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Best practice recommendations for medically assisted reproduction in patients with known cardiovascular disease or at high risk of cardiovascular disease

A consensus statement supported by the UK Maternal Cardiology Society (UKMCS), British Fertility Society, MacDonald Obstetric Medicine Society (MOMS), British Cardiovascular Society (BCS), British Cardiovascular Intervention Society (BCIS), British Society for Heart Failure (BSH), Scottish Obstetric Cardiac Network (SOCN), Royal College of Obstetricians and Gynaecologists (RCOG), Association of Anaesthetists, Fertility UK, Primary Care Cardiovascular Society (PCCS), Obstetric Anaesthetists Association (OAA), Association of Inherited Cardiac Conditions (AICC)

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PRACTICE AND POLICY

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Kate English[a], Charlotte Frise[b], Johanna Trinder[c], Matthew Cauldwell[d], Maggie Simpson[e], Dawn Adamson[f], Chris Elton[g], Gwenda Burns[h], Meenakshi Choudhary[i], Mike Nathanson[j], Leema Robert[k], Jim Moore[l], Pat O'Brien[m] and Jyotsna Pundir[n]

[a]Department of Congenital Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK; [b]Department of Obstetrics, Queen Charlotte's and Chelsea Hospital, London, UK; [c]St Michael's Hospital, Bristol, Bristol; [d]Department of Obstetrics, St George's Hospital, London, UK; [e]Cardiology, NHS Greater Glasgow and Clyde, Glasgow, UK; [f]Department of Cardiology, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK; [g]Department of Anaesthesia, Leicester Royal Infirmary, Leicester, UK; [h]Fertility Network UK, Greenwich, UK; [i]Newcastle Fertility Centre at Life, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK; [j]Department of Anaesthesia, Nottingham University Hospitals NHS Trust, Nottingham, UK; [k]Department of Clinical Genetics, Guys and St Thomas' NHS Foundation Trust, London, UK; [l]Department of Primary Care, NHS Gloucestershire Clinical Commissioning Group, Brockworth, UK; [m]Department of Obstetrics, University College London, London, UK; [n]Reproductive Medicine, St Bartholomew's Hospital, London, UK

ABSTRACT

Increasing numbers of people are seeking assisted conception. In people with known cardiac disease or risk factors for cardiac disease, assisted conception may carry increased risks during treatment and any subsequent pregnancy. These risks should be assessed, considered and minimized prior to treatment.

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KEYWORDS
Assisted conception; cardiac disease; sub-fertility

Background

Subfertility is common, affecting approximately one in seven couples, and the numbers of people seeking assisted conception has doubled in the last 20 years. In 2019, 53,000 patients in the UK had In Vitro Fertilisation (IVF) in order to achieve a pregnancy. Increasing numbers of older patients are having IVF; currently almost 40% of patients are aged 38 or over (Human Fertilisation and Embryology Authority, 2019). Patients seeking fertility treatment may have known cardiovascular disease (acquired, inherited or congenital) or cardiovascular risk factors such as diabetes, hypertension and obesity, all of which increase with age. Current data from the British Heart Foundation show that 9% of women living in England between the ages of 35–44 years have established hypertension, 32% are obese (Body Mass Index $\geq$30 kg/m^2) and 3% have known diabetes (British Heart Foundation, 2019).

CONTACT Kate English kateenglish@nhs.net Department of Congenital Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK.
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It is known that pregnancy carries an increase in mortality and morbidity risk for patients with cardiovascular disease (Roos-Hesselink et al., 2019) but there is very little published data giving information about the risks of fertility treatment itself for these patients or for those at high risk of cardiovascular disease (Dayan et al., 2014; Kim et al., 2020; Quien et al., 2022; Skorupskaite et al., 2022). The MBRRACE-UK reports (Mothers and Babies: Reducing Risk through Audit and Confidential Enquiries) into maternal deaths consistently show that cardiovascular disease is the commonest cause of death for pregnant women in the UK, and several of the chapters in the 2021 report emphasise the need for guidance on maternal medical assessment and screening prior to assisted reproduction, particularly for older women who are at higher risk of co-morbidities such as cardiovascular disease (MBRRACE-UK, 2021). This document aims to address this, as there is no current guidance about how these patients should be investigated and optimised prior to undertaking fertility treatment, and no guidance to suggest when or how their fertility treatment should be modified to reduce complications that may be exacerbated by their underlying condition. A recent cohort study of almost 2.5 million patients showed no increased risk of later CVD associated with use of Assisted Reproductive Technology (ART) in later life, which may be reassuring to those concerned about long term impacts (Magnus et al., 2023).

As the population of patients with congenital heart defects reaching reproductive age increases (Bouma & Mulder, 2017), it is equally important that they have access to appropriate support for subfertility if the risks allow, and issues such as fertility preservation are considered prior to major surgical interventions which may considerably increase future pregnancy risk (e.g., a mechanical heart valve). Anecdotally, there are also reports of patients being denied fertility treatment after their risk is deemed incorrectly to be prohibitively high.

Aims

This document aims to provide best practice recommendations to promote

- Development of relationships between MAR units and their local cardiology teams and networks, regional maternal medicine networks and regional pregnancy heart teams (Team of experts in obstetrics, cardiology, obstetric anaesthesia and high-risk midwifery, providing holistic care to pregnant women with cardiac disease).
- Thorough and accurate multi-disciplinary risk assessment and counselling to aid shared decision making before undertaking MAR and subsequent pregnancy in women with cardiovascular disease.
- Assessment and optimisation of risk factors before undertaking MAR and subsequent pregnancy in women with risk factors for cardiovascular disease.
- Facilitation of safe MAR in patients with known cardiovascular disease by appropriate modification of treatment pathways.
- Timely referral for expert care once pregnancy is achieved.

Governance

Best Practice Recommendations vary in their style and format across different specialities, Royal Colleges and organisations. Given the multi-speciality nature of this document, it has been written bearing in mind these different styles and formats. The multi-disciplinary authorship team were nominated by their respective professional bodies following an approach by the UKMCS to the President, chief executive or equivalent of each professional body. Authors were asked to consider sections of the recommendations dependent upon their particular areas of expertise, and the consensus document was created drawing on the current evidence base, published guidance and expert opinion. Each professional body was asked to give preliminary feedback and finally approval to the recommendations.

The evidence base behind each recommendation is given in accordance with the classification shown in Tables 1 and 2. As with any guidance or consensus statement, the responsibility to make appropriate and accurate decisions, and to give due consideration of the patient's condition and in consultation with the patient remains with the responsible clinician.

Table 1. Classes of recommendation.

	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/ efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy	Should be considered
Class IIb	Usefullness/efficacy is less well established by evidence / opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful	Is not recommended

Table 2. Levels of evidence.

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Implementation

These recommendations are made in attempt to help prevent poor pregnancy outcomes for mothers and babies. Implementation is achieved in different ways in different health economies depending upon local network arrangements and current provision and expertise. Local leadership teams in reproductive medicine, maternal medicine networks, cardiac networks, and primary care will need to work together to manage implementation.

