What's new in obstetrics and gynecology

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The following represent additions to UpToDate from the past six months that were considered by the editors and authors to be of particular interest. The most recent What's New entries are at the top of each subsection.

PRENATAL OBSTETRICS

Revised criteria for pregnancy morbidity in antiphospholipid antibody syndrome (September 2023)

Obstetric antiphospholipid syndrome (APS) is sometimes used to describe patients with pregnancy morbidity, a positive test for antiphospholipid antibodies within three years of the pregnancy morbidity, and findings not attributable to another APS domain. The American College of Rheumatology and European Alliance of Associations for Rheumatology have recently updated the classification criteria for pregnancy morbidity in APS [1]. Changes included more explicit criteria for gestational age and placental insufficiency (table 1). (See "Antiphospholipid syndrome: Obstetric implications and management in pregnancy", section on 'Adverse pregnancy outcomes defining APS'.)

Respectful, equitable, supportive maternity care (August 2023)

Respectful, equitable, and supportive maternity care is a basic human right that is not always achieved. In a recent survey of mothers in the United States, 90 percent of respondents were satisfied with the care they received during pregnancy, but 20 percent overall reported mistreatment, including requests for help refused or not responded to, physical privacy violated, and verbal abuse [2]. Approximately 30 percent of all respondents and 40 percent of

Black, Hispanic, and multiracial respondents reported discrimination during maternity care. Multiple organizations have developed strategies that encourage a culture of respectful, equitable, and supportive maternity care. These strategies can be useful to providers, patients, and health care systems. (See "Prenatal care: Second and third trimesters", section on 'Respectful, equitable, and supportive maternity care'.)

Pessary placement for short cervical length does not reduce preterm birth (July 2023)

Previous meta-analyses of randomized trials comparing use of a cervical pessary versus no pessary (with or without vaginal progesterone) for asymptomatic patients at high risk for preterm birth (PTB) have found that a pessary did not result in a statistically significant reduction in spontaneous PTB; however, the trials had many limitations. In a recent well-designed randomized trial of over 500 patients with cervical length <20 mm, placement of an Arabin pessary at 16 to 23 weeks of gestation also demonstrated no benefit over usual care; the rate of PTB or fetal death <37 weeks was nearly the same for both groups [3]. Strengths of this trial were inclusion of a very high-risk population, exclusion of patients with a history of PTB, and routine use of vaginal progesterone in both groups. These findings further support our practice of not using a pessary to reduce PTB in patients with a short cervix. (See "Cervical insufficiency", section on 'Pessary'.)

Impact of warning signs about cannabis use (June 2023)

The rising prevalence of cannabis use has raised questions regarding best methods of public education about potential risks of use during pregnancy. In a study that surveyed pregnant and recently pregnant women residing in states with legal recreational cannabis, point-of-sale warning signs about risks of cannabis use in pregnancy were not associated with reduced pregnancy use [4]. Although 42 percent of pregnant users agreed that warning signs give important information, 32 percent thought they scare people too much, only 30 percent trusted the information in the signs, and only 26 percent believed signs stop people from using cannabis during pregnancy. This study highlights the need for obstetric providers to provide education about potential risks of cannabis use during pregnancy. (See "Substance use during pregnancy: Overview of selected drugs", section on 'Perceived lack of risk'.)

Early pregnancy diagnosis of gestational diabetes (June 2023)

The benefit of treating gestational diabetes (table 2) diagnosed before 20 weeks of gestation has not been established. In a trial comparing immediate treatment of such patients versus retesting at 24 to 28 weeks and starting treatment at that time if diagnostic criteria are met, immediate treatment did not reduce rates of large-for-gestational age infants or pregnancy-related hypertension [5]. These findings have prompted stakeholders to review their early

pregnancy diabetes screening protocols. Treatment of overt diabetes (table 3) diagnosed in early pregnancy is still recommended. (See "Gestational diabetes mellitus: Screening, diagnosis, and prevention", section on 'Management of patients after an early pregnancy GTT'.)

Anticoagulation does not prevent recurrent pregnancy loss in patients with inherited thrombophilia (June 2023)

Increasing data support the lack of benefit of anticoagulation for improving live birth rates among patients with an inherited thrombophilia who have experienced recurrent pregnancy loss. In one of the largest randomized trials, which included 326 such patients, treatment with low molecular weight heparin (LMWH) throughout pregnancy did not improve live birth, miscarriage, preterm birth, or small for gestational age birth rates compared with standard care [6]. In pregnant patients with an inherited thrombophilia, we use LMWH to prevent venous thromboembolism, as described in the tables (table 4A-B). (See "Inherited thrombophilias in pregnancy", section on 'Anticoagulation'.)

Disease relapse among pregnant SLE patients (June 2023)

Patients with systemic lupus erythematosus (SLE) are known to have a higher risk of relapse during pregnancy. In a multivariate analysis of pregnancies in patients with SLE, patients with a low C4 prior to conception had an increased risk of relapse during pregnancy [7]. Moreover, patients who experienced flare during pregnancy were more likely to have a low C4 during each trimester compared with patients who did not flare. Pregnant SLE patients with a low C4 may benefit from closer disease monitoring throughout pregnancy. (See "Pregnancy in women with systemic lupus erythematosus", section on 'Exacerbation of SLE'.)

