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Pregnancy and Cardiovascular Disease (N Scott, Section Editor)

Contraception for the Cardiac Patient: a Cardiologist's Primer

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Abstract

Purpose of review Cardiovascular disease (CVD) is the number one cause of maternal mortality in the USA. There are many cardiac conditions which pose significant risk to maternal health, and these women should be offered options to avoid unwanted pregnancies. Individualized contraceptive counseling focusing on woman's desire for future pregnancy, comorbid conditions, and desire for hormone or non-hormonal (contraceptive) options is paramount to avoid adverse or unwanted side effects. The purpose of this review is to give general guidance on prescribing both hormonal and non-hormonal contraceptives for providers caring for women with heart disease.

Recent findings Specific recommendation for the use of either non-hormonal or hormonal contraception requires knowledge of the types of contraceptive options available, cost, failure rates, and contraindications to use. Newer progestin-only options have become available and should be considered first-line therapy for women with cardiovascular disease.

Summary The physiologic burden of pregnancy on the cardiovascular system can cause significant maternal morbidity and mortality for women with underlying CVD. These women should be offered safe and effective options for birth control, and both cardiology and obstetrical providers alike should possess fundamental knowledge of appropriate options.

Introduction

The maternal mortality rate (MMR) in the USA stands at 16.9 per 100,000 and is higher than that of any other industrialized nation [1]. In response to this alarming trend, two-thirds of states have established maternal mortality review committees. Childbirth is the sixth highest cause of mortality in women ages 20–34 [2]. Of these childbirth-related deaths, cardiovascular disease has been found to be the leading cause [2,3]. Advances in cardiovascular treatment and surgery have enabled children born with congenital cardiac anomalies to survive into adulthood, with many of these women desiring fertility. Delayed childbearing, coupled with rising rates of diabetes, obesity, and other traditional cardiovascular risk factors, have also contributed to the growing trend of maternal deaths. Optimizing medical comorbidities and cardiovascular care prior to pregnancy is essential, and this responsibility falls upon both the obstetrician and the cardiologist alike. In order to reduce the burden of unintended pregnancies and optimize timing of pregnancy for women with heart disease, providers who care for these women must have knowledge of safe and effective contraceptive options.

Both over-the-counter and prescription contraceptive methods are widely available in the USA to assist women in preventing unwanted or unintended pregnancies. The benefits of family planning are vast, including fewer teen pregnancies, fewer abortions, higher educational attainment rates, lower incidence of sexually transmitted diseases, lower preterm birth rates, reduction in maternal morbidity, reduction in neonatal and maternal mortality, and greater economic growth [4–6]. More than 99% of American women aged 15–44 report having used some method of birth control at some point during their reproductive lives [7]. However, lack of knowledge regarding available options and correct use, misperceptions and exaggerated concerns about safety, restrictions barring minors from consenting to contraceptive services, limited insurance coverage, and cost continue to pose major barriers to women in obtaining effective contraception [8].

Choosing a particular contraceptive method is a highly individualized decision; each woman should retain autonomy and the ability to choose a method that is compatible with her personal values, level of comfort, reproductive desires, and underlying medical issues. There are both barrier and hormonal forms of pregnancy prevention, and each comes with its unique risk and benefit profile. Methods differ in terms of effectiveness, side effect profile, drug interactions, use of hormones, cost, confidentiality concerns, and the degree of control women have over their use.

Cardiologists as women's reproductive health providers

The ever-changing climate of medicine has altered and expanded the physician role into new arenas. For example, as obstetricians are stepping into new positions as mental healthcare providers, so too are cardiologists expected to

have a breadth of knowledge regarding contraception and contraceptive counseling. Ideally, this counseling would be performed jointly by an experienced cardiologist and obstetrician. However, many facilities do not have the capability of maintaining a joint cardio-obstetrics clinic. Women with underlying cardiovascular disease often view their cardiologist as being their primary care provider, and this touch point may be the only opportunity to discuss family planning topics. As well, many young women with congenital heart disease do not enter into gynecologic care until early adulthood and therefore may go without contraceptive counseling until that time. Adolescence is an optimal time to initiate the discussion surrounding contraception, as only one-quarter of teens engaging in sexual behavior are reported to utilize any form of protection against sexually transmitted diseases or pregnancy [9]. Without contraception, up to 85% of women will experience an unintended pregnancy within a year [10]. As the sole healthcare provider to many adolescents with heart disease, cardiologists should view each visit as an opportunity to discuss family planning issues. This will require a familiarity with the different types of available contraceptive options, their risk and safety profiles, efficacy rates, and any contraindications to use, particularly in cardiac disease states. The aim of this review is to provide a quick reference to enhance cardiologists' comfort level in discussing family planning and contraceptive options in women with cardiovascular disease.