Over-arching recommendations

Recommendation: All reproductive medicine units should develop strong links with one or more local cardiology teams, regional obstetric physicians and pregnancy heart teams to help ensure the safe care of patients with, or at high risk of, cardiovascular disease. (Class IIb, C)

Recommendation: All patients should have an assessment of their cardiovascular risk before starting MAR. (Class IIb, C)

Recommendation: Alternative options to family formation should be discussed, including no treatment, use of donor gametes, surrogacy or adoption. (Class IIb, C)

Recommendation: The risks of poor neonatal outcomes are increased both in patients with known cardiovascular disease, and in MAR-conceived pregnancies, so the increased neonatal risks should be considered in pre-treatment assessment and counselling. (Class IIa, B)

Recommendation: Patients with cardiovascular disease requesting MAR should not be turned down for treatment on the basis of assumed cardiovascular risk, until the case has been discussed in an MDT involving the pregnancy heart team and the reproductive medicine unit. (Class IIa, C)

Recommendation: Women with known cardiovascular disease or at high risk of cardiovascular disease seeking cross border MAR should be provided with clear information about benefits versus risks of MAR, including the risks of becoming unwell while abroad, and the importance of single embryo transfer to help them make an informed decision. (Class IIb, C)

Patients with cardiac disease requesting MAR

Background

The risks of pregnancy in patients with cardiovascular disease are well described in international registries (Roos-Hesselink et al., 2019; Silversides et al., 2018), but the risks of the use of MAR remain largely unreported outside of small case series from single centres (Dayan et al., 2014; Kim et al., 2020; Quien et al., 2022; Skorupskaite et al., 2022). Given the lack of evidence, it is important that all current expertise is shared, and complex management decisions are not taken by a single clinician in isolation.

Pre-implantation genetic testing

A number of monogenic diseases are identified in cardiac patients, and pre-implantation genetic testing for genetic conditions should be discussed in any patient with a serious inheritable cardiac condition (e.g., but not limited to Loeys Dietz syndromes, Marfan syndrome, Di George syndrome, Anderson Fabry disease, Catecholaminergic Polymorphic Ventricular tachycardia), where the pathogenic gene variant is known and listed as approved on the Human Fertilisation and embryology Authority (HFEA) website (https://www.hfea.gov.uk/pgt-m-conditions/).

Patients requiring PGT for the above indications should be first referred to regional Genetics service who would then initiate an onward referral to a reproductive medicine unit licensed by HFEA to offer PGT for that condition.

Risk stratification

Recommendation: Pre-implantation Genetic Testing should be offered to men and women with an inheritable cardiac condition where the pathogenic gene variant is known and who meet local and national eligibility criteria for PGT. (Class IIa, C)

The stratification of patients with cardiovascular disease by their level of risk associated with pregnancy is well described, and these patient groupings can be used to consider the potential risks of MAR, but with some additional caveats which are specific to the MAR process itself, and the risks of complications in the resultant pregnancy.

The modified World Health Organisation (mWHO) classification of maternal cardiovascular risk during pregnancy is shown in Supplementary Table 3 (European Society of Gynecology (ESG), Association for European Paediatric Cardiology (AEPC), German Society for Gender Medicine (DGesGM), Regitz-Zagrosek et al., 2011). The risks of both the MAR treatment cycle and the risks of the resultant pregnancy

and delivery should be considered during pre-treatment multidisciplinary assessment and counselling by the pregnancy heart team.

Clinicians should be mindful that some patients with congenital heart lesions are lost to follow-up rather than purposefully discharged, so all should be treated as at least mWHO Class I.

If the male partner is affected by cardiac disease, consideration of the safety of semen sample production may cause concern. In the overwhelming majority of cases this will be very low risk as the metabolic and cardiovascular demands of self-stimulation sexual activity are modest. Therefore, if no restrictions have been placed on sexual activity by the patients' own cardiologist or general practitioner, no specific precautions appear necessary (Cheitlin, 2003; Levine et al., 2012).

mWHO Class I

- Small or mild: pulmonary stenosis, patent ductus arteriosus, mitral valve prolapse
- Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage)
- Atrial or ventricular ectopic beats, isolated

In this patient group, there is likely to be no detectable increase in risk of maternal mortality and no/only mildly increased risk in morbidity during assisted conception and resultant pregnancy.

Recommendation: Patients with known cardiovascular disease in mWHO Class I should have a minimum of a local cardiology assessment *including specific pre-pregnancy counselling* in the 2 years prior to embarking on MAR. If no concerns are raised by the cardiologist, no specific precautions need to be taken by the reproductive medicine or anaesthetic teams. (Class IIa, C)

mWHO Class II

- Unoperated atrial or ventricular septal defect
- Repaired tetralogy of Fallot
- Most arrhythmias (supraventricular arrhythmias)
- Turner syndrome without aortic dilatation
- Essential hypertension well-controlled on medical therapy*

In this patient group, there is likely to be only a small increased risk of maternal mortality or moderate increase in morbidity during MAR and resultant pregnancy.

Recommendation: Patients with known cardiovascular disease in mWHO Class II should have had a cardiology assessment *including specific pre-pregnancy counselling* by a pregnancy heart team in the 12 months prior to embarking on MAR. If there are haemodynamically significant cardiovascular lesions which are treatable, treatment should be undertaken before embarking on an assisted conception pathway. A multi-disciplinary team discussion including the pregnancy heart team and reproductive medicine team should be undertaken before the patient starts treatment. Alterations to medical treatment or assisted reproduction pathways may be considered (Class IIa, C).

mWHO Class II–III

- Mild left ventricular impairment (Ejection Fraction (EF) >45%)
- Hypertrophic cardiomyopathy
- Native or tissue valve disease not considered WHO I or IV (mild mitral stenosis, moderate aortic stenosis)
- Marfan or other Heritable thoracic aortic disease (HTAD) syndrome without aortic dilatation
- Aorta <45 mm in bicuspid aortic valve pathology
- Repaired coarctation
- Atrioventricular septal defect
- Fully re-vascularised coronary artery disease *
- Essential hypertension with sub-optimal control with medical therapy*

In this patient group there is likely to be an intermediate increased risk of maternal mortality and moderate to severe increase in morbidity during MAR and resultant pregnancy. Patients with previous coarctation repairs are particularly at risk of hypertensive disorders of pregnancy and it should be recognised that these are more common in IVF pregnancies (Qin et al., 2016).

Recommendation: Patients with known cardiovascular disease in mWHO Class II–III, should have had a cardiology assessment *including specific pre-pregnancy counselling* by a pregnancy heart team in the 12 months prior to embarking on MAR. If there are haemodynamically significant cardiac lesions or issues (such as poorly controlled hypertension) which are treatable, this should be undertaken before starting MAR. A multidisciplinary team discussion including the pregnancy heart team and reproductive medicine team is recommended before the patient starts treatment. Alterations to medical treatment or assisted reproduction pathways should be considered (Class IIa, C).

mWHO Class III

- Moderate left ventricular impairment (EF 30–45%)
- Previous peripartum cardiomyopathy without any residual left ventricular impairment
- Mechanical heart valve @

- Systemic right ventricle with good or mildly decreased ventricular function
- Fontan circulation. If otherwise the patient is well and the cardiac condition uncomplicated.
- Unrepaired cyanotic heart disease #
- Other complex heart disease
- Moderate mitral stenosis
- Severe asymptomatic aortic stenosis
- Moderate aortic dilatation (40–45 mm in Marfan syndrome or other HTAD; 45–50 mm in bicuspid aortic valve, Turner syndrome Aortic size index (ASI) 20–25 mm/m^2, tetralogy of Fallot <50 mm)
- Ventricular tachycardia
- Ischaemic heart disease, not fully revascularized, but no symptoms *

Patients in mWHO Class III carry a significantly increased risk of maternal mortality or severe morbidity during assisted conception and resultant pregnancy.

In some patients in this group, the pregnancy risk to mother or baby may be felt to be prohibitively high, but ovarian stimulation, oocyte retrieval and embryo formation for use in a surrogate may be possible. In this instance, it is very likely that alterations to the standard pathways will be required.

