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Contraceptive Strategies in Women With Heart Failure or With Cardiac Transplantation

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Abstract

Purpose of Review We describe contraception for two groups of women: (1) women with heart failure and (2) women with cardiac transplantation.

Recent Findings Medical Eligibility Criteria for contraceptive agents address women with peripartum cardiomyopathy and women with valvular heart disease (Curtis et al. MMWR Recomm Rep 65:1–103, 2016). Recommendations for women with other forms of heart failure are extrapolated from these populations. Recommendations for women with cardiac transplantation have shifted since the 1980s: use of long-acting reversible contraception has increased, and there is a better understanding of the interactions between contraceptive and immunosuppressive regimens.

Summary Women with heart failure may utilize long-acting reversible contraception and permanent sterilization. Modifications should be made according to the specific etiology of the heart failure. In women with cardiac transplantation, pregnancy is high risk and should be avoided altogether for 1–2 years after transplantation. In uncomplicated transplantation, almost all forms of contraception are allowable. In complicated transplantation, combined hormonal contraceptives are contraindicated, and de novo IUD insertion is not recommended.

Keywords Contraception · Cardiac transplantation · Heart failure · Cardiomyopathy · Estrogen and progesterone · Intrauterine device

Introduction

Women with heart failure and women who have undergone cardiac transplantation represent two populations in whom pregnancy can be a high risk proposition [1, 2]. Preconception counseling is essential on several fronts: (1) prevention of unplanned pregnancy, (2) counseling about potential maternal and neonatal risks of pregnancy to determine whether pregnancy is advisable/feasible, (3) optimization of timing of pregnancy, and (4) adjustment of medication regimens for fetal safety prior to conception. Genetic counseling may be appropriate for women who have an underlying heritable etiology of their cardiac dysfunction. Many women with either heart failure or cardiac transplantation have a pregnancy risk that is prohibitive [3, 4]. Effective contraception is as important for their future well-being and survival as their cardiac regimen.

In order to adequately counsel women with heart failure or cardiac transplantation on appropriate contraceptive strategies, cardiologists must be familiar with the different contraception options that are currently available. They should be able to balance the contraceptive efficacy versus the cardiac safety of different contraceptive methods. In order to do so, they must be familiar with the potential for adverse cardiac side effects of contraceptive agents, including adverse effects on blood pressure control, fluid retention, risk of thrombosis, risk of infection, and risk of arrhythmia.

The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have published Medical Eligibility Criteria (MEC) for contraceptive use [5••, 6•, 7•]. Taken together, these documents make recommendations for women with peripartum cardiomyopathy, valvular heart disease, ischemic heart disease, hypertension, hyperlipidemia, and solid organ transplantation. Recommendations for other forms of heart failure and for

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cardiac transplantation, specifically, are extrapolated from these guidelines. In addition, several post-transplant registries, including the National Transplantation Pregnancy Registry, have provided data on post-transplantation pregnancy outcomes and counseling on contraceptive options for women with cardiac transplantation [8•].

Forms of Contraception

Without any form of contraception, about 85% of women will experience an unintended pregnancy within a year [6•]. Knowledge and utilization of contraceptive methods is essential for prevention of unplanned pregnancy.

Barrier Methods

Barrier forms of contraception include use of spermicides, calendar methods, withdrawal methods, use of sponge, female and male condom use, and use of a diaphragm or cervical cap. The advantage of these methods is that they are safe for all forms of cardiac disease and are easily reversible with respect to fertility. Condoms provide protection against sexually transmitted diseases. The difficulty with barrier methods is the relatively inferior contraceptive efficacy compared to other forms. With typical use, barrier methods have a failure rate ranging from 12 to 28% within a year. With perfect use, the failure rate can be reduced to 2–5% per year [6•]. For advanced cardiac disease, in which pregnancy carries a mortality risk, the efficacy of barrier methods is insufficient protection [9]. In the post-cardiac transplant patient, barrier methods are insufficient protection, especially within the first 1–2 years of transplant, during which time the woman is at high risk for graft rejection [10].

Combined Estrogen and Progesterone Contraceptives

Combined estrogen and progesterone contraceptives include combined oral contraceptive (COCs), contraceptive patch, and the vaginal ring.

