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# Diagnostic Cardiovascular Imaging and Therapeutic Strategies in Pregnancy

## *JACC* Focus Seminar 4/5

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**ABSTRACT**

The prevalence of cardiovascular disease (CVD) in pregnancy, both diagnosed and previously unknown, is rising, and CVD is a leading cause of maternal morbidity and mortality. Historically, women of child-bearing potential have been underrepresented in research, leading to lasting knowledge gaps in the cardiovascular care of pregnant and lactating women. Despite these limitations, clinicians should be familiar with the safety of frequently used diagnostic and therapeutic interventions to adequately care for this at-risk population. This review, the fourth of a 5-part series, provides evidence-based recommendations regarding the use of common cardiovascular diagnostic tests and medications in pregnant and lactating women. (J Am Coll Cardiol 2021;77:1813–22) © 2021 by the American College of Cardiology Foundation.

Previously in this 5-part review series of cardiovascular disease (CVD) in pregnancy, we covered the approach to the cardio-obstetrics patient from risk stratification and delivery planning through postpartum care (Part 1), congenital and heritable disorders (Part 2), and acquired CVDs (Part 3). Here in part 4 of this review series we discuss the use of diagnostic cardiac imaging in pregnancy and considerations for the use of cardiovascular contrast agents and medications in pregnancy and lactation. We conclude with a brief review of the history of the inclusion of pregnant women in research studies to better understand the current state of the evidence and the clinical dilemmas facing the cardio-obstetrics team when weighing maternal and fetal risks related to diagnostic testing and therapeutic interventions.

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**ABBREVIATIONS AND ACRONYMS**

**ACOG** = American College of Obstetricians and Gynecologists

**CT** = computed tomography

**CVD** = cardiovascular disease

**GBCA** = gadolinium-based contrast agent

**IVC** = inferior vena cava

**MRI** = magnetic resonance imaging

**TEE** = transesophageal echocardiography

**TTE** = transthoracic echocardiography

## DIAGNOSTIC CARDIAC IMAGING IN PREGNANCY

This section highlights the current approaches to the use of cardiac imaging modalities during pregnancy. In general, diagnostic testing strategies to evaluate known or suspected CVD in pregnancy are similar to those used in nonpregnant women but should take into consideration additional safety measures to maximize fetal well-being (1,2). Detailed guidance on the use of diagnostic imaging during pregnancy and lactation is available from the American College of Obstetricians and Gynecologists (ACOG) (3). A basic principle guiding the use of imaging is a primary assessment of the patient's clinical need. If the indication for imaging is appropriate and will alter clinical management, then imaging during pregnancy should be considered. Obtaining accurate diagnostic data for appropriate maternal care is necessary for optimal fetal outcomes. When pregnancy-safe imaging procedures such as ultrasound and magnetic resonance imaging (MRI) without gadolinium-based contrast agents (GBCAs) are available and can provide the appropriate diagnostic data, they should be the preferred modality. For computed tomography (CT), nuclear medicine, or invasive coronary angiography, exposure to ionizing radiation is often the chief consideration when weighing the balance of risks and benefits. For these modalities, a frank discussion with the patient may help to facilitate the decision to use an imaging modality that would expose her and the fetus to ionizing radiation (**Central Illustration**) (4). In addition, if the decision is made to proceed with imaging, protocols should be adapted and individualized to minimize radiation exposure. Any elective procedures involving exposure to ionizing radiation are not recommended during pregnancy and should be deferred.