@ *Consideration of the **significant and conflicting risks of bleeding and valve thrombosis** at the time of egg collection should be made in patients with mechanical heart valves and haematology input is vital to manage the period of time around egg collection as safely as possible.*

 # Bleeding risk is also increased in cyanotic heart disease, because of poor tissue quality, and haemostatic abnormalities. Cyanotic patients are often at risk of paradoxical emboli, so care regarding air emboli should be taken during venous cannulation.

** Some lesions/conditions which the authors felt were important are not included in the mWHO classification. The authors have allocated these patients to a category in accordance with perceived risk. These conditions are marked in the text and tables (* not included in original mWHO classification)* (European Society of Gynecology (ESG), Association for European Paediatric Cardiology (AEPC), German Society for Gender Medicine (DGesGM), Regitz-Zagrosek et al., 2011).

Recommendation: It is recommended that patients with known cardiovascular disease in mWHO Class III have a cardiology assessment *including specific pre-pregnancy counselling* by a pregnancy heart team in the 6 months prior to starting MAR. If there are haemodynamically significant cardiac lesions which are treatable, this should be undertaken before starting MAR.
A multidisciplinary team discussion including the pregnancy heart team and reproductive medicine team is recommended before the patient starts treatment. Alterations to the standard pathways of care should be implemented (Class I, C).

mWHO Class IV

- Pulmonary arterial hypertension
- Severe systemic ventricular dysfunction (EF <30% or New York Heart Association (NYHA) class III–IV)
- Previous peripartum cardiomyopathy with any residual left ventricular impairment
- Severe mitral stenosis
- Severe symptomatic aortic stenosis
- Systemic right ventricle with moderate or severely decreased ventricular function
- Severe aortic dilatation (>45 mm in Marfan syndrome or other HTAD, >50 mm in bicuspid aortic valve, Turner syndrome ASI >25 mm/m^2, tetralogy of Fallot >50 mm)
- Vascular Ehlers–Danlos
- Severe (re)coarctation
- Fontan with any complication
- Ischaemic heart disease with ongoing symptoms or documented ischaemia *
- Accelerated/malignant hypertension *

Patients in mWHO Class IV carry a very significantly increased risk of maternal mortality or severe morbidity during assisted conception and resultant pregnancy. It is likely that the risks of assisted conception and resultant pregnancy in patients in this category will be too high to safely embark upon MAR. Other options such as surrogacy ± donor egg or adoption should be discussed.

Recommendation. It is recommended that patients with known cardiovascular disease in mWHO Class IV seeking MAR should have had an up-to-date cardiology assessment with a pregnancy heart team and a multidisciplinary team discussion including the pregnancy heart team and the assisted reproduction team. If there are haemodynamically significant cardiac lesions which are treatable, this may be undertaken, and may reduce their risk category. However, in many patients in this group, there will be no treatment options which will sufficiently modify their risk profile to reduce their risk category. While pregnancy risk to mother or baby is likely to be prohibitively high, ovarian stimulation, oocyte retrieval and embryo formation for use in a surrogate may occasionally be possible and these options should be considered and discussed. In this instance, it is expected that alterations to the standard pathways will be required. (Class I, C)

Recurrence of congenital or inherited heart disease in offspring

There is an increased risk of congenital heart disease in the biological offspring of affected mothers and to a lesser extent fathers, but no convincing evidence that assisted conception increases this risk further. In patients with inherited cardiac conditions there is also a risk of recurrence in their offspring. Recurrence risk

in offspring should be discussed at pre-treatment counselling (Øyen et al., 2022; Schofield et al., 2017).

Patients with risk factors for cardiovascular disease

The 2021 MBRRACE report identified that some patients who had undergone MAR and died of cardiovascular disease had pre-existing cardiovascular risk factors which had not been identified prior to pregnancy (MBRRACE-UK, 2021). While data is available about the prevalence of cardiovascular risk factors in patients of reproductive age, the prevalence among patients pursuing MAR is not known (British Heart Foundation, 2019). There is a lack of consensus about what, if any, investigations to perform prior to MAR and how this might influence the treatment protocols used in the IVF process.

While the presence of cardiovascular risk factors increases the chance of a pregnancy being complicated by atherosclerotic vascular disease, events also occur in women with no risk factors, or undiagnosed risk factors and patients can also present with acute coronary syndromes due to spontaneous coronary artery dissection and thrombo-embolic coronary occlusion.

Atherosclerotic disease risk assessment

The majority of patients (78%) seek help for sub-fertility and subsequent referral for MAR through their primary care team (https://www.hfea.gov.uk/about-us/news-and-press-releases/2018-news-and-press-releases/our-national-patient-survey-results/) (Human Fertilisation and Embryology Authority, 2018). Other patients may access MAR services through direct self-referral. In the majority of cases therefore it is appropriate for initial risk assessment to be performed in primary care prior to a referral for fertility treatment being made. MAR services accepting direct self-referral without primary care filtering should ensure that initial risk assessment is performed prior to starting treatment. In those patients who seek fertility treatment abroad, risk factor assessment should still be promoted by UK care providers even if not mandated by the treating centre.

Irrespective of the source of the original referral, it is ultimately the responsibility of the fertility treatment centre to ensure that patients have been appropriately screened for cardiac disease and risk factors, prior to commencing a treatment cycle.

Recently updated WHO data show diabetes as the strongest predictor variable for myocardial infarction or coronary heart disease (CHD) death in women (hazard ratio (HR) 2.92), current smoking status confers a HR of 2.87, systolic blood pressure a HR of 1.37 per 20 mmHg increase over 120 mmHg, increasing age a HR of 1.67 per 5 years, total cholesterol a HR of 1.23 per 1 mmol/L increase, and Body Mass Index (BMI) a HR of 1.14 per 1 kg/m^2 increase over 25 kg/m^2 (WHO CVD Risk Chart Working Group, 2019).

There are widely available risk calculators for cardiovascular disease which can estimate an individual's 10-year or lifetime risk, assisting primary care physicians to make decisions about primary prevention strategies, but these risk calculators are not designed to make an assessment of risk associated with pregnancy or MAR, and therefore cannot be used for this purpose.

For the purposes of this document, cardiovascular risk factors are considered to be:

- diabetes,
- current smoker or recent ex-smoker (within 12 months or $>$ 5 pack year history in last 10 years),
- hypertension,
- known hyperlipidaemia,
- obesity (BMI $>$ 30 kg/m^2)
- family history of ischaemic heart disease in a first degree relative under 60 years of age

Recommendation: It is recommended that all patients are assessed for cardiovascular risk factors before commencing MAR. (Class I, C)

Patients with increased risk for atherosclerotic cardiovascular disease are defined as

a. Type 1 or Type 2 diabetes
   OR
b. 3 non-diabetes vascular risk factors (as listed above) and are under 35 years of age
   OR
c. 2 non-diabetes vascular risk factors (as listed above) and are over 35 years of age

+ 'Physician with expertise in the management of medical disorders in pregnancy' - this could be an obstetric physician, obstetric cardiologist or obstetrician with maternal medicine interest depending upon local arrangements.

Recommendation: It is recommended that patients with increased risk for atherosclerotic cardiovascular disease[@] are referred for review by a physician with expertise in the management of medical disorders[+] in pregnancy prior to starting MAR. (Class I, C)

Patients with diabetes or at high risk of diabetes

Diabetes is the strongest predictive factor for the development of coronary artery disease (WHO CVD Risk Chart Working Group, 2019), and this risk should be explored and counselled alongside the other pregnancy risks associated with diabetes. All patients with diabetes should be referred early to an obstetric diabetes service when pregnancy is confirmed.

