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Gynaecological health in adult congenital heart disease women: Addressing menorrhagia, infertility, contraception, menopause

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ABSTRACT

Developments in medical and surgical techniques have improved survival in women with congenital heart disease (CHD) with most now surviving well into adulthood. Reproductive health amongst these women is underexplored and needs more attention. Women with CHD are known to have more menstrual dysfunction than the general population and have higher maternal and fetal risks when they become pregnant. Adequate and timely preconception counselling, including contraception within a multidisciplinary team (MDT) are essential to optimise pre pregnancy cardiac status and improve pregnancy outcomes. Counselling regarding fertility, sexuality, contraception and menopause is necessary and should start early, around 12–13 years, and as they transition into adult services. Fertility seems to be reduced in women with complex CHD and consideration for assisted reproduction technique (ART) should be assessed by the MDT as risks associated with ART including ovarian hyperstimulation syndrome, bleeding, thrombosis and infection can have profound effects on women with complex cyanotic CHD.

1. Introduction

Congenital heart disease (CHD) affects around 1% of all livebirths worldwide. Due to early diagnosis and improved treatment, (surgical and medical) survival of patients with CHD has improved over the recent years, and up to 84% of adolescents and young adults (AYA) with CHD currently survive to 40 years of age [1]. Reproductive health in these women therefore needs more consideration and is still relatively unexplored. The common subtypes of CHD include bicuspid aortic valve, ventricular septal defect, and atrial septal defect, which are relatively mild and have a good prognosis. The more severe subtypes include hypoplastic left heart syndrome, cyanotic heart disease and pulmonary atresia, which have a worse prognosis.

The European Society of Cardiology (ESC) and the American Heart Association (AHA) guidelines provide information on the management and care of adults with CHD (including pregnancy specific guidance) and describe the risks and treatments of the different types of CHD [2,3]. However, there has been less attention on gynaecological health including the occurrence of menstrual dysfunction, sexuality, contraception, fertility requiring assisted reproduction techniques (ART) and menopause in patients with adult CHD [4]. In this review we will discuss each of these areas in detail (Table 1). Due to a lack of randomised studies, guidance is based on information from small studies and expert opinion.

2. Menstrual dysfunction

A few studies have previously reported an increased incidence of menstrual dysfunction in women with complex CHD including delayed menarche, dysmenorrhea, irregular menstruation, and menorrhagia especially in those taking anticoagulants. A study by Khajali et al. showed that the age of menarche was later in women with CHD compared with general population [5]. The authors reported that the median age of menarche was 14.5 years in women with complex CHD compared with 13 years in those with simple acyanotic CHD. Drenthen et al. suggested that low cardiac output (single ventricle pathologies), chronic systemic venous congestion, and hypoxemia may affect the supply of oxygen and nutrients essential for the development of ovarian function, which may be the cause for a delayed menarche in women with cyanotic heart disease [6]. It is believed that ovarian blood flow is essential for normal ovarian function. Nao Konagai et al. demonstrated an association between impaired hemodynamics and menstrual

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Table 1
Reproductive health issues with age in women with congenital heart disease.

Life stage	Problems needing attention
Adolescence	• Menstrual dysfunction • Sexuality • Contraception • Education
Young Adulthood	• Menstrual dysfunction • Sexuality • Contraception • Education • Pregnancy planning – preconception counselling • Subfertility/infertility
Childbearing	• Education • Effect of pregnancy on heart disease • Risks in pregnancy – cardiac complications and obstetric and neonatal risks • Inheritance and Genetics (if applicable) • Contraception • Interpregnancy interval
Late adulthood	• General health - diet and exercise • Effect of pregnancy on long term health • Menstrual dysfunction
Older age	• Menopause • Acquired medical conditions and effect on congenital heart disease

problems as hypothesized by Drenthen et al. [7].

Canobbio et al. reported that menstrual patterns in women with acyanotic CHD were similar to the general population, unlike those with cyanotic CHD's who have a higher prevalence of amenorrhea, oligomenorrhea, polymenorrhea, menorrhagia or breakthrough bleeding [8]. Menstrual cycle disorders were observed in 68% AYA with CHD compared to 13–23% reported in the general population [9]. The most frequent menstrual dysfunction was frequent menstrual bleeding, which was observed in 32% AYA with CHD (compared to 2% in general population) [9]. Special consideration should be given to AYA who are on anticoagulation (due to mechanical heart valves, for arrythmia or on prophylaxis (single ventricle) as they have a higher risk of menorrhagia compared to the general population [10]. Women on a vitamin K antagonist have a two - threefold increased risk of menorrhagia.