Combined oral contraceptives (COCs) include a combination of estrogen (various dosages) and progestins (four different generations). The most common estrogen used in COCs is ethinyl estradiol. Older COCs used 50 mcg of ethinyl estradiol. Progressively newer COCs have utilized lower doses (ranging from 10 to 35 mcg). Estrogen inhibits ovulation, thickens cervical mucus, and alters endometrial receptivity. The progestins in COCs act by thickening cervical mucus, altering endometrial receptivity, and impairing tubal motility. They have a less reliable effect on inhibition of ovulation than the estrogen component [11]. Desogestrel and drospirenone (third- and fourth-generation progestins, respectively) have been shown to effectively suppress ovulation, but neither is available in the USA in a progestin-only pill formulation [12]. First-generation progestins were derived from testosterone, and second-generation progestins are an estrane derivative of testosterone. Thus, they have a higher rate of androgenic side effects, such as hirsuitism, acne, bloating, fluid retention, and lowering of HDL cholesterol [13, 14]. Third- and fourth-generation progestins are significantly less androgenic, and fourth-generation progestins have partial anti-androgenic and anti-mineralocorticoid activity. The latter promotes natriuresis and a slight lowering of blood pressure [12, 15]. Drosperinone containing COCs does not raise blood pressure, even in women who are hypertensive at baseline [12, 16].

COCs have a failure rate of 9% (with typical use) and 0.3% (with perfect use) in the first year [6•]. The estrogen component of COCs achieves a high contraceptive efficacy, but it can cause a number of adverse cardiac sequelae. These risks are attributed to the estrogen component by comparison with progestin-only pills, which, in general, have not been associated with the risks described below.

Estrogen use can raise blood pressure; although the typical blood pressure elevation is mild (5–10 mmHg), some women can develop overt hypertension. Blood pressure effects are rapidly reversible with discontinuation of the medication [17, 18].

Estrogen is thought to promote fluid retention. The exact mechanism of this effect for COCs is not definitive. Estrogen stimulates hepatic synthesis of angiotensin, which ultimately leads to an increase in aldosterone levels, and hence sodium and water retention [19]. In post-menopausal women, estradiol administration altered renal sensitivity to arginine vasopressin, leading to plasma volume expansion [20, 21].

The estrogen component of COCs has been associated with a small increased risk of ischemic stroke with a thrombotic mechanism, with an absolute risk of 11.3 cases per 100,000 women-years in young women (< 44 years) [22]. The risk of ischemic stroke increases with age.

COCs with low (20 mcg) to medium (30–40 mcg) dose estrogen preparations are associated with a small increased relative risk for myocardial infarction (RR 1.44 for low dose and RR 1.88 for medium dose), thought to be mediated by arterial thrombosis, rather than atherosclerotic plaque accumulation [23].

COC use is associated with a two- to fourfold increased risk of venous thromboembolism (VTE) [24, 25]. For VTE, both the estrogen and progestin components may have an influence on overall risk. Third- and fourth-generation COCs containing desogestrel, gestodene, or drospirenone are associated with a higher VTE risk than second-generation COCs that contain levonorgestrel or noresthisterone [26, 27].

Endogenous and exogenous estrogen and progestins are known to affect the QT interval [28]. Estrogen lengthens the QT interval. Progestins differ in their effects of QTc due to differing androgenic potential (first-, second-, and third-

generation progestins shorten the QT, while fourth-generation progestins do not) [29]. While COCs that utilize first-, second-, and third-generation progestins have no net effect on the QTc, COCs that utilize fourth-generation progestins (e.g., drosperinone) have been shown to lengthen the QTC by 4 ms (presumed unopposed estrogen effect) [28]. Whether the change in QTc translates into an increase in adverse cardiac outcomes has yet to be determined; an initial study in the Rochester-based LQTS (long QT syndrome) Registry showed no difference in cardiac events in COC users compared to non-COC users [30].

The contraceptive patch releases ethinyl estradiol (35 mcg/day) and norelgestromin (derivative of a third generation progestin, 0.15 mg/day). The hormones do not go through first pass metabolism through the liver. Patch efficacy is similar to COCs (9% unintended pregnancy within 1 year typical use and 0.3% perfect use); compliance and achievement of perfect use may be better for the patch than for COCs [6•]. There have been reports of a potential small increase in VTE risk and arterial thrombotic risk for users of the patch compared to users of COCs, but the evidence is not yet definitive [31].