Recommendation: All women with known diabetes should be referred for assessment with a physician expert in the management of diabetes in pregnancy prior to starting MAR. MAR should only be commenced in patients with diabetes once satisfactory glycaemic control has been achieved. (Class 1, C)
Recommendation: An HbA1c is recommended in all patients aged over 35 years, those with obesity (BMI of 30 kg/m^2 or greater), those with a family history of diabetes in first degree relatives, previous history of gestational diabetes, and all patients of an ethnicity other that White Caucasian before starting MAR. (Class I, C)

It is estimated that there are 1 million people in the UK with undiagnosed diabetes (Whicher et al., 2020). The contact made with health services by patients seeking MAR is a vital point at which intervention may occur to facilitate diagnosis, reducing their risk during MAR, subsequent pregnancy and lifelong.

a. If HbA1c above threshold for diagnosis of type 2 diabetes mellitus, blood glucose monitoring should be started and treatment instituted, as well as modification of risk factors such as weight and diet. Good glycaemic control should be achieved before starting MAR.
b. If HbA1c consistent with pre-diabetes, provide advice about lifestyle modification.
c. All patients with an increased HbA1c should be counselled about the risks of hyperglycaemia in pregnancy and the development of gestational diabetes. The need for good glucose control should be explained and where necessary, dietary advice given to help the patients achieve normoglycaemia.
d. All patients with pre-diabetes should be advised that they require an oral glucose tolerance test in pregnancy.

Smoking

Smoking is a potent risk factor for atherosclerotic disease, and also reduces fertility and the success of MAR (Berthiller & Sasco, 2005; WHO CVD Risk Chart Working Group, 2019).

Recommendation: It is recommended that all patients who continue to smoke should be advised to stop and offered smoking cessation support. (Class I, A)

Hypertension

Hypertension plays an important role in the development of premature atherosclerosis, predisposes to adverse pregnancy outcomes, and is very easy to assess with a non-invasive blood pressure reading (Bramham et al., 2014; WHO CVD Risk Chart Working Group, 2019). All patients with pre-existing hypertension should be referred early to high-risk obstetric services when pregnancy is confirmed.

Recommendation: All patients should have a blood pressure measurement within the year prior to commencing MAR. If hypertension is identified, according to thresholds in the NICE Hypertension in Pregnancy guideline, (NICE, 2019) treatment should be started with pregnancy-appropriate antihypertensive agents and screening for secondary causes considered. MAR should only be commenced in patients with hypertension once blood pressure control is satisfactory. (Class I, C)

Hyperlipidaemia

Patients with elevated lipid levels are at increased risk of developing atherosclerotic disease as they age, but it is not known to increase the risks of MAR or pregnancy per se. Patients with familial hypercholesterolaemia are at significantly higher risk of developing atherosclerosis in early life (Graham & Raal, 2021; WHO CVD Risk Chart Working Group, 2019).

Recommendation: Patients known to have familial hyperlipidaemia, hypertriglyceridaemia, or on lipid-lowering agents other than a statin, should be referred for medical review by a metabolic medicine team, prior to starting MAR. (Class IIb, C)

Obesity

Obesity is a risk factor for atherosclerotic disease, and is known to be associated with increased rates of pre-eclampsia, gestational diabetes, caesarean delivery, severe maternal morbidity and maternal mortality. The impact of obesity should be considered in assessing atherosclerotic risk, and a patients' overall risk profile before commencing MAR (Denison et al., 2019).

Recommendation: Obese women should be given advice on weight management and lifestyle changes, and should be encouraged to lose weight before starting MAR. (Class IIb, C)

History of ischaemic heart disease in a first degree relative under 60 years of age

Having a positive family history of atherosclerotic disease in a first degree relative at a young age is known to be associated with increased risk of vascular disease. In itself, it is not a contra-indication to MAR, but should be taken into consideration when assessing the patients' overall risk as above.

Inherited cardiac disease risk assessment

The MBRRACE reports (EMBRRACE UK 2021) detail a number of cases where inherited cardiac conditions are not detected pre-pregnancy despite there being a clear family history. Therefore, all patients should be asked about relatives

- who have died suddenly and unexpectedly
- who had cardiovascular disease <50 years of age or
- who have had conditions such as aneurysms, dissections or required interventions e.g. cardiac surgery or implantable cardiac defibrillator

Recommendation: It is recommended that a thorough assessment of family history of cardiovascular disease is obtained prior to commencing MAR, to assess the likelihood of inherited heart disease. Class I, C)

Patients at high risk for an inherited cardiac condition are those with a family history of an inherited cardiac condition such as inherited arrhythmia syndromes, cardiomyopathy, aortopathy, or sudden cardiac death. Discussion with the local Inherited Cardiac Conditions service may provide or signpost to useful information about the condition, family history and genetic results.

Recommendation: It is recommended that patients at high risk for inherited cardiac conditions are discussed with the local pregnancy heart team or local ICC team prior to starting MAR. (Class I, C)

Medically assisted reproduction (MAR) methods, and their implications in patients with cardiovascular disease

MAR consists of different methods used to achieve pregnancy according to the particular circumstances of the person seeking pregnancy. Different methods of treatment induce different physiological changes, and therefore pose different risks to the patient, dependent upon the nature of the cardiac disease (Fujitake et al., 2020; Li et al., 2013). The specific concerns associated with MAR in women with cardiac disease or at risk of cardiac disease are;

- Risks of ovarian hyperstimulation syndrome (OHSS)
- Risks of MAR in women requiring anticoagulation
- Risks of resultant pregnancy
- Risks associated with multiple pregnancy

Before initiating any HFEA regulated MAR treatments, patients are required to fill out a 'Welfare of Child' patient history form, providing comprehensive information about cardiac conditions and the potential risk of inheritance.

Ovulation induction (OI) with or without intrauterine insemination (IUI)

OI is used in patients with ovulatory disorders such as polycystic ovarian syndrome. OI with clomiphene citrate/letrozole aiming for growth of a single follicle should not pose any additional risk compared with natural conception, therefore, treatment should strictly aim for mono-follicular growth (Teede et al., 2018; Wang et al., 2019). Gonadotrophins are used for OI in those who do not respond to first-line treatment with clomiphene citrate/letrozole, but this is more likely to result in the development of multiple follicles, increasing the risk of multiple pregnancy. OI cycle should be cancelled if more than one follicle develops. In the event of cycle cancellation due to multiple follicles, patients should be recommended to avoid unprotected sexual intercourse, to prevent multiple pregnancy.

Recommendation: Ovulation induction may be used in patients with cardiac disease following satisfactory cardiac review (see section 4), but it is recommended to monitor closely for development of multiple follicles, to avoid the risk of multiple pregnancy. (Class 1, B)

In-vitro Fertilisation

Controlled ovarian stimulation (COS)

The aim of COS in IVF is to stimulate the ovaries to form multiple follicles, enabling the collection of multiple oocytes to create embryos. COS results in some degree of hyper-stimulation, however OHSS is characterized by cystic enlargement of the ovaries and increased vascular permeability. In OHSS, patients can become critically unwell due to the shift of fluid into third spaces and up to a 100-fold increase in venous thrombo-embolism (VTE) risk. It is a potentially life-threatening condition in its severe form, resulting in hospitalization in 1.9% of cases (Humaidan et al., 2010).

Even without OHSS, ovarian stimulation results in a rise in endogenous steroid levels and is associated with alteration in cardiovascular parameters such as left ventricular ejection fraction and end diastolic volume as well as a significantly increased risk of VTE (Li et al., 2013; Sennström et al., 2017).