Anti Mullerian Hormone (AMH) is produced by the ovarian granulosa cells in the preantral and small antral follicles. Serum AMH levels reflect the ovarian reserve and are therefore useful for assessing ovarian functional status. AMH levels may indicate incipient ovarian insufficiency in women with normal menstrual cycles. Previous studies have shown that serum AMH levels were statistically significantly lower in women with CHD compared to healthy controls. This difference was noted more in older women (>35 years of age) and those with a Fontan circulation [9].

Menstrual problems have often been inadequately addressed in AYA with CHD. Considering the diversity of adult CHD patients, individualised information and advice should be provided at an earlier age (around 12–13 years) and as they transition into adulthood. Progesterone (tablets and Levonorgestrel releasing intra uterine device (LNG IUD)) is considered safe and effective for treatment of menorrhagia. The common side effects of acne, breast tenderness, nausea, headaches, mood changes, breakthrough bleeding and irregular bleeding should be discussed before starting treatment. The menstrual irregularities especially irregular cycles and primary/secondary amenorrhea may play a role in subfertility and difficulty in conceiving in women with cyanotic CHD.

2.1. Sexual health

Sexual function is impaired in AYA with CHD. On all sexual function scores, women with CHD score less than the general population and younger women seem to be more affected. Women with CHD have reduced libido, more pain (dyspareunia) and more insecurity and fear, likely due to their heart disease. Males with CHD have worse erectile function, orgasmic function and intercourse satisfaction. Around 11% women with CHD reported feeling unattractive due to their surgical scar at the time of sexual intercourse [11].

Fear regarding the use of contraceptives, passing on their heart disease, and of the effect of both pregnancy and delivery on their heart disease seems to affect many women with CHD. Physicians caring for such women should therefore discuss with, and counsel them about issues relating to sexuality and reproduction in early adolescence, with an awareness of the adolescent's developing understanding and maturity. In a previous study, only around 21% of AYA with CHD had appropriate knowledge of the most suitable contraceptive method considering their condition [12].

3. Subfertility, infertility

Subfertility/infertility affects up to 15–18% couples in the developed world. Infertility can be due to male factor, female factor or be unexplained. Available data suggest that fertility is reduced in women with CHD especially with cyanotic complex CHD like Fontan palliation. In patients with simple or moderate CHD, fertility does not appear to be affected, although both men and women with CHD have lower birth rates compared to those without CHD, independent of the CHD severity [13]. The lower incidence of live births is possibly due to underlying genetic factors, extra cardiac anomalies, drugs like anticoagulants and psychological factors [14].

The most well studied and understood syndrome associated with infertility and CHD is probably Turner syndrome (TS). In TS, the cardiac defects commonly seen are bicuspid aortic valve, aortic coarctation, and septal defects, there is also an increased risk of aortic dissection. Women with TS with the combination of bicuspid aortic valve, coarctation of aorta, aortic dilatation and hypertension are at greatest risk of aortic dissection [15]. The absence of normal ovarian tissue means that women with TS have premature ovarian insufficiency, and can only conceive with reproductive assistance, usually ovum donation. Pregnancy is contraindicated if the aortic size index exceeds 25 mm/m^2 with aortic root repair considered if the aortic size is between 20 and 24 mm/m^2.

Investigations for infertility include routine blood tests, semen analysis, pelvic ultrasound, tests for ovulation and tubal patency. Tubal patency is assessed via hysterosalpingography (HSG), which involves passing a tube through the cervix and injecting fluid into the uterine cavity to outline its shape and show whether the fallopian tubes are patent. Cervical manipulation while inserting the dye can cause a vasovagal reaction that may be life threatening in some patients with complex CHD. Such procedures needing instrumentation of the cervix should be performed in a hospital setting suitable for women with complex CHD (Fontan palliation, pulmonary artery hypertension) with anesthetic support, cardiovascular monitoring, and adequate analgesia. Hysteroscopy may be indicated to assess the uterine cavity and treat intrauterine adhesions or resect a fibroid/septum. Particular attention should be paid on the fluid balance during the hysteroscopy as excess fluid can lead to heart failure.