**HIGHLIGHTS**

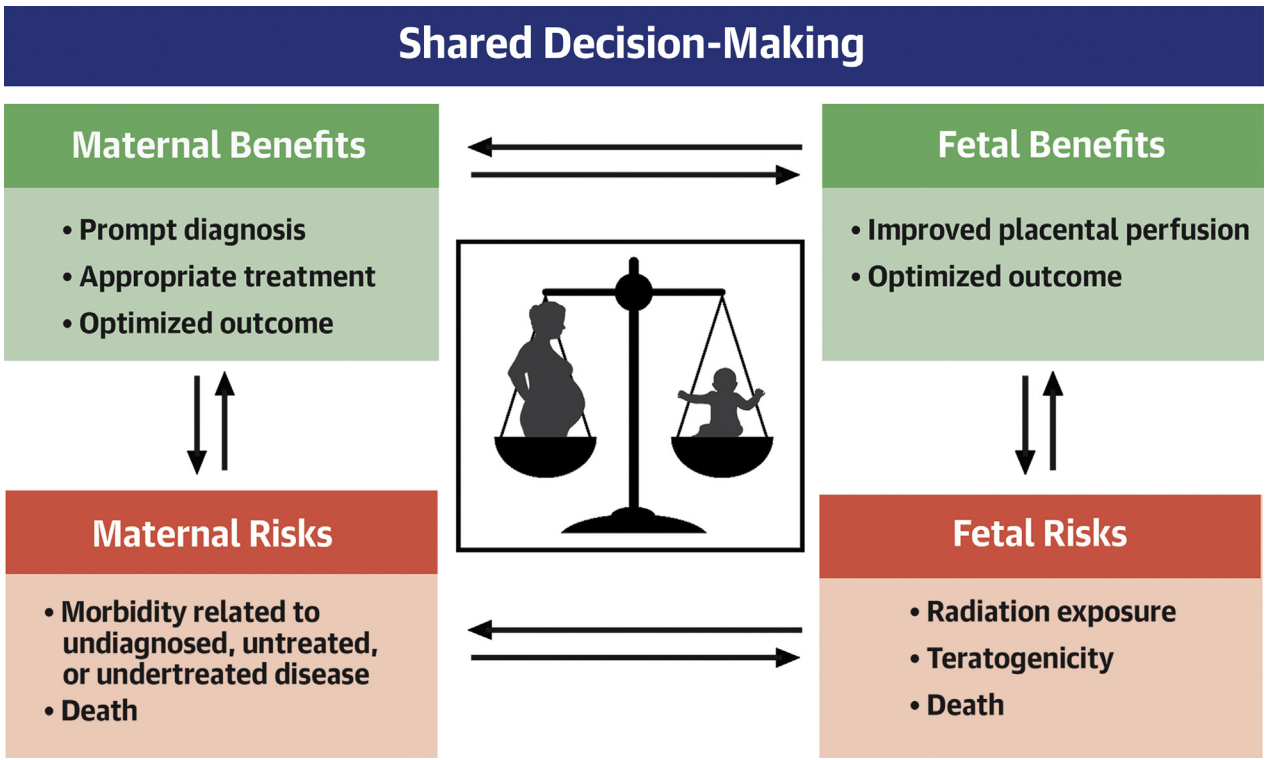
- Pregnant women represent a complex but not necessarily vulnerable population.
- Ultrasound and magnetic resonance without gadolinium-based contrast are preferred over other imaging modalities for pregnant woman to avoid radiation exposure.
- When imaging that involves ionizing radiation is necessary during pregnancy, the strategy should be designed to minimize exposure.
- Although almost every drug administered to a mother crosses the placenta, fetal drug concentration may be similar to, higher than, or lower than the maternal concentration.

**CONSIDERATIONS FOR POSITIONING A PREGNANT PATIENT DURING DIAGNOSTIC TESTING.** The maternal vascular system undergoes a number of physiological adaptions to the pregnant state that vary by trimester and have been described in Part 1 of this series. An important additional hemodynamic phenomenon that must be taken into consideration when performing diagnostic imaging studies, such as echocardiography, is the positional effect of the gravid uterus on the inferior vena cava (IVC). IVC compression occurs in the majority of women during the third trimester, and, as a result, maternal cardiac output decreases by up to 30% when supine compared to that in the left lateral decubitus position. Decreases in maternal blood pressure and concomitant increases in heart rate are also seen, and in a minority of patients (8%) symptomatic supine hypotensive syndrome can occur (5,6). Although the size and position of the uterus and fetus affect the degree of IVC compression, additional factors such as azygos venous flow rate also have an impact on maternal hemodynamics and subsequently placental and fetal perfusion (7,8).

The combination of displacement of the heart (upward and lateral) secondary to the enlarged uterus along with preferred positioning in the left lateral decubitus may improve echocardiographic image quality, although this can be offset by a decrease the intracostal space leading to a limited acoustic window. For examinations performed during the first and second trimesters when fundal height usually is below the umbilicus and IVC compression is minimal, patient positioning is rarely an issue. However, during the third trimester and at term, avoidance of supine positioning and subcostal imaging is recommended. If necessary, supine positioning should be limited to brief periods of time (<3 to 7 min) (5). Traditionally in both pregnancy and echocardiography, the left lateral decubitus position is preferred. However, recent studies suggest that maternal cardiac output does not drop significantly in the right lateral compared to the left lateral position, so the right can be used if necessary (9).