New guidelines on pregnancy/postpartum mental health screening (May 2023)

Updated guidelines from the American College of Obstetricians and Gynecologists now suggest screening patients for depression and anxiety at the initial prenatal visit, later in pregnancy, and at postpartum visits using a standardized, validated tool [8]. Updated guidelines on treatment and management of mental health conditions include screening for bipolar disorder before initiating pharmacotherapy for anxiety or depression, if not previously done [9]. Perinatal Psychiatry Access Programs are a useful resource for obstetric providers managing these patients. (See "Prenatal care: Initial assessment", section on 'History' and "Overview of the postpartum period: Normal physiology and routine maternal care", section on 'Screening'.)

Obstetric outcomes of transgender men (May 2023)

Transgender men are capable of pregnancy, but their obstetric outcomes have not been well studied. A United States database study comparing birth outcomes of nearly 2000 transgender men with 2.7 million cisgender people reported similar rates of severe morbidity and preterm birth for both groups [10]. Transgender men experienced lower rates of cesarean birth despite an overall increased prevalence of chronic medical conditions, anxiety, and depression. While study limitations included potential gender misclassification and a low frequency of severe morbidity, we discuss these reassuring findings with transgender men desiring or experiencing pregnancy. (See "Sexual and gender minority women (lesbian, gay, bisexual, transgender, plus): Medical and reproductive care", section on 'Transgender individuals'.)

Cerclage placement at 24 to 27 weeks of gestation (May 2023)

Cerclage placement at 24 to 28 weeks of gestation is controversial because of concerns that efficacy has not been proven and procedure-related complications may lead to an extremely preterm birth (PTB). In a meta-analysis of individual patient-level data from four randomized trials of cerclage versus no cerclage in 131 singleton pregnancies at 24+0/7 to 26+6/7 weeks of gestation, cerclage did not result in statistically significant reductions in PTB <37, 34, 32, or 28 weeks nor improvement in any neonatal outcome [11]. PTB <37 weeks was not reduced even in subgroups with cervical length ≤15 mm or ≤10 mm. However, confidence intervals were wide, and modest benefits or harms cannot be excluded. In the absence of reassuring data of efficacy and safety, we do not perform cerclage at ≥24 weeks of gestation. (See "Transvaginal cervical cerclage", section on 'Upper and lower gestational age thresholds for cerclage placement'.)

Biomarker test approved for predicting preeclampsia progression (May 2023)

In stable patients with a hypertensive disorder of pregnancy, it is difficult to predict when severe features of preeclampsia (sFP) will develop. Assessment of the antiangiogenic factor, soluble fms-like tyrosine kinase 1 (sFlt-1), and the proangiogenic factor, placental growth factor (PlGF), in maternal blood may be useful. In the PRAECIS study of hospitalized patients with a hypertensive disorder of pregnancy between 23+0 and 34+6 weeks of gestation, those with sFlt-1:PlGF below the threshold had <5 percent chance of developing sFP within two weeks, while those above the threshold had a 65 percent chance of developing sFP [12]. Based on these findings, in May 2023, the US Food and Drug Administration approved use of the sFlt-1:PlGF test for pregnant patients hospitalized for a hypertensive disorder of pregnancy [13]. Clinicians may find use of this test along with other laboratory tests and clinical assessments helpful for managing these patients. (See "Preeclampsia: Antepartum management and timing of delivery", section on 'Inpatient versus outpatient care'.)

Caffeine consumption and congenital anomalies (May 2023)

The safety of caffeine consumption during pregnancy is an ongoing concern. An update of the 1997-2011 US National Birth Defects Study compared children born with versus without congenital anomalies stratified by maternal self-reported pre- and early pregnancy caffeine intake and found associations with 10 congenital anomalies [14]. However, causality is unlikely given the lack of dose-response relationships, small effect size (odds ratios 1.2 to 1.7), residual confounding, retrospective subjective ascertainment of caffeine consumption, likelihood of chance due to the large number of estimates, and other study limitations. We continue to suggest that individuals who are attempting to conceive or pregnant limit caffeine consumption to less than 200 to 300 mg per day until more conclusive data are available. (See "Caffeine: Effects on reproductive outcomes in females", section on 'Congenital anomalies'.)

Interruption of endocrine therapy for an attempt at pregnancy after breast cancer (May 2023)

There are few data informing the risks of interrupting adjuvant endocrine therapy for breast cancer survivors desiring pregnancy. In a study in 516 patients with early breast cancer who had received adjuvant endocrine therapy for 18 to 30 months and desired pregnancy, endocrine therapy was interrupted upon enrollment, and pregnancy occurred in 74 percent [15]. The three-year rate of breast cancer events was 8.9 percent, which was similar to the rate in an external control group who met study entry criteria aside from desire for pregnancy and treatment interruption (9.2 percent). These data suggest that endocrine therapy interruption for pregnancy does not increase short-term risks of breast cancer recurrence, but longer-term data are required. We typically advise women to wait for at least two years before attempting pregnancy to ensure that the patient does not have early cancer recurrence prior to a pregnancy attempt. (See "Approach to the patient following treatment for breast cancer", section on 'Fertility and pregnancy after breast cancer'.)

Vitamin B12 supplementation does not reduce preterm birth (April 2023)

Cohort studies have reported that lower maternal vitamin B12 levels (particularly gross deficiency) are associated with a higher risk of preterm birth, suggesting that supplementation may improve pregnancy outcome. However, in a placebo-controlled randomized trial of vitamin B12 supplementation during pregnancy conducted in Nepal in which most participants were at least marginally vitamin B12 deficient, supplementation did not improve gestational age at birth or birth weight [16]. For individuals with vitamin B12 deficiency, which is uncommon in the United States, vitamin B12 supplementation is indicated for maternal health. It is administered parenterally if malabsorption is the cause and orally to those with normal absorption. (See "Nutrition in pregnancy: Dietary requirements and supplements", section on 'Vitamin B12'.)

