### Fertility Preservation and Care in Women Diagnosed with Cancer

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**Ovarian reserve:** girls born with ≈1 million follicles, and number decreases throughout lifetime; primordial, preantral, and antral follicles vulnerable to radiation and chemotherapy; treatment for cancer may lead to difficulty conceiving and early ovarian failure (OF); OF characterized by amenorrhea that begins during therapy and does not resolve; in some patients, menses resume but loss of oocytes results in risk for infertility and early OF, and for delayed onset of premature ovarian failure (POF; early menopause defined as occurring <40 yr of age)

**Chemotherapy:** type and dose of chemotherapy affect risk for fertility impairment, as do location and dose of radiation and age of patient; chemotherapeutic agents classified as high, moderate, or low risk, but agents most often used in combination; after treatment with adriamycin plus cyclophosphamide for breast cancer, risk for OF reported 0% if patient <30 yr of age, but likely high if >40 yr of age; taxanes permit use of lower dose of cyclophosphamide, but 4-fold increase in OF seen with use of taxanes

**Pelvic radiation:** risk of OF depends on radiation dose and age of patient; effective sterilizing dose (ESD) defined as dose that induces acute OF in 97.5%; ESD 20.3 Gy at birth, then decreases with age; with total body irradiation, risk for OF high

**Advising patients:** impaired fertility difficult to predict; data inadequate because studies use different definitions and often report OF, not infertility; however, patient may be provided with approximate risks for OF and infertility; patients with cancer often asked to wait 2 yr after treatment to conceive; pregnancy contraindicated in women receiving tamoxifen or aromatase inhibitors, and standard duration of therapy may exceed reproductive life

**Options before treatment:** informed consent for cancer therapy should address possibility of infertility; interested patients should be referred to reproductive specialist early; cryopreservation of embryos and oocytes standard of care; other methods investigational

**Cryopreservation:** gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone) given on day 2 of menses; when follicles ≈14 mm, gonadotropin-releasing hormone (GnRH) antagonist used to prevent premature ovulation; ovulation triggered with human chorionic gonadotropin or leuprolide (Lupron); leuprolide decreases risk for ovarian hyperstimulation and expedites return of ovaries to normal size and shape, allowing cancer treatment to start earlier; eggs retrieved, guided by transvaginal ultrasonography (TVUS), under sedation; process requires 10 to 14 days

**Levels of estradiol:** peak levels of estradiol 200 to 600 pg/mL in natural cycle but 2 to 3 times higher when multiple follicles stimulated; safe peak level of estradiol in patients with breast cancer unknown; to increase safety, tamoxifen or aromatase inhibitors such as letrozole given during ovarian stimulation to suppress production of estrogen or block estrogen at level of breast tissue; study of 42 patients suggested that when tamoxifen or letrozole given, ovarian stimulation does not increase rate of recurrence of breast cancer

**Rates of pregnancy:** frozen embryos — less likely than fresh embryos to result in pregnancy; in young patients, pregnancy rate per cycle 60% with fresh and 40% with frozen embryos; in women >40 yr of age, pregnancy rate per cycle 30% with fresh and 20% with frozen embryos; frozen eggs — review found rates of pregnancy same as when frozen embryos used

**Timing:** traditional approach — initial consultation includes assessment of antinullianer hormone (AMH) and TVUS; ovarian stimulation initiated in early follicular phase; process requires 2 to 6 wk depending on phase of menstrual cycle; random start — refers to starting ovarian stimulation at random time of cycle; in retrospective study, random start required more days of stimulation than conventional start (11 vs 9 days), but no differences seen in outcome of cycle or number of eggs or embryos; with random start, process may be completed in 2 to 2.5 wk without compromising outcome; cryopreservation done before treatment because chemotherapy may decrease number of retrievable eggs; possibility that exposed oocytes could yield abnormal offspring

**Experimental interventions:** cryopreservation of ovarian tissue — entails laparoscopic removal of entire ovary or part of ovary; option for prepubertal as well as postpubertal girls; may be initiated after start of chemotherapy; few live births reported; reimplantation might restore hormonal function, but might also reintroduce malignant cells; procedure reserved for patients for whom time does not permit ovarian stimulation and those at high risk for OF after treatment; GnRH analogues — goal to create pseudopenubertal state and reduce damage to immature eggs; some studies show no benefit; 281 premenopausal