The contraceptive vaginal ring releases ethinyl estradiol (15 mcg/day) and etonogestrel (derivative of a third-generation progestin, 0.12 mg/day). The ring is self-inserted into the vagina by the woman and changed weekly for 3 weeks, followed by a 1-week, ring-free interval. It comes in one size only and does not require fitting. Ring efficacy is similar to COCs and contraceptive patches (9% unintended pregnancy within 1 year typical use and 0.3% perfect use) [6•]. Risk of VTE and stroke appears similar between the vaginal ring and COCs [23, 32]. Risk of MI is uncertain due to a low event rate.

Progesterone-Only Contraception

Progesterone-only contraception includes (1) progesterone-only pills, (2) depot medroxyprogesterone acetate (DPMA) injections, and (3) progestin implants.

Progesterone-only pills (POPs) provide an alternative oral form of contraception for women who are unable to tolerate the risks of COCs. In the USA, norethindrone is the main progestin used in POPs. Norethindrone POPs are not associated with blood pressure elevations, increased risk of VTE, fluid retention, changes in lipid profile, or QTc prolongation [21, 29, 33, 34]. However, norethindrone does not reliably suppress ovulation; it mainly thickens cervical mucus and alters endometrial receptivity. In addition, in order to work effectively, POPs must be taken at the same time each day. As such, the failure rate of norethindrone POPs is likely to be > 9% per year in highly fertile women with typical use. In other parts of the world, desogestrel POPs are available. Desogestrel is able to suppress ovulation with a similar efficacy to COCs, and the timing of its administration is not as stringent as norethindrone POPs. POPs may cause unpredictable breakthrough bleeding that ultimately affects compliance [35].

Depot medroxyprogesterone acetate (DMPA) is an injectable form of progesterone-only contraception that is effective for 3 months. It can be delivered via intramuscular or subcutaneous routes. DMPA effectively suppresses ovulation, in addition to thickening cervical mucus and altering endometrial receptivity. Failure rates are 6% within 1 year with typical use and 0.2% with perfect use [6•]. Delayed return for a repeat injection after 3 months was the usual cause of contraceptive failure. Although breakthrough bleeding can occur initially, sustained use of DMPA usually leads to amenorrhea. DMPA has not been associated with adverse effects on blood pressure, fluid retention, or QTc prolongation. However, there have been some studies that have suggested that VTE risk is increased; the strength of this evidence is regarded as weak [31]. Long-term DMPA use has been shown to induce unfavorable changes in serum lipid profiles [36, 37]. These include an increase in total cholesterol, triglycerides, and low-density lipoprotein, as well as a reduction in high density lipoprotein. The changes in lipid profile are thought to increase overall cardiovascular risk, but whether this translates into adverse clinical outcomes has yet to be determined. DMPA can also cause a decrease in bone mineral density because it induces a hypoestrogenic state [38].

Progesterone-only implants are another effective form of long-acting reversible contraception. In many countries, including the USA, a single rod, etonogestrel-releasing system is available. It was originally marketed as Implanon; the rod was modified to be radio-opaque for easier removal and was remarketed as Nexplanon. Prior to 2002, a six-rod levonorgestrel system was used (Norplant); it is no longer available. Outside the USA, a two-rod levonorgestrel system (Jadelle or Sino-implant) is available. Etonogestrel implants stay efficacious for 3 years, and their failure rates are very low—0.05% risk of pregnancy within the first year of use [6•]. In fact, etonogestrel implant efficacy is higher than that of permanent sterilization. Etonogestrel implant use has not been found to increase the risk of hypertension, hyperlipidemia, myocardial infarction, ischemic stroke, or VTE in trials [31, 39]. It does not induce fluid retention, and progesterone contraception does not seem to lead to QTc prolongation [40, 41]. However, because etonogestrel is a metabolite of desogestrel, a third-generation progestin that may be associated with increased VTE risk, its package insert lists current or past thrombosis as a contraindication. Progestin implants can cause significant unscheduled bleeding, which can limit their tolerability, despite their excellent efficacy [42].