Laparoscopy may be indicated for diagnosis and treatment of subfertility (tubal adhesions, endometriosis). The pneumoperitoneum created causes an increased intra-abdominal pressure, which can impact cardiac output by reducing the venous return and elevating cardiac afterload. The Trendelenburg position can further compromise respiratory function, causing CO_2 retention and increasing pulmonary vascular resistance. Positional changes can cause significant hypoxemia, hypotension, and hemodynamic instability, which are poorly tolerated by women with complex CHD. If necessary, laparoscopic surgery can be performed with minimal abdominal inflation under regional or local anesthesia. Women with complex CHD like Fontan circulation and pulmonary artery hypertension or Eisenmenger's should have operative procedures like hysteroscopy or laparoscopy in an inpatient setting with an experienced cardiac obstetric team after discussion with a multi-

disciplinary team (MDT), to define risks and strategies to minimise potential complications [16,17].

Treatment of infertility involves ART including intrauterine insemination (IUI) with ovarian stimulation, in-vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI). ART can be complicated by ovarian hyperstimulation syndrome (OHSS), bleeding, infection, arterial and venous thrombo-embolism (VTE), multifetal pregnancy, pre-eclampsia, and preterm delivery. All these are associated with increased risk among patients with CHD.

IVF usually requires superovulation, the process where the ovaries are stimulated develop at least 2-3 follicles to release eggs for fertilisation in the laboratory. One of the most common complications of superovulation is OHSS, which is caused by the release of VEGF by the hyper stimulated ovaries [18]. The VEGF increases the permeability of pelvic and abdominal vessels leading to marked fluid shifts, intravascular volume loss resulting in hypotension, hemoconcentration and potentially life-threatening thromboembolic disease. Even mild forms of OHSS may be poorly tolerated in women with ventricular dysfunction, left ventricular outflow tract obstruction, Fontan palliation, or pulmonary arterial hypertension. The risk of OHSS can be reduced by careful cycle monitoring, using low-dose follicle-stimulating hormone in combination with a gonadotropin-releasing hormone antagonist, freezing all embryos, or only transferring a single embryo. ART is associated with multiple pregnancies that induces a more marked cardiovascular adaptation which can precipitate cardiac decompensation in women with significant left-outflow tract obstruction or severe left ventricular systolic dysfunction.

Before considering ART in patients with CHD, it is recommended that a thorough pre-conception assessment with counselling be carried out so that the impact of a pregnancy on the heart disease and vice versa can be determined and discussed. Currently, several risk stratification models are used, including the CARPREG I, CARPREG II, ZAHARA and the modified World Health Organization (mWHO) risk stratification model, which uses cumulative knowledge of lesion-specific risk to divide patients into four risk groups [19]. These scores provide estimates of the likelihood of a major adverse cardiovascular event in pregnancy, so that advice can be provided to women who are contemplating pregnancy. If pregnancy is considered safe, the pros and cons should be discussed in detail including risks of ART.

Cardiac disease is the leading cause of indirect maternal deaths in the developed world [18]. Risk stratification and preconception counselling within an MDT is extremely important for women with CHD who are at risk of developing complications including heart failure, arrythmias, thromboembolic events, cerebrovascular events, and endocarditis. Conversely, women with CHD have a higher rate of adverse obstetrical (8.4%) and fetal and neonatal events (24%) compared with the general population. They have an increased risk of miscarriage, preeclampsia (especially with pulmonary atresia, pulmonary artery hypertension), fetal growth restriction and preterm delivery. The risk of transmission of heart disease to offspring ranges from 3% to 5% in patients for whom a genetic cause is not known, to 50% in those with an autosomal dominant condition, such as Marfan syndrome or Noonan syndrome, who should be considered for preimplantation genetic diagnosis prior to ART.

Surrogacy and adoption are valid options in women with complex congenital anomalies. In host surrogacy, the mother's egg is harvested and can be associated with risks during ovarian stimulation and egg collection. In complex CHD cases straight surrogacy with the use of surrogate mothers' egg may be a safer option. The outcome of infertility treatment in adult CHD patients as compared to normal women is not well described. In a series of 20 patients with cardiovascular disease, pregnancy following infertility treatment was associated with some complications in 73% subjects [20].