**TRANSTHORACIC ECHOCARDIOGRAPHY.** As in nonpregnant patients, transthoracic echocardiography (TTE) is the mainstay of cardiac imaging in

**CENTRAL ILLUSTRATION** **Shared Decision-Making Is the Cornerstone of Providing Optimal Care to Pregnant Women**

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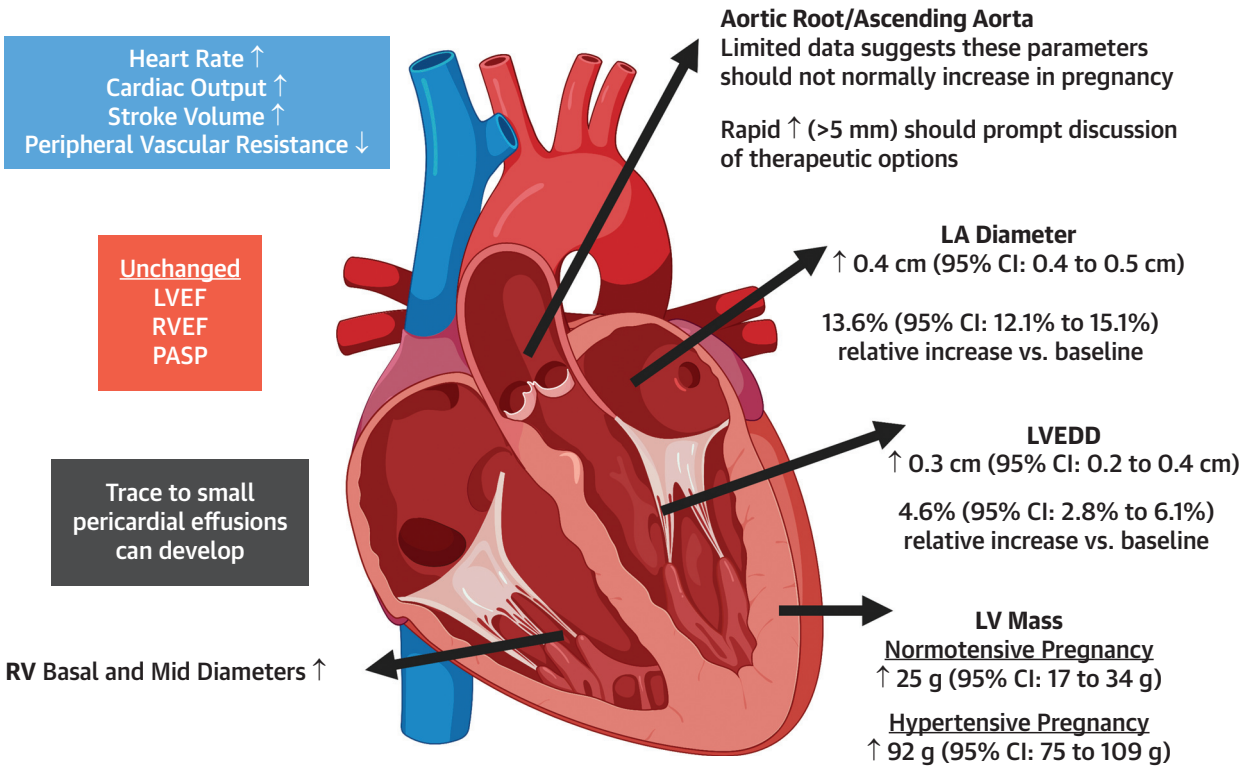
When choosing diagnostic tests and medications for pregnant and lactating women, the interplay between maternal and fetal/infant risks and benefits must be carefully considered. Shared decision-making in consultation with the patient and cardio-obstetrics team is essential for optimal outcomes.

pregnant patients, and the indications for its use vary widely based on the clinical scenario. ACOG recommends TTE be performed in all pregnant women with pulmonary hypertension, valvular disease, congenital heart disease or aortopathies (even if presumed corrected), or cardiomyopathies, as well as in those with a history of exposure to cardiotoxic chemotherapeutic agents (10). Additional common uses include evaluation of wall motion and ventricular function as well as serial monitoring of valvular and congenital disorders. An individualized approach to the timing of serial examinations during pregnancy and in the postpartum period is recommended (10).

Remarkable physiological adaptions in cardiac structure occur in response to the increased plasma volume that is a hallmark of pregnancy (**Figure 1**) (11–13). Most initially become apparent in the second trimester and peak during the third trimester, resulting in a pattern of concentric remodeling that should not be mistaken for pathology. A greater increase in left ventricular mass and relative wall thickness is seen in pregnancies affected by hypertensive disorders compared to normotensive pregnancies (12). The effects of pregnancy on stenotic and regurgitant valvular diseases are reviewed in detail in Part 2 of this series.