Metabolism and side effects of hormonal contraceptives

As with many steroids, estrogen and progesterone exert various metabolic effects throughout the body. Their directional effect on lipid profiles, hemostatic variables, and even carbohydrate metabolism is dependent upon the route of administration, dosage, and type of hormone (Fig. 1). Metabolism of the various exogenous estrogens is similar to endogenous estradiol in that they undergo extensive first-pass metabolism in the cytochrome P450 CYP3A system, leading to the formation of several active metabolites. Over 95% of orally administered estrogen is metabolized by the enterohepatic system prior to reaching systemic circulation. Concentration can be affected by other medications including St. John's Wort, many antiepileptics, benzodiazepines, bosentan, and warfarin [11,12]. Estrogens are known to increase blood pressure, promote fluid retention through stimulated hepatic synthesis of angiotensin leading to increased aldosterone levels, increase VLDL and HDL, decrease LDL, increase levels of sex hormone binding globulin, and increase liver proteins leading to changes in the procoagulation/fibrinolytic balance [12–16]. As such, exogenous or synthetic estrogen has been associated with an increase in ischemic stroke, myocardial infarction, venous thromboembolism, and a lengthening in the QT interval [17–20]. The risk for a thrombotic event rises with increasing estrogen doses, varies by the type of progestin (highest with the 3rd and 4th generation), and is highest for the first 3 months of use [18,21].

Unlike estrogens, progestins have differing first-pass metabolism rates. Progestin-only contraception does not seem to have the same negative effects on the coagulation cascade as estrogen or combined formulations and therefore can be used in women with higher risks for cardiovascular or thrombotic events [10,22]. The first- and second-generation progestins (norethindrone and