Respiratory syncytial virus vaccination in pregnancy (April 2023)

Respiratory syncytial virus (RSV) is a major cause of morbidity and mortality in infants. In a phase 3 placebo-controlled randomized trial including almost 7000 pregnant people between 24 and 36 weeks of gestation, a single intramuscular injection of RSV prefusion F protein-based vaccine reduced the rate of severe RSV-associated lower respiratory tract illness in infants up to 180 days after birth [17]. The rate of nonsevere RSV-associated illness also trended lower. Rates of preterm birth trended higher in the vaccinated group, but this was not statistically significant. These data suggest effective passive immunity in infants. In August 2023, the US Food and Drug Administration approved the nonadjuvanted recombinant RSV vaccine for pregnant individuals between 32 and 36 weeks of gestation [18]. Recommendations from the United States Centers Disease Control and Prevention and other expert organizations are pending. (See "Immunizations during pregnancy", section on 'Vaccines under investigation'.)

FDA withdraws approval for Makena (April 2023)

In 2002, the US Food and Drug Administration (FDA) approved use of Makena (generic name hydroxyprogesterone caproate) during pregnancy for prevention of recurrent spontaneous preterm birth (sPTB) based on data from a randomized trial, but required a postmarketing trial for confirmation of benefit. In 2023, additional analysis of data from these two trials and other data led the FDA to withdraw its approval of Makena for preventing recurrent sPTB [19]. Pregnant people currently taking Makena may continue or discontinue treatment; the FDA did not identify any harms for either approach. However, medication supply may be limited. Vaginal progesterone does not appear to be an effective alternative for prevention of recurrent PTB; therefore, no pharmacologic prophylaxis is available for this purpose. (See "Progesterone supplementation to reduce the risk of spontaneous preterm labor and birth", section on 'Singleton pregnancy with prior preterm birth'.)

Malaria prevention regimens and pregnancy outcomes in East Africa (March 2023)

Intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP) is important for reducing malaria-associated adverse birth outcomes, but dihydroartemisinin-piperaquine (DP) is a promising alternative in areas with SP resistance. A randomized trial of nearly 4700 pregnant women without human immunodeficiency virus (HIV) infection in East Africa randomly assigned participants to receive IPTp with: SP alone, DP alone, or DP with azithromycin [20]. Compared with SP alone, DP resulted in a 41 percent reduction in clinical malaria but a higher composite rate of adverse pregnancy outcomes (low birth weight, small for gestational age, preterm birth, death: 28 versus 23 percent). Thus, while DP-IPTp may have superior antimalarial effects in areas with SP resistance, SP-IPTp may have other benefits on

pregnancy outcomes. Further study of malaria prevention tools in areas with SP resistance is needed. (See "Malaria in pregnancy: Prevention and treatment", section on 'Intermittent preventive treatment in pregnancy (IPTp)'.)

INTRAPARTUM AND POSTPARTUM OBSTETRICS

Intravenous iron during pregnancy (May 2023)

Oral iron is generally used to treat iron deficiency in pregnancy, especially during the first trimester. However, intravenous (IV) iron may be indicated in some cases and has the advantage of providing the entire dose in a single infusion. In a new open-label trial from Malawi that randomly assigned 862 pregnant individuals at a median gestational age of 22 weeks with hemoglobin <10 g/dL to receive IV or oral iron, the IV iron group had a lower incidence of iron deficiency at all time points and a lower incidence of anemia that reached statistical significance at some time points [21]. IV iron is especially useful for severe anemia and later in pregnancy when rapid repletion is needed. (See "Anemia in pregnancy", section on 'Oral versus IV iron'.)

Multicomponent intervention for postpartum hemorrhage (May 2023)

Postpartum hemorrhage (PPH) is a major cause of maternal morbidity and mortality globally. In a randomized trial comparing a multicomponent intervention for PPH versus usual care in nearly 100,000 vaginal births at secondary-level hospitals across Africa, using a calibrated blood-collection drape and a bundle of first-line treatments (eg, uterine massage, uterotonic medications, tranexamic acid) reduced the composite outcome (blood loss ≥1000 mL, laparotomy for bleeding, maternal death from bleeding) by 60 percent (1.6 versus 4.3 percent) [22]. The efficacy of the intervention likely derived from improved detection of PPH coupled with consistent implementation of the evidence-based treatment bundle. Although the trial was conducted in low- and middle-income countries, a similar approach has been suggested for high-income countries. (See "Overview of postpartum hemorrhage", section on 'Early recognition, assessment, and intervention'.)

Family well-being after gestational carrier pregnancy (April 2023)

Data on child and family psychological well-being after gestational carrier pregnancy has been limited to studies with short-term follow-up. Now, a longitudinal study that administered standardized interviews and questionnaires to 65 mothers and 20-year-old children conceived with assisted reproductive technology (ART), including 22 with gestational carrier pregnancy, reported similar outcomes in young adult psychological adjustment, maternal well-being

(measured by anxiety and depression), and couple relationship quality for the ART and 52 unassisted conception groups [23]. This study provides the longest psychological follow-up data of ART families and shows that their well-being, including those who used a gestational carrier, appears to be at least as good as natural conception families. (See "Gestational carrier pregnancy", section on 'Psychological'.)