In patients with cardiac disease, even mild OHSS could precipitate cardiovascular compromise (Humaidan et al., 2010). Human chorionic gonadotrophin (hCG), either exogenous or endogenous, is the triggering factor of the syndrome (Mocanu et al., 2007), therefore, embryo transfer and successful implantation can worsen OHSS further due to endogenous hCG production (Humaidan et al., 2010).

Several primary and secondary risk factors for OHSS have been identified which can help identify those patients at particularly high risk of OHSS (Table 3) (Fiedler & Ezcurra, 2012).

Measures should be considered in all patients to minimise the risk of OHSS, but in patients with cardiac disease, in particular those patients at higher risk of OHSS, more careful and individualised COS needs to be undertaken, even if it is at the cost of a slightly lower chance of success.

Natural cycle/minimal stimulation protocols are associated with much poorer success rates compared with standard traditional protocols, therefore it is appropriate to use strictly monitored standard protocols.

Type of down-regulation or pituitary desensitisation/LH suppression regimen

The influence of endogenous luteinising hormone (LH) and follicle stimulating hormone (FSH) on the ovaries needs to be prevented in an IVF cycle, so two alternative medications are used. Gonadotrophin releasing hormone (GnRH) *agonists* ('long cycle') prevent the LH surge by causing downregulation of pituitary receptors, whereas GnRH *antagonists* ('short protocol') cause competitive blockade of receptors resulting in the immediate suppression of the LH surge. Evidence suggests that GnRH antagonist protocol has similar clinical efficacy in terms of live birth rate compared to use of an agonist protocol, with the added benefit of a lower risk of OHSS (Al-Inany et al., 2016).

Type of gonadotrophins

In COS the two most commonly used FSH preparations in the UK are urinary human menopausal gonadotrophins (hMG) and recombinant follicle stimulating hormone (r-FSH). There is no difference between live birth rate between r-FSH and hMG (Humaidan et al., 2010). Older data suggested no difference between OHSS rate, but recently published RCTs showed significantly lower risk of OHSS using hMG compared to r-FSH (Witz et al., 2020). Thus, in high ovarian responders, use of hMG may be preferred to r-FSH.

Dose of gonadotrophins (based on predicted ovarian response)

Individualised COS with tailoring of FSH dose using patient characteristics predictive of OHSS (Table 3) is advised. A recent Cochrane review has shown that, in predicted high responders, lower doses of FSH seemed to reduce the overall incidence of moderate and severe OHSS (Lensen et al., 2018). Therefore, in

Table 3. Risk factors/predictive factors for OHSS (adapted from Fiedler & Ezcurra, 2012).

Primary risk factors (patient related)	Secondary risk factors (ovarian response-related)
· High basal AMH	· On day of hCG trigger
· Young age	High number of follicles
· Previous OHSS	High or rapidly rising E2 levels
· PCO like ovaries	· hCG trigger
	· Number of oocytes retrieved
	· VEGF levels
	· Elevated inhibin-B levels
	· hCG administration for LPS
	· Pregnancy (increase in endogenous hCG)

AFC = antral follicle count; AMH = anti-Müllerian hormone; E2 = oestradiol; hCG = human chorionic gonadotropin; LPS = luteal phase support; OHSS = ovarian hyperstimulation syndrome; PCOS = polycystic ovary syndrome; VEGF = vascular endothelial growth factor.

high responders, a lower dose of FSH should be preferred to minimize OHSS risks and over-response.

Choice of oocyte maturation trigger

Human chorionic gonadotrophin (hCG) has been used for many years for the final oocyte maturation trigger. More recently, however, a Cochrane meta-analysis of 3 randomised controlled trials in 212 patients who were at risk of hyper-response to ovarian stimulation, the use of an agonist trigger resulted in a significantly lower risk of moderate to severe OHSS compared to hCG trigger (Youssef et al., 2014). The use of an antagonist cycle followed by an agonist trigger is an effective way of reducing OHSS risk. GnRH agonist trigger use, however, may have an impact on ongoing pregnancy following fresh transfer due to early luteolysis so it is advised that all embryos are frozen in a cycle where an agonist trigger has been used, followed by frozen embryo transfer (segmentation of treatment cycle).

Recommendation: When undertaking IVF in patients with cardiovascular disease or risk factors for cardiovascular disease, specific steps to avoid OHSS are recommended. (Class 1, B)
Steps should be taken to minimise the risk of OHSS

1. GnRH antagonist protocol is preferred for pituitary desensitization as it offers an option to avoid the hCG trigger.
2. Controlled ovarian stimulation should aim to use standard or lower dose of FSH to avoid OHSS.
3. In predicted high responders the use of highly purified hMG is probably preferable to recombinant FSH.
4. Controlled ovarian stimulation cycles should be intensely monitored with frequent blood tests for oestradiol and ultrasound monitoring of the follicles.
5. Cryopreservation of viable oocytes/embryos (FAE) with segmentation of treatment cycle allows the maternal hyperoestrogenaemic state to recover prior to a potential pregnancy.
6. Natural cycle frozen embryo transfer is preferable over medicated cycle in women with regular periods to minimise the risk of hypertensive disorder in subsequent pregnancy.

Luteal support

Luteal support with progesterone supplementation in IVF cycles achieves a higher live birth rate (van der Linden et al., 2015), and studies have shown no detrimental effect of progesterone on cardiovascular health (Mittal et al., 2022) so luteal support can be used as normal in patients with cardiac disease.

Frozen versus fresh embryo transfer

Cryopreserving all embryos resulting from a fresh cycle reduces the risk of OHSS and therefore should be considered in higher risk patients where OHSS is a particular concern. Segmentation of fresh cycle with freeze all eggs or embryos (FAE) followed by frozen embryo transfer cycle is preferred (Busnelli et al., 2022).

Regimen for frozen embryo transfer cycle

Frozen embryo transfer (FET) can be performed in a natural cycle or in a medicated cycle, starting with oestrogen and followed by additional progesterone. A recently published systematic review and meta-analysis (Busnelli et al., 2022) suggested a higher risk of hypertensive disorders in pregnancies following medicated compared to natural cycle FET, therefore it is advisable to consider natural cycle FET in patients with cardiac disease with regular periods to minimise the risks of hypertensive disorders in the resulting pregnancy.

VTE and arterial thrombosis risk during IVF

IVF is associated with a significantly increased risk of VTE in the resultant pregnancy. This risk is further increased in the event of OHSS, which also pre-disposes to arterial thrombus formation (Henriksson et al., 2013). This can be of particular concern to certain patients with cardiac disease who may already be more prone to thrombotic complications.

A more than eightfold increase in VTE during the first trimester of fresh embryo transfer pregnancies is reported, with no such increase in the incidence of VTE during frozen-thawed embryo transfer (FET) pregnancies. The ovarian stimulation, with its oestradiol surge, seems to be a necessary prerequisite to trigger the increase in VTE risk; therefore, segmentation of treatment cycle with FAE followed by frozen embryo transfer in patients already at high risk of VTE is recommended (Olausson et al., 2020).

Recommendation: In patients with known cardiovascular disease, or risk factors for cardiovascular disease specific consideration of measures to minimise the risk of VTE and arterial thrombosis should be considered in pre-treatment multi-disciplinary discussion including a haematologist. In patients at high risk, segmentation of the treatment cycle should be considered. (Class 1, C)

Bleeding risk at egg collection in patients who require full anticoagulation for cardiac indications

Some patients with cardiovascular disease are fully anticoagulated and this poses a significant risk for bleeding complications at the time of egg collection and in the 7–10 days afterwards. In some patients, full anticoagulation may be relatively safely interrupted for a short period of time around the time of egg collection. In other patients, particularly those with mechanical heart valves (MHV), safe management of

anticoagulation versus bleeding risk from the ovarian bed during IVF is very challenging. There is very little data to guide practice (European Society of Gynecology (ESG), Association for European Paediatric Cardiology (AEPC), German Society for Gender Medicine (DGesGM), Regitz-Zagrosek et al., 2018; Skorupskaite et al., 2022; Yinon et al., 2006).

