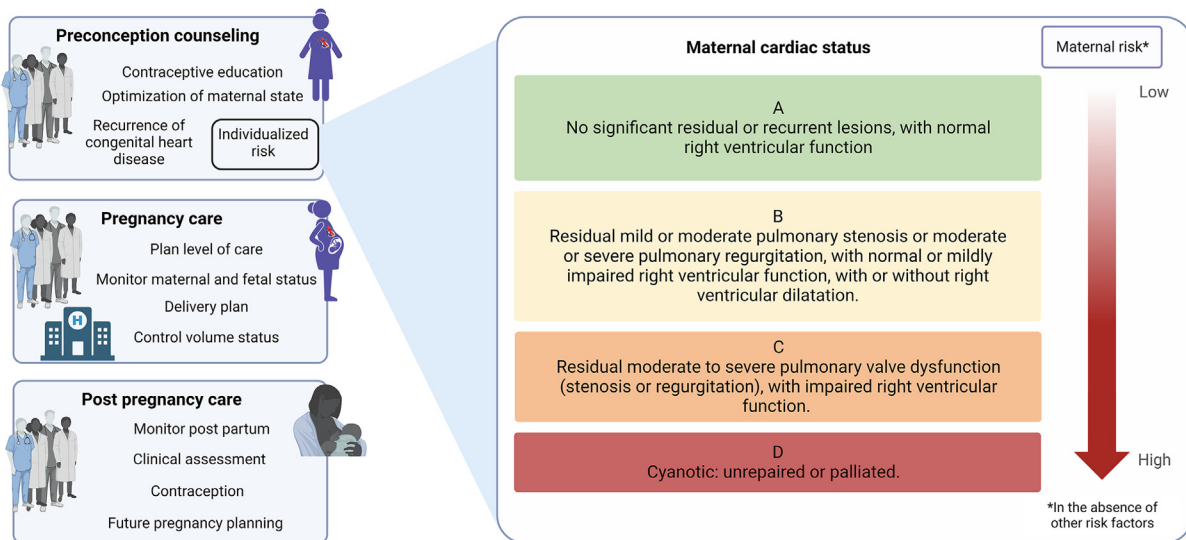## Review

Pregnancy Considerations in Tetralogy of Fallot

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PREGNANCY CONSIDERATIONS IN TETRALOGY OF FALLOT

ABSTRACT

The majority of women with repaired tetralogy of Fallot are able to tolerate pregnancy with a low risk of cardiovascular events. However, proactive contraceptive advice, prepregnancy counselling, and care by a pregnancy heart team with expertise in congenital heart disease are key to ensuring a good outcome for mother and baby. Maternal and fetal risks are increased in the presence of severe valvular stenosis, poorly tolerated arrhythmia, significant ventricular dysfunction, and cyanosis. It is unusual to see cyanotic adults with tetralogy of Fallot,

RÉSUMÉ

La majorité des femmes présentant une tétralogie de Fallot réparée tolèrent une grossesse et sont exposées à un faible risque d'événements cardiovasculaires. Cependant, des conseils sur la contraception, des consultations avant la grossesse et des soins prodigués par une équipe spécialisée en cardiopathies congénitales permettront de garantir de bons résultats pour la mère et l'enfant. Les risques pour la mère et l'enfant sont accrus en cas de sténose valvulaire sévère, d'arythmie mal tolérée, de dysfonction ventriculaire

Many people aspire to have children at some point in their lives, and adults with repaired tetralogy of Fallot are no exception. Their expectation to participate fully in society

through working, enjoying leisure activities, and having a family life reflects the successes of childhood repair and ongoing specialist surveillance through adulthood. With expert care throughout, from prepregnancy planning, through pregnancy and birth and into the puerperium, most women with repaired tetralogy of Fallot can tolerate pregnancy without significant cardiac complications.

Prepregnancy evaluation is a fundamental pillar for patients with tetralogy of Fallot and includes contraceptive education, optimization of the maternal state before pregnancy, and

whether unoperated or shunt palliated; pregnancy risks are greatly reduced by completing their repair before pregnancy is undertaken. The multidisciplinary pregnancy heart team should make a risk-stratified pregnancy care plan using a combination of published scoring systems and an individualized assessment of the patient's comorbidities. Low-risk patients may have the majority of their care and give birth in local units, whereas those at high risk should be managed and give birth in a tertiary centre with high-level expertise and intensive care facilities. Age-appropriate conversations about future childbearing and safe and reliable contraception should be part of routine follow-up from teenage years, so that women with tetralogy of Fallot can control their own fertility and make informed decisions about having children.

importante ou de cyanose. Les cas de cyanose chez les adultes atteintes de la tétralogie de Fallot sont toutefois rares, qu'elles aient subi ou non une anastomose palliative, et les risques associés à la grossesse sont considérablement réduits si la réparation est effectuée avant la grossesse. Pendant la grossesse, l'équipe multidisciplinaire spécialisée en cardiologie et obstétrique doit élaborer un plan de soins stratifié en fonction des risques, à l'aide de systèmes d'évaluation reconnus et une évaluation personnalisée des maladies concomitantes de la patiente. Les patientes à faible risque peuvent normalement recevoir leurs soins et accoucher dans des établissements locaux, tandis que celles à risque élevé doivent être prises en charge et accoucher dans un centre de soins tertiaire doté d'un haut niveau d'expertise et d'installations de soins intensifs. Dès l'adolescence, lorsque des patientes atteintes de la tétralogie de Fallot se présentent pour une consultation de routine, il est important de discuter de la procréation et de l'utilisation de méthodes de contraception sûres et fiables en utilisant un langage adapté à leur âge afin qu'elles sachent ce qu'il faut faire pour éviter une grossesse et puissent prendre une décision éclairée quant à l'éventualité d'avoir un enfant.

individualized risk stratification counselling (Fig. 1).[1-3] Patients should have expert individualized care within the framework of a multidisciplinary pregnancy heart team during the prepregnancy, prenatal, delivery, and the early and late postnatal periods. After delivery, the majority of patients can expect to make a full recovery with no major long-term haemodynamic deterioration. This review aims to provide a comprehensive description of contraception and pregnancy education, risk stratification, counselling, and management with current recommendations for care.