IUDs and IUSs

Intrauterine devices (IUDs), coated with copper, and intrauterine systems (IUSs), coated with the progestin, levonorgestrel,

are among the most commonly used form of long-acting reversible contraception. The IUDs and IUSs induce a sterile inflammatory reaction within the uterus that is toxic to sperm and ova and impairs implantation. Copper has an additive toxic effect on sperm; levonorgestrel thickens cervical mucus and alters endometrial receptivity. An IUD/IUS will not disrupt an already implanted pregnancy. Copper IUDs provided effective contraception (failure rate with typical use 0.8% in 1 year) for up to 10 years; Levonorgestrel IUSs are approved for use over a 5-year period and are equally efficacious (typical failure rate 0.2% in first year) [6•]. Unscheduled bleeding is significantly less with an IUD/IUS compared to progestin implants and tends to improve over time. Menstrual bleeding with the copper IUD can be heavier; in contrast, the levonorgestrel IUS tends to lessen menstrual flow or even cause amenorrhea [43]. IUD/IUS use is not associated with blood pressure elevation, increase in VTE, increase in ischemic stroke, fluid retention, or QTc prolongation [31].

Female and Male Sterilization

Sterilization is useful for those who desire permanent forms of contraception. Failure rates are very low (0.5% in the first year for female sterilization and 0.15% in the first year for male sterilization) [6•]. Female sterilization, also known as tubal ligation or tubal occlusion, can be accomplished by a variety of techniques: (1) postpartum sterilization via a cesarean incision for cesarean delivery or via a mini-laparotomy following a vaginal delivery or (2) interval sterilization via a laparoscopic, hysteroscopic (tubal occlusion device), or mini-laparotomy approach. In each of these cases, surgical and anesthetic risk has to be taken into account before recommending this form of contraception to women. Male sterilization involves vasectomy. Vasectomy is perhaps the safest method of contraception, especially for the woman, assuming that she will not have any other male partners. However, for women with very advanced cardiac disease who have a tangible short-term mortality risk, vasectomy may be a poor choice for a man who has a reasonable chance of having a future partner [44].

Emergency Contraception

Women who have had unprotected intercourse or who have experienced failure of another method of contraception (e.g., condom rupture, inadvertent missed contraceptive pill) have the option of emergency contraception to avoid pregnancy. Options for emergency contraception include (1) placement of a copper IUD, (2) levonorgestrel (1 dose of 1.5 mg, or 2 doses of 0.75 mg, administered 12 h apart), (3) anti-progestins—ulipristal and mifepristone (mifepristone not available in the USA), and (4) combined estrogen and progesterone oral contraceptive pills in adjusted dosages. Use of antacids, histamine H2 blockers, and proton pump inhibitors may reduce the absorption of ulipristal; a copper IUD is preferred in women who take these medications concurrently. The copper IUD is the most efficacious (failure rate of 0.04 to 0.19%), followed by ulipristal or mefepistone (failure rate 1.4%), followed by levonorgestrel (failure rate 2–3%). Although a COC made specifically for emergency contraception is not available, several COC pills used for regular contraception can be taken together to equal 100 mcg of ethinyl estradiol and 0.5 mg of levonorgestrel. This same combination should be repeated in 12 h (total dose of 200 mcg ethinyl estradiol and 1 mg levonorgestrel). Once implantation has occurred, none of the emergency contraceptive options are effective [45, 46].

WHO and CDC MEC for Contraceptive Use

The 2010 and 2015 WHO-medical eligibility criteria (MEC) documents and the 2016 CDC-MEC document both utilize a four-point scale to grade advisability of contraceptive use (Table 1) [5••, 6•, 7•].

A simplified schema for contraceptive choices in patients with heart failure or cardiac transplantation is shown in Fig. 1.

Considerations in the Heart Failure Patient

It is important to recognize that the term “heart failure” encompasses a diverse range of conditions, each of which has specific risks with respect to contraceptive use. We will consider contraceptive recommendations for common forms of heart failure in women of child-bearing age: (1) peripartum cardiomyopathy, (2) idiopathic dilated cardiomyopathy, (3) ischemic cardiomyopathy, (4) hypertrophic cardiomyopathy, (5) hypertensive heart disease with diastolic dysfunction, (6) valvular cardiomyopathy, (7) chemotherapy-associated cardiomyopathy, and (8) cardiomyopathy associated with arrhythmias. Cardiomyopathy due to complex congenital cardiac disease is beyond the scope of this review.