Recommendation: In patients with known cardiovascular disease who are fully anticoagulated, the high risks of egg collection must be considered by the whole multi-disciplinary team (including a haematologist) and the patient before starting treatment. If IVF is undertaken, ovarian stimulation should be minimised, and a detailed protocol for management of anticoagulation at the time of egg collection put in place. This is of particular concern in patients with mechanical heart valves. (Class 1, C)

Elective single embryo transfer

Singleton pregnancies carry lower risk for baby and mother and should be recommended. In patients with cardiovascular disease or risk factors for cardiovascular disease, a multiple pregnancy could create additional risk in a patient with cardiac disease (Kametas et al., 2003; Ombelet et al., 2006). Patients seeking MAR in countries where single embryo transfer is not the norm should be counselled about the increased risks (Jaspal et al., 2019).

Recommendation: In all patients with cardiovascular disease or risk factors for cardiovascular disease, single embryo transfer is recommended. (Class I, B)

Management once pregnancy is confirmed

Once ongoing pregnancy is confirmed after MAR, the patient should be referred for care to their local obstetric team, and additionally all mWHO Class II and above, or high risk of atherosclerotic or inherited cardiac disease, should be referred to the regional pregnancy heart team. The receiving team should be fully aware of the additional risks posed by an MAR pregnancy on cardiovascular health during pregnancy and beyond and the interaction between this and fetal wellbeing.

Recommendation: Pregnancies resulting from MAR should be managed in accordance with the recommendations for their mWHO risk category. Caregivers should be aware of the increased pregnancy risks associated with MAR pregnancy. (Class IIb, C)

HFEA confidentiality issues

HFEA Confidentiality issues should be revisited to address multi-disciplinary team (MDT) care for these patients including the Consent of disclosure. This issue must be addressed at the very beginning of treatment cycle following current HFEA regulations.

Anaesthetic considerations

During fertility treatment, the procedures for which sedation, regional or general anaesthesia are required are laparoscopic assessment of tubal patency, hysteroscopy, trans-vaginal oocyte recovery (TVOR), surgical sperm retrieval and occasionally for embryo transfer. Complication rates of less than 1% are reported from TVOR, including infection, bleeding, interference with an ovarian cyst, accidental damage to other structures (bowel, uterus, iliac vessels), and patient discomfort (Levi-Setti et al., 2018).

The most invasive procedure is laparoscopy, and the potential cardiovascular and ventilatory implications should be considered before treatment is commenced (Atkinson et al., 2017).

Embryo transfer involves cervical visualisation and insertion of a small catheter. There is a small chance of vagal stimulation from cervical manipulation, but in practice this is encountered extremely rarely.

The pathophysiological impact of the required interventional procedures and the associated anaesthesia/sedation is likely to be considerably *less* than the impact of any resultant pregnancy and delivery. Therefore, any patient considered 'fit' to carry a pregnancy to term (or near term) should be suitable for assisted reproduction procedures such as TVOR and laparoscopy.

Anaesthetic considerations regarding management of labour and delivery of a successful ongoing pregnancy, should be considered at the time of pre-pregnancy counselling.

Recommendation: It is recommended that in mWHO Class III or IV patients who are being considered for MAR, anaesthetic assessment of the safety and feasibility of planned procedures including laparoscopy and trans-vaginal oocyte recovery under sedation/GA, should be part of the pre-treatment multi-disciplinary discussion and planning. (Class I, C)

Recommendation: Published guidance including the 2013 Academy of Medical Royal Colleges (AoMRC, 2021) multi-disciplinary guidelines on sedation practice, updated in 2021 (www.aomrc.org.uk/2021), Guidelines on Day Case Surgery 2019 (Bailey et al., 2019); Standards of Monitoring during Anaesthesia and Recovery in 2021 (Klein et al., 2021); and Immediate Post-Anaesthesia Recovery in 2013 (Membership of the Working Party, Whitaker et al., 2013), should all be adhered to during MAR. (Class 1, C)

Co-location to other services

The care provided should be patient centred. Most patients will be safe to undergo the above procedures required in local centres. The small number of higher risk patients may need to be cared for in locations other than stand-alone fertility units, where rapid access to critical care support would be possible if needed.

Recommendation: The co-location of support services including critical care facilities should be considered when planning MAR in patients with known cardiovascular disease, or at high risk of cardiovascular disease. An agreed escalation plan should be documented in high-risk patients to facilitate rapid assessment and treatment in the event of a complication. (Class IIa, C)

Conclusion

Patients with known cardiovascular disease or at high risk of cardiovascular disease will continue to seek MAR in increasing numbers. It is important that the potential risks of MAR itself, and the subsequent pregnancies are understood by caregivers and patients, and those risks are minimised by careful assessment, pre-pregnancy optimisation and modification of MAR pathways. Optimisation of outcomes in terms of active patient choice, maternal safety, live-birth rate, and good neonatal outcomes will require a multi-disciplinary approach.

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Data availability statement

There is no patient associated or original data to share.

References

Academy of Medical Royal Colleges (AoMRC). (2021). https://www.aomrc.org.uk/wp-content/uploads/2021/02/Safe_sedation_practice_for_healthcare_procedures_update_0521.pdf#:~:text=Sedation%20for%20therapeutic%20and%20investigative%20procedures%20in%20healthcare,required%20for%20the%20safe%20delivery%20of%20effective%20sedation

Al-Inany, H. G., Youssef, M. A., Ayeleke, R. O., Brown, J., Lam, W. S., & Broekmans, F. J. (2016). Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. *The Cochrane Database of Systematic Reviews*, *4*(4), CD001750. https://doi.org/10.1002/14651858.CD001750.pub4

Atkinson, T. M., Giraud, G. D., Togioka, B. M., Jones, D. B., & Cigarroa, J. E. (2017). Cardiovascular and ventilatory consequences of laparoscopic surgery. *Circulation*, *135*(7), 700–710. https://doi.org/10.1161/CIRCULATIONAHA.116.023262

Bailey, C. R., Ahuja, M., Bartholomew, K., Bew, S., Forbes, L., Lipp, A., Montgomery, J., Russon, K., Potparic, O., & Stocker, M. (2019). Guidelines for day-case surgery 2019: Guidelines from the Association of Anaesthetists and the British Association of Day Surgery. *Anaesthesia*, *74*(6), 778–792. https://doi.org/10.1111/anae.14639

Berthiller, J., & Sasco, A. J. (2005). Tabagisme (actif ou passif) en relation avec la fertilité, la procréation médicalement assistée et la grossesse [Smoking (active or passive) in relation to fertility, medically assisted procreation and pregnancy]. *Journal de Gynécologie Obstétrique et Biologie de la Reproduction*, *34* (1), 47–54. https://doi.org/10.1016/S0368-2315(05)82970-9

Bouma, B. J., & Mulder, B. J. (2017). Changing landscape of congenital heart disease. *Circulation Research*, *120*(6), 908–922. https://doi.org/10.1161/CIRCRESAHA.116.309302

Bramham, K., Parnell, B., Nelson-Piercy, C., Seed, P. T., Poston, L., & Chappell, L. C. (2014). Chronic hypertension and pregnancy outcomes: Systematic review and meta-analysis. *BMJ (Clinical Research ed.)*, *348*, g2301. https://doi.org/10.1136/bmj.g2301