Epidemiology of Tetralogy of Fallot

Tetralogy of Fallot is the most common cyanotic congenital heart disease in children beyond the neonatal period, with an incidence of 3-5 per 10,000 live births or 7%-10% of all birth defects.[4] The etiology of the condition is multifactorial, but it is highly prevalent in specific genetic conditions such as 22q11.2 deletion syndrome, with a prevalence of 6% in a tetralogy of Fallot cohort. Other associated genetic conditions include trisomy 21, 18, 13, and Alagille syndrome.[5-7]

Evolution of Surgical Repair of Tetralogy of Fallot and Effect on Late Sequelae

The approach to surgical repair has evolved since the first palliative systemic to pulmonary shunt in 1944 and the first corrective surgery in 1954, to contemporary strategies that aim for complete repair in the first year of life, with either a transannular patch, valve-sparing procedure, or valved conduit placement.[4] In the current era, patients with tetralogy of Fallot undergo reparative surgery in early life, with excellent survival,[8] to the extent that they reach adulthood with near normal functional capacity and quality of life, with the expectation of having employment and regular social networks, and the choice to build a family like their unaffected counterparts.

Although patients with repaired tetralogy of Fallot have excellent long-term survival, the long-term morbidity is significant. In patients of childbearing age, morbidity most often relates to the status of the pulmonary valve.[8] Those who had initial repair with a transannular patch are likely to have severe pulmonary regurgitation with subsequent dilatation of the right ventricle (RV),[9] and some will already have undergone additional pulmonary valve replacement. Others will have
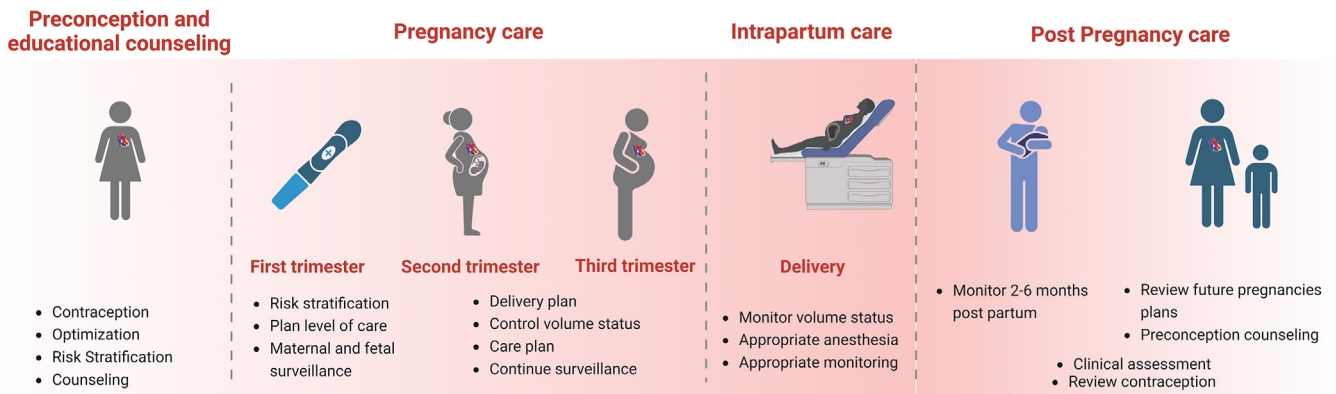

Preconception and educational counseling
- Contraception
- Optimization
- Risk Stratification
- Counseling

Pregnancy care

First trimester
- Risk stratification
- Plan level of care
- Maternal and fetal surveillance

Second trimester
- Delivery plan
- Control volume status
- Care plan
- Continue surveillance

Third trimester

Intrapartum care

Delivery
- Monitor volume status
- Appropriate anesthesia
- Appropriate monitoring

Post Pregnancy care
- Monitor 2-6 months post partum
- Clinical assessment
- Review contraception
- Review future pregnancies plans
- Preconception counseling

Figure 1. Pregnancy in patients with tetralogy of Fallot. Created with BioRender.com.

residual valvular dysfunction that may affect RV function.[9] Arrhythmia may also contribute to morbidity in women of childbearing age; an Australian cohort found that 17% of patients with tetralogy of Fallot have atrial arrhythmias 30 years after initial repair.[10] Although less common in younger adults, left ventricular or RV dysfunction is an important predictor of pregnancy-related morbidity.[11]

Survival to adulthood without repair or palliation is rare, both because surgical intervention is widely available in high- and middle-income countries and because childhood mortality is high in unrepaired tetralogy of Fallot. Nonetheless, a small percentage with favourable physiology who were beyond the reach of the medical system survive into adulthood with uncorrected anatomy.[12] Patients with unrepaired tetralogy of Fallot and those who have only undergone palliation with a systemic to pulmonary shunt remain cyanotic and will develop heart failure and complications of cyanosis during adulthood. Pregnancy in these patients carries high maternal and fetal morbidity[13–15] in comparison with the successful pregnancy outcomes seen in patients with repaired tetralogy of Fallot.

As in other conotruncal anomalies, some patients with tetralogy of Fallot have dilatation of the ascending aorta, likely related to increased flow in the aorta during fetal and early life. This dilatation does not carry the risks associated with bicuspid aortic valve or familial aortopathies, and the incidence of aortic complications is extremely low.[16]

For the purposes of pregnancy risk and management, 4 broad phenotypes may be considered, understanding that overlap or evolution between groups may occur and that additional cardiac lesions may coexist. In the absence of other risk factors, the risks of pregnancy increase from the lowest in group A to highest in group D:

A. No significant residual or recurrent lesions, with normal RV function.
B. Residual mild or moderate pulmonary stenosis or moderate or severe pulmonary regurgitation, with normal or mildly impaired RV function, with or without RV dilatation.
C. Residual moderate to severe pulmonary valve dysfunction (stenosis or regurgitation), with impaired RV function.
D. Cyanotic: unrepaired or palliated.

Physiological Adaptations During Pregnancy and Delivery

The ability of a patient with tetralogy of Fallot to tolerate a pregnancy safely depends largely on whether her heart is able to respond to the physiological demands of pregnancy. These physiological changes start early in the first trimester, leading to a hyperdynamic state capable of supporting the growing fetus as pregnancy progresses. A successful maternal and fetal outcome is dependent on achieving and sustaining a rise in cardiac output by increasing stroke volume and heart rate.