4. Contraception

Advice regarding contraception is important for AYA with CHD [21,22]. In a study of 536 women with CHD, 43% had never been counselled about contraception and since unintended pregnancies account for up to 50% of pregnancies between 15 and 45 years and 80% in teenagers <18 years, this is a dangerous omission. Unplanned pregnancies in women with CHD can have potentially dangerous and harmful consequences for the woman. Similarly, many of the drugs used in the management of CHD have teratogenic effects on the developing fetus, meaning planning a pregnancy is essential. Advice regarding contraception is extremely important for women classified as mWHO III and IV since pregnancy is very high risk in those with conditions classified as mWHO class III and should be avoided in mWHO Class IV (Table 2). Pregnancy should be planned, with adequate preconception counselling and investigations to optimise health, stratify risks, avoid teratogenic medication and after an MDT discussion in all women with CHD especially with mWHO Class III and IV defects [19]. Taking effective and safe contraception is therefore essential and a critical part of the care of women with CHD.

The choice of contraception needs to be individualised depending on the underlying lesion, risks, and effectiveness of the method of contraception and the duration for which it is required (Table 3). Current contraceptive options involve combined oestrogen and progesterone (most common pill formulations (combined oral contraceptive pill (COCP), vaginal ring and patch), progesterone only (pill, implant, LNG IUD) and hormone free methods (barrier methods like condoms, cervical caps, diaphragms, withdrawal method, copper IUD, sterilisation).

Barrier methods, withdrawal before ejaculation and calendar method have a high failure rate and hence not recommended. Oestrogen increases the risk of VTE and is known to increase blood pressure and hence not recommended in patients with pre-existing heart disease or hypertension. Progesterone only preparations (POP), the "Mini pill", is a safe choice for women with CHD [23]. Progesterone only contraceptives work by thickening the cervical mucus and preventing sperm penetration and reduction of endometrial receptivity, preventing implantation. The mechanism of action depends on the method used (IUD, pills, implants). POP commonly used is the higher dose of progesterone (Desogestrel 75 mg, [Cerazette]), which is more reliable as it inhibits ovulation. Its contraceptive efficacy is similar to the COCPs and is safe for use in women with CHD. Depot medroxyprogesterone acetate (DMPA) can be used by intramuscular injections every three months. Subdermal implants containing Levonorgestrel or etonorgestrel is another option that maintains contraceptive efficacy for 3–5 years and are effective reversible contraceptive methods that are safe for women with CHD.

The two common forms of reversible intrauterine device (IUD) are the Copper IUD and LNG IUD. LNG IUD is one of the safest and most effective contraceptives. LNG IUD offers other non-contraceptive

Table 2
Contraindications for pregnancy in women with congenital heart disease (mWHO Class IV).

Pregnancy contraindicated (mWHO Class IV)
1 Pregnancy contraindicated (mWHO Class IV)Pulmonary arterial hypertension
2 Severe systemic ventricular dysfunction (EF <30% or NYHA class III–IV)
3 Previous peripartum cardiomyopathy with residual left ventricular impairment.
4 Severe mitral stenosis
5 Severe symptomatic aortic stenosis
6 Systemic right ventricle with moderate or severely decreased ventricular function
7 Severe aortic dilatation Marfan's or heritable thoracic aortic disease with aortic dimensions >4.5 cm, Bicuspid aortic valve with aortic dimensions >5.0 cm, Turner syndrome with an aortic size index of >2.5 cm/m^2 Tetralogy of Fallot >50 mm
8 Vascular Ehlers–Danlos
9 Severe (re) coarctation
10 Fontan with any complication
mWHO – modified World Health Organization Classification.
EF – ejection fraction
NYHA – New York Heart Association

Table 3
Contraceptive choices for women with congenital heart disease.

Type of contraceptive	Failure rate (Typical %)	Effective period	Mechanism of action	Safety and Side effects
Barrier Methods				
Male Condoms, Female Condoms, Diaphragm Withdrawal	15 21 16 27	When used as per manufacturer's advice	Prevent sperms from entering the uterus	Safe to use High failure rate (15-28%) Protect from STI/PID
Implant (Nexplanon)	0.05	3 years	Inhibits ovulation, thickens cervical mucus	Highly effective (>99%)) No protection from STI Side effects: irregular bleeding, acne, mood changes, headache Needs local anesthetic for insertion.
LNG IUD (Mirena)	0.2	5 years	Cervical mucus thickening, anovulation, prevents implantation	Highly effective (>99%)) No protection from STI Used for endometrial protection, management of heavy menstrual bleeding, dysmenorrhea. Inserted with local anesthetic, can cause vasovagal
Copper IUD	0.8	5 /10 years (device dependent)	Inhibits fertilization and implantation	Highly effective (>99%)) No protection from STI Side effects: increased menstrual blood loss, Increased risk of infection (PID) Used as emergency contraceptive Insertion same as LNG IUD
Progesterone only Pill (Desogestrel)	8	Take daily for it to work (as per Manufacturers advice)	Inhibits ovulation, cervical mucus thickening	Moderately effective No protection from PID Side effects: irregular and breakthrough bleeding, acne, mood changes, headache, breast sensitivity