British Heart Foundation. (2019). BHF statistics Compendium 2019. https://www.bhf-statistics-compendium-2022.pdf

Busnelli, A., Schirripa, I., Fedele, F., Bulfoni, A., & Levi-Setti, P. E. (2022). Obstetric and perinatal outcomes following programmed compared to natural frozen-thawed embryo transfer cycles: A systematic review and meta-analysis. *Human Reproduction (Oxford, England)*, *37*(7), 1619–1641. https://doi.org/10.1093/humrep/deac073

Cheitlin, M. D. (2003). Sexual activity and cardiovascular disease. *The American Journal of Cardiology*, *92*(9A), 3M–8M. https://doi.org/10.1016/s0002-9149(02)03367-2

Dayan, N., Laskin, C. A., Spitzer, K., Mason, J., Udell, J. A., Wald, R. M., Siu, S. C., Iten-Scott, T., & Silversides, C. K. (2014). Pregnancy complications in women with heart disease conceiving with fertility therapy. *Journal of the American College of Cardiology*, *64*(17), 1862–1864. https://doi.org/10.1016/j.jacc.2014.07.977

Denison, F. C., Aedla, N. R., Keag, O., Hor, K., Reynolds, R. M., Milne, A., & Diamond, A. (2019). Care of women with obesity in pregnancy: Green-top Guideline No. 72. *BJOG: An International Journal of Obstetrics & Gynaecology*, *126*(3), e62–e106. https://doi.org/10.1111/1471-0528.15386

European Society of Gynecology (ESG), Association for European Paediatric Cardiology (AEPC), German Society for Gender Medicine (DGesGM), Regitz-Zagrosek, V., Blomstrom Lundqvist, C., Borghi, C., Cifkova, R., Ferreira, R., Foidart, J. M., Gibbs, J. S., Gohlke-Baerwolf, C., Gorenek, B., Iung, B., Kirby, M., Maas, A. H., Morais, J., Nihoyannopoulos, P., Pieper, P. G., Presbitero, P., Roos-Hesselink, J. W., … ESC Committee for Practice Guidelines (2011). ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC).

European Heart Journal, *32*(24), 3147–3197. https://doi.org/10.1093/eurheartj/ehr218

Fiedler, K., & Ezcurra, D. (2012). Predicting and preventing ovarian hyperstimulation syndrome (OHSS): The need for individualized not standardized treatment. *Reproductive Biology and Endocrinology: RB&E*, *10*(1), 32. https://doi.org/10.1186/1477-7827-10-32

Fujitake, E., Jaspal, R., Monasta, L., Stampalija, T., & Lees, C. (2020). Acute cardiovascular changes in women undergoing in vitro fertilisation (IVF), a systematic review and meta-analysis. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *248*, 245–251. https://doi.org/10.1016/j.ejogrb.2020.01.033

Graham, D. F., & Raal, F. J. (2021). Management of familial hypercholesterolemia in pregnancy. *Current Opinion in Lipidology*, *32*(6), 370–377. https://doi.org/10.1097/MOL.0000000000000790

Henriksson, P., Westerlund, E., Wallén, H., Brandt, L., Hovatta, O., & Ekbom, A. (2013). Incidence of pulmonary and venous thromboembolism in pregnancies after in vitro fertilisation: Cross sectional study. *BMJ (Clinical Research ed.)*, *346*, e8632. https://doi.org/10.1136/bmj.e86326

Humaidan, P., Quartarolo, J., & Papanikolaou, E. G. (2010). Preventing ovarian hyperstimulation syndrome: Guidance for the clinician. *Fertility and Sterility*, *94*(2), 389–400. https://doi.org/10.1016/j.fertnstert.2010.03.028

Human Fertilisation and Embryology Authority. (2019). Fertility treatment 2019: Trends and figures. https://www.hfea.gov.uk/about-us/publications/research-and-data/fertility-treatment-2019-trends-and-figures/#Section1

Human Fertilisation and Embryology Authority. (2018). Our national patient survey results | HFEA. https://www.hfea.gov.uk/about-us/news-and-press-releases/2018-news-and-press-releases/our-national-patient-survey-results/

HFEA. (n.d). https://www.hfea.gov.uk/pgt-m-conditions/ https://www.hfea.gov.uk/media/h1jhkpy2/2023-09-21-pgt-m-full-approved-condition-list.xlsx

Jaspal, R., Prior, T., Denton, J., Salim, R., Banerjee, J., & Lees, C. (2019). The impact of cross-border IVF on maternal and neonatal outcomes in multiple pregnancies: Experience from a UK fetal medicine service. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *238*, 63–67. https://doi.org/10.1016/j.ejogrb.2019.04.030

Kametas, N. A., McAuliffe, F., Krampl, E., Chambers, J., & Nicolaides, K. H. (2003). Maternal cardiac function in twin pregnancy. *Obstetrics and Gynecology*, *102*(4), 806–815. https://doi.org/10.1016/s0029-7844(03)00807-x

Kim, Y. Y., Levine, L. D., Partington, S. L., Patel, P. A., Ruckdeschel, E., Senapati, S., & Gracia, C. R. (2020). Successful in vitro fertilization in women with Fontan physiology. *Journal of Assisted Reproduction and Genetics*, *37*(12), 3017–3023. https://doi.org/10.1007/s10815-020-01969-2

Klein, A. A., Meek, T., Allcock, E., Cook, T. M., Mincher, N., Morris, C., Nimmo, A. F., Pandit, J. J., Pawa, A., Rodney, G., Sheraton, T., & Young, P. (2021). Recommendations for standards of monitoring during anaesthesia and recovery 2021: Guideline from the Association of Anaesthetists. *Anaesthesia*, *76*(9), 1212–1223. https://doi.org/10.1111/anae.15501

Lensen, S. F., Wilkinson, J., Leijdekkers, J. A., La Marca, A., Mol, B. W. J., Marjoribanks, J., Torrance, H., & Broekmans, F. J. (2018). Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI). *The Cochrane Database of Systematic Reviews*, *2*(2), CD012693. https://doi.org/10.1002/14651858.CD012693.pub2

Levi-Setti, P. E., Cirillo, F., Scolaro, V., Morenghi, E., Heilbron, F., Girardello, D., Zannoni, E., & Patrizio, P. (2018). Appraisal of clinical complications after 23,827 oocyte retrievals in a large assisted reproductive technology program. *Fertility and Sterility*, *109*(6), 1038–1043.e1. https://doi.org/10.1016/j.fertnstert.2018.02.002

Levine, G. N., Steinke, E. E., Bakaeen, F. G., Bozkurt, B., Cheitlin, M. D., Conti, J. B., Foster, E., Jaarsma, T., Kloner, R. A., Lange, R. A., Lindau, S. T., Maron, B. J., Moser, D. K., Ohman, E. M., Seftel, A. D., & Stewart, W. J. (2012). Sexual activity and cardiovascular disease: A scientific statement from the American Heart Association. *Circulation*, *125*(8), 1058–1072. https://doi.org/10.1161/CIR.0b013e3182447787

Li, Y., Sun, X., Zang, L., Zhang, Q., Li, J., & Zou, S. (2013). Correlation between steroid hormonal levels and cardiac function in women during controlled ovarian hyperstimulation. *Endocrine*, *44*(3), 784–789. https://doi.org/10.1007/s12020-013-9953-7

Magnus, M. C., Fraser, A., Håberg, S. E., Rönö, K., Romundstad, L. B., Bergh, C., Spangmose, A. L., Pinborg, A., Gissler, M., Wennerholm, U. B., Åsvold, B. O., Lawlor, D. A., & Opdahl, S. (2023). maternal risk of cardiovascular disease after use of assisted reproductive technologies. *JAMA Cardiology*, *8*(9), 837–845. https://doi.org/10.1001/jamacardio.2023.2324