There is a rapid rise in stroke volume from the first trimester, plateauing in the third trimester, to an approximately 45%-50% rise above baseline in a singleton pregnancy.[17] Heart rate increases by 10-20 bpm during pregnancy, mainly in the third trimester, contributing to the rise of cardiac output (Fig. 2). The highest heart rate and

cardiac output are seen during labour before normalizing in the postpartum period. Heart rate returns to baseline in 2 weeks, while cardiac output falls to its baseline by 16 weeks postpartum.[18]

Systemic and pulmonary vasodilation start early in the first trimester, with a steady decrease in peripheral vascular resistance reaching a nadir near the 20th week, at 25%-30% from the baseline, before rising again later in the third trimester, returning to baseline in the first weeks of the puerperium.[19] The increase in vascular compliance is reflected by small changes in blood pressure, the mean blood pressure falling 5-710 mm Hg below the initial value.

Total blood and plasma volume also rise during gestation,[20] and an acceleration of erythropoiesis increases the red blood cell count. However, as the fetus grows, the 50%-60% expansion in plasma volume is not matched by erythropoiesis, leading to dilutional "physiological" anaemia. Of note, maternal iron stores are preferentially directed to the fetus, so true iron deficiency anaemia is also common, and may be poorly tolerated if maternal cardiac reserve is limited.

Both left ventricular and RV mass increase during pregnancy, with an increase in left ventricular wall thickness seen on echocardiography of 25%-30%. The changes are driven by volume loading and vascular endothelial growth factor and return to baseline within 6 months after pregnancy.[21]

Pregnancy carries an increased risk of thrombosis, particularly pertinent to patients with arrhythmia, mechanical valves, or cyanosis. The highest rate of thromboembolic complications is described in the third trimester and postpartum period, particularly following caesarean section.[22]

Cardiac output reaches its peak during labour and delivery, rising by 80%, in association with transient 300-500 mL autotransfusions from the placenta during uterine contraction.[18] There is a further autotransfusion during the third stage of labour when the placenta is delivered. Pain and stress contribute to these changes, raising heart rate and blood pressure, and can be mitigated with good pain management, particularly regional analgesia. The haemodynamic changes around the time of delivery are more marked and rapid with caesarean section than with vaginal birth; vaginal birth with regional analgesia and passive descent of the fetus is the mode of delivery associated with the least haemodynamic stress.

Most of these adaptations persist for 48 hours after delivery, during which time patients with vulnerable ventricular function may develop heart failure. Although the major fluid shifts and circulatory changes have resolved after 48 hours, it is not until around 6 weeks postpartum that the circulation is fully returned to baseline.

Contraception and Prepregnancy Assessment and Counselling

Age- and development-appropriate discussion about future potential childbearing and contraception should start from teenage years, before sexual activity begins. The opportunity for discussion should be offered at each visit, evolving appropriately to the individual's needs and wishes, educating and empowering the patient to control their own fertility.[23]
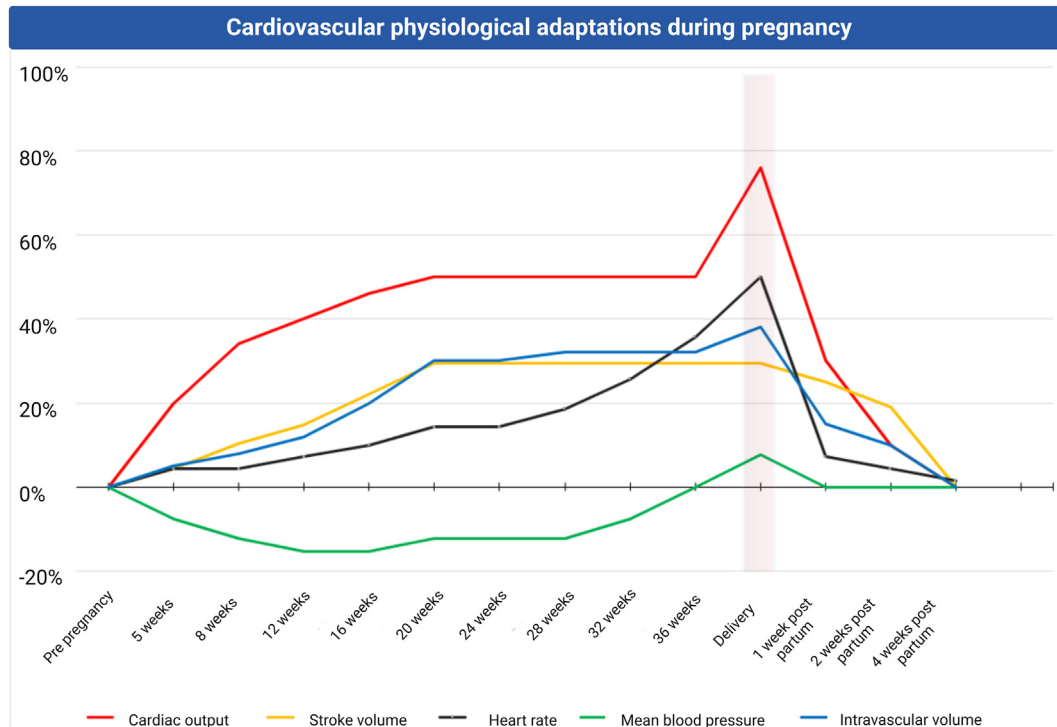
Figure 2. Cardiovascular physiological adaptations during pregnancy. Adapted from Hunter and Robson,[17] Mahendru et al.,[19] Halpern et al.,[22] Shen et al.,[65] and Loerup et al.[66] Created with BioRender.com.

More focused preconception counselling should be offered when the patient starts to consider a pregnancy.

Although there is no reported maternal mortality described in patients with repaired tetralogy of Fallot in the current era, the occurrence of morbidity is higher than in the unaffected population (3%-10%).[24] Therefore, prepregnancy counselling provides specific benefits to this population and should comprise the following components (Fig. 3):

(1) Understanding the patient's aims for childbearing
(2) Assessment and optimizing their condition
(3) Counselling with regard to maternal and fetal risk
(4) Outline of expected care plan during pregnancy and birth
(5) Alternatives to pregnancy, if appropriate
(6) Contraception

It is important to understand what the patient wishes to achieve with respect to pregnancy—the timescale, including whether they need fertility treatment or are seeking genetic testing or surrogacy.

Contraception

Effective and cardiovascularly safe contraception is key for patients with heart disease, for whom fertility control may be a matter of maternal safety, as well as normal family planning.

