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Review

Gynecological health of females with congenital heart disease

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Abstract

Because of major advances in diagnostic and surgical methods, females with congenital heart disease (CHD) now survive into and beyond their reproductive years. Management of pregnancy in this patient population is well described, but gynecologic management such as menstruation, contraception and menopause have received scanty attention. Accordingly, the gynecologic health issues confronting these patients are described.

Menstrual patterns in acyanotic females with CHD are similar to the general population, but cyanotic females have menstrual irregularities including amenorrhea, which implies anovulation and an increased risk of uterine carcinoma. Anticoagulants predispose to heavy vaginal bleeding and corpus luteum rupture. Contraceptives must be selected according to individual patient profiles. Hormone replacement therapy is warranted for relief of menopausal symptoms as in the general population and should be relatively safe because estrogen dose is low.

Keywords: Congenital heart disease; Menstruation; Contraception

Increasing numbers of females with congenital heart disease (CHD) have reached childbearing age, and experience with pregnancy in this patient population has increased accordingly [1,2]. Conversely, experience in and management of gynecologic health—contraception, menstruation and menopause—has lagged far behind. The following discussion focuses on common gynecologic issues in females with CHD based largely on experience in the Ahmanson/UCLA Adult Congenital Heart Disease Center.

1. Menstruation

Menarche, the clinical indicator of the level of hypothalamic maturation and the ability to conceive, occurs in the normal female population at a mean age of 12.3 years [3]. In females with *acyanotic* congenital heart disease, menarche reportedly occurs somewhat later at 13 years, and in *cyanotic* females occurs still later at 13.9 years—statistically significant differences when compared to age-matched controls [4]. Menstrual patterns in females with acyanotic CHD are similar to those of the general population, but cyanotic females tend to have shorter or longer cycle lengths with a greater frequency of menstrual irregularities such as missed periods and break-through bleeding [4].

Comparatively little is known about postoperative menstrual patterns in women with cyanotic CHD. Cyanotic females who underwent a Fontan operation in childhood (<10 years of age) reportedly experience menarche as the same age as the normal female population [5]. Cyanotic females repaired after menarche (≥ 12 years of age) resume normal menstrual patterns within 6 months of surgery. However, cyanotic females operated upon 6–10 years *after* the menarche have a greater frequency of menstrual irregularities, especially amenorrhea [5]. What accounts for these abnormal menstrual patterns has not been established. Dysfunctional bleeding characterized by heavy periods, missed periods or amenorrhea in women of child bearing age usually indicates an anovulatory state, which is accompanied by a three-fold increase in the risk of endometrial cancer because of unopposed estrogen production that results in continuous endometrial stimulation and hyperplasia that predispose to endometrial carcinoma [3,6,7]. Chronic anovulation can also be accompanied by menorrhagia and iron-deficient anemia, the control of which

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may require surgical intervention. For females with cyanotic CHD, blood loss destabilizes the increase in red cell mass—erythrocytosis—that is a desirable adaptive response to systemic arterial hypoxemia [8]. Iron-deficient anemia causes fatigue and muscle weakness best treated with oral iron replacement that must be monitored closely because the increase in circulation erythropoietin predisposes to a rapid and excessive rise in hematocrit [8]. Anovulatory patients requires a thorough gynecologic evaluation including a detailed menstrual history supplemented by a pelvic examination and pap smear and documentation of anovulation by charting daily basal body temperature for two cycles. If abnormal cycles persist, serum progesterone level should be determined in the anticipated luteal phase. Women over 35 years of age or younger women who experience anovulation for greater than 6 months should be biopsied to rule out endometrial hyperplasia or carcinoma. The recommended treatment for anovulation is cyclic progestin or hormonal therapy utilizing estrogen and progestin. Amenorrhea requires investigation for pregnancy, thyroid disease, hyperandrogenism, polycystic ovaries and hyperprolactinemia. Abnormal *ovulatory* bleeding requires evaluation for anatomic causes such as endometrial hyperplasia, cervical or endometrial carcinoma, endometrial polyp, myomata adenomyosis or endometriosis. Additionally, one must be cognizant of potential effects of pharmacologic agents used in the management of cardiovascular disease may have on the menstrual cycle. For example, while anticoagulants have been a source of concern in pregnancy [9–11], there should be equal concern of the untoward effects of anticoagulants, including the potential risk of vaginal bleeding in females with rigid prosthetic valves or chronic atrial fibrillation [12]. Menorrhagia is the major complication of long-term anticoagulants, which can be managed in the short-term with high-dose progestins or dilatation and curettage. For prolonged menstrual suppression, Depo Provera or the progestin secreting intrauterine device may be considered. For women in whom pregnancy is not desired or in whom the risk is prohibitive, endometrial ablation or hysterectoscopy should be considered. Hemoperitoneum due to rupture of the corpus luteum is a potential complication in premenopausal women with poorly controlled prothrombin levels, and the clinical presentation with insidious shoulder pain, lower abdominal pain and rectal pain and constipation can be misleading [13–15]. Even if hemoperitoneum is detected early and successfully treated without surgical intervention, there appears to be an increased risk of recurrence. Skin and soft tissue necrosis, while uncommon, typically occurs in perimenopausal and post-menopausal women on anticoagulants. Necrosis develops in areas of abundant subcutaneous fat such as thigh and breast [16]. Symptoms begin with localized pain progressing from a flush to ecchymosis, edema, hemorrhagic infarction, eschar formation and tissue sloughing.