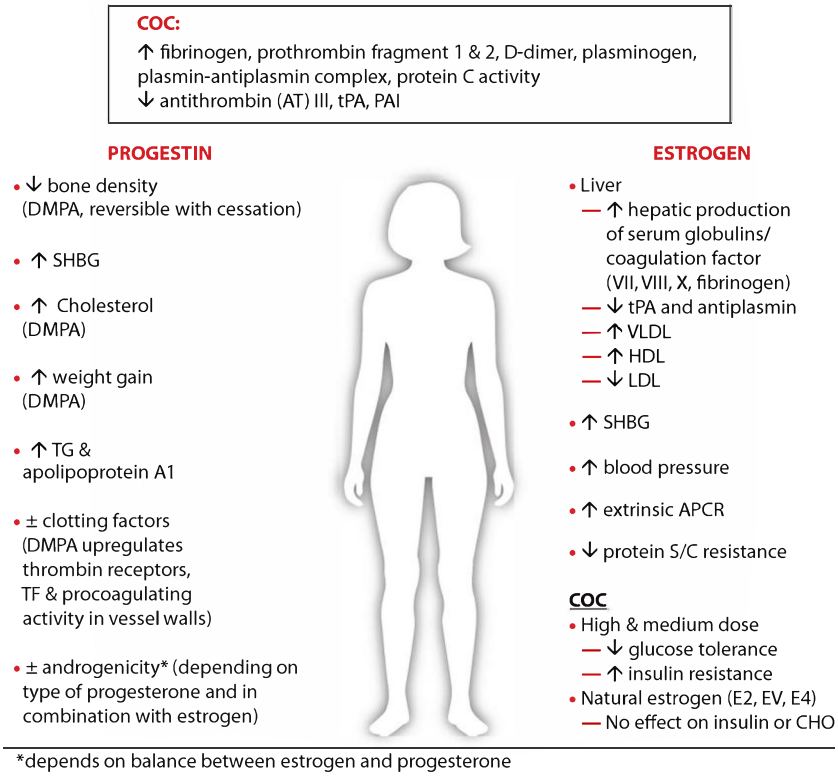

Fig. 1. Metabolic effects of hormonal contraception. DMPA, depomedroxyprogesterone acetate; SHBG, serum hormone-binding globulin; TG, triglycerides; MPA, medroxyprogesterone acetate; TF, tissue factor; tPA, tissue plasminogen activator; VLDL, very low density lipoprotein; HDL, high density lipoprotein; LDL, low density lipoprotein; APCR, activated protein C resistance; E2, estradiol; EV, estradiol valerate; E4, estetrol; CHO, carbohydrates; CHC, combined hormonal contraceptives; PAI, plasminogen activator inhibitor.

levonorgestrel) are estrane derivatives of testosterone with a higher rate of androgenic side effects and thus are more likely to cause bloating, fluid retention, lowering of HDL, and acne than the third- and fourth-generation medications [23].

Types of contraceptive methods and efficacy

The WHO and the US Medical Eligibility Criteria for Contraceptive Use (USMEC) are classification guidelines developed to guide contraceptive management in women with comorbidities. Although the USMEC (Table 1) gives guidance for women with cardiovascular disease, it does not distinguish between women solely with cardiovascular disease from those with multiple comorbidities. However, the WHO guidelines encompass cardiac disease with other comorbid conditions. Both guidelines can be utilized when deciding upon the safest and most efficacious contraceptive method in a woman with multiple comorbidities. All possible contraceptive options must be weighed against the risk of pregnancy, and the appropriate type of contraception should be implemented so as to prevent or mitigate any future pregnancy-associated complications.

Table 1. United States Medical Eligibility Criteria (MEC) for Contraceptive Use

1 = A condition for which there is no restriction for the use of the contraceptive method
2 = A condition for which the advantages of using the method generally outweigh the theoretical or proven risks
3 = A condition for which the theoretical or proven risks usually outweigh the advantages of using the method
4 = A condition that represents an unacceptable health risk if the contraceptive method is used

Contraceptives are classified on the basis of those that contain exogenous hormones and those that do not, the latter of which may act either as a barrier to sperm entry or inhibit sperm activity/viability. Within the class of hormonal contraceptives, there are two main types: those that contain a combination of estrogen and progestin and those with progestin alone (Table 2). The most commonly used form of estrogen is ethinyl estradiol (EE), which was the first formulation used when the pill was introduced to the market in 1960. Only recently have three new estrogen formulations been developed to further alter the metabolic side effects mentioned above. There are four generations of progestins, each one with progressively fewer androgenic properties [23–26]. This is important to consider when prescribing first- and second-generation progestin-containing hormonal contraceptives, as the adverse effects may include higher risk of CV morbidity [23]. In this case, it may be more appropriate to choose a third- or fourth-generation progestin with less androgenic side effects or even those that have partial anti-androgenic and anti-mineralocorticoid activity. The following section delineates the types of contraceptive options by their mechanism of action, effectiveness, and safety in women with heart disease.

Most effective, with fewest contraindications: intrauterine devices, implants, and sterilization

The long-acting reversible contraceptive methods (IUDs and progesterone implants) or LARCs are the most effective at pregnancy prevention [27]. There are five different types of intrauterine devices on the market in the USA, four of which are progesterone-containing devices and one containing copper. The 4 progesterone-containing IUDs differ according to their physical size, length of suggested use, and the amount of progestin released daily. All are T-shaped devices with various levels of progestin (Mirena LNG-20, Liletta LNG-18.6, Kyleena LNG-19.5, and Skyla LNG-13.5) contained in a polydimethylsilicone sleeve and release a set amount of hormone daily. Depending on the brand, these forms of contraception can be left in place for up to 5 years (Mirena® 5 years, Liletta® 4 years, Kyleena® 5 years, and Skyla® 3 years) [27,28]. Within the first year of use, the progestin-containing IUDs have a higher efficacy rate than female sterilization [28,29]. The failure rate decreases only slightly with prolonged use to 0.2% [28]. The primary mechanism of action prevents fertilization by causing a change in the amount and viscosity of the cervical mucus, inhibiting sperm entry into the uterine cavity. Progestin-containing IUDs also act on the uterine lining to induce decidualization (thinning of the endometrial lining) and atrophy. Finally, at higher doses and during the first few months of use, the progestin effect also inhibits ovulation [30–33]. For the non-hormonal

copper IUD (ParaGard®), the mechanism of action results from an increase in copper ions, enzymes, prostaglandins, and macrophages that impair sperm function and thereby inhibit fertilization [34,35]. The copper T380A IUD is approved for use for up to 10 years and may also be used for emergency contraception if placed up to 7 days after unprotected intercourse [36].