Patients with heart failure of all varieties may require medications that are contraindicated during pregnancy. This makes unplanned pregnancy particularly undesirable. Specifically, women should be counseled that angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists are strictly contraindicated during pregnancy. Although beta blockers are not contraindicated, atenolol use is not preferred during pregnancy, and use of beta blockers may have additional theoretical adverse fetal effects, including intrauterine growth retardation. Warfarin has adverse fetal effects and requires substitution with other agents during specific periods of fetal development and at the time of labor and delivery. Diuretic use during pregnancy can have adverse effects on amniotic fluid volume [2]. Cardiac conditions for which pregnancy is contraindicated are listed in Table 2 [9].

Table 1 WHO and CDC scale for advisability of contraceptive use

1	A condition for which there is no restriction to use
2	A condition for which the advantages of use outweigh the theoretical or proven risks
3	A condition for which the theoretical or proven risks outweigh the advantages
4	A condition for which the method should not be used

In general, barrier methods are considered safe in all forms of heart failure. Although data on emergency contraception in heart failure patients is lacking, copper IUD is considered safe for most forms of cardiac disease, and the limited doses of anti-progestins (ulipristal and mifepristone) and levonorgestrel make the risk of these agents in this population small relative to the risk of unintended pregnancy [5••].

Recommendations for peripartum cardiomyopathy (PPCM) are well elucidated in CDC-MEC. Combined estrogen and progesterone combinations, including pill, patch, and vaginal ring, are not advisable in patients with a history of PPCM (CDC-MEC 4). Blood pressure elevation, fluid retention, increased thrombogenicity, and the potential for QTc prolongation may all adversely affect patients with PPCM. Progestin-only contraception, including POP, implant, and DMPA injection, is allowed and advisable (CDC-MEC 1 in patients with mild/moderate cardiac limitations and CDC-MEC 2 in patients with more advanced heart failure symptoms) [5••]. One caveat to this recommendation is that contraceptive efficacies of POP, implant, and DMPA are not equal. In patients with severe cardiomyopathy for whom pregnancy could be life-threatening, the efficacy of progestin-only contraception from highest to lowest is implant > DMPA > POP [47]. Furthermore, outside the USA, the thrombogenicity of desogestrel POPs is still under investigation; if a woman with PPCM has high thrombotic potential, desogestrel POP may carry additional risk [48, 49]. Copper IUD and levonorgestrel IUS are both allowed for women with PPCM, with CDC-MEC 2. Some concern was raised that IUD/IUS insertion could induce a profound vagal reaction and thus provoke arrhythmias in these patients [9]. There are no direct data for women with idiopathic dilated cardiomyopathy. Recommendations for these women are extrapolated from and parallel the recommendations for women with PPCM.

Women with an ischemic cardiomyopathy secondary to known atherosclerotic disease should not use combination estrogen and progesterone contraception (pill, patch, or vaginal ring) (CDC-MEC 4). Initiation of POPs and progestin implants are allowed (CDC-MEC 2), but if a woman develops an ischemic cardiomyopathy while using POPs or an implant, the risk of continuation is deemed high due to hypoestrogenic effects (CDC-MEC 3). DMPA use is not advised (CDC-MEC 3). Copper IUDs are strongly recommended in this population (CDC-MEC 1); levonorgestrel IUS is recommended (CDC-MEC 2), but if a woman develops ischemic cardiomyopathy while using the levonorgestrel IUS, continuation is not recommended (CDC-MEC 3) due to a theoretical adverse effect on lipid profile [5••].