Barrier methods. Male and female condoms carry no cardiovascular risk and help to prevent sexually transmitted diseases. However, they are operator dependent and have a high failure rate (12.6% at 1-year typical use), particularly in young adults.[25,26]

Hormonal methods (Fig. 4)

Oestrogen-containing methods. The combined oral contraceptive pill is popular due to its beneficial effects in regulating menstruation. If taken consistently it has a high contraceptive efficacy (1% failure rate per year with perfect use), although the failure rate is higher with typical use (9%). All oestrogen-containing methods (the combined pill, oestrogen patch, and sponge) carry an increased risk of venous and arterial thrombosis.[27,28] They are therefore relatively contraindicated in patients with arrhythmia and severe ventricular dilatation and should not be used in those with cyanosis or a mechanical valve.

Progestogen-only methods. They do not carry the same risk of thrombosis associated with oestrogens, and all are cardiovascularly safe. However, contraceptive efficacy and menstrual effects may limit their use. Most progestogen-only methods may cause irregular bleeding in their first months of use, which usually settles to be acceptable to the patient.[29]

- Progestogen-only pills:
  - The standard minipill has less good contraceptive efficacy at around 9% failure rate per year, as it does not prevent ovulation and has a narrow timing window. Its use should therefore be primarily for low-risk patients who are spacing planned pregnancies.[29]
  - Drospirenone and desogestrel pills both prevent ovulation and have a similar contraceptive efficacy to the combined pill. They are good options for patients who need to avoid pregnancy and do not wish to use a long-acting method.[30]
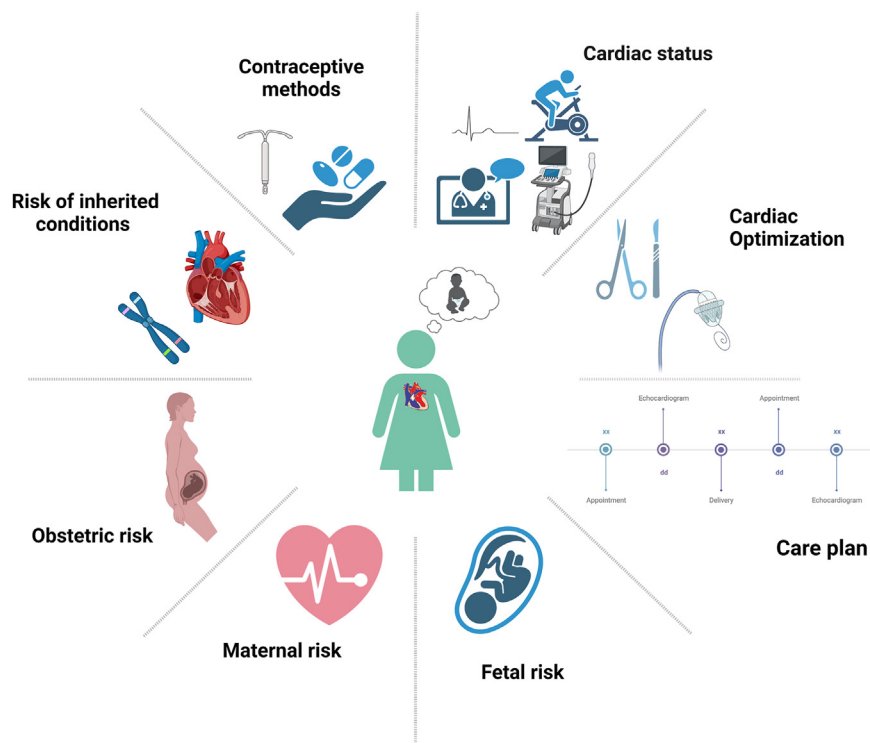
Figure 3. Preconception education and counselling. Created with BioRender.com.

- Long-acting progestogen-only methods (<1.4% failure rate at 1 year with typical use[26]):
  - Progestogen-eluting intrauterine devices (IUDs) (eg, Mirena, Kyleena, and Jaydess) are more reliable than sterilization and normally have a beneficial effect on menstruation. They last between 3 and 8 years. Insertion can be unpleasant and carries a small risk of a vagal response during cervical manipulation. As a result, patients with unrepaired or palliated tetralogy of Fallot and cyanosis should have the device fitted in a hospital setting with anaesthetic availability.[28]
  - DepoProvera is a 3-monthly intramuscular injection. It has good efficacy as long as repeat injections are performed on time. There may be bruising at the site of injection in women taking anticoagulants, and unwanted progestogen-associated side effects such as mood swings and weight gain may be more common than with other long-acting methods.[29]
  - Nexplanon subdermal implant is an unobtrusive small flexible plastic rod inserted into the medial side of the upper arm. It lasts 3 years and has a similar efficacy to sterilization. The side effect profile is similar to the progestogen IUD, and there are no cardiac risks at insertion.[29]
- Morning-after pill: There are 2 types of morning-after pill; both are safe for all patients with heart disease and both are available at pharmacies without prescription.[29]
  - Levonorgestrel (Plan B): progestogen only, most effective if taken within 12 hours of unprotected sex; failure rate is 2.2%.
  - Ulipristal (Ella): selective progesterone receptor modulator, can be taken up to 5 days after unprotected sex, most effective when taken early; failure rate is 1.4%.
- Copper IUDs are favoured by some women who want reliable contraception but who do not wish to use hormonal contraception. Insertion risks are the same as for the progestogen-eluting IUDs, but they tend to increase menorrhagia and dysmenorrhoea.[27]

Prepregnancy Assessment

Assessment requires a full understanding of previous maternal cardiac history and current status, comorbidities, medications, examination, and updated investigations. The assessment should enable the clinician to determine how residual or recurrent issues impact pregnancy risk and whether they require intervention before pregnancy. Investigations should include the following:

- A baseline electrocardiogram (ECG) establishes heart rhythm and QRS duration, which correlates with RV dilatation and dysfunction.[31] In addition, QRS fragmentation has been correlated with the presence of ventricular arrhythmias.[32]
- A current echocardiogram is a key part of prepregnancy assessment, showing biventricular size and function, atrial size, residual shunts, and significant
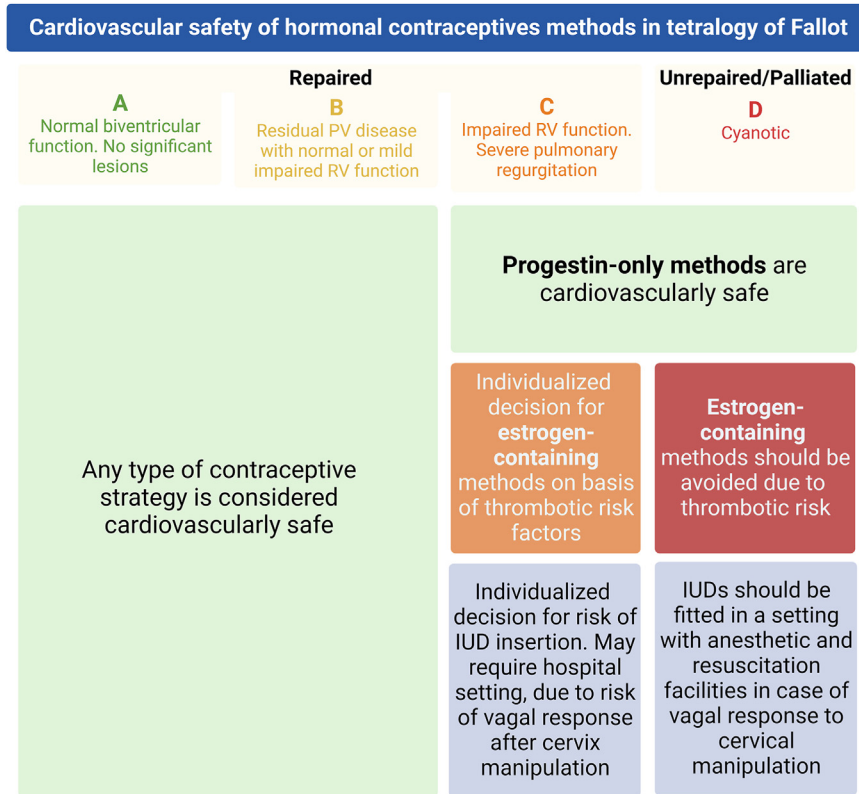
Cardiovascular safety of hormonal contraceptives methods in tetralogy of Fallot

	Repaired		Unrepaired/Palliated
A Normal biventricular function. No significant lesions	**B** Residual PV disease with normal or mild impaired RV function	**C** Impaired RV function. Severe pulmonary regurgitation	**D** Cyanotic

Progestin-only methods are cardiovascularly safe

Any type of contraceptive strategy is considered cardiovascularly safe

Individualized decision for **estrogen-containing** methods on basis of thrombotic risk factors	**Estrogen-containing** methods should be avoided due to thrombotic risk
Individualized decision for risk of IUD insertion. May require hospital setting, due to risk of vagal response after cervix manipulation	IUDs should be fitted in a setting with anesthetic and resuscitation facilities in case of vagal response to cervical manipulation

Figure 4. Summary of cardiovascular safety of hormonal contraceptive methods in patients with tetralogy of Fallot. IUD, intrauterine device; PV, pulmonary valve; RV, right ventricle. Created with BioRender.com.

valve lesions, and can be used for comparison as pregnancy progresses.[21]

- Cardiopulmonary exercise testing provides evidence of the patient's physical performance and can be considered a surrogate for the ability to increase cardiac output during pregnancy. The estimation of heart rate response has been correlated to outcomes in pregnancy.[33,34]
- Advanced imaging such as cardiac computed tomography or magnetic resonance imaging is useful to assess the RV volumes and function if visualization by echocardiography is limited.[35] Magnetic resonance imaging is also useful for patients with severe pulmonary reguritation and a dilating RV to determine whether the threshold for pulmonary valve replacement has been reached, indicating the need for prepregnancy intervention.

Prepregnancy Risk Stratification and Counselling

Maternal risk. There are 3 widely used risk-scoring algorithms validated in patients with congenital and acquired heart conditions that aim to anticipate the expected maternal cardiovascular course during pregnancy according to the anatomy, prior interventions and events, medications, functional class, and other variables. In patients with tetralogy of Fallot, they may be used along with individualized assessment to provide appropriate counselling.

The modified classification of the World Health Organization is in widespread use, as it simplifies cardiac patients into 4 categories with respective increased risk of events, according to the complexity of the anatomy and their status.[1] Patients with tetralogy of Fallot can be classified as modified classification of the World Health Organization II, III, and IV (Fig. 5). The ZAHARA (**Z**wangerschap bij **A**angeboren **HARtA**fwijkingen) study found that patients with a history of arrhythmia, New York Heart Association functional class >II, severe atrioventricular valvular insufficiency, and use of cardiac medication[3] have worse outcomes during pregnancy. The CARPREG II (**CAR**diac disease in **PREG**nancy) study showed increased risk with previous cardiovascular events, reduced systemic ejection fraction, New York Heart Association III or IV, cyanosis, high-risk aortopathy, late first prenatal visit, noncardiac comorbidities, fertility treatment, poor patient compliance, and poor access to good quality of care.[2]

In practical terms, the best estimation of maternal risk in pregnancy is achieved by applying 1 or more of the scoring systems and individualizing the risk assessment to consider the whole of the patient's clinical situation. Taking into account these risk scoring systems and other published data, the anticipated maternal cardiovascular risks for patients in groups A-D can be further considered:

A. No significant residual or recurrent lesions, with normal biventricular function. These patients have only a small increase in the chance of developing arrhythmia or heart failure in comparison with normal population.

Use of risk stratification models in tetralogy of Fallot

Tetralogy of Fallot patients (Groups)	CARPREG II		mWHO		ZAHARA	
	Score	Maternal cardiac risk (%)	Score	Maternal cardiac risk (%)	Score	Maternal cardiac risk (%)
(A) Repaired with no significant residual lesions	0-1	<5	I	<5	<0.50	<3
(B) Repaired with residual significant PR, dilated RV, normal biventricular function	2	5-10	II	5-10	0.75	7.5
(C) Repaired with residual significant PS/PR, dilated RV with impaired RV function	3	15	II-III	10-20	2.25	17.5
(C) Repaired with residual significant valve lesions and mild-moderate biventricular dysfunction or previous cardiac event or arrhythmia	4	20-25	III	20-30	2.25	17.5
(D) Cyanotic (unrepaired or palliated), or NYHA III-IV, with previous cardiac event or arrhythmia or ventricular dysfunction	>4	40-45	IV	>40	>2.51	>43

Figure 5. Examples of the use of different scoring systems to stratify the maternal risk of pregnancy in tetralogy of Fallot.[1–3] CARPREG II, CARdiac disease in PREGnancy; mWHO, modified classification of the World Health Organization; NYHA, New York Heart Association; PR, pulmonary regurgitation; PS, pulmonary stenosis; RV, right ventricle; ZAHARA, Zwangerschap bij Aangeboren HARtAfwijkingen. Created with BioRender.com.