There are numerous other advantages to the various types of LARC. The progestin-containing IUDs decrease heavy menstrual bleeding by up to 98% and cause complete cessation of menses in up to 44% of users after 6 months of use [31,37]. This is ideal for women who experience heavy menstrual cycles resulting in anemia and/or those on anticoagulation. Progestin-containing IUDs are also approved for the treatment of dysmenorrhea, endometriosis, and adenomyosis and have been shown to decrease the incidence of endometrial polyps and both endometrial and ovarian cancers [37,38]. These cancer preventative effects even extend to the copper IUD with a yet unknown mechanism of action [37]. The typical and perfect use rates are similar as this type of contraception is user-independent [27]. Multiple studies have found that the progestin-containing IUDs and copper IUD have similar efficacy and safety profiles in both adults and adolescents [39]. Therefore, IUDs should be considered first-line contraceptive therapy not only for adult women with cardiovascular risk factors but also for adolescents with congenital cardiac disease.

The most common side effects for the progestin-containing IUD include pain at the time of insertion, irregular and/or intermenstrual bleeding, and hormone-related menstrual symptoms such as breast tenderness, headaches, and acne [31]. There are some randomized controlled trials reporting decreased pain and easier insertion with the use of misoprostol placed the night prior to the procedure [40]. The copper IUD has a higher rate of dysmenorrhea and heavy menstrual bleeding and therefore should not be considered in women on anticoagulation as the rates of blood loss can increase by up to 65% [31,41]. Uterine perforation at the time of placement is uncommon (1 per 1000 placements) but can result in migration of the IUD into surrounding structures and subsequent surgery to remove the device [42,43]. Expulsion after placement occurs at a rate of 2 to 10% and is more common in the first 3 months of use, which puts women unknowingly at risk for unintended pregnancies [27,31]. Although current guidelines do not recommend antibiotic prophylaxis prior to IUD insertion for high-risk cardiac patients, there is a slight increased risk of pelvic inflammatory infection within the first month of use and has been associated with endocarditis in case reports of women with congenital heart disease [44,45]. It is the opinion of these authors that pre-procedural antibiotics may be considered for women in whom the associated morbidity of infective endocarditis is unacceptably high compared to the risks of antibiotic use.

Manipulation of the cervix can result in a vagal reaction in 5% of women, and in patients with a fixed cardiac output or decreased ventricular function, this can be life-threatening. For those women who risk cardiovascular collapse due to a vasovagal reaction (i.e., Fontan circulation, severe aortic stenosis, Eisenmenger's, severe left ventricular dysfunction) with IUD insertion, the etonogestrel subdermal implant is a safe and highly effective progestin-only alternative that is approved for use up to 3 years. It is a single-rod implant that contains 68 mg of the progestin etonogestrel and 15 mg of barium sulfate so as to be identified on X-ray or ultrasound. A trained clinician is required for insertion into the medial aspect of the proximal arm which may limit