**TRANSESOPHAGEAL ECHOCARDIOGRAPHY.** The elevation in progesterone during pregnancy decreases gastric motility and increases relaxation of the lower esophageal sphincter, which in concert with increased intra-abdominal pressure from a gravid uterus lead to a heightened risk of emesis and aspiration in pregnancy (14). As a result, after 18 weeks' gestation, anesthesiologists consider pregnant women's fasting status to be "full stomach" regardless of the actual duration of fasting. Although the potential risks and benefits must be weighed on an individual basis, endotracheal intubation is frequently recommended for transesophageal echocardiography (TEE) after the first trimester due to the

**FIGURE 1 Changes to Cardiac Structure and Function in Pregnancy**




Expected alterations in commonly measured cardiac dimensions and hemodynamic parameters during pregnancy. CI = confidence interval; LA = left atrium; LV = left ventricle; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; PASP = pulmonary arterial systolic pressure; RV = right ventricle; RVEF = right ventricular ejection fraction; ↑ = increase; ↓ = decrease.

increased risk of aspiration of gastric contents in pregnant women; consultation with a cardiac anesthesiologist is recommended. An additional maternal consideration when providing either general or monitored anesthesia care is the coupling of increased oxygen requirement/maternal hyperventilation with reduced functional residual capacity, which can result in a very rapid onset of hypoxemia and acidosis during periods of apnea.

TEE is otherwise performed as in nonpregnant patients, although in late pregnancy care should be taken to ensure the patient is in the left lateral decubitus position and not supine to avoid unnecessary pressure on the IVC as previously discussed. Additional fetal concerns during the administration of anesthesia for TEE are 3-fold and include potential teratogenesis from anesthetic agents, fetal hypoxia, and miscarriage/preterm birth. Midazolam is not recommended for use during the first trimester, although other sedatives and hypnotic agents can be used (15). Maternal/fetal medicine consultation for fetal monitoring should be considered if the fetus is a viable age (>22 to 24 weeks' gestation).

**EXERCISE STRESS TESTING.** Submaximal exercise testing during pregnancy can be a useful assessment of cardiovascular response to exertion. In addition to the standard precautions and contraindications to exercise stress testing that apply to nonpregnant adults, Table 1 lists absolute and relative contraindications to exercise specific to pregnancy according to ACOG (16). It should also be taken into consideration that non-weight-bearing exercise on a recumbent bike is preferred to the treadmill, particularly for women who are unaccustomed to exertion. This will remove the influence of gestational weight gain and allow for better stability and reduction of fall risk. A minimum of 4 min of exercise is necessary for a diagnostic test, and the intensity of exercise should be individualized, with subjective assessments of perceived exertion used to guide the testing. There are currently no normative values to identify a dysfunctional response to aerobic exercise in

**TABLE 1 Contraindications to Submaximal Exercise Stress Testing in Pregnant Women**

| |
|---|
| Absolute contraindications |
| Persistent vaginal bleeding, especially in the second and third trimesters |
| Incompetent cervix, history of cerclage placement |
| Known hemodynamically significant cardiovascular disease |
| Multiple gestation |
| Placenta previa after 26 weeks |
| Pre-eclampsia/gestational hypertension |
| Preterm labor |
| Premature rupture of membranes/amniotic fluid leakage |
| Restrictive lung disease |
| Relative contraindications |
| Severe anemia |
| Bronchitis |
| Poorly controlled diabetes or hypertension |
| Dyspnea before exertion |
| Dizziness/presyncope |

**TABLE 2 Potential Fetal Effects of Radiation Exposure and Excess Risk of Cancer by Fetal Radiation Dose**

| Dose (mGy) | Low-Risk Model | Intermediate-Risk Model | High-Risk Model |
|---|---|---|---|
| 10 | 1/4,545 | 1/3,571 | 1/1,667 |
| 20 | 1/2,272 | 1/1,786 | 1/834 |
| 30 | 1/1,515 | 1/1,190 | 1/556 |
| 40 | 1/1,136 | 1/892 | 1/417 |
| 50 | 1/909 | 1/714 | 1/334 |

pregnant women, and use of standard age- and sex-matched referent values or comparison to the patient's pre-pregnancy response is recommended (17,18).

**CARDIAC MRI.** Cardiac MRI is used less frequently but can provide important supplement information about cardiac and particularly vascular structures and function. It is most commonly utilized in pregnant women to measure aortic dimensions (19), although it also is useful for assessment of wall motion and ventricular function when ultrasound is non-diagnostic. Similar to echocardiography, normative values for cardiac indexes in pregnancy and the postpartum state have been published (13). GBCAs are not necessary for imaging of the aorta or for the majority of other indications in pregnancy. They should be used with extreme caution and only in situations in which the potential benefit clearly justifies the potential risk to the fetus. The potential risks associated with GBCA use in pregnancy are discussed in the GBCAs section.