B. Residual mild or moderate pulmonary stenosis or moderate or severe pulmonary regurgitation, with normal or mildly impaired RV function, with or without RV dilatation.

The risk of developing complications such as arrhythmia or ventricular dysfunction in pregnancy is small, although assessment should include a consideration as to whether pre-pregnancy intervention is warranted.[36] RV dilatation secondary to pulmonary regurgitation is well tolerated in pregnancy; however, whether RV dilatation progresses as a result of pregnancy remains uncertain, with differing reports.[36–38] No difference in pregnancy outcome has been reported whether or not pulmonary valve replacement was performed before pregnancy,[38] and in practical terms, the effect of pregnancy on a well-functioning dilated RV is likely to be small. Pregnancy is not associated with degeneration of right-sided bioprosthetic valves.[39]

C. Residual moderate to severe pulmonary valve dysfunction (stenosis or regurgitation), with impaired RV function.

These patients usually have good functional status before pregnancy; however, the cardiovascular stress of gestation can lead to decompensation, and so their risk of heart failure or arrhythmia during pregnancy is increased by 4%-10% and 1.6%-2%, respectively, with a 1% risk of embolic events.[40,41] They should therefore have full prepregnancy assessment, and

if they meet the standard criteria for pulmonary valve replacement, consideration should be given to prepregnancy intervention.[42]

D. Cyanotic: unrepaired or palliated.

In the modern era, it is rare for patients in high- and middle-income countries to present at childbearing age without complete repair. If such patients are seen for pre-pregnancy assessment, they should be offered repair before undergoing pregnancy, as maternal, fetal, and obstetric risks are very high in this situation and include maternal heart failure and arrhythmia, haemorrhage, fetal loss, prematurity, and impaired fetal growth.[12,43]

Maternal and fetal risk increases with the degree of cyanosis with a risk of major cardiovascular morbidity of 19%-37%; close tertiary centre follow-up is needed.[1,12]

Tetralogy of Fallot patients with a dilated aorta should be evaluated on an individual basis; in general, it carries a low risk and is not comparable to the hereditary aortopathies. Aortic dissection is extremely rare with only a few case reports, outside of pregnancy.[44] There are no data to support prophylactic aortic intervention before pregnancy, and if surgery is performed to replace a dilated aortic root, it is usually carried out at the same time as another indicated surgical procedure.[16] Nonetheless, most pregnancy heart teams advise precautions to reduce cardiac stress at the time of delivery if the aorta is >5 cm.[1,45]

Obstetric risk. The miscarriage rate in patients with tetralogy of Fallot is comparable with unaffected population.[46] Similarly, women with tetralogy of Fallot do not have an increased risk of developing common obstetric complications, such as pre-eclampsia (0.5%-8%), gestational hypertension, and gestational diabetes. General recommendations for screening and preventive measures apply to this group of patients in the same way as their counterparts, including prenatal vitamins, folic acid supplements, and avoiding anaemia.

The risk of obstetric haemorrhage has been reported to be increased in women with heart disease; however, the risk of ante- and postpartum haemorrhage is not elevated for acyanotic patients with repaired tetralogy of Fallot who are not taking anticoagulants, and whose labour is managed with standard uterotonic care during the third stage (delivery of the placenta).[47] The risk of intra- and postpartum haemorrhage is increased for patients with tetralogy of Fallot who are cyanotic; they should be advised to give birth in a tertiary centre with a specialist pregnancy heart team.

Fetal risk. There is a 3%-4.8% risk of recurrence of congenital heart disease in children of parents with tetralogy of Fallot compared with 0.8% in the general population.[48] A fetal echocardiogram between weeks 16 and 22 is recommended to screen for congenital heart defects.[49] If a parental 22q11.2 deletion is present, the chance inheriting the affected chromosome is 50%, with high risk of an associated congenital heart defect.

Historical data suggest that intrauterine growth restriction and preterm birth are increased in infants born to mothers with repaired tetralogy of Fallot with impaired RV function and poor maternal outcomes,[46] possibly in relation to the uteroplacental circulation.[50] There is a paucity of data on contemporary fetal outcomes; however, in general, uncomplicated pregnancies in healthy mothers have a good chance of leading to full-term, well-developed newborns.

Patients with unrepaired tetralogy of Fallot have the highest risk of poor fetal outcome, with a 10%-20% risk of spontaneous abortion, 10%-16% stillbirth, 40%-49% small for gestational age, and 40%-50% risk of preterm birth.[12,43] The degree of maternal cyanosis and ventricular dysfunction are the strongest risk factors for poor fetal outcome.

Fetal outcomes can be affected by maternal medications, so these should be reviewed at the time of prepregnancy counselling. Consideration should be given to stopping medications that are associated with fetal embryopathy or other adverse fetal effects, or to prescribing alternative drugs, either before conception or as soon as conception is confirmed. Commonly used cardiovascular medications that carry fetal risk include oral anticoagulants, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, statins, and amiodarone. Aspirin is safe in pregnancy, as are β-blockers, with most centres preferring bisoprolol or metoprolol.[1,51]

Location of Care

The choice of location of care depends on a number of factors including maternal and fetal risk, the expertise and facilities available, geographical factors, and maternal choice.

The pregnancy heart team in a tertiary centre includes the maternal fetal medicine obstetrician, anaesthetist, obstetric cardiologist, midwife, and health allies familiar with the patient's congenital heart condition. All members of the care team should participate in the construction of a care plan, following the premise that a multidisciplinary approach results in better maternal and fetal outcomes.[52] Women who live far from a tertiary centre, but who require higher levels of care than can be provided locally, may need to relocate in the latter stages of pregnancy. This may be a financial and psychosocial burden on the patient and her family, and should therefore be planned in advance.

After initial assessment by the pregnancy heart team, those in groups A and B who are at low risk of pregnancy complications may reasonably choose to have their care and give birth at their local centre. If this is not the tertiary centre, they should have a care plan that details the steps to follow in case escalation of care is required, including the criteria to trigger escalation, who and how to contact the team at the tertiary centre, and how to arrange the transfer of care process.