2. Contraception

Contraception counseling should be an integral part of any adolescent or adult congenital heart disease program regardless of whether or not the patient is known to be sexually active. Data from the National Survey of Family Growth reported in 1994 that 49% of all pregnancies were unintended in women aged 15–44 years, with 54% electively aborted [17]. The proportion of unintended pregnancy among teenagers younger than 18 years was 82–83% [18].

2.1. Oral contraceptives

There is no contraceptive that is both completely effective and completely free from side effects in females with CHD. Oral contraceptives prevent pregnancy by inhibiting gonadotropin secretion via the pituitary and hypothalamic centers. The contraceptive effect is based upon three mechanisms: suppression of the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH); suppression of the LH surge and the resulting ovulation; alteration of cervical mucus that renders it less penetrable by sperm; and changes of the endometrium that render it less conducive to implantation. Current oral contraceptives maintain efficacy and minimize complications because of the relatively *low* steroid concentrations. Two categories of oral contraceptives in current use include progestin only preparations, and agents with low dose estrogen combined with varying amounts of progestin referred to as combined oral contraceptives (COC).

The earlier forms of high dose estrogen-based contraceptives increased the risks of thromboembolism and fluid retention, thus making them unacceptable for women with right-to-left shunts, pulmonary vascular disease, prosthetic devices or other materials susceptible to thrombus formation [19]. Thromboembolic effects are primarily attributed to the estrogenic component of the formulation, but studies report a minimal increase in platelet activation and in coagulability associated with products containing less than 50 μg of estrogen [19,20]. The dose of estrogen in the current multiphasic COC preparation is between 20 and 35 μg of ethinyl estradiol per tablet.

The progestin only "Mini Pill" containing 0.35 mg of norethindrone acetate taken daily offers a good alternative when estrogen is contraindicated. Progestin only pills thicken cervical mucus, decrease permeability and are accompanied by a thin endometrium, which resists implantation. Additionally, the mini pill inhibits ovulation approximately 30% of the time and has no measurable impact on clot formation or platelet behavior. Untoward side effects include breakthrough vaginal bleeding, amenorrhea and occasionally a diuretic response [21–23]. Failure rates tend to be higher than with the COC, particularly in the first year. In order to ensure efficacy, the mini pill must be taken regularly at the same time each day, because cervical impermeability diminishes approximately 22 h after administration. Owing to the need for a

rigid daily regimen, the mini pill is not a good choice for forgetful adults or for the average adolescent.