**CARDIAC IMAGING THAT UTILIZES IONIZING RADIATION.** Ionizing radiation includes gamma rays from nuclear medicine procedures such as single-photon emission computed tomography or positron emission tomography and x-ray radiation from CT, general radiography, or fluoroscopy. The primary concern when exposing a pregnant woman to ionizing radiation at the levels expected from medical imaging is fetal exposure resulting in an elevated risk of childhood cancer, not teratogenesis (20,21). For exposure to a newborn child, the lifetime attributable risk of developing cancer is estimated to be 0.4% per 10-mGy (1-rad) dose to the baby. The potential risks in utero for the second and third trimesters and part of the first trimester may be comparable, but this is only an estimate (22). The relative risk of childhood cancer in an irradiated fetus may be as high as 2-fold, but this must be weighed against the failure to diagnose a potentially serious disease (20). It also is important to keep in mind that the absolute risk to the fetus remains small (Table 2). Exposure to the fetus primarily occurs when the uterus is within the direct beam, although indirect scatter can also result in fetal exposure. From an Image Wisely Taskforce, the added cancer risk to the fetus following exposure to 10 mGy of radiation is estimated to range from 0.022% to 0.06% (Table 3).

Radiation exposure exceeding a threshold of 50 mGy should be avoided in order to avert potential nonstochastic effects of radiation to the fetus (23). Table 4 lists dose ranges associated with commonly performed cardiac diagnostic and therapeutic imaging techniques, including chest radiography, fluoroscopy, CT angiography, and ventilation/perfusion scan (23,24). For every patient, pregnant or not, the lowest possible exposure dose should be a goal (i.e., the principle of ALARA [as low as reasonably achievable]), and the Image Wisely website from the American College of Radiology has extensive material for dose modification suggestions for CT imaging of the pregnant patient (22). The reductions in radiation exposure must be balanced to avoid reduced image quality whereby there is insufficient information for the diagnosis in question. Importantly, it is standard practice for all imaging laboratories to have operating procedures for exposing women of child-bearing age to ionizing radiation. These should be added if none currently exist. When time allows, consultation with a radiology or imaging specialist can be considered, particularly when considering the use of nuclear medicine compounds in pregnant or lactating women (3,25).

**CARDIAC CATHETERIZATION AND INVASIVE ELECTROPHYSIOLOGICAL PROCEDURES.** An in-depth description of diagnostic and therapeutic cardiac

**TABLE 3 Summary of Possible In Utero Induced Deterministic Radiation Effects by Gestational Age and Radiation Dosage**

| Gestational Age (Weeks) | <50 mGy | 50–100 mGy | >100 mGy |
|---|---|---|---|
| 0 to 2 | None | None | None |
| 3 to 4 | None | Probably none | Possible spontaneous abortion |
| 5 to 10 | None | Scientifically uncertain and probably too subtle to be clinically detectable | Possible malformation risk increases with increasing dose |
| 11 to 17 | None | Scientifically uncertain and probably too subtle to be clinically detectable | Risk of diminished IQ increases with increasing dose |
| 18 to 27 | None | None | IQ deficits not detectable at diagnostic doses |
| >27 | None | None | None applicable to diagnostic medicine |

IQ = intelligence quotient.

procedures during pregnancy is covered in Part 3 of this series.

## CVD MEDICATION USE DURING PREGNANCY AND LACTATION

A comprehensive evaluation of all cardiovascular medications used during pregnancy is beyond the scope of this paper and was recently reviewed (26). This section highlights important physiological effects of pregnancy on pharmacokinetics and pharmacodynamics and discusses commonly used cardiovascular medications and contrast agents.

**PHARMACOKINETIC CONSIDERATIONS FOR PREGNANT AND LACTATING WOMEN.** Pregnancy is a hemodynamically complex period with marked increases in volume of distribution and cardiac output. As a result of these changes as well as delays in gastric emptying, increased hepatic and renal clearance, and decreased albumin and plasma binding proteins, pharmacokinetics are altered in the pregnant state. Given the complex interplay among these variables, the effective dose of a drug during pregnancy may be higher or lower than in the nonpregnant state and may change throughout the course of pregnancy, with increased clearance of certain medications requiring escalation of dose. Slow titration of medications as well as use of the lowest possible effective dose are recommended to minimize adverse maternal and fetal effects of necessary medications.