Table 2. Contraceptive options according to type of hormone

Estrogen derivatives			
Estrogen component	Dosing of estrogen	Route of administration	Pharmacologic effect
Estradiol valerate (E2V) (natural)	3/2/2/1 mg (26 tablets +2 place- bo)	- Oral	- Ensures adequate endometrial proliferation and stability - Less effect on hepatic proteins and hemostatic parameters
Ethinyl estradiol (synthetic)	- Oral:	10 mcg/20 mcg/25 mcg/30 mcg/ 35 mcg/50 mcg - Patch: 30 mcg/day or 35 mcg/day - Ring: 13 mcg/ day/15 mcg/ day	- Oral - Transdermal patch - Transvaginal ring
- Headache - Nausea/vomiting - DVT/VTE			
Progestin derivatives			
Progestin component	Doses of progestin	Route of administration	Pharmacologic effect
Norethindrone acetate (greater bioavailability than norethindrone)	- 1 mg -1.5 mg -2.5 mg	- Oral	- Thickening of cervical mucus making cervix less penetrable by sperm
Norethindrone	- 0.4 mg - 0.5 mg - 0.75 mg - 1 mg		- Tubal motility impairment and decrease in tubal peristalsis
Ethynodiol diacetate (metabolizes to norethindrone)	- 1 mg	- Oral	
Norgestrel	- 0.3 mg - 0.5 mg	- Oral	
Levonorgestrel	- 0.05/0.75/0/1.25 mg - 0.1 mg - 0.15 mg	- Oral	
Desogestrel	- 0.15 mg - 0.1/0.125/0.15 mg	- Oral	
Norgestimate	- 0.25 mg - 0.18/0.215/0.25 mg	- Oral	- Suppression of ovulation - Thickening of cervical mucus

Table 2. (Continued)

			- Changes in endometrium altering implantation - Tubal motility impairment and decrease in tubal peristalsis
Drospirenone	- 3 mg	- Oral	
Dienogest	- 0/2/3/0 mg	- Oral	
Nomegestrol acetate	- 2.5 mg with 1.5 mg of estradiol hemihydrate	- Oral	
Etonogestrel	- Ring (Nuvaring): 120 mcg/day + EE 15 mcg/day	- Ring: 1 ring × 3–4 weeks	- Suppression of ovulation - Thickening of cervical mucus - Changes in endometrium which alters implantation
Norelgestromin	- Transdermal patch (Xulane): 150 mcg/day + EE 20 mcg/day	- Transdermal patch: 1 patch every week × 3 weeks	- Suppression of ovulation - Thickening of cervical mucus - Changes in endometrium which alters implantation
Segesterone	- Vaginal ring (Annovera): 150 mcg/day + EE 13 mcg/day - But one ring provides contraception for 13 28-day cycles	- Vaginal ring: insert ring × 3 weeks followed by 1 week without ring in place. The ring is then re-inserted for first 21 days of the next 28-day cycle. One system provides contraception for 13 cycles	- Suppression of ovulation - Thickening of cervical mucus - Changes in endometrium which alters implantation
Medroxyprogesterone acetate	150 mq IM every 11–13 weeks	- Injection	- Suppression of
- Amenorrhea or menstrual irregularities - Weight gain (variable (2–7 kg) - Bone density decreases; reversible upon discontinuation - Allergic reaction			
Long-acting reversible contraceptives			
Long-acting reversible contraceptive	Active ingredient	Pharmacologic effect (or mechanism of action?)	Effect on lipid profile
Etonogestrel implant	Etonogestrel 90 pg/ml per day	- Near 100% suppression of ovulation - Thickened cervical mucus to prevent sperm penetration into the upper genital tract	- Neutral effect
	Levonorgestrel (20 mcg per day)	- Thickening of cervical mucus	- Neutral effect

Table 2. (Continued)

Levonorgestrel iUD (Mirena)		- Suppression of endometrium - Impairs sperm function by changes in immune intrauterine environment - Impairs ovulation	
Levonorgestrel IUD (Liletta)	Levonorgestrel (20 mcg per day)		
Levonorgestrel IUD (Kyleena)	Levonorgestrel (12 mcg per day)		
Levonorgestrel IUD (Skyla)	Levonorgestrel (8 mcg per day)		
Copper T 380A IUD (ParaGard)	None/copper	- Toxic intrauterine environment causing destruction of sperm/ova, impaired implantation - Inflammation prevents fertilization, increases phagocytosis by sperm	No effect
Progestin-only pills			
Type of progestin	Dosing	Route of administration	Pharmacologic effect
Norethindrone	0.35 mg	- Oral	- Thickening of cervical mucus - Decreases ovulation in a proportion of cycles - Reduces activity of fallopian tube cilia - Alteration of endometrium, possibly inhibiting implantation