2.2. Implantable contraceptive

Low-dose progestin implants inhibits ovulation, thickens the cervical mucus and suppresses growth and development of the endometrium thus producing an unfavorable endometrial lining. Implants, which consist of flexible silastic capsules, are surgically inserted in subcutaneous tissue of the inner surface of the upper arm, and is a consideration for women in whom pregnancy is contraindicated but who are not prepared to undergo permanent sterilization. Levonorgestrol implant known as "Norplant" is a long acting (5 years effect after insertion) low dose (36 mg) synthetic progestin, which contains no estrogenic activity. Untoward effects include irregular menstrual bleeding, weight gain, headache, acne and breast tenderness. There is evidence of an effect on lipids, but with prolonged use, lipoproteins return to preinsertion levels [24]. Norplant production was temporarily suspended due to reported increase in failure rates from specific lots [25], but is still available on a limited basis. Etonogestrel (Implanon) provides contraceptive protection for up to 3 years and is a single synthetic rod containing 68 mg of etonogestrel, an active metabolite of desogestrel [26]. Implanon, which is available in the United Kingdom and other European countries and is soon expected to be available in the United States, has been associated with irregular menstrual bleeding and amenorrhea [26]. Implants are costly to insert and may be difficult to remove because of embedding and scarring around insertion sites [24].

2.3. Injectable contraceptive

An alternative to oral and implantable contraceptives is the progestin only intramuscular injection of depomedroxyprogesterone acetate (DMPA) known as Depo Provera. In addition to the thickening of cervical mucus and alteration of the endometrium, this agent raises the circulating level of the progestin that effectively blocks the LH surge and prevents ovulation. Depo injections are given in a dosage of 150 mg every 3 months deep in the gluteal or deltoid muscle by the Z-track technique. A highly effective contraceptive method that is free from the side effects of estrogen, Depo Provera provides an attractive alternative for women at risk of thromboembolism, and in whom compliance may be a concern. While highly effective, the side effects of irregular menstrual bleeding, weight gain (approximately 2.3 kg during the first year of use), morning headaches and depression may make the agent undesirable. There is additional concern regarding the risk of osteoporosis associated with amenorrhea in long-term users [27]. Data suggest that prolonged hypoestrogenism due to the drug may temporarily suppress skeletal bone mineralization, which is of particular concern in adolescents [28].

A new injectable contraceptive containing 25 mg of medroxyprogesterone acetate and 5 mg of estradiol, "Lunelle", has recently been approved by the FDA [29]. This monthly injectable contraceptive produces a predictable cycle and a return in fertility within 2 weeks of cessation. Contraindications for Lunelle are the same as for other progestin–estrogen combined contraceptives. Lunelle should not be prescribed for women 35 years and older who smoke, and should be discouraged for smokers younger than 35 years [29]. A shortcoming of all contraceptives that require repeated deep intramuscular injection is the potential risk of bleeding in women on antiplatelet agents or long-term anticoagulant.

2.4. Intrauterine devices

Although an effective contraceptive method, the use of intrauterine devices (IUD) has declined because of the risk of pelvic inflammatory disease. IUD-related infections have been attributed to transient microbiologic contamination of the endometrium at the time of insertion [30–33], a risk that is incurred within the first 20–30 days. Infections occurring 3–4 months after insertion are believed to be due to acquired sexually transmitted disease (STD) rather than the direct result of the IUD [30]. The infection rate from 1 month after insertion through the full lifespan of the device has been reported to be 1.4 cases per 100 years and is virtually absent in women with no risk factors for STDs [31,32]. Infective endocarditis associated with IUDs is rare, occurring less than once per million patient-years, but remains a consideration in women with high risk substrates. Two grams of amoxicillin should be given 1 h before insertion and upon removal of the device [34]. IUDs probably should also be avoided in women at risk for endometriosis [33]. IUDs should be inserted with caution in women with bradycardia or conduction defects because a vagal response has been reported at the time of implantation [30]. Other side effects include increased menstrual cramps and pain, and iron deficiency anemia from increased menstrual blood loss. Owing to the increased risk of infertility, IUDs are not recommended for nulliparious females, particularly teenagers, but are suited for women in a monogamous relationship after child bearing is completed.

There are two models of IUDs, the ParaGard T380A, a copper bearing device, and the hormone releasing IUDs, Progestasert and Mirena. The ParaGard model is effective for 10 years, with a failure rate of 0.7% in the first year, diminishing to 0.0% in the 10th year, and an expulsion rate of approximately 5% in the first year. Reasons for removal include for bleeding or pain, which occurs in 3–12% of women over 10 years with the highest percentage in the first 3 years. The Progestasert, which releases 65 μg progesterone/day, causes less cramping and blood loss than ParaGard, but its utility is limited by the need for yearly reinsertions. The newer progestin-containing IUD "Mir-

ena'' releases 20 μg/day of levonorgestrel and is effective for 5 years [35]. Mirena can initially cause abnormal bleeding or spotting, but after 3–6 months hypomenorrhea or amenorrhea usually results; dysmenorrhea declines. The first year failure rate of the Progestasert is 2% but of the Mirena only 0.3%.