Knowledge of the safety, efficacy, and side effects of cardiac medications on both mother and fetus is essential when caring for pregnant and postpartum patients. The placenta is a complex organ that serves many roles, including nutrient transfer, waste removal, and hormone secretion. Although almost every drug administered to a mother eventually crosses the placenta, fetal drug concentration may be similar to, higher than, or lower than the maternal concentration. It is important to note that in addition to direct fetal drug effects, medications may impact the fetus through alterations of uteroplacental blood flow (27). In 2015, the U.S. Food and Drug Administration implemented an updated Pregnancy and Lactation Labeling Rule that eliminated the letter category system (A, B, C, D, and X). The new system requires summaries describing the risks and benefits of drugs and biological products when used in pregnancy and lactation to be described in the package insert (28). LactMed, a frequently updated online database, is a useful reference for checking medication compatibility with lactation (29).

**TABLE 4 Average Radiation Exposure From Common Cardiac Imaging Procedures**

| Imaging Modality | Fetal Dose (mGy) |
|---|---|
| Ultrasound | 0 |
| MRI | 0 |
| CXR | 0.002–0.1 |
| CT chest or CT pulmonary angiography | 0.03–0.66 |
| V/Q scan | 0.32–0.74 |
| Low-dose perfusion scintigraphy | 0.1–0.5 |
| Fluoroscopy (diagnostic/therapeutic angiography, balloon valvuloplasty) | 3–20 |
| PET CT | 10–50 |

CT = computed tomography; CXR = chest x-ray; MRI = magnetic resonance imaging; PET = positron emission tomography; V/Q = ventilation/perfusion.

**USE OF COMMON CARDIOVASCULAR MEDICATIONS IN PREGNANT AND LACTATING WOMEN.** Hypertension and heart failure are the most commonly encountered CVDs that require medication use in pregnancy, and they can be associated with significant risk to both mother and fetus. Several evidence-based medical therapies that are the foundation of treatment for nonpregnant patients are contraindicated for use in pregnancy due to their potential teratogenic effects during the first trimester. Table 5 lists recommended medications to treat these conditions. Anticoagulants are another medication class commonly used during pregnancy (Table 6). Although many women receiving therapeutic anticoagulation during pregnancy have a chronic indication for its use, some women will require initiation of one of these agents during gestation. Additional information regarding anticoagulant use around the time of delivery can be found in Part 2 of this review series and a recent comprehensive review of venous thromboembolism associated with pregnancy (30).

**USE OF IMAGING CONTRAST AGENTS IN PREGNANT AND LACTATING WOMEN. Agitated saline.** Administration of intravenous agitated saline is routinely used in the nonpregnant adult to provide right heart contrast and is an integral part of the diagnostic workup of right-to-left intra-cardiac shunting and evaluation of extracardiac shunt due to pulmonary arteriovenous malformation (31). Because air microbubbles are short-lived and diffuse into the lungs from the pulmonary circulation, their administration is quite safe in the absence of shunting. In pregnancy there is a concern that, in the presence of a shunt, the microbubbles of air could travel to the placenta, resulting in placental infarction and fetal distress. In general, the recommendation is to defer the use of agitated saline contrast until the postpartum period, or to use alternative imaging modalities such as cardiac MRI without GBCA if needed to diagnose intracardiac and extracardiac shunting in pregnancy (31).

**Left ventricular ultrasound-enhancing agents.** Left ventricular contrast can be clinically useful to evaluate for intracardiac thrombus and to improve endocardial border definition and assessment of systolic function and regional wall motion. There are no empiric data on the safety of any of the 3 left ventricular contrast agents (Definity, Lantheus Medical Imaging, North Billerica, Massachusetts; Optison, GE Healthcare, Marlborough, Massachusetts; or Lumason, Bracco Diagnostics Inc., Monroe Township, New Jersey) in human pregnancy or lactation, although no evidence of fetal harm has been observed in animal studies (32). Prescribing information suggests that relevant fetal exposure is not expected due to the very short half-life of these agents and recommends their use be considered only if clinically needed by the mother during pregnancy and lactation (33–36).

**Iodinated contrast.** Intravenous iodinated contrast can cross through the placenta and enter the fetal circulation and amniotic fluid; therefore, its use in pregnancy should be limited to situations in which the diagnostic information obtained will alter care (37). Importantly, intravenous contrast should not be withheld if an additional scan with contrast might be needed as a follow-up study, which would expose the woman and fetus to additional radiation. For breastfeeding women, ACOG recommends that breastfeeding be continued without interruption, as these agents are excreted into the breast milk at very low levels (3,36). Oral contrast agents are not absorbed and, although rarely indicated for cardiovascular imaging procedures, do not have any potential for real or theoretical harm to a pregnant woman or her fetus.