PID: pelvic inflammatory disease; STI: sexually transmitted infection; LNG IUD: Levonorgestrel intra-uterine device.

benefits including reduction of heavy menstrual bleeding, iron deficiency anaemia, pelvic pain (especially in women with endometriosis), and prevention of endometrial hyperplasia. Infective endocarditis prophylaxis is not needed for insertion of these devices. As previously discussed, IUD insertion may need to be performed in a hospital setting especially for Fontan and Eisenmenger syndrome patients, patients with pre-existing arrythmias, long QT syndrome or impaired ventricular function due to risks of vasovagal reaction during insertion, [24,25] Barrier contraceptives have a high failure rate but can prevent the spread of sexually transmitted infections. A combination of barrier contraception and LNG IUD is ideal. The commonly used LNG IUD (Mirena) is effective for 5 years after insertion and can be inserted in an outpatient setting with a local anesthetic. For emergency contraception, copper IUD, LNG or ulipristal acetate (UPA) are safe with no increased risk of thrombosis. In women with Eisenmenger syndrome or primary pulmonary hypertension, laparoscopic or mini laparotomy tubal ligation under local anesthesia can be considered for permanent contraception. Alternatively, vasectomy for the partner can be discussed.

5. Menopause

'Menopause' is defined as absence of menses for 12 consecutive months. As more women with CHD live until their 50s, the effect of menopause in these women will need to be considered by gynaecologists [26]. Adults with complex CHD have been shown to have a reduced total body bone mineral density compared to healthy individuals [27]. They are more likely to have acquired heart disease or a deterioration of their CHD, making management more challenging. Hormone replacement therapy (HRT) is usually given as a combination of oestrogen and progesterone, unless a hysterectomy has been performed in which case oestrogen can be given alone. It is most commonly given as a tablet, but for women with an increased risk of thrombosis transdermal routes are preferred, using patches, gel or spray, as they have a lower risk of thrombosis. This issue is greatest concern in women with Fontan's procedure or those with a mechanical heart valve.

Although HRT went into disrepute in 2002, when women's health initiative showed increased risk of coronary artery disease and breast cancer when the combination of oestrogen and progesterone were used together for HRT [28]. Since then, various studies have shown that HRT is safe and beneficial in postmenopausal women. In principle, the lowest dose of oestrogen should be used to improve symptoms and reduce the risk of osteoporosis.

5.1. Post menopausal ACHD

The number of adults over the age of 65 years with CHD is increasing due to improved surgical and medical management. A lot of these women have simple CHDs like septal defects [29]. The healthcare needs of these women have not been well defined in literature. They may also have acquired heart disease including coronary artery disease, and other medical problems, gynaecological malignancies, and pelvic floor dysfunction with uterine prolapse or stress incontinence which needs addressing, with the knowledge of the underlying CHD [30].

6. Conclusion

Gynaecological health in women with CHD needs more attention. Individualised counselling needs to commence from 12 to 13 years of age and continue to the transition to adult services. Through this time, discussion around menstrual dysfunction, contraception, fertility and pregnancy can commence and develop at a rate dependent on the developmental stage of the young person. Menstrual disorders including delayed menarche may be amongst the first topics but of extreme importance is the need to plan and support reliable contraception alongside barrier contraceptives to reduce the risk of sexually transmitted infection. Advice regarding contraception is paramount for women classified as mWHO III and IV since pregnancy is very high risk or contraindicated respectively. For some women with CHD experiencing infertility, ART poses a marked risk and needs discussion within an MDT. Women with cyanotic CHD have high risk pregnancies with increased rates of both maternal and fetal complications and awareness needs to be raised prior to the time they are trying to conceive. Ultimately, women on their gynaecological journey, which begins in menarche, and continues until well after childbearing need clear advice and information to assist them make personal health and fertility choices.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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