Race-based differences in screening for substance use in pregnancy (April 2023)

Substance use disorders are an underdiagnosed problem with significant medical implications during pregnancy. In a study that used logistic regression models including race and history of substance use and adjusting for age and other factors, Black patients with a history of substance use had a higher predicted probability of undergoing urine toxicology testing at delivery than comparable White patients, but White patients had a higher predicted probability of a positive test result [24]. This study highlights the need for universal screening of pregnant people for substance use to avoid differential testing for a problem that is known to impact patients of all ages, races/ethnicities, and socioeconomic demographics. (See "Substance use during pregnancy: Screening and prenatal care", section on 'Concerns for bias'.)

Prophylactic tranexamic acid at cesarean birth (April 2023)

Administration of tranexamic acid to patients having a postpartum hemorrhage reduces mortality due to bleeding, but a benefit from routine prophylactic administration at cesarean is uncertain. In a randomized trial including 11,000 patients undergoing cesarean birth at 31 hospitals, administration of tranexamic acid immediately after umbilical cord clamping slightly reduced rates of "maternal death or transfusion" and "intraoperative blood loss >1 L" compared with placebo, but the reductions were not statistically significant [25]. The tranexamic acid group was less likely to need intervention in response to bleeding complications and had a slightly smaller decrease in hemoglobin levels. One UpToDate author administers prophylactic tranexamic acid before making the skin incision for cesarean, as this timing was most effective in a recent meta-analysis [26]. (See "Management of the third stage of labor: Prophylactic pharmacotherapy to minimize hemorrhage", section on 'After cesarean birth'.)

Hemolytic disease of the fetus and newborn due to anti-M (April 2023)

Hemolytic disease of the fetus and newborn (HDFN) due to maternal alloantibodies against the M antigen (anti-M) is usually mild, but severe HDFN can occur when the alloantibody is a high-titer IgG (or a mixture of IgM and IgG) that is active at 37°C. In a new series of 17 infants with HDFN due to anti-M, fetal or neonatal anemia was severe enough in 14 cases to warrant transfusion, even when maternal antibody titers were higher at 4°C than at 37°C [27]. The risk of low birthweight and premature birth was increased relative to infants with HDFN caused by

antibodies against RhD and ABO antigens. This series is a reminder that severe fetal anemia can complicate pregnancies with anti-M. (See "Management of non-RhD red blood cell alloantibodies during pregnancy", section on 'MNS'.)

Preventing postpartum overdose (April 2023)

Overdose is a leading cause of pregnancy-related deaths in the year following delivery. In a population-based study of individuals with Medicaid insurance in the United States (2006 to 2013), those with opioid use disorder (OUD) had a high incidence of opioid overdose death compared with the general obstetric population (118 versus 5 per 100,000 deliveries); their all-cause postpartum death rate was also high (316 versus 51 per 100,000 deliveries) [28]. However, postpartum use of medication for OUD (MOUD) was associated with a 60 percent reduction in the odds of opioid overdose death. We follow patients with OUD closely and continue MOUD postpartum to support retention in treatment of OUD and prevent return to use. (See "Opioid use disorder: Overview of treatment during pregnancy", section on 'Continue MOUD'.)

Ventilatory support of critically ill pregnant patients with COVID-19 (March 2023)

Limited data are available in pregnant females who are critically ill with COVID-19. In a cohort study of 91 such patients, lung mechanics and ventilatory parameters during advanced respiratory support were similar to nonpregnant patients with COVID-19 [29]. Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score was the only risk factor for invasive mechanical ventilation. Fetal delivery was induced in nearly two-thirds of patients and mainly for maternal reasons. Delivery did not improve ventilatory parameters other than the arterial oxygen tension to fraction of inspired oxygen ratio. These findings suggest that the approach to advanced respiratory support for critically ill patients with COVID-19 is similar for pregnant and nonpregnant patients. (See "Critical illness during pregnancy and the peripartum period", section on 'COVID-19'.)

OFFICE GYNECOLOGY

Fezolinetant, a neurokinin 3 receptor antagonist for hot flashes (August 2023)

Hormone therapy remains the most effective treatment for hot flashes. However, a new class of nonhormonal drugs, neurokinin 3 receptor (NK3R) antagonists, appears to be a reasonable alternative for those who cannot take hormone therapy. The first NK3R antagonist to be approved and available for clinical use is fezolinetant. In one trial of over 500 postmenopausal women with moderate-to-severe hot flashes, fezolinetant significantly reduced hot flash

frequency and severity when compared with placebo [30,31]. After 12 weeks of therapy, the mean reductions in hot flash frequency for fezolinetant 45 mg, 30 mg, or placebo were 64, 59, and 45 percent, respectively. Women receiving fezolinetant 45 mg also had significant improvements in sleep disturbances when compared with placebo. (See "Menopausal hot flashes", section on 'Neurokinin 3 receptor antagonist'.)

Nonhormonal therapies for menopausal hot flashes (August 2023)

The 2023 nonhormonal therapy position statement from the North American Menopause Society (NAMS) suggests a number of treatment options for hot flashes in women who cannot take hormone therapy [32]. These include cognitive behavioral therapy, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, oxybutynin, gabapentin, and fezolinetant. Nonhormonal therapies that NAMS does not recommend for vasomotor symptoms include paced respiration, supplements/herbal remedies, cooling techniques, avoiding triggers, exercise, yoga, mindfulness-based intervention, relaxation, soy, cannabinoids, acupuncture, and clonidine. (See "Menopausal hot flashes", section on 'NAMS 2023 recommendations'.)