Those in group C who are at modestly increased risk of maternal cardiac complications may choose to have their care and give birth at the tertiary centre, or they may opt for shared care with a local centre closer to home, so that they are known in both institutions if maternal complications indicate a need to change their birth plan.

Patients in group D and patients with other cardiac or noncardiac comorbidities, who are at high risk of maternal and fetal complications, should have close follow-up by the high-risk pregnancy heart team in a tertiary centre with the availability of noninvasive and invasive monitoring, intensive care, mechanical cardiac support, and advanced care for the newborn.[1]

Care During Pregnancy

Most patients should be seen by the obstetric cardiologist at least once per trimester.[52] At each clinic visit with the cardiologist, symptoms and signs should be reviewed, and an ECG and echocardiogram are indicated to assess the cardiac response to the volume overload and stress of the pregnancy. A Holter monitor is indicated if symptoms suggest arrhythmia. Serial serum N-terminal pro-brain natriuretic peptide levels in patients with cyanosis, myocardial dysfunction, or other cardiac risk features have prognostic value and are a useful addition to clinical assessment.[53] Particular attention should be paid during the second and third trimesters when haemodynamic changes in volume status can lead to heart failure or arrhythmias.

The maternal-fetal obstetrician will assess fetal well-being as per guideline recommendations, including surveillance of the growth curve, weight, and placental Doppler flow to anticipate fetal complications in the case of high-risk maternal features such as ventricular dysfunction and cyanosis.

Specific Situations—Arrhythmias, Heart Failure, and Cyanosis

Pregnancy is a proarrhythmogenic state, and pregnant patients with repaired tetralogy of Fallot may experience arrhythmias for the first time.[54] They may have increased

premature beats or nonsustained runs of supraventricular arrhythmia, or sustained atrial arrhythmia, including atrial fibrillation or flutter. Most arrhythmias can be controlled with β-blocker treatment, though those with haemodynamic instability will benefit from prompt electrical direct current cardioversion. Direct current cardioversion is safe in pregnancy, and no major complications have been described.[55] Fetal monitoring before and after the procedure is recommended, although the risk of fetal arrhythmias or premature labour is deemed extremely low.[56] In the case of atrial fibrillation, guidelines recommend therapeutic anticoagulation with low-molecular-weight heparin until after birth when consideration can be made to switch to an oral anticoagulant.[1]

Patients who develop heart failure should be under the care of a tertiary centre and treatment should include diuretics and afterload-reducing medication such as hydralazine. Bed rest and tertiary centre hospital admission may be necessary. Depending on the severity of symptoms and myocardial dysfunction, early delivery may be required, with escalation of care to include intensive care and mechanical support. These latter 2 interventions are very rarely needed for patients with repaired tetralogy of Fallot unless there is coexistent severe left ventricular dysfunction.

Patients who are cyanotic with unrepaired or palliated circulations are at increased risk of heart failure as pregnancy progresses. The vasodilation of pregnancy is associated with an increase in right to left shunting and a fall in oxygen saturation, particularly on exercise. Although usually well tolerated by the patient, the increased hypoxia is deleterious to fetal outcome, and bed rest may be advised. The risk of thrombosis is increased in the presence of maternal cyanosis, so prophylactic anticoagulation is advised if the patient is immobile, bearing in mind that the risk of haemorrhage is also increased in this patient group.

Cardiac medications during pregnancy

Although many medications routinely used during pregnancy are relatively safe, the benefits and risks to the mother and fetus must be carefully weighed. Cardiovascular drugs most commonly used by patients with heart disease cross the placenta and expose the fetus to their pharmacologic effects. After delivery, the newborn and nursing infant may be exposed to drugs that pass into breast milk. During pregnancy, drugs such as adenosine, β-blockers, digoxin, nitroglycerin, hydralazine, and calcium channel blockers have benign profiles. During breastfeeding, spironolactone and angiotensin-converting enzyme inhibitor such as enalapril may be safely added.[51]

Intrapartum Care

Delivery—care plan

A care plan summarizes the maternal cardiac condition and describes the particular maternal, fetal, and obstetric risks, detailing the instructions for all stages of labour and early postpartum management. This should be shared between the patient and all other members of the health care team. The mode of administration and the type of analgesia should be discussed between the patient and the obstetric, anaesthetic,

and cardiology team. A multidisciplinary approach to intrapartum care provides a good understanding of the physiological changes that occur during vaginal and surgical delivery, and considers the drugs used during the second and third stages of labour and the obstetric techniques available.[57]

Group A and B patients whose pregnancy has progressed without complications may be considered low risk and give birth with no special cardiac precautions in a local unit with standard facilities, or with midwife led care. In general, group C patients should be advised, and group D patients strongly encouraged, to give birth at a tertiary centre with expertise in congenital heart disease and intensive care facilities.

There are few cardiac contraindications to vaginal birth, so unless the patient has decompensated heart failure and is too unwell to labour, the only indications for caesarean section are usually noncardiac complications or maternal choice.

Induction of labour may be performed, depending on cardiac status and obstetric criteria. Induction may be achieved mechanically (cervical ripening balloon and artificial rupture of membranes) and/or with pharmacologic agents including vaginal or oral prostaglandins such as misoprostol or dinoprostone, or intravenous oxytocin infusion.[1,58]

Maternal monitoring during labour should be individualized.[57] Patients with cyanosis or poor ventricular function require the most intensive monitoring, including fluid balance, telemetry, and pulse oximetry, with consideration given to invasive central venous and arterial monitoring. At the time of delivery, the obstetric anaesthesia team should be actively involved, avoiding sudden changes in blood pressure or heart rate. Epidural anaesthesia controls 95% of pain and ameliorates haemodynamic changes, decreasing the adrenergic response to pain. Fluid management should aim to maintain euvolaemia, particularly in patients with cyanosis and impaired ventricular function.

The second stage of labour is usually well tolerated, and patients can push without cardiovascular complications. Assistance in the second stage is not mandated for the majority of patients with tetralogy of Fallot. The key to a safe birth is regular review by a senior clinician during labour, particularly if there is a change in maternal or fetal status, with instrumental intervention only if there is any new maternal compromise, or for fetal or obstetric indications. For patients with tetralogy of Fallot and severe aortic dilatation (>5 cm), it is reasonable to limit pushing, whether through an assisted second stage during vaginal birth or offering caesarean section.[45]

For patients at high risk of cardiovascular complications, vaginal birth with regional analgesia and passive descent of the fetus is the mode of delivery associated with the least haemodynamic stress. However, each case must be individualized, and complex situations and decision-making mean that there is a trend towards caesarean section in situations such as heart failure, significant arrhythmia, and anticoagulation.