2.5. Vaginal ring

Approved for use by the Food and Drug Administration (FDA) in 2001, the vaginal ring (NuvaRing) slowly releases 15 μg of ethinyl estradiol and 120 μg etonogestrel daily [36]. A flexible transparent ring of about 2.1 in. in diameter is left in place for 3 weeks, then removed for 1 week after which bleeding may occur. After one ''ring-free'' week, a new ring is inserted. The ring may be removed during intercourse, but if left in place for more than 3 h, a second method of contraception must be used. To be effective, the ring must be in place for 7 days. The failure rate is approximately 1–2% [37]. Side effects and contraindications are the same as with any combined estrogen/progestin contraceptive. Additionally, there may be localized vaginal irritation and discharge.

2.6. Transdermal patch

The ''Patch'' (Evra) is another progestrin/estrogen contraceptive combination, which was approved by the FDA in 2001, and every 24 h releases 0.6 mg norelgestromin, the active metabolite of norgestimate and 0.75 mg ethinyl estradiol. The patch is applied every week for a 3-week period followed by one ''patch-free'' week during which break-through bleeding may occur. The efficacy rate is reported to be 1.24 pregnancies per 100 women [38]. Side effects include breast tenderness, which resolves with subsequent cycle use, headache and local skin irritation. Approximately 2% of patches detach. It is not known whether the lack of first pass metabolism in the liver results in a lower incidence of thromboembolic events.

2.7. Barrier methods

For women who are cyanotic or who have undergone intracardiac repair but are left with residual shunts, conventional barrier methods are often recommended. Although accompanied by the lowest risk of complications, barrier methods carry a greater risk of an unwanted pregnancy particularly among teenagers, and should be used only by motivated females.

The diaphragm remains the safest and most commonly employed barrier method of female contraception. Used with spermicide, an effectiveness rate of approximately 80% has been demonstrated in clinical trials [39]. Both diaphragm and condom provide a 50% reduction in the occurrence of sexually transmitted pelvic inflammatory disease. Occasional side effects and complications include vaginal irritation due to the latex rubber or the spermicide, recurrent cystitis, pelvic discomfort and cramps [24]. Complaints are often associated with an ill-fitting diaphragm or prolonged retention beyond 24 h. The failure rate of condoms alone is 2% theoretical and 12% in actual usage. Only the latex and polyurethane condoms protect against sexually transmitted diseases. The female condom, which is much more costly and has a poor acceptance rate, consists of a polyurethane vaginal pouch with an internal and external ring. The internal ring is placed like a diaphragm and the external ring is placed over the labia. A lubricant is provided to decrease friction, which often causes the pouch to slip from the vagina during intercourse. Other barrier methods include spermicides in the form of jelly, foam, films or suppositories or sponges and cervical caps. While considered to be less reliable, if used conscientiously and in combination with a second barrier method such a condom, the effectiveness can approximate the level of efficacy of oral contraceptives [40,41]. Therefore, regardless of the method used, efficacy associated with the combination of two barrier methods is underscored.

Equally important to note is the role that condoms and spermicides play in protecting against sexually transmitted diseases, HIV and hepatitis B. The commercially available synthetic latex condoms provide far better protection against HIV and hepatitis B virus compared to natural-skin (sheep) condoms.

2.8. Emergency contraception

Emergency contraception is employed to reduce the risk of pregnancy after unprotected coitus. Often referred to as the ''morning-after pill'' or post-coital contraception, the most commonly used emergency contraceptive methods are the combined estrogen/progestin referred to as the Yuzpe regimen, and the progestin only regimen of oral contraceptive pills referred to as Plan B. The high estrogen-containing Yuzpe regimen consists of four tablets each containing 0.05 mg of ethinyl estradiol and 0.25 mg of levonorgestrel marketed as Preven®. Plan B, the preferred regimen for women with cardiac disease, includes a high-dose preparation of 0.75 mg of levonorgestrel. The total dose of levonorgestrel is equivalent to 20 mini pills. Both regimens, which consist of two doses of contraceptive steroids taken 12 h apart, can reduce the risk of pregnancy up to 120 h after unprotected vaginal intercourse, but are more effective when the first dose is taken within 72 h. Of the two regimens, the progestin-only (Plan B) is more effective with a failure rate of approximately 1%, is theoretically safer for women at risk of thrombosis and better tolerated, with less nausea and vomiting [42,43]. These products should not be administered to an individual who is already pregnant.