**TABLE 5 Antihypertensives and Heart Failure Medications in Pregnancy**

| Hypertension |
|---|
| First-line |
| Nifedipine ER |
| Labetalol |
| Alpha-methyldopa |
| Second-line |
| Hydralazine |
| Isosorbide dinitrate |
| Nitroglycerine |
| Amlodipine |
| Furosemide* |
| HCTZ* |
| Clonidine transdermal patch† |
| Contraindicated |
| ACE inhibitors, ARBs, direct renin inhibitors, aldosterone antagonists |
| **Heart Failure** |
| Metoprolol |
| Carvedilol |
| Furosemide* |
| Bumetanide* |
| Torsemide* |
| Metolazone* |
| Hydralazine |
| Isosorbide dinitrate |
| Nitroglycerine |
| Dopamine |
| Dobutamine |
| Norepinephrine |
| Digoxin |
| Contraindicated |
| ACE inhibitors, ARBs, aldosterone antagonists, ivabradine, sacubitril/valsartan |

*Monitor for volume depletion to ensure adequate placental perfusion. †Consider using in women with hyperemesis gravidarum who are unable to tolerate oral medications.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HCTZ = hydrochlorothiazide.

**GBCAs.** Gadavist (Bayer HealthCare, Wayne, New Jersey) (38) is the only contrast agent approved by the Food and Drug Administration for use specifically in cardiac MRI, although in practice many other GBCAs are used. There are no studies of Gadavist use in pregnant women, and whether Gadavist crosses the human placenta is unknown. However, other GBCAs are water soluble, cross the placenta, and transfer into the fetal circulation and amniotic fluid where they remain for an indefinite amount of time. Limited published human data on exposure to GBCAs during pregnancy did not show adverse effects in exposed neonates. Because GBCAs are water soluble, there is little excretion into breast milk, and breastfeeding should not be interrupted after GBCA administration (3,36).

**TABLE 6 Anticoagulants for Use in Pregnancy and Lactation**

| | Advantages | Disadvantages | Special Consideration | Lactation |
|---|---|---|---|---|
| UFH | UFH does not cross the placenta, has an acute reversal agent (protamine), and is favored for patients with renal failure.<br>UFH is also favored for patients with pulmonary embolism and hemodynamic compromise. | Requires frequent monitoring of PTT to determine therapeutic window. | UFH should be used 36 h before induction or cesarean section because it has a shorter half-life than LMWH.<br>UFH drip should be stopped 4 to 6 h before anticipated delivery and restarted 6 h after delivery if no bleeding complications occur. | UFH is not found in breast milk in any significant amount. There is no contraindication to its use in lactation. |
| Enoxaparin (LMWH) | Does not cross the placenta, and is convenient for outpatient use.<br>Lower risk of heparin-induced thrombocytopenia, major bleeding, and osteoporosis compared to UFH. | Requires twice daily injections.<br>Higher cost. | Metabolism is primarily by renal excretion, and caution should be used in patients with impaired renal function.<br>As pregnancy progresses there is altered metabolism, and frequent dose adjustments may be required. Follow peak and trough anti-Xa levels meticulously during pregnancy. | Enoxaparin is not found in breast milk in any significant amount; therefore, there is no contraindication to its use in lactation. |
| Fondaparinux | Fondaparinux is associated with minimal transplacental passage. Recommended by ACOG in the setting of heparin-induced thrombocytopenia or heparin allergy. | Few data on its use in pregnancy are available. | | |
| VKAs | Pregnant women can be switched back to warfarin in the second and third trimesters until delivery. | Crosses the placenta and is a known teratogen. Administration >5 mg/day associated with neurodevelopmental deficits, fetal bleeding, and miscarriage. | Women who are taking VKAs before pregnancy generally need to be switched to LMWH as soon as pregnancy is confirmed, with very few exceptions. An alternative approach is switching to LMWH before conception. | Warfarin is not found in breast milk in any significant amount and can be resumed postpartum. |