Mifepristone for treatment of adenomyosis (August 2023)

Symptomatic uterine adenomyosis is typically treated with nonsteroidal anti-inflammatory drugs, the 52 mg levonorgestrel-releasing intrauterine device, or surgery, but use of other hormonal medications (eg, oral contraceptive pills, gonadotropin-releasing hormone analogs, mifepristone) has been described. In a randomized trial including over 130 premenopausal patients with adenomyosis based on imaging, mifepristone (10 mg orally daily) resulted in greater improvement in dysmenorrhea, blood loss, and uterine volume compared with placebo after 12 weeks of treatment [33]. Further studies are needed to determine the long-term efficacy of mifepristone in such patients before it can be used routinely for this indication. (See "Uterine adenomyosis", section on 'Alternative hormone strategies'.)

Cabergoline after second-trimester pregnancy loss or termination (June 2023)

Breast symptoms (engorgement, tenderness, milk leakage) after second-trimester pregnancy loss or termination are common, but pharmacotherapy to suppress engorgement and lactation is limited. In a randomized placebo-controlled trial of approximately 70 patients with pregnancy loss or termination at 18 to 26 weeks of gestation, cabergoline (1 mg orally within four hours of fetal expulsion/extraction) substantially reduced breast symptoms on days 2 through 14 of follow-up [34]. Side effects were similar between groups, but the trial was not powered to detect small differences. When counseling patients about breast symptoms after second-trimester pregnancy loss or termination, we discuss the option of cabergoline as well as

nonpharmacologic measures (eg, ice, compression with a tight sports bra, avoiding breast stimulation). (See "Overview of second-trimester pregnancy termination", section on 'Postprocedure considerations' and "Overview of the postpartum period: Normal physiology and routine maternal care", section on 'Breast engorgement'.)

Prednisone use during in vitro fertilization (May 2023)

Prednisone is often used during in vitro fertilization (IVF) to improve the chances of implantation, and thereby live birth, in patients with a prior unsuccessful embryo transfer. However, a randomized trial comparing oral prednisone with placebo in over 700 patients <38 years of age with two or more unsuccessful embryo transfers reported similar live birth rates in both groups after frozen-thawed embryo transfer [35]. We do not prescribe prednisone during IVF cycles, including for patients with prior unsuccessful embryo transfer. (See "In vitro fertilization: Overview of clinical issues and questions", section on 'No proven effect'.)

Surgical management of incomplete miscarriage (April 2023)

Hysteroscopic resection of retained intrauterine tissue after miscarriage has been proposed as an alternative to vacuum aspiration because it may preserve fertility better. However, a randomized trial comparing the two procedures in 563 patients found similar live birth rates and median times to conception for both procedures at two years' follow-up [36]. Hysteroscopic resection required additional equipment, took longer, and could not be completed in all cases. We continue to use vacuum aspiration to manage patients with retained products of conception. (See "Pregnancy loss (miscarriage): Counseling and comparison of treatment options and discussion of related care", section on 'Surgical management'.)

GYNECOLOGIC ONCOLOGY

Updated endometrial cancer staging system (July 2023)

An updated version of the International Federation of Gynecology and Obstetrics (FIGO) staging for endometrial cancer was published in June 2023 (table 5 and table 6) [37]. The new version includes histologic types, tumor patterns, and molecular classification (if performed) reflecting the complexities of endometrial carcinoma and its underlying biology and behavior. It also aims to better define prognostic groups and help guide treatment decisions. Ongoing studies will further refine the role of molecular classification in treatment strategies for endometrial cancer. (See "Overview of resectable endometrial carcinoma", section on 'Staging and surgical treatment'.)

Prognosis of pregnancy-associated cancers (July 2023)

Studies have yielded mixed results in regard to whether cancers diagnosed during pregnancy or in the postpartum period have a higher risk of mortality. In a retrospective analysis of 24,307 premenopausal patients with cancer, there was an increased risk of mortality with cancers diagnosed during pregnancy (adjusted hazard ratio [HR] 1.8) and during the first postpartum year (adjusted HR 1.5) compared with cancers not associated with pregnancy [38]. However, results varied across cancer sites, with increased mortality observed among breast, ovarian, and stomach cancers diagnosed during pregnancy and melanoma, breast, and brain cancers diagnosed postpartum. Details regarding treatments administered were not provided, which may limit interpretation of this study. We encourage multidisciplinary management of cancers diagnosed during pregnancy. (See "Gestational breast cancer: Treatment", section on 'Maternal health' and "Adnexal mass: Evaluation and management in pregnancy", section on 'Prognosis'.)

OTHER GYNECOLOGY

Assisted reproductive technology outcomes in euthyroid women with thyroid peroxidase (TPO) antibodies (March 2023)

A 2022 meta-analysis of observational studies showed higher rates of adverse assisted reproductive technology (ART) outcomes in euthyroid women with, compared to without, thyroid peroxidase (TPO) antibodies, although the findings were limited by the low quality of the evidence [39]. In a subsequent retrospective study of 449 TPO antibody-positive and 2945 antibody-negative Chinese women undergoing in vitro fertilization or intracytoplasmic sperm injection, there was no difference in oocyte retrieval, fertilization, embryo utilization, blastocyst formation, pregnancy rate, or live birth rate between the two groups [40]. Although the new study was larger than most previous studies and attempted to control for numerous potential confounding factors, it was retrospective in design and has similar limitations as previous observational studies. The association between thyroid autoimmunity and adverse ART outcomes remains uncertain. (See "Overview of thyroid disease and pregnancy", section on 'Pregnancy outcomes'.)

