing multiple tests. The first few milliliters of fluid are discarded to reduce the risk of maternal cell contamination. Some centers provide local anesthesia, but it is not possible to numb the uterus.

- **POSSIBLE COMPLICATIONS OF AMNIOCENTESIS:**

Maternal complications of amniocentesis include vaginal leakage of amniotic fluid, spotting, uterine cramping and infection. There is up to a 1 in 200 (0.5%) chance for complications resulting in a miscarriage when amniocentesis is performed prior to 24 weeks' gestation; a recent study found risk to be as low as 1 in 1,600. When performed after 24 weeks' gestation there is up to a 1 in 100 (1%) risk of complications resulting in preterm labor. Chorioamnionitis, an intrauterine infection, is also a risk.

- **DIAGNOSTIC TESTING: AMNIOCENTESIS AND CVS:**

Multiple results of testing are available with amniocentesis and CVS. Fetal karyotype takes about 10-14 days and is 99.9% accurate with amniocentesis. There is a 1 to 2% chance of an ambiguous result with CVS, requiring further analysis. With an amniocentesis, detection of open neural tube defects is available within 2-3 days by measurement of amniotic fluid AFP and, if elevated, acetylcholinesterase. It is also important to remember that normal results do not guarantee a healthy baby!

25. INVASIVE TESTING IS AN OPTION:

Not all parents want testing during pregnancy, while some parents want testing to prepare emotionally. It may give them time to grieve for the loss of the expected baby and prepare for a different set of expectations. Medically, they can prepare by considering specialized delivery arrangements if needed, meeting specialists who will care for the baby, or planning for perinatal hospice, if available and needed. Other parents may want put a plan in place for adoption or choose to terminate a pregnancy.

26. PSYCHOLOGICAL ADJUSTMENTS TO PREGNANCY AFTER INFERTILITY:

In addition to physical changes, women face a number of psychological adjustments to pregnancy after infertility.

- **COMMON RESPONSES AND CONCERNS:**

  For many couples, as well as their healthcare providers, a pregnancy after a long struggle with infertility is viewed as a premium pregnancy. This may add medical and psychological stressors. Women may have high levels of anxiety and be excessively vigilant, worrying that the pregnancy may fail. Some may use denial as a coping mechanism and may not invest emotionally in the pregnancy. For some women there is an increased risk of depression and anxiety.

- **MANAGING EXPECTATIONS:**

  To help patients manage expectations, they need validation and emotional support. Prior negative outcomes can make it difficult to imagine a successful pregnancy and birth. Patients may need more frequent medical visits for reassurance.

- It is important to begin refocusing patient education from infertility to pregnancy, providing the patient with anticipatory guidance and information.

- Many women experience a sense of isolation, feeling that they are no longer a part of the infertile world, but not fitting into the fertile world. It is often hard for them to transition to an obstetrical practice and leave the infertility practice that has been so much a part of their lives.

- Many are reluctant to share their news and may delay telling others; some have guilt about their ambivalent feelings.

- The threat of loss with multifetal reduction, miscarriage, perinatal loss, and stillbirth can remain throughout the pregnancy.

- Many women feel they aren't entitled to express complaints about pregnancy discomforts or have negative thoughts or experiences in their pregnancy because of their infertility.

- Parenting after infertility also has challenges. Repetitive negative experiences trying to achieve pregnancy can stifle the ability to anticipate the parenting role.

- Because of the difficulties of infertility, some parents develop a desire for an "idealized child"with unrealistically high expectations for the child and for themselves as parents.

- There may be a tendency for parents to be more concerned and more protective of their children conceived after infertility.

- Medical problems of children, such as prematurity, low birthweight, or long-term developmental or behavioral problems that are more common in children conceived after infertility treatment can increase the difficulties of parenting.

27. EARLY PREGNANCY LOSS:

Early pregnancy loss signifies an unanticipated, physically traumatic event representing the death of a future child and disruption of reproductive plans. It is important to recognize that loss is real at any gestational age, whether a failed fertility cycle, miscarriage, perinatal loss, reduction, or termination. The loss must be validated and considered equally important to the couple experiencing the loss. The emotional impact of early loss can be as severe as a loss later in pregnancy or after the birth of a child.

Pregnancy loss has a different impact on men and women. Women can feel a lack of support, isolation, guilt, feelings of failure and inadequacy, ambivalence, and fear about future pregnancies. Men can feel helpless, experience denial, wish to protect their partner, need to be in control, express feelings of anger more easily than sadness, use work as an escape, or be reluctant to talk about feelings for fear of upsetting their partner. Single parents by choice and same-sex couples may experience infertility and pregnancy loss differently, based on their role expectations as parents.

28. GRIEF COUNSELING:

Grief work is intense and painful for both the patient and caregiver. It is a process with no shortcuts, and it is important to acknowledge that all losses are significant. Talking frequently and in detail about the loss is important. There may be profound feelings of guilt and inadequacy. Nurses can help patients by normalizing the grief process and being aware of how different cultures grieve.

Counseling can include helping couples create rituals for expression of grief, such as planting a tree or lighting a candle to remember the loss. Patients may need referrals for support and Resources. It is important to acknowledge that they will get through the experience, not over it.

29. REFERRAL FOR OBSTETRIC CARE:

Referral to obstetric care occurs after a viable intrauterine pregnancy has been confirmed by ultrasound, generally in late first trimester. For some patients, particularly those with a high- order multiple gestation, referral to a maternal-fetal medicine (MFM) specialist may be indicated. Other patients at risk who may benefit from an MFM referral include patients with medical or surgical disorders, and healthy women at high risk of pregnancy complications. Once a patient is ready for transfer to obstetric care, the content of what is to be included in records should be discussed with the patient. There may be confidentiality issues related to donor gametes or the use of ART therapy itself.

30. PATIENT RESOURCES:

There are multiple resources available for patients including the ASRM, Resolve, ACOG and AIUM.

- **SUMMARY:** In summary, Early diagnosis, and appropriate assessment and management are important for pregnancies after infertility. Patient education, counseling and anticipatory guidance are essential. These pregnancies have increased risks for ectopic pregnancy and miscarriage. All multiple gestations, including twins, have substantial maternal, fetal and perinatal risks. There are many options for first- and second-trimester aneuploidy screening and diagnosis. Women face a number of psychological adjustments to pregnancy after infertility.

WISH YOU BEST OF LUCK FOR

MODULE -12- QUIZ