Women with hypertrophic cardiomyopathy (HCM) have a different risk factor profile during pregnancy than women with left ventricular systolic dysfunction. Pregnancy is generally well tolerated by women with HCM [50]. The WHO and CDC do not have specific recommendations for women with

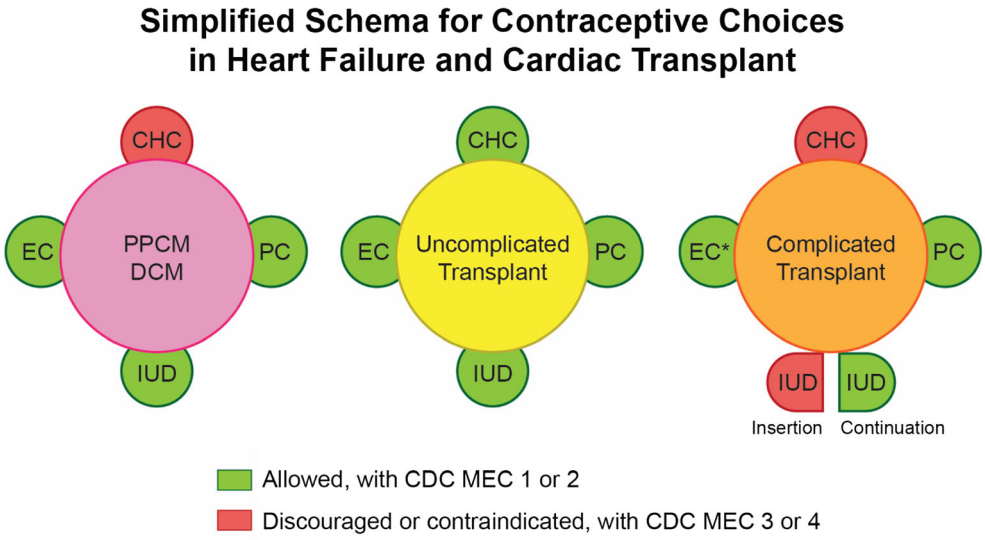

Fig. 1 Simplified schema for contraceptive choices in heart failure and cardiac transplant

*Copper IUD is not recommended for EC in complicated transplant

Abbreviations: PPCM, peripartum cardiomyopathy; DCM, dilated cardiomyopathy; CHC, combined hormonal contraceptives, including estrogen + progestin pills, patch or vaginal ring; PC, progesterone only contraception, including progesterone only pill, Depot-medroxyprogesterone acetate injection, and implant; IUD, intrauterine device or intrauterine system; EC, emergency contraception, including copper IUD, ulipristal acetate, levonorgestrel, or combined oral contraceptive pill

Table 2 Cardiac conditions for which pregnancy is contraindicated

Severely reduced left ventricular ejection fraction (LVEF < 30%)
New York Heart Association III or IV symptoms
Pulmonary hypertension of any cause
Prior peripartum cardiomyopathy with any residual impairment of left ventricular systolic function
Marfan syndrome with a dilated aorta > 4.0 cm

HCM. However, many women with HCM have concomitant hypertension, and some have significant arrhythmia risk that necessitates placement of an implantable cardiac defibrillator (ICD). The effects of estrogen on blood pressure, fluid retention, and QTc may not be desirable in this population, and combined estrogen and progesterone contraception may not be advisable.

Women with hypertensive heart disease (and potentially clinically significant diastolic dysfunction) should not use combination estrogen and progesterone contraception (CDC-MEC 3–4). POPs and progestin implants are allowed (CDC-MEC 1–2, depending on level of BP control). DMPA is allowed for women with controlled hypertension (CDC-MEC 2) but should not be used in uncontrolled hypertension (BP > 160/100 mmHg) or in women with multiple atherosclerotic risk factors (CDC-MEC 3) [5••].

Women with valvular disease are divided into uncomplicated valvular disease and complicated valvular disease in WHO-MEC. Those with uncomplicated disease may use any form of contraception. In CDC-MEC, complicated valvular disease was defined as valve disease with pulmonary hypertension, increased risk for atrial fibrillation, or associated with bacterial endocarditis. Complicated valve disease is thought to have an increased risk of thrombosis, and as such, combination estrogen and progesterone contraception is not advised (CDC-MEC 4). Once valve disease causes a true cardiomyopathy with left ventricular systolic dysfunction, estrogen containing contraception has the additional risks described in the PPCM and idiopathic dilated cardiomyopathy populations. All forms of progestin-only contraception are allowed for both uncomplicated and complicated valve disease (CDC-MEC 1). With advanced LV systolic dysfunction, progestin-only contraception would still be allowed (CDC-MEC 2). Copper IUD and levonorgestrel IUS are both allowed (CDC-MEC 1); according to the American Heart Association guidelines and the European Society of Cardiology guidelines, antibiotic prophylaxis of endocarditis is not required for IUD/IUS insertion or removal [5••, 51].