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Topic 8350 Version 12227.0

GRAPHICS

Pregnancy morbidity associated with APS

≥3 consecutive otherwise unexplained* prefetal deaths (<10 weeks 0 days) and/or early fetal deaths (10 weeks 0 days to 15 weeks 6 days)
or
≥1 fetal death (16 weeks 0 days to 34 weeks 0 days) alone (ie, no preeclampsia with severe features or placental insufficiency with severe features¶)
or
Preeclampsia with severe features (<34 weeks 0 days) with or without fetal death
or
Placental insufficiency with severe features (<34 weeks 0 days)¶ with or without fetal death

APS: antiphospholipid syndrome; aPL: antiphospholipid antibodies.

* If a detailed analysis of fetal morphology or genetic studies is not performed or unavailable, reasonable clinical judgment that the loss is unexplained should be used based on careful history and review of available medical records.

¶ Placental insufficiency with severe features is defined by fetal/newborn growth restriction (estimated fetal weight <10th percentile for gestational age or postnatal birth weight <10th percentile for gestational age) in the absence of fetal-neonatal syndromes or genetic conditions associated with growth restriction **and** at least one of the following severe features:

- Abnormal or nonreassuring fetal surveillance test(s) suggestive of fetal hypoxemia (eg, nonreactive nonstress test, low biophysical profile score [0 to 4 out of 10])
- Abnormal Doppler velocimetry suggestive of fetal hypoxemia (eg, absent or reversed end-diastolic flow in the umbilical artery)
- Severe fetal/newborn growth restriction (eg, estimated fetal or postnatal birth weight <3rd percentile for gestational age)
- Oligohydramnios (eg, amniotic fluid index ≤5 cm, deepest vertical pocket <2 cm)
- Placental histology showing maternal vascular malperfusion (eg, placental thrombosis/infarction, inadequate remodeling of the uterine spiral arteries [decidual vasculopathy], decreased vasculosyncytial membranes, increased syncytial knots, or decidual inflammation)

  NOTE: Maternal vascular malperfusion can be detected in the placentas of aPL-negative patients with growth restriction and/or preeclampsia and in normal pregnancies, thus these findings are not specific for APS. Whether to send the placenta for histopathologic evaluation is a clinical judgment. Postdelivery histopathologic placental examination is performed when the clinician believes that the information may aid understanding of obstetric, fetal, or neonatal abnormalities. Refer to UpToDate content on placental examination for more information.

Although placental abruption has been associated with placental insufficiency, APS is not associated with placental abruption, and placental abruption is not a defining morbidity for APS.

Adapted from: Barbhaiya M, Zuily S, Naden R, et al. 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthritis Rheumatol 2023.

Graphic 142539 Version 1.0

IADPSG and ADA criteria for a positive two-hour 75-gram oral glucose tolerance test for the diagnosis of gestational diabetes

Two-hour 75-gram oral glucose tolerance test thresholds	
Fasting	92 mg/dL (5.1 mmol/L)
OR	
One hour	180 mg/dL (10 mmol/L)
OR	
Two hour	153 mg/dL (8.5 mmol/mol)

The diagnosis of gestational diabetes mellitus is made at 24 to 28 weeks of gestation when ≥1 plasma glucose value is at or above these thresholds.

IADPSG: International Association of the Diabetes and Pregnancy Study Groups; ADA: American Diabetes Association.

Graphic 61208 Version 20.0

American Diabetes Association criteria for the diagnosis of diabetes

1. A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.* **OR**
2. FPG ≥126 mg/dL (7 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.* **OR**
3. 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.* **OR**
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

A1C: glycated hemoglobin; NGSP: National Glycohemoglobin Standardization Program; DCCT: Diabetes Control and Complications Trial; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test.

* In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Graphic 61853 Version 18.0

Approach to anticoagulation for pregnant individuals with inherited thrombophilia

Clinical setting		Antepartum management	Postpartum management
Lower-risk thrombophilia*	With personal history of previous VTE	Unprovoked VTE or VTE associated with a hormonal risk factor: Anticoagulation (low-dose heparin)	Anticoagulation (low-dose heparin)
		VTE associated with a nonhormonal temporary provoking risk factor and no other risk factors for VTE: No antepartum anticoagulation	Anticoagulation (low-dose heparin)
	No personal history of VTE	Surveillance for VTE without anticoagulation. Anticoagulation may be warranted for individual patients with additional factors that place them at greater risk of thrombosis (eg, prolonged immobility, first-degree relative with unprovoked VTE under age 50 years).	Anticoagulation (low-dose heparin) for patients who have a cesarean birth
Higher-risk thrombophilia¶	With previous VTE and on long-term anticoagulation	Anticoagulation (therapeutic-dose heparin)	Anticoagulation (therapeutic-dose heparin)
	With previous VTE not on long-term anticoagulation	Anticoagulation (intermediate- or therapeutic-dose heparin)	Anticoagulation (intermediate- or therapeutic-dose heparin)
	No personal history of previous VTE and not on chronic anticoagulation	Anticoagulation (low- or intermediate-dose heparin)	Anticoagulation (intermediate-dose heparin)

Low molecular weight heparin is generally preferred to use of unfractionated heparin. Refer to UpToDate content regarding use proximate to labor and birth. Postpartum anticoagulation can generally be started 4 to 6 hours after a vaginal birth or 6 to 12 hours after a cesarean birth, unless

there is significant bleeding or risk for significant bleeding. It is generally continued for six weeks postpartum in patients who did not have a VTE during the pregnancy and who do not have indications for chronic anticoagulation.