A total of 10%-28% of patients with tetralogy of Fallot have a caesarean section, with leading determinants being patients' choice and obstetric indications. No increased risk of adverse fetal outcomes were documented.[11,40,41] It should be noted that caesarean section incurs a higher haemorrhagic risk, with more rapid fluid shifts, and increased risk of infection and embolic events than vaginal birth.[47]

The third stage of labour is the period between the delivery of the baby and the delivery of the placenta. Historically, women with congenital heart conditions are reported to have higher rates of postpartum bleeding; this may be contributed to by a reluctance to use adequate doses of oxytocin, given the concern for possible cardiac effects. However, most patients with congenital heart disease, including tetralogy of Fallot, can receive standard doses of oxytocin with good tolerance, resulting in rates of blood loss comparable to those of patients with structurally normal hearts.[47] In case of severe bleeding, prostaglandin E2 analogs such as sulprostone, misoprostol, and carboprost can be used[1,57] in conjunction with fluid resuscitation and escalation of interventional care.

Antibiotic prophylaxis is not indicated for patients with tetralogy of Fallot with or without prosthetic valves, independent of mode of delivery. Standard hygiene and aseptic measures should be taken.[1]

High-risk scenarios

Heart failure. Severe maternal systemic ventricular dysfunction is uncommon in patients of childbearing age with tetralogy of Fallot, as is decompensated right heart failure. However, it presents a very high risk during delivery, and the patient should be monitored closely for at least 48 hours post partum in a facility with the ability to provide intensive therapeutic unit care and mechanical support.

Cyanosis. Cyanosis carries a high risk of severe intrapartum and postpartum haemorrhage, as well as a risk of paradoxical embolism. Close monitoring is indicated, and birth should be in a tertiary level unit with intensive therapeutic unit facilities with a pregnancy heart team with expertise in congenital heart disease. Air filters should be used in intravenous lines to avoid paradoxical emboli. In this scenario, vaginal birth is preferable as it carries a lower risk of bleeding, but fetal compromise frequently requires delivery by caesarean section, in which case great care should be taken to achieve haemostasis and a surgical drain should be placed. Close monitoring for at least 48 hours of partum on a high dependency unit is indicated.[59]

Postpartum Care

Breastfeeding

Patients should be encouraged to breastfeed given the known benefits for the mother and baby.[60] If domperidone is used to facilitate the milk supply, women considered at risk of arrhythmia should have standard monitoring of the QT segment on ECG.[61] The puerperium is the period after childbirth when maternal physiological and anatomic changes return to the nonpregnant state; it takes up to 6 months. Patients who had complications during pregnancy should be closely followed during this time. Postpartum patients should visit their cardiologist for clinical review. They should be encouraged to use reliable contraception and discuss the importance of planning for any future pregnancies.

Infertility

The prevalence of infertility in patients with tetralogy of Fallot does not differ from that of the general population.[41] Liaison between the obstetric cardiologist and fertility specialist is important, although the risks of fertility treatment are low for most with acyanotic repaired tetralogy of Fallot. Women with impaired left or right ventricular function have poor tolerance of ovarian hyperstimulation syndrome, a condition where there is rapid accumulation of fluid, causing ascites and effusions. This condition is rare with modern ovarian stimulation protocols, but the fertility team should be aware to modify the protocol in high-risk patients and consider delayed embryo implantation.[62,63] Only one embryo should be implanted to avoid multiple gestation, a scenario that increases maternal and fetal risks.[62]

Preimplantation Genetic Testing

Preimplantation genetic testing may be possible for patients with serious disease-causing single gene mutations and may be considered for those with 22q11.2 deletion syndrome to avoid the 50% risk of recurrence. The availability and cost of the process may vary between jurisdictions, and discussions need to be sensitive and respectful of patient choice.[64]

Surrogacy

If pregnancy carries a prohibitively high risk, surrogacy can be explored using eggs from the mother herself or from a donor. The maternal risk for obtaining eggs is much lower than with pregnancy, but ovarian stimulation techniques should be modified to minimize the risk of hyperstimulation, and egg retrieval should be performed in a setting with adequate resuscitation facilities. In many jurisdictions, only altruistic surrogacy is permitted; it may be difficult to find a surrogate, and costs may be prohibitive.

Summary and Conclusion

Patients with repaired tetralogy of Fallot expect to lead a good quality of life and participate in all aspects of society, including family life. The cardiology team should offer age-appropriate discussions regarding childbearing and contraception from teenage years so that girls and women can make informed decisions about their fertility. Formal pre-pregnancy counselling should be offered to all patients with tetralogy of Fallot who wish to consider a pregnancy, and once pregnant, they should be seen by a specialist pregnancy heart team.

The majority of women with tetralogy of Fallot are able to tolerate pregnancy with only a modestly increased risk of cardiovascular complications. This low maternal risk includes those with pulmonary regurgitation and a well-functioning dilated RV. Although specialist assessment is important to care planning, many can safely give birth in community obstetric units close to home.

Women at high risk include those with cyanosis, ventricular dysfunction, severe valvular disease, and poorly tolerated arrhythmia. They should be offered care throughout their pregnancy and delivery by a specialist pregnancy heart team at a tertiary centre.

Key Messages

- Most patients with repaired tetralogy of Fallot
  - tolerate the cardiovascular demands of pregnancy even in the presence of significant valvular regurgitation.
  - have <20% of cardiovascular events in pregnancy with a very low risk of maternal mortality.
  - have up to 4.8% risk of recurrence of congenital heart disease, or 50% risk in the presence of 22q11.2 deletion syndrome.
- Maternal and fetal risks are high in patients with tetralogy of Fallot complicated by
  - cyanosis.
  - significant right or left ventricular dysfunction.
  - severe valvular stenosis.
- Multidisciplinary care by a specialist pregnancy heart team optimizes maternal and fetal outcomes.

Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a review article that does not use identifiable data, and therefore the institutional review board did not require patient consent.

Funding Sources

No funding was received for this study.

Disclosures

The authors have no conflicts of interest to disclose.

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