Estrogen derivatives			
Estrogen component	Androgenicity	Effect on lipid profile	Side effects
Estradiol valerate (E2V) (natural)	None	- Increases total cholesterol - Decreases LDL - Increases HDL - No change in VLDL or triglycerides	- Headache - Nausea/vomiting - DVT/VTE
Ethinyl estradiol (synthetic)	None	- Increases production of VLDL, HDL, and triglycerides - Enhances removal of LDL	- Headache - Nausea/vomiting - DVT/VTE
Progestin derivatives			
Progestin component	Androgenicity	Effect on lipid profile	Side effects
Norethindrone acetate (greater bioavailability than norethindrone) Norethindrone	Moderate	- Decreases HDL and HDL2 - Increases LDL	- Acne - Weight gain

Table 2. (Continued)

Ethynodiol diacetate (metabolizes to norethindrone)	Low		- Acne - Weight gain
Norgestrel	High	- Decreases HDL - Increases LDL	- Acne - Weight gain - Unwanted hair growth
Levonorgestrel	High	- Decreases HDL-C and HDL2-C - Increase in apolipoprotein B	- Acne - Weight gain - Unwanted hair growth
Desogestrel	Low	- Increase HDL	- Decreases acne - Decreases hirsuitism
Norgestimate	Low	- Decreases LDL	- Decreases acne - Decreases hirsuitism
Drospirenone	Low	- Increases HDL-C - Increases triglycerides - Decreases LDL- C	- Anti-mineralocorticoid diuretic effect may lower blood pressure (SBP 7–8 mmHg)
Dienogest	Low	- Increases triglycerides - Increases apolipoprotein A1	- Anti-androgenic properties
Nomegestrol acetate	Low	- Neutral effects	- Anti-androgenic properties
Etonogestrel	Low	- Increases triglycerides, HDL-C - Increases apolipoprotein AI - Decreases apolipoprotein B	- Headache - Vaginal discharge or foreign body sensation - Irregular bleeding - Breast discomfort
Norelgestromin	Low	- Increases HDL, HDL3, total cholesterol - Increases triglycerides - Decreases LDL/HDL	- Patch: local skin reaction - Breast discomfort (22%) - Headache (22%) - Nausea (8%)
Segesterone	Low	- Neutral effects	- Headache - Vaginal discharge or foreign body sensation - Irregular bleeding - Breast discomfort
Medroxyprogesterone acetate	Moderate	- Increases total cholesterol and LDL; self-limited in first few weeks and improves over time	- Amenorrhea or menstrual irregularities - Weight gain (variable (2–7 kg) - Bone density decreases; reversible upon discontinuation - Allergic reaction

Table 2. (Continued)

Long-acting reversible contraceptives			
Long-acting reversible contraceptive		Androgenicity	Side effects
Duration of use			
Etonogestrel implant	Low	- Local site irritation, soreness, placement-related risks - Migration of implant (rare) - Unpredictable bleeding (11%) - Acne (12%)	3–4 years (manufacturer vs new studies)
Levonorgestrel iUD (Mirena)	High	- Amenorrhea - Unpredictable bleeding - Cramping - Uterine perforation - Pregnancy complications in event of failure, including ectopic pregnancy - IUD expulsion (3–6% in first year) - Weight gain (10%, mean 1 kg) - Pelvic infection (< 1%)	5–7 years (manufacturer vs new studies)
Levonorgestrel IUD (Liletta)			6–7 years (manufacturer vs new studies)
Levonorgestrel IUD (Kyleena)			5 years
Levonorgestrel IUD (Skyla)			3 years
Copper T 380A IUD (ParaGard)	None	- Heavier, longer, or more uncomfortable menses - Uterine perforation - Pregnancy complications in event of failure, including ectopic pregnancy - IUD expulsion (3–10% in first year) - Pelvic infection (< 1%)	12–20 years (manufacturer vs new studies)
Progestin-only pills			
Type of progestin		Androgenicity	Effect on lipid profile
Side effects			
Norethindrone	Moderate	- Minimal effect	- Irregular bleeding - Melasma - Headache