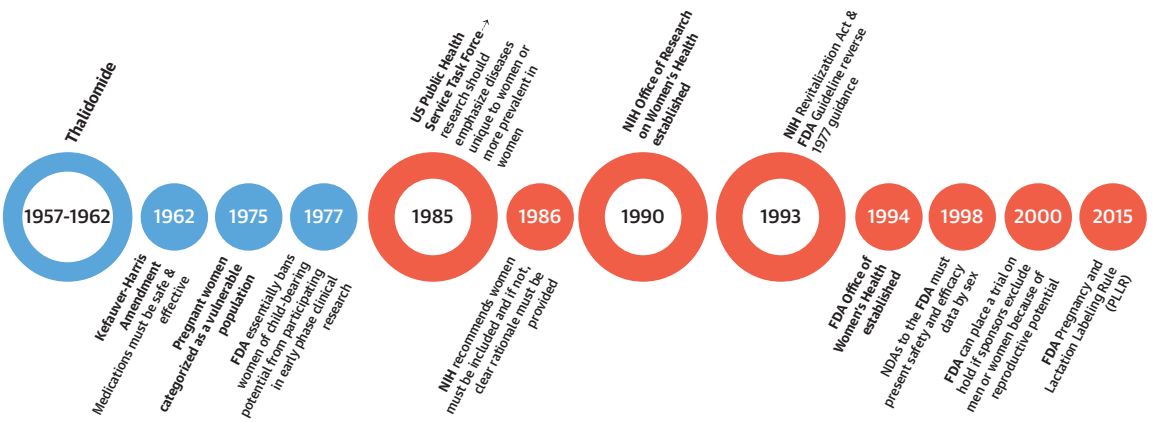
Direct oral anticoagulants (DOACs) are contraindicated. Rivaroxaban crosses the placental barrier and therefore is contraindicated in pregnancy. Other DOACs have not been evaluated. Pregnant women were excluded from DOAC trials. If a patient has an appropriate indication for anticoagulation, she should be switched to heparin products or warfarin during pregnancy and during lactation.

ACOG = American College of Obstetricians and Gynecologists; LMWH = low-molecular-weight heparin; PTT = partial thromboplastin time; UFH = unfractionated heparin; VKA = vitamin K antagonist.

## KNOWLEDGE GAPS IN THE CARE OF PREGNANT WOMEN WITH CVD

Pregnant women and women of child-bearing age have often been under-represented in or excluded from CVD clinical trials (Figure 2) (39). This has led to persistent knowledge gaps in the CVD evidence base, relating to both the treatment of pregnancy-specific CVD as well as the treatment of CVD in women who are pregnant, postpartum, or of reproductive age

**FIGURE 2 Timeline of Important U.S. Milestones Affecting Women's Participation in Research**




Key milestones related to the inclusion or exclusion of women from participation as research subjects as well as important regulations related to the study of pregnancy and lactation. FDA = Food and Drug Administration; NDA = new drug application; NIH = National Institutes of Health; US = United States.

(39,40), as exemplified throughout this review series by the paucity of large trials in the evidence base supporting the use of various pharmacological therapies and diagnostics. The conduct of both clinical care and research on CVD in pregnancy is complex, but these complexities must be confronted, and the ethical obligation to improve care for pregnant women must not be ignored. In recognition of the low levels of enrollment of women in clinical trials, in 1993 the National Institutes of Health Revitalization Act (Public Law 103-43) was passed, mandating the inclusion of women and minorities in all research funded by the National Institutes of Health. However, this has done little to encourage the conduct of research specifically addressing CVD in the context of pregnancy.

Although pregnant women are "scientifically complex" secondary to physiological differences intrinsic to the state of pregnancy and the potential for fetal harm (41), they are not necessarily a "vulnerable" population. Vulnerability implies a compromised ability to protect one's interests and provide informed consent, a definition that the majority of pregnant women do not meet. It is important to recognize that both involvement in clinical trials and the provision of non-evidence-based clinical care are not without risk. Thus, as the prevalence of CVD in pregnancy continues to grow over time, efforts to improve the quality of care delivered to these women also must intensify. The cost of an overly conservative approach is failure to improve care for anyone (42).

## CONCLUSIONS

The choice of diagnostic testing and therapeutic medications for pregnant and lactating women can be complex, but it is important to recognize that it is inappropriate to deem pregnant women a vulnerable population by default. When considering a nonelective diagnostic imaging procedure or therapeutic medication as part of the care for a pregnant or lactating woman, the choice of strategy must weigh both maternal and fetal/infant health and should factor in the patient's preferences in a process of shared decision-making. As described in this 5-part series, delivering care to pregnant and lactating women is best done in the context of a cardio-obstetrics team-based setting. However, all clinicians should be familiar with the safety of frequently used diagnostic and therapeutic interventions for pregnant women with and at high risk for CVD in order to adequately care for this growing population.

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