Insertion of a copper intrauterine device (IUD) within 5–7 days after unprotected intercourse may also serve as an emergency contraceptive but should only be deployed in

females who meet the screening criteria for safe use of such a device [44].

2.9. Tubal occlusion

When pregnancy is contraindicated, as in women with Eisenmenger syndrome or primary pulmonary hypertension, laparoscopic or mini laparotomy tubal ligation under local anesthesia is recommended [45]. For females who are married or in a committed relationship, vasectomy for the partner is an alternative. For sexually inactive young single woman who favors tubal ligation, the long-term consequences of this emotional and irreversible decision must to be thoughtfully discussed. It may be preferable to postpone tubal ligation until mature judgment can be exercised. The emotional price of immature and premature decisions weighs heavily in the balance.

2.10. Choice of contraceptive

The selection of a contraceptive method for the female with CHD must be individualized, taking into account the primary cardiac defect, related surgical interventions, and post-operative residua and sequelae (Table 1). Women who have undergone successful early surgical repair for malformations such as atrial septal defect, patent ductus arteriosus, or ventricular septal defect with few or no post-operative residua or sequelae should be treated similarly to the general population.

Estrogen-based contraceptives and IUDs are contraindicated for women in whom risk of thrombosis or embolism. Residual and sequelae are obligatory after complex intracardiac repair such as the Fontan, Mustard or Rastelli procedure. Consideration must be given to the presence and degree of residual shunting, and whether or not prosthetic materials are in place. Accordingly, COC pills or IUDs are not advised. Fluid retaining progesterone-based contraceptives should be used cautiously in patients with impaired ventricular function.

Sex differences in pharmacokinetics are increasingly being recognized as important considerations in clinical pharmacology [41]. Therapeutic responses may be altered by body mass, by hormone fluctuations during a woman's life span, and by differences in drug concentration, elimination and metabolism. There is also concern about drug interactions and oral contraceptives. Plasma levels of the combined oral contraceptive pill may be decreased by certain antimicrobials such griseofulvin and rifampicin [46]. There are reports of COC pill failure following short-term use of antibiotics for dental and dermatological procedures [47,48]. Less clear is the evidence of failure rates during administration of ampicillin, tetracycline or cephalosporins, [46,49]. Although the risk of antibiotics in women taking COC pill is uncertain, the serious consequence of an unwanted pregnancy mandates that physicians and other health care providers make appropriate enquires, and if a potential threat to contraceptive efficacy is suspected, patients should be advised to use extra contraceptive protection during the COC pill cycle in which an antibiotic is taken. If long-term use of antibiotics is required, the patient is best advised to choose an alternative contraceptive method.

Drugs that affect liver metabolism, such as phenytoin and carbamazepine, can affect the efficacy of hormonal

Table 1
Recommendations for contraception in females with congenital heart disease

Defect/residua	COCs	Mini Pill	Norplant	Depo Provera	IUD	Barrier
I. Surgically repaired defects						
A. No residua: ASD/VSD/PDA	+	+	+	+	+	+
B. Residual shunt and/or obstruction	–	+	+	+	+	+
C. Prosthetic valves, conduits, baffles	–	+	+	+	–	+
D. Residual pulmonary and/or systemic hypertension	–	+	+	+	–	+
II. Unrepaired defects, postoperative residua						
A. Small VSD	+	+	+	+	+	+
B. Mild to moderate residual shunts (ASD, VSD, PDA)	–	+	+	+	–	+
C. Residual systemic or pulmonary hypertension (coarctation of aorta)	–	+	+	+	–	+
D. Complex cyanotic defects (TA, SV, TR)	–	+	+	+	–	+
III. Defects complicated by						
A. Cyanosis	–	+	+	+	–	+
B. Ventricular dysfunction	–	+/–	+/–	+/–	–	+
C. Atrial fibrillation/flutter	–	+	+	+/–	–	+
D. Eisenmenger physiology	–	+	+	+	–	+

ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; VHD, valvular heart disease; TA, tricuspid atresia; SV, single ventricle; TR, truncus arteriosus; COCs, low dose combine oral contraceptives.
**Recommend administration of antibiotic prophylaxis during with insertion.

contraception because of increased metabolism of the estrogenic component in the OCP [50]. Because it is undesirable to raise the estrogen dose in women with congenital heart disease, OCPs are best avoided in women receiving anticonvulsants other than sodium valproate.