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### Educational Objectives

The goals of this program are to improve diagnosis and treatment of abnormal placentation and infertility in women with cancer. After hearing and assimilating this program, the clinician will be better able to:

1. Discuss options for preservation of fertility with a patient undergoing treatment for cancer.
2. Offer a prognosis for a patient previously treated for cancer who seeks consultation regarding her fertility.
3. Lead a multidisciplinary team in planning delivery for a patient with placenta accreta.
4. Diagnose abnormal placentation.
5. Discuss the controversial role of ureteral stents in patients with abnormal placentation.

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### Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, members of the faculty and planning committee reported nothing to disclose. In her lecture, Dr. Chung presents information related to the off-label or investigational use of a therapy, product, or device. In her lecture, Dr. Esakoff presents information related to the off-label or investigational use of a therapy, product, or device.
women with breast cancer randomized to chemotherapy alone vs chemotherapy plus triptorelin every 4 wk; menopause significantly less likely in patients receiving triptorelin (25% vs 9%); leuprolide may be recommended even when embryos or eggs frozen; agent unlikely to cause harm and may help

Options after treatment: return of menses does not guarantee normal fertility; ovarian reserve testing recommended (FSH and estradiol on day 3 of cycle, ovarian volume and antral follicle count, and AMH); tests most helpful when abnormal; when tests normal, age best predictor of outcome; patients should attempt pregnancy as early as feasible; predictive values of these tests not validated in patients with cancer, but AMH probably good marker of reproductive longevity and ovarian function

Retrieval of eggs: ideally performed ≥6 mo after chemotherapy, when primordial follicles unaffected by chemotherapy reach antral stage; indicated for patients with risk or evidence of diminished ovarian reserve or impending POF

Indicators of ovarian failure: FSH >20 mIU/mL on 2 occasions, undetectable AMH, no follicles on TVUS, and amenorrhea lasting >12 mo; options for such patients donated eggs or embryos or adoption

Surgical causes of infertility: hysterectomy — if ovaries intact, oocytes may be removed and implanted in gestational carrier; oophoropexy — for patients who have undergone oophoropexy before radiation (ovaries placed above anterior superior iliac spine or higher), abdominal retrieval of eggs or laparoscopic approach required; BRCA mutations — carriers advised to have bilateral salpingo-oophorectomy, typically by 40 yr of age; such women may undergo several cycles of treatment to freeze numerous eggs; trachelectomy — 60% to 80% of women can become pregnant after trachelectomy, but 10% to 15% have cervical stenosis

Management of Abnormal Placation

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Epidemiology: incidence of placenta accreta rising, likely because of increase in cesarean deliveries; definitions — type of abnormal placentation depends on depth of invasion of trophoblast; accreta invades endometrium but not Nitabuch layer, increta invades myometrium, and percreta invades beyond serosa; incidence — placenta accreta occurs in 1 in 533 pregnancies, but accreta accounts for 10% of obstetric mortality and most cesarean hysterectomies; risk factors — previous uterine surgery, placenta previa, advanced maternal age, and parity ≥3; among patients without placenta previa in index pregnancy, incidence of accreta low in those with <5 previous cesarean deliveries and 4.5% in those with ≥5 cesareans; however, in patients with placenta previa, incidence of accreta 10% if 1 previous cesarean delivery, 40% if 2 cesareans, and 60% if 3 cesareans; accreta associated with risk for cystotomy, ureteral injury, pulmonary embolism, need for ventilator, and admission to intensive care unit (ICU)

Diagnosis: ultrasonography — primary method of prenatal diagnosis; normal hypeoechoic boundary between placenta and bladder not seen in patients with accreta; however, sensitivity and specificity of this finding low (7% and 6%); other signs presence of lacunae (100% sensitivity after 15 wk and 97% to 100% specificity), hypervascularity on color Doppler (84%-100% sensitive), and myometrial thickness <1 mm or loss of visualization of myometrium (21% to 91% specific); data on accuracy of 3-dimensional ultrasonography mixed; magnetic resonance imaging — controversial; may not be superior to ultrasonography, but may be useful when percreta suspected, accreta in unusual location, or ultrasonography negative but clinical suspicion high; overall, ultrasonography associated with sensitivity of 77% to 93%, specificity of ≥90%, and high negative predictive value