accessibility. The primary mechanism of action is to inhibit ovulation. Similar to the progestin-containing IUD, it also thins the endometrial lining and thickens the cervical mucus [30,46]. The etonogestrel implant has an extremely low failure rate, comparable to that for permanent sterilization [28]. It is an excellent choice for adolescent females, as uptake and continuation rates are high [47]. Side effects are again similar to the LNG IUD, with most commonly reported side effects being headache, weight gain, acne, and emotional lability [48]. It is an alternative option to the LNG IUD, and a choice for women who are on anticoagulation as amenorrhea occurs in 22 to 29% of users [49,50]. However, up to 20% also experience irregular and/or intermenstrual bleeding, and this should be taken into consideration when deciding between the two forms of contraception [51]. Other non-cardiac contraindications include current or recent history of breast cancer, severe decompensated liver cirrhosis, hepatocellular carcinoma, and unexplained vaginal bleeding prior to investigation [10,22]. There is no permanent effect on bone mineral density, and the risk of venous thromboembolism, myocardial infarction, or stroke is not increased compared to non-users [18,35]. The efficacy remains high even in women in higher BMI categories [31].

Female sterilization is an option for women who have completed childbearing or in those for whom pregnancy presents an unacceptably high risk. This can be achieved either via laparoscopy, through an open abdominal incision, or at the time of cesarean delivery. The risk of failure with sterilization is dependent upon the technique, approach, and age of the patient, with an overall quoted efficacy of > 99.5% [10,52–55].

Moderately effective with moderate contraindications: depot medroxyprogesterone acetate injection, combined hormonal contraceptive pills, and progestin-only pills

Depot medroxyprogesterone acetate or DMPA is an injectable form of progestin-only contraception that is highly effective and with minimal contraindications. It is an optimal choice for women with heavy menstrual bleeding, hepatic disease, or any other contraindication to the estrogen component of CHCs [37]. It is administered intramuscularly at a dose of 150 mg/dL and given at 3-month intervals. Its long-acting efficacy is a direct effect of the pharmacologically active drug that can persist in the tissue for long periods of time [32]. The failure rates are similar to the previously mentioned LARCs at 0.2% [10,22]. The higher failure rate is likely due to non-compliance of returning for repeat injections and can be as high as 44–68% in some users [32,56]. The mechanism of action is similar to all other forms of systemic progesterone in that it inhibits ovulation and causes atrophy of the uterine lining. Added benefits of this form of contraception include amenorrhea and endometrial protection. Other side effects include irregular bleeding, weight gain, and delayed return of fertility [32,57,58]. There is transient but decreased bone density in women with prolonged use, alteration in lipid profiles (increased cholesterol and triglycerides with concomitant decrease in HDL), and slightly increased risk for a venous thromboembolic events [58–60].

The progestin-only pill, alternatively known as the "mini-pill," contains 0.35 mg of the progestin norethindrone and can be offered as an alternative oral contraceptive option when estrogen is contraindicated. The mechanism of action and side effect profile is similar to all the progestins; however, the failure rate of this type of contraception is reported between 9 and 15% as its

gonadotropin-inhibitory effect relies on perfect compliance and has to be taken at the same time every day [22,61,62].

Combined hormonal contraceptives (CHC) include any oral, vaginal, or transdermal form that contains both an estrogen and progestin component. Overall efficacy is from suppression of follicle-stimulating hormone (FSH), suppression of luteinizing hormone (LH) and the LH surge that triggers ovulation, alteration in the cervical mucus, and decidualization of the endometrium [33]. There are various formulations of both the estrogen and progestin components that will lead to desired and undesired (side) effects. Failure rates of 0.3% with perfect use and 9% with typical use have been documented, again largely due to the user-dependent requirement of timely daily dosing [63]. CHCs carry side effects that may render them inappropriate choices for women with cardiovascular disease. Estrogen has been known to raise blood pressure and should be used with caution in patients with hypertension. Although the pharmacokinetic effects of estrogen suggest an increase in fluid retention, the effects are likely of minimal clinical significance and should not preclude use in women with cardiovascular disease as the sole contraindication. More importantly, multiple studies have found a threefold increase in ischemic stroke, fivefold increase in myocardial infarction, and up to fourfold increase in VTE. These risks increase with increasing doses of estrogen [35,64–66]. The progestin component (gestogene, desogestrel, cyproterone acetate, and drospirenone-containing combination contraceptives) when combined with estrogen may independently increase the risk of VTE; however, when used without estrogen, this does not increase the risk of VTE above baseline [67]. The concomitant use of cardiac medications such as warfarin or bosentan must be considered when choosing contraception, as these interact with the CYP3A4 system and can decrease the efficacy of CHC as mentioned above. In women with underlying cardiovascular risk factors, alternative forms to CHC should be considered.