2.10.1. Termination of pregnancy

Once a decision to terminate a pregnancy is reached, it is important to act swiftly because the choice of procedure is determined by the duration of pregnancy. If there is discrepancy between dates and uterine size, ultrasound should be performed. Abortion at 12 weeks of gestation or earlier is preferred because cardiac output begins to increase by 8 weeks. Dilation and suction curettage under local anesthesia (paracervical block) is the method employed for first trimester termination, and carries a very low complication rate when performed by an experienced obstetrician in an operating room rather than in an outpatient setting.

Medical abortion utilizing oral antiprogesterone agents such as RU486 (Mefipristone) and vaginally administered Misoprostol (prostaglandin E1 analog) are as effective as suction curettage if performed within the first 7 weeks of gestation [51,52]. Because expulsion and bleeding occur at home, the process is not controlled, so the systemic vasodilation afforded by the PGE could potentially be risky for women with Eisenmenger syndrome or primary pulmonary hypertension.

Second trimester termination methods include medical and surgical procedures. Intrauterine instillation of prostaglandin (E2 or F) and hypertonic urea results in uterine contractions and expulsion of the fetus, but labor can take up to 20 h, is painful, requires in-patient care, and there is the risk of retention of the placenta, hemorrhage and infection. Accordingly, dilatation and evacuation of fetus and placenta are more frequently used for termination of second-trimester pregnancies. With introduction of a small dilator, called Laminaria, the cervix is slowly dilated, most of which occurs in the first 6 h, with maximum dilation usually occurring 12–24 h followed by evacuation. The complication rate associated with laminaria is low.

3. Menopause

The number of women with CHD who are currently reaching menopause is increasing [53,54]. The 32nd Bethesda Conference on adult CHD reported that 80% of patients in two centers were 40 years or older [55]. Accordingly, responsible physicians must not only be sensitive to the emotional and physical effects of menopause, but must make a judgment regarding hormone replacement therapy (HRT). Menopause by definition is the absence of menses for 12 consecutive months. However, estrogen production begins to decline over a period of several years before complete cessation. It is estimated that women begin menopausal transition at about 47 years and have their last menses at about age 51 [56]. It is during this transitional period that symptoms commonly associated with menopause develop. Nulliparous women tend to experience menopause earlier than multiparous. The principal goal of HRT has been deliver the lowest effective dose of estrogen/progestin to relieve menopausal symptoms and to potentially reduce the risk of coronary artery disease (CAD) and osteoporosis. While earlier reports emphasized the benefits of HRT for prevention of coronary artery disease, more recently, these beneficial effects of HRT have been called into question [57–59]. The Women's Health Initiative (WHI) stopped the HERS trial of combined hormones/estrogen/progestin in women with an intact uterus because of the increased risk of breast cancer, stroke, and pulmonary embolism [60]. The current recommendation is neither to begin nor continue HRT for the prevention of cardiovascular disease. Another trial examining estrogen only therapy is ongoing with results expected in 2005.

Currently, hormone replacement regimens include unopposed estrogen or combined estrogen/progestin therapies [61]. Unopposed estrogen is not recommended for women who have a uterus. In the United States, systemic estrogen is available in oral or transdermal form with a starting dose of 0.625 mg of conjugated estrogen or the equivalent being recommended (Table 2). However, lower doses of estrogen (0.45 mg of conjugated estrogen) when combined with a progestin (1.5 mg