Proposed placenta accreta index (PAI): calculated using point values assigned to lacunae, number of cesarean deliveries, location of placenta, bridging vessels, and hypervascularity; if PAI >1, risk for placental invasion 10%, and if PAI >8, risk 96%  

Antepartum management: principles — patients should receive antenatal iron supplementation, and delivery should occur at facility equipped to manage massive transfusion; antenatal testing not indicated because accreta not associated with intrauterine growth restriction or fetal death; study — evaluated multidisciplinary program including admission at 30 to 34 wk, planned cesarean hysterectomy at 34 to 35 wk, preoperative consultation with pulmonary critical care, urology, blood bank, anesthesia, nursing, neonatal ICU, prospective planning for maternal and neonatal care, and coordination of care by maternal-fetal medicine (MFM); compared with patients treated before program started, multidisciplinary care associated with less blood loss and fewer emergent deliveries; although multidisciplinary group delivered at earlier gestational age, neonatal outcomes similar

Timing of delivery: planned delivery associated with less blood loss and fewer complications than emergent delivery; decision analysis comparing 9 strategies found that delivery at 34 wk optimal; delivery should not be delayed to achieve fetal lung maturity; 27% of emergent deliveries avoided by doing planned delivery by 34 wk; experts recommend dorsal lithotomy position to permit assessment of vaginal bleeding and easier surgical access; patient should be padded and positioned carefully; type of skin incision based on body habitus and surgical history

Surgical management: gold standard planned cesarean hysterectomy; if conservative management elected, placenta should be left in situ; attempts at removal may cause bleeding; total or subtotal hysterectomy permissible

Conservative management: entire placenta may be left in situ, or some tissue may be left and uterine artery embolization (UAE) performed; adjuvant medical therapy includes methotrexate, GnRH analogues, mifepristone, and misoprostol

Outcomes: rates of treatment failure 15% after conservative therapy alone (leaving entire placenta in situ), 23% when methotrexate given, and 25% when UAE performed; overall, 80% had successful outcomes; complications fever in one-third, endometritis in 18%, and disseminated intravascular coagulation (DIC) in 6%; recurrence rate of accreta 60% in another study. 92% of patients required additional therapy (medical, surgical, or UAE) after conservative management, but overall success rate =80%; treatment failure associated with fever in 15% and DIC in 12%; in retrospective study of 167 women, conservative treatment successful in 80% and others required hysterectomy; 6% had severe maternal morbidity such as sepsis, peritonitis, vesicouterine fistula, or necrosis of uterus; spontaneous reabsorption of placenta observed in 75%; 25% needed hysteroscopic resection or curettage; median time to resorption 13.5 wk, but could take up to 60 wk; summary — conservative management indicated only if blood loss minimal, patient wants to preserve fertility, adequate support available to manage treatment failures, and patient willing to continue surveillance until placenta resorbed

Other techniques: occlusion of internal iliac arteries after delivery of fetus may decrease morbidity; accomplished with placement of balloon catheters through femorals immediately before cesarean delivery; alternatively, interventional radiologist may obtain access peroperatively and do UAE after fetus delivered; literature inconsistent; some studies report less blood loss, fewer transfusions, and shorter duration of surgery, but others show increase in complications including thrombosis, dissection, hematoma, abcess, necrosis, and pseudoaneurysm;
alternatively, UAE after completion of hysterectomy associated with success rate of 60% to 70%; fewer most common complication; outcomes after UAE include return of menses in 83% and pregnancy in 15%; 18% have abnormal placenta.

Guidelines: American Congress of Obstetricians and Gynecologists states cathether occlusion or UAE may be used, but evidence insufficient to make firm recommendation for such therapies.

Experimental interventions: include argon beam coagulation of remaining placental tissue, circumferential sutures on uterine serosa around bleeding area, and partial excision of uterine wall with repair of defect.