Chemotherapy-associated cardiomyopathy occurs in the setting of exposure to cardiotoxic agents, such as (but not limited to) trastuzumab, pertuzumab, ado-trastuzumab-emtansine, doxorubicin, liposomal doxorubicin, epirubicin, and idarubicin [52]. For patients who are undergoing treatment for hormone-sensitive breast cancer, combination estrogen and progesterone contraception, progesterone-only contraception, and levonorgestrel IUS are all not advisable [53]. Choice of contraception for other forms of cancer will depend on the patient's cardiac function, cardiovascular risk factor profile, and thrombosis risk.

Cardiomyopathy can occur in the setting of specific arrhythmias. Atrial fibrillation and atrial flutter can lead to a cardiomyopathy, especially in the setting of sustained tachycardia. If LV dysfunction is significant, contraceptive recommendations should follow the guidelines outlined for PPCM (above). In women who are anticoagulated for atrial fibrillation or flutter, there may be an additional consideration: bleeding risk. Of the two forms of intrauterine contraception, copper IUD is associated with heavier menstrual bleeding than levonorgestrel IUS [43]. Hence, the levonorgestrel IUS may be better tolerated. Interestingly, DMPA injection has not been found to carry additional risk of hematoma formation in the setting of systemic anticoagulation. Women who have a risk of ventricular arrhythmias (e.g., Long QT syndrome, hypertrophic cardiomyopathy, ischemic cardiomyopathy with scar formation, dilated cardiomyopathy or PPCM with severely reduced LV systolic function) have a theoretical risk from exposure to contraceptive agents that lead to QT prolongation. Fourth-generation COCs carry this theoretic risk; whether this translates into an actual clinical risk of increased cardiac events remains to be determined [30]. Many women in this group already have contraindications for estrogen containing contraception, above and beyond the potential arrhythmia risk.

Cardiac Transplantation

Pregnancy in women who have received a heart transplant is feasible but is considered high risk [1, 3, 10, 54]. Women with cardiac transplant have to consider the effects of immunosuppressive medications on their baseline health, the potential for genetic transmission of the original cardiac defect to the fetus, the impact of pregnancy on acute rejection and on graft function, and the expectation of maternal survival (independent of pregnancy risk). There is a strong recommendation to avoid pregnancy for at least 1 year following transplantation, during which time the risk of rejection is higher [55]. Given all of these considerations, discussions about contraception are paramount, beginning well before transplantation.

The effects of typical immunosuppressive medications has relevance to choice of contraception. The four most common classes of immunosuppressive medications and their side effects are shown in Table 3 [56•, 57].

When choosing a contraceptive regimen, one should consider both the general recommendations for women with solid organ transplantation as well as the presence of other cardiovascular co-morbidities, including hypertension, hyperlipidemia, fluid retention, and diabetes.

Pregnancy risks in women with cardiac transplants are an important part of the discussion about the need for an effective contraception plan. The National Transplantation Pregnancy Registry provides data to quantify pregnancy risk in cardiac transplant patients, which varied according to the immunosuppressive regimen (Table 4) [8•].

Contraception recommendations for cardiac transplant recipients follow the general recommendations for solid organ transplant [56•, 58, 59•, 60]. Solid organ transplants are divided into two groups: uncomplicated and complicated. In uncomplicated transplant, almost all forms of contraception are allowable (in the absence of other cardiovascular co-morbidities). Specifically, combined estrogen and progesterone pills, patch, and vaginal ring are considered safe (CDC-MEC 2). All forms of progestin-only contraception (POP, implant, and DMPA injection) are allowed in uncomplicated transplant (CDC-MEC 2). Finally, copper IUD and levonorgestrel IUS are classified according to de novo insertions (initiation) versus continuation of existing devices. In uncomplicated transplant, both initiation and continuation of IUD and IUS are allowed (CDC-MEC 2). All forms of emergency contraception are allowed—copper IUD is CDC-MEC 2; levonorgestrel, ulipristal, and COC for emergency contraception are all CDC-MEC 1 [5••].