Table 2
Currently used estrogen and progestin preparations

1. Estrogen	
A. Conjugated estrogen 0.3, 0.45 or 0.625 p.o. QD	
B. Estropipate 0.625 mg p.o. QD	
C. Esterified estrogen 0.3 or 0.625 p.o. QD	
D. Micronized estradiol 0.5 or 1 mg p.o. QD	
E. 17β Estradiol transdermal system 0.025 or 0.0375 or 0.05	
F. Ethinyl estradiol 5 μg	
2. Progestin/progesterone	
A. Medroxyprogesterone acetate (MPA)	1.5, 2.5 or 5 mg p.o. QD 10 mg p.o. QD 14–25*
B. Progesterone oral micronized or suppository	100 mg p.o. QD 200 mg p.o. QD 12–25**
C. Norethindrone acetate	0.5–1 mg p.o. QD
3. Transvaginal estrogen preparations for atrophic vaginal symptoms	
A. Conjugated estrogen vaginal cream 1 g, 2–3 times/week for 2 months then as needed	
B. Estradiol vaginal cream 0.5–1 g, 2–3 times/week for 2 months then as needed	
C. Estradiol vaginal ring (Estring)—replace every 3 months	
D. Estrogen suppositories (Vagifem)—2–3 times/week per vagina as needed	

* Taken day 14 through 25.
** Taken day 12 through 25.

hydroxy progesterone acetate) have been found to relieve vasomotor symptoms and prevent bone loss [62]. Protocols set by the American College of Obstetrics and Gynecology and American College of Physician recommend the addition of cyclic or of daily progestin administration for women with an intact uterus to reduce risk of endometrial cancer [63]. Progestin (medroxyprogesterone acetate or norethindrone acetate) is usually prescribed in oral form, while progesterone is available in other forms including oral (micronized), vaginal or rectal suppositories.

Given the results of the WHI report, the decision to prescribe HRT must consider the individual needs of each patient weighing the benefits against the risks. For the woman with CHD, the decision to prescribe HRT must also take into account the cardiac primary defect, what if any surgical intervention has taken place, and her clinical status at the time of evaluation. Since the dose of estrogen in HRT is one quarter the dose found in oral contraceptives, the majority of females with CHD can safely receive these agents and be evaluated as the general population. However, for those at risk of thromboembolism, HRT should not be recommended given the recent WHI reports of a 41% increase in stroke and a two-fold greater rate of venous thromboembolism (VTE), in women receiving estrogen plus progestin therapy [60].

The standard estrogen replacement dose, for example 0.625 mg of Premarin is approximately one quarter of the estrogenic potency of the 20 μg of ethinyl estradiol in an oral contraceptive pill. It is possible that estrogen administration via a transdermal patch may be safer as this mode bypasses the liver and may be less procoagulant than other agents. There is, however, no specific clinical evidence for this recommendation in women with or without CHD. It is recommended that one prescribe the lowest dose of systemic HRT that will address the vasomotor symptoms associated with estrogen deficiency. If there are residual complaints of vaginal dryness or dyspareunia, the vaginal atrophy symptoms can be treated with vaginal estrogen in the form of cream, tablets or ring. As noted above, estrogen doses lower than 0.625 mg of conjugated estrogen are probably effective in reducing bone loss if combined with a progestin [62]. For those women with a history of thrombosis, embolism or bleeding HRT is ill-advised. Over-the-counter phytoestrogen or selective serotonin reuptake inhibitors can be used to alleviate menopausal symptoms such as hot flashes but controlled trials reporting their effectiveness are mixed. In the asymptomatic female, it is reasonable to avoid HRT and utilize other agents such as bisphosphonates to prevent osteoporosis, unless the latter are contraindicated due to reflux, hiatal hernia or impaired renal function. Transvaginal estrogen may then be used for vaginal atrophy and SSRIs for mood changes associated with the perimenopause or early menopause.

4. Conclusion

Because increasing numbers of females with congenital heart disease are reaching childbearing age, practitioners responsible for the care of adolescents or adults must be aware not only of the risks of pregnancy associated with varying types of CHD, and must also be aware of issues involving the entire reproductive cycle in order to provide appropriate care, counseling and education.

As young girls reach reproductive age, discussions regarding menstrual function, contraception and pregnancy should begin and, when sexually active, they should be referred to a gynecologist who specializes in adolescent gynecology. For adult females, these issues should be addressed in the initial evaluation and at follow-up. Sexually active females and women over 21 should be followed regularly by a gynecologist, in consultation with the primary care cardiologist.

Despite impressive surgical advances in congenital heart disease, cure in the literal sense is seldom achieved. Accordingly, most if not all female patients require long-term care and counseling on reproductive issues including their menstrual cycle, pregnancy, contraception and menopause.

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