Uterine stents: controversial; theoretical concerns urinary tract injury, stent migration, deformity, and reflex anuria; in review of 3000 gynecologic procedures, stents did not decrease incidence of injury to ureter, potential benefits immediate recognition of ureteral injury and less blood loss if procedure shortened; however, stents rigid and may make ureter difficult to push away or alter location of ureter; iatrogenic injury occurs in 1% of insertions.

Anesthetic management: experts recommend regional anesthesia for delivery, and half suggest induction of general anesthesia for hysterectomy.

Hematologic management: massive transfusion protocol mainstay of treatment; early administration of fresh frozen plasma, platelets, and packed red blood cells (PRBCs) in 1:1:1 ratio beneficial; limited early and aggressive use of crystalloids and colloids recommended; goal to prevent DIC; autologous donation not recommended except in alloimmunized patients whose blood may be difficult to crossmatch; factor VII reserved for uncontrollable hemorrhage because it may cause thrombosis; use of cell salvage machine (cell saver) — reasonable; severe hypotension occasionally reported; with current filtering technology, amniotic fluid embolism not concern, but consider risk for alloimmunization from fetal red cells.

Other studies: scheduled delivery probably best approach; attempting to remove placenta invades morbidity; ureteral stents do not change incidence of ureteral injury but reduce incidence of composite outcome of admission to ICU for ≥24 hr, transfusion of ≥4 units of PRBCs, coagulopathy, ureteral injury, and early reoperation; in survey of MFM in the United States, most believed hysterectomy only option; 32% had tried conservative management, one-third had used ureteral stents, and one-third had used balloon catheters.

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Suggested Reading


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Estimated time to complete the educational process:

Audio Digest Educational Objectives on page 1

Take pretest 5 minutes

Listen to audio program 10 minutes

Review written summary and suggested readings 60 minutes

Take posttest 35 minutes

Take posttest 10 minutes
1. The effective sterilizing dose of radiation is the dose that induces:
   (A) Premature ovarian failure in 50% of patients
   (B) Acute ovarian failure in 97.5% of patients
   (C) Impairment of fertility resulting in need for assisted reproduction
   (D) Level of antimullerian hormone <1.0 ng/mL

2. Which of the following practices is thought to increase the safety of ovarian stimulation in patients with breast cancer?
   (A) Stimulating follicles in the early follicular phase
   (B) Stimulating follicles using a random start
   (C) Using gonadotropin-releasing hormone (GnRH) to trigger ovulation
   (D) Giving letrozole during ovarian stimulation

3. When fresh embryos are used, what is the rate of pregnancy per cycle in patients ≥40 yr of age?
   (A) 10%  (B) 20%  (C) 30%  (D) 40%

4. Which of the following techniques for preserving fertility in patients about to undergo treatment for cancer are considered experimental?
   1. Use of GnRH analogue to create pseudopubertal state
   2. Cryopreservation of eggs
   3. Cryopreservation of embryos
   4. Cryopreservation of ovarian tissue
   (A) 1,2  (B) 1,4  (C) 2,3  (D) 2,4

5. Evaluation of ovarian reserve includes all the following tests, EXCEPT:
   (A) Luteinizing hormone
   (B) Estradiol
   (C) Ovarian volume
   (D) Antral follicle count

6. Approximately what percentage of women are able to become pregnant after tracheectomy?
   (A) 10%  (B) 40%  (C) 70%  (D) Not known

7. Placenta accreta is associated with increased risk for all the following, EXCEPT:
   (A) Fetal death
   (B) Ureteral injury
   (C) Pulmonary embolism
   (D) Cystotomy

8. Which of the following is the most reliable sign of placental accreta?
   (A) Loss of hypoechoic boundary between placenta and bladder
   (B) Lacunae in placenta
   (C) Hypervascularity on color Doppler
   (D) Myometrial thickness <1 mm

9. A review of 3000 gynecologic procedures showed that ureteral stents did not decrease the incidence of injury to the ureter.
   (A) True  (B) False

10. Which of the following methods for surgical management of abnormal placentation is standard care?
    (A) Autologous donation
    (B) Factor VII
    (C) Cell salvage machine (cell saver)
    (D) Massive transfusion protocol

Answers to Audio Digest Obstetrics/Gynecology Volume 62, Issue 16: 1-D, 2-A, 3-B, 4-D, 5-D, 6-C, 7-A, 8-B, 9-B, 10-A