VTE: venous thromboembolism; FVL: factor V Leiden; PGM: prothrombin G20210A gene mutation; AT: antithrombin.

* Lower-risk thrombophilias include heterozygosity for FVL or PGM and heritable deficiencies of protein C or protein S.

¶ Higher-risk thrombophilias include AT deficiency, homozygosity for FVL or PGM mutation, double heterozygosity for FVL and PGM, and protein C deficiency in combination with another hereditary defect. Some women with heterozygous deficiencies may be at higher risk based on their personal and family history.

Graphic 95707 Version 12.0

Heparin dosing during pregnancy

Indication	Dose level	Type of heparin	Dosing for specific agents
VTE prevention	Low dose (also called prophylactic dose) May require modifications for extremes of body weight	LMW heparin	Enoxaparin 40 mg SUBQ once daily **or** Dalteparin 5000 units SUBQ once daily
		UFH	5000 units SUBQ every 12 hours
	Intermediate dose*	LMW heparin	Enoxaparin 40 mg SUBQ once daily, increase as pregnancy progresses to 1 mg/kg once daily **or** Dalteparin 5000 units SUBQ once daily, increase as pregnancy progresses to 100 units/kg once daily
		UFH	First trimester: 5000 to 7500 units SUBQ every 12 hours Second trimester: 7500 to 10,000 units SUBQ every 12 hours Third trimester: 10,000 units SUBQ every 12 hours
VTE treatment	Therapeutic dose	LMW heparin	Enoxaparin 1 mg/kg SUBQ every 12 hours **or** Dalteparin 100 units/kg SUBQ every 12 hours
		UFH	Can be given as a continuous IV infusion or SUBQ dose every 12 hours. Titrated to keep the aPTT in the therapeutic range.

This table applies to VTE in pregnant individuals, with the exception of individuals with a prosthetic heart valve, which is discussed separately in UpToDate.

- **Dose level** – Prevention typically uses low or intermediate dose, but therapeutic dose may be used for prevention in selected cases (eg, individuals with recurrent unprovoked thrombotic

events [with or without hereditary thrombophilia or antiphospholipid antibody syndrome] who are receiving long-term anticoagulation with warfarin or a direct oral anticoagulant such as rivaroxaban 20 mg daily or apixaban 5 mg twice daily).

- **Choice of agent** – LMW heparin is recommended for most patients. UFH is used when there may be a need for rapid discontinuation, such as for delivery or perioperatively or in individuals with severely reduced kidney function (eg, CrCl <30 mL/min). Only one heparin product is given at any point in time. Confirm the absence of preservatives (eg, benzyl alcohol) in the heparin product chosen.

Refer to UpToDate for anticoagulation indications, choice of dose level, duration of pharmacologic therapy, and timing of switches between LMW heparin and UFH.

VTE: venous thromboembolism; LMW: low molecular weight; SUBQ: subcutaneously; UFH: unfractionated heparin; IV: intravenous; aPTT: activated partial thromboplastin time; ACCP: American College of Chest Physicians; ACOG: American College of Obstetricians and Gynecologists; CrCl: creatinine clearance.

* Our "intermediate" dose level differs from that used in society guidelines (eg, ACCP, ACOG). Some clinicians prefer to use a different "intermediate" dose level such as enoxaparin 40 mg SUBQ every 12 hours; however, this entails a significant increase in the number of injections over the course of the pregnancy.

Courtesy of Kenneth A Bauer, MD.

Graphic 140440 Version 3.0

Cancer of the endometrium: 2023 FIGO staging*¶

Stage	Description
Stage I	Confined to the uterine corpus and ovary[Δ]
IA	Disease limited to the endometrium **or** non-aggressive histological type (ie, low-grade endometroid) with invasion of less than half of myometrium with no or focal LVSI **or** good prognosis disease IA1 Non-aggressive histological type limited to an endometrial polyp **or** confined to the endometrium IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[Δ]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[◇]
IC	Aggressive histological types[§] limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma without extrauterine extension **or** with substantial LVSI **or** aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[◇] of non-aggressive histological types
IIC	Aggressive histological types[§] with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[Δ] IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[¥] IIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIIC1ii Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis

	IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

FIGO: International Federation of Gynecology and Obstetrics; ITCs: isolated tumor cells; EEC: endometrioid carcinoma; LVSI: lymphovascular space involvement; SLN: sentinel lymph node.

* Endometrial cancer is surgically staged and pathologically examined. In all stages, the grade of the lesion, the histological type and LVSI must be recorded. If available and feasible, molecular classification testing (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all patients with endometrial cancer for prognostic risk-group stratification and as factors that might influence adjuvant and systemic treatment decisions.

¶ In early endometrial cancer, the standard surgery is a total hysterectomy with bilateral salpingo-oophorectomy via a minimally invasive laparoscopic approach. Staging procedures include infracolic omentectomy in specific histological subtypes, such as serous and undifferentiated endometrial carcinoma, as well as carcinosarcoma, due to the high risk of microscopic omental metastases. Lymph node staging should be performed in patients with intermediate-high/high-risk patients. SLN biopsy is an adequate alternative to systematic lymphadenectomy for staging proposes. SLN biopsy can also be considered in low-/low-intermediate-risk patients to rule out occult lymph node metastases and to identify disease truly confined to the uterus. Thus, the ESGO-ESTRO-ESP guidelines allow an approach of SLN in all patients with endometrial carcinoma, which is endorsed by FIGO. In assumed early endometrial cancer, an SLN biopsy in an adequate alternative to systematic lymphadenectomy in high-intermediate and high-risk cases for the purpose of lymph node staging and can also be considered in low-/intermediate-risk disease to rule out occult lymph node metastases. An SLN biopsy should be done in association with thorough (ultrastaging) staging as it will increase the detection of low-volume disease in lymph nodes.