Least efficacious, minimal to no contraindications: barrier methods, spermicide, and natural family planning

Examples of these methods include condoms, spermicides, female sponges, female diaphragms, female condoms, and cervical caps. These methods are associated with the highest failure rates and account for up to 5% of all unplanned pregnancies. These should be a last resort as far as contraceptive options in women with cardiovascular disease. The efficacy is dependent upon perfect use and with some forms, proper fitting performed by a gynecologist.

Emergency contraception

In all women, but particularly those in whom pregnancy poses an unacceptably high risk of adverse outcomes, emergency contraception should be discussed at every visit. There are several different forms of emergency contraception, but the most effective is placement of a copper IUD. If inserted within 7 days of unprotected intercourse, the risk of pregnancy is reduced by more than 99% [22]. It is important to counsel the patient on the currently available products on the market (Table 3 from Lee et al.), timing of intended use following unprotected intercourse, most common side effects, efficacy in larger BMI status, safety profile during breastfeeding (for those in the postpartum period),

Table 3. Comparison of available emergency contraception methods

EC method	Mechanism of action	Dosing	Efficacy	Use by overweight women	Common side effects	Notable drug interactions
Ulipristal acetate pill	Selective progesterone receptor modulator; delays or inhibits ovulation	30 mg orally, once as soon as possible following unprotected intercourse	98% within 72 h [31] and 62–85% within 120 h of unprotected intercourse [27–30]	Greater efficacy than LNG ECPs but little efficacy when BMI > 35 kg/m^2 [34]	Headache, nausea, and vomiting [28, 29]	Cytochrome P450 3A4 inducers and progestin-containing hormonal contraceptives may reduce ECP efficacy [37, 38]
Levonorgestrel pill	Delays or inhibits ovulation and luteal function	1.5 mg orally, once as soon as possible following unprotected intercourse	52–94% within 72 h of unprotected intercourse [31]	Little efficacy when BMI > 26 kg/m^2 [34]	Headache, nausea, and vomiting [28, 29]	Cytochrome P450 3A4 inducers may reduce ECP efficacy [37]
Combined ECPs	Delays or inhibits ovulation	Dosing depends on the pill used; several pills taken in two doses 12 h apart [39]	Least effective EC, 74% within 72 h of unprotected intercourse [40]	No prior studies, but likely little efficacy when BMI > 26 kg/m^2	Nausea and vomiting [41]	Cytochrome P450 3A4 inducers may reduce ECP efficacy [37]
Copper IUD	Prevents fertilization or implantation	IUD placement within 5 days after unprotected intercourse	99% when a Cu-IUD is placed up to 5 days after unprotected intercourse [3]	Equally efficacious in overweight women given local mechanism of action	Short-term uterine cramping and changes in menstrual cycle [42]	None

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and the rapidity of fertility resumption [68,69]. Furthermore, these products are not abortifacients and should not be used outside the recommended exposure window. There are currently no cardiac conditions for which the risks of use of emergency contraception outweigh potential benefit [22].

Summary

There are numerous contraceptive options available to women with cardiovascular disease. The personalization of birth control to patients' cardiovascular conditions remains key and should be the most important consideration when prescribing contraception. The nuances of timing, efficacy, duration of use, and side effects will also influence decision-making in this complex group of women.

Compliance with Ethical Standards

Conflict of Interest

Karen L. Florio declares that she has no conflict of interest. Monica Kao declares that she has no conflict of interest. Traci Johnson declares that she has no conflict of interest. Heidi A. Tuttle declares that she has no conflict of interest. Darcy White declares that she has no conflict of interest. Lynne Nelson declares that she has no conflict of interest. Neil Patel declares that he has no conflict of interest. Devon Ramaeker declares that he/she has no conflict of interest. Sue Kendig declares that he/she has no conflict of interest. Laura Schmidt declares that she has no conflict of interest. Anna Grodzinsky declares that she has no conflict of interest. Katherine Economy declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent Statement

This article does not contain any studies with human or animal subjects performed by any of the authors.

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