Although almost all forms of contraception are allowable in uncomplicated transplant, typical immunosuppressive regimens can result in a high rate of hypertension, hyperlipidemia, and diabetes [61–65]. Since multiple cardiovascular risk factors are commonly present in cardiac transplant recipients, the use of combined hormonal contraception may not be feasible. Similarly, use of DMPA may be problematic due to its effects of lipid profile. As such, IUD/IUS has become one of the most commonly recommended contraceptive methods in the transplant population [58, 66, 67]. Historically, this was not the case—in the 1980s, IUD/IUS use in the post-transplant population was strongly discouraged, if not altogether contraindicated due to concerns that (1) immunosuppressive regimens would make an IUD ineffective, and (2) IUDs would result in pelvic infections in post-transplant patients [68, 69]. Clinical experience has shown that these concerns are largely unfounded; it is important to note this shift in clinical practice over the past 30 years.

Complicated transplants are defined as those that show evidence of graft failure, rejection, or transplant vasculopathy. Complicated transplants have several notable restrictions with respect to contraceptive selection. Combined estrogen and progesterone contraception (pill, patch, or vaginal ring) are all contraindicated due to their effect on overall cardiovascular risk. IUD and IUS are classified according to de novo insertion versus continuation of an existing device. Complicated transplants often require an increase in their immunosuppressive regimens, which increases their risk of infection. As such, de novo IUD/IUS insertion is not recommended (CDC-MEC 3). However, continuation of an existing device is not thought to pose an additional infection risk and is therefore allowed (CDC-MEC 2). All forms of progesterone-only contraception (POP, implant, and DPMA injection) are permissible (CDC-MEC 2) [5••]. However, if a patient with a complicated transplant has evidence of dyslipidemia or bone loss, DPMA injection may aggravate these conditions [38, 70]. The contraceptive efficacy of norethindrone-based POP may not be sufficient in this population; desogestrel-based POP (in countries where it is available) has better efficacy [12]. In complicated transplant patients who require emergency contraception, copper IUD insertion is not recommended (CDC-MEC 3). However, ulipristal, levonorgestrel, and combined oral contraceptive pill combinations are all allowed (CDC-MEC 1) [5••].

For cardiac transplant recipients who do not intend to ever undergo pregnancy, permanent sterilization options may be preferred. For female sterilization, anesthesia and surgical risk have to be considered. For male sterilization, the mortality of the female transplant recipient should be taken into account: if the man is likely to have another partner in his lifetime, vasectomy may not be a wise option.

Table 3 Immunosuppressive medications used post-cardiac transplant

Class	Examples	Major side effects
Steroids	Methyprednisolone, prednisolone, prednisone	Fluid retention, diabetes, hypertension, hyperlipidemia, myopathy, osteoporosis
Calcineurin inhibitors	Cyclosporine A, tacrolimus	Hypertension, nephrotoxicity, dyslipidemia, diabetes
Mammalian target of rapamycin (mTOR) inhibitors	Everolimus, sirolimus	Hyperlipidemia, fluid retention, bone marrow suppression, impairment of wound healing
Antimetabolites	Mycophenolate mofetil, azathioprine	Diarrhea, leucopenia; contraindicated during pregnancy (teratogenic)

Table 4 Pregnancy risks in heart transplant recipients

Complication during pregnancy	Frequency (%)[a]
Hypertension	31–52
Preeclampsia	10–30
Diabetes	0–4
Infection	8–21
Rejection episode	3–22
Graft loss within 2 years	0–6
Livebirths	50–71
Stillbirths	0–4
Miscarriage	17–42

[a] Frequency range is due to varied immunosuppressive regimens

Conclusion

Contraception counseling is an important conversation for a cardiologist to have with his/her patients, especially those with heart failure or cardiac transplantation. In order to effectively consider which contraceptive strategy maximizes efficacy and minimizes risk, cardiologists have to be familiar with the common forms of contraception and their side effects. In addition, cardiologists should be aware of existing guideline recommendations for choice of contraceptive agents in patients with cardiovascular conditions and solid organ transplantation. Since many cardiac conditions for which contraception counseling is required do not have direct data-driven recommendations, cardiologists will have to use their knowledge of specific contraceptive agents to tailor a strategy for their individual patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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