Δ Low-grade EECs involving both the endometrium and the ovary are considered to have a good prognosis, and no adjuvant treatment is recommended if all the below criteria are met. Disease limited to low-grade endometrioid carcinomas involving the endometrium and ovaries (Stage IA3) must be distinguished from extensive spread of the endometrial carcinoma to the ovary (Stage IIIA1), by the following criteria: (1) no more than superficial myometrial invasion is present (<50%); (2) absence of extensive/substantial LVSI; (3) absence of additional metastases; and (4) the ovarian tumor is unilateral, limited to the ovary, without capsule invasion/rupture (equivalent to pT1a).

◇ LVSI as defined in WHO 2021: extensive/substantial, ≥5 vessels involved.

§ Grade and histological type:

- Serous adenocarcinomas, clear cell adenocarcinomas, mesonephric-like carcinomas, gastrointestinal-type mucinous endometrial carcinoma, undifferentiated carcinomas, and carcinosarcomas are considered high-grade by definition. For EECs, grade is based on the proportion of solid areas: low grade = grade 1 (≤5%) and grade 2 (6 to 50%); and high grade =

grade 3 (>50%). Nuclear atypia excessive for the grade raises the grade of a grade 1 or 2 tumor by one. The presence of unusual nuclear atypia in an architecturally low-grade tumor should prompt the evaluation of p53 and consideration of serous carcinoma. Adenocarcinomas with squamous differentiation are graded according to the microscopic features of the glandular component.

- Non-aggressive histological types are composed of low-grade (grade 1 and 2) EECs. Aggressive histological types are composed of high-grade EECs (grade 3), serous, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type carcinomas, and carcinosarcomas.
- It should be noted that high-grade EECs (grade 3) are a prognostically, clinically, and molecularly heterogenous disease, and the tumor type that benefits most from applying molecular classification for improved prognostication and for treatment decision-making. Without molecular classification, high-grade EECs cannot appropriately be allocated to a risk group and thus molecular profiling is particularly recommended in these patients. For practical purposes and to avoid undertreatment of patients, if the molecular classification is unknown, high-grade EECs were grouped together with the aggressive histological types in the actual FIGO classification.

¥ Micrometastases are considered to be metastatic involvement (pN1 [mi]). The prognostic significance of ITCs is unclear. The presence of ITCs should be documented and is regarded as pN0(i+). According to TNM8, macrometastases are >2 mm in size, micrometastases are 0.2 to 2 mm and/or >200 cells, and isolated tumor cells are ≥0.2 mm and ≤200 cells. Based on staging established by FIGO and the American Joint Committee on Cancer AJCC Cancer Staging Manual, 8th ed (Springer 2017).

Graphic 141918 Version 3.0

2023 FIGO endometrial cancer stage with molecular classification*

Stage designation	Molecular findings in patients with early endometrial cancer (stages I and II after surgical staging)
Stage $IAm_{POLEmut}$	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage $IICm_{p53abn}$	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

LVSI: lymphovascular space involvement; MMRd: mismatch repair deficiency; NSMP: no specific molecular profile; p53abn: p53 abnormal.

* When feasible, the addition of molecular subtype to the staging criteria allows a better prediction of prognosis in a staging/prognosis scheme. The performance of complete molecular classification (*POLEmut*, MMRd, NSMP, p53abn) is encouraged in all cases of endometrial cancer for prognostic risk-group stratification and as potential influencing factors of adjuvant or systemic treatment decisions. Molecular subtype assignment can be done on a biopsy, in which case it need not be repeated on the hysterectomy specimen. When performed, these molecular classifications should be recorded in all stages.

- Good prognosis: pathogenic *POLE* mutation (*POLEmut*)
- Intermediate prognosis: MMRd/microsatellite instability and NSMP
- Poor prognosis: p53abn

When the molecular classification is known:

- FIGO stages I and II are based on surgical/anatomical and histological findings. In case the molecular classification reveals *POLEmut* or p53abn status, the FIGO stage is modified in the early stage of the disease. This is depicted in the FIGO stage by the addition of "m" for molecular classification, and a subscript is added to denote *POLEmut* or p53abn status, as shown below. MMRd or NSMP status do not modify early FIGO stages; however, these molecular classifications should be recorded for the purpose of data collection. When molecular classification reveals MMRd or NSMP, it should be recorded as stage Im_{MMRd} or stage Im_{NSMP} and stage IIm_{MMRd} or stage IIm_{NSMP}.
- FIGO stages III and IV are based on surgical/anatomical findings. The stage category is not modified by molecular classification; however, the molecular classification should be recorded if known. When the molecular classification is known, it should be recorded as stage IIIm or stage IVm with the appropriate subscript for the purpose of data collection. For example, when molecular classification reveals p53abn, it should be recorded as stage $IIIm_{p53abn}$ or stage IVm_{p53abn}.

From: Berek JS, Matias-Guiu X, Creutzberg C, et al. FIGO staging of endometrial cancer: 2023. Int J Gynecol Obstet 2023.

Graphic 141963 Version 1.0

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