MBRRACE-UK. (2021). Maternal Report 2021. https://www.npeu.ox.ac.uk/assets/downloads/mbrrace-uk/reports/maternal-report-2021/MBRRACE-UK_Maternal_Report_2021_-_FINAL_-_WEB_VERSION.pdf

Membership of the Working Party:, Whitaker, D. K., Booth, H., Clyburn, P., Harrop-Griffiths, W., Hosie, H., Kilvington, B., Macmahon, M., Smedley, P., Verma, R., & Association of Anaesthetists of Great Britain and Ireland (2013). Immediate post-anaesthesia recovery 2013: Association of Anaesthetists of Great Britain and Ireland. *Anaesthesia, 68*(3), 288–297. https://doi.org/10.1111/anae.12146

Mittal, M., McEniery, C., Supramaniam, P. R., Cardozo, L., Savvas, M., Panay, N., & Hamoda, H. (2022). Impact of micronised progesterone and medroxyprogesterone acetate in combination with transdermal oestradiol on cardiovascular markers in women diagnosed with premature ovarian insufficiency or an early menopause: A randomised pilot trial. *Maturitas*, *161*, 18–26. https://doi.org/10.1016/j.maturitas.2022.01.012

Mocanu, E., Redmond, M. L., Hennelly, B., Collins, C., & Harrison, R. (2007). Odds of ovarian hyperstimulation syndrome (OHSS) - time for reassessment. *Human Fertility (Cambridge, England)*, *10*(3), 175–181. https://doi.org/10.1080/14647270701194143

NICE. (2019). Hypertension in pregnancy: Diagnosis and management NICE guideline [NG133]. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwioisKd6vyBAxVEhv0HHdt_AZgQFnoECCUQAQ&url=https%3A//www.nice.org.uk/guidance/ng133/resources/hypertension-in-pregnancy-

diagnosis-and-management-pdf-66141717671365&usg=AOvVaw1XrPlNwAkWn7ngj_q0yJvD&opi=89978449

Olausson, N., Discacciati, A., Nyman, A. I., Lundberg, F., Hovatta, O., Westerlund, E., Wallén, H. N., Mobarrez, F., Bottai, M., Ekbom, A., & Henriksson, P. (2020). Incidence of pulmonary and venous thromboembolism in pregnancies after in vitro fertilization with fresh respectively frozen-thawed embryo transfer: Nationwide cohort study. *Journal of Thrombosis and Haemostasis: JTH*, *18*(8), 1965–1973. https://doi.org/10.1111/jth.14840

Ombelet, W., Martens, G., De Sutter, P., Gerris, J., Bosmans, E., Ruyssinck, G., Defoort, P., Molenberghs, G., & Gyselaers, W. (2006). Perinatal outcome of 12,021 singleton and 3108 twin births after non-IVF-assisted reproduction: A cohort study. *Human Reproduction (Oxford, England)*, *21*(4), 1025–1032. https://doi.org/10.1093/humrep/dei419

Øyen, N., Boyd, H. A., Carstensen, L., Søndergaard, L., Wohlfahrt, J., & Melbye, M. (2022). Risk of congenital heart defects in offspring of affected mothers and fathers. *Circulation. Genomic and Precision Medicine*, *15*(4), e003533. https://doi.org/10.1161/CIRCGEN.121.003533

Qin, J., Liu, X., Sheng, X., Wang, H., & Gao, S. (2016). Assisted reproductive technology and the risk of pregnancy-related complications and adverse pregnancy outcomes in singleton pregnancies: A meta-analysis of cohort studies. *Fertility and Sterility*, *105*(1), 73–85.e1–6. https://doi.org/10.1016/j.fertnstert.2015.09.007

Quien, M. M., Hausvater, A., Maxwell, S. M., & Weinberg, C. R. (2022). Assisted reproductive technology outcomes in women with heart disease. *Frontiers in Cardiovascular Medicine*, *9*, 842556. https://doi.org/10.3389/fcvm.2022.842556

Regitz-Zagrosek, V., Roos-Hesselink, J., Bauersachs, J., Blomström-Lundqvist, C., Cífková, R., De Bonis, M., Iung, B., Johnson, M. R., Kintscher, U., Kranke, P., Marthe Lang, I., Morais, J., Pieper, P. G., Presbitero, P., Price, S., Rosano, G. M. C., Seeland, U., Simoncini, T., Swan, L., Warnes, C. A. (2018). 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *European Heart Journal, 39*(34):3165–3241. https://doi.org/10.1093/eurheartj/ehy340.

Roos-Hesselink, J., Baris, L., Johnson, M., De Backer, J., Otto, C., Marelli, A., Jondeau, G., Budts, W., Grewal, J., Sliwa, K., Parsonage, W., Maggioni, A. P., van Hagen, I., Vahanian, A., Tavazzi, L., Elkayam, U., Boersma, E., & Hall, R. (2019). Pregnancy outcomes in women with cardiovascular disease: Evolving trends over 10 years in the ESC Registry Of Pregnancy And Cardiac disease (ROPAC). *European Heart Journal*, *40*(47), 3848–3855. https://doi.org/10.1093/eurheartj/ehz136

Schofield, S. J., Doughty, V. L., van Stiphout, N., Franklin, R. C. G., Johnson, M. R., Daubeney, P. E. F., & Cullinan, P. (2017). Assisted conception and the risk of CHD: A case-control study. *Cardiology in the Young*, *27*(3), 473–479. https://doi.org/10.1017/S1047951116000743

Sennström, M., Rova, K., Hellgren, M., Hjertberg, R., Nord, E., Thurn, L., & Lindqvist, P. G. (2017). Thromboembolism and in vitro fertilization - A systematic review. *Acta Obstetricia et Gynecologica Scandinavica*, *96*(9), 1045–1052. https://doi.org/10.1111/aogs.13147

Silversides, C. K., Grewal, J., Mason, J., Sermer, M., Kiess, M., Rychel, V., Wald, R. M., Colman, J. M., & Siu, S. C. (2018). Pregnancy outcomes in women with heart disease: The CARPREG II Study. *Journal of the American College of Cardiology*, *71*(21), 2419–2430. https://doi.org/10.1016/j.jacc.2018.02.076

Skorupskaite, K., Joy, E., Balen, A., Agarwal, K., Cauldwell, M., & English, K. (2022). Assisted reproduction in patients with cardiac disease: A retrospective review. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *276*, 199–203. https://doi.org/10.1016/j.ejogrb.2022.07.020

Teede, H. J., Misso, M. L., Costello, M. F., Dokras, A., Laven, J., Moran, L., Piltonen, T., & Norman, R. J. (2018). Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Human Reproduction (Oxford, England)*, *34*(2), 388–1618. https://doi.org/10.1093/humrep/dey256

van der Linden, M., Buckingham, K., Farquhar, C., Kremer, J. A., & Metwally, M. (2015). Luteal phase support for assisted reproduction cycles. *The Cochrane Database of Systematic Reviews*, *2015*(7), CD009154. https://doi.org/10.1002/14651858.CD009154.pub3

Wang, R., Li, W., Bordewijk, E. M., Legro, R. S., Zhang, H., Wu, X., Gao, J., Morin-Papunen, L., Homburg, R., König, T. E., Moll, E., Kar, S., Huang, W., Johnson, N. P., Amer, S. A., Vegetti, W., Palomba, S., Falbo, A., Özmen, Ü., … Mol, B. W. (2019). First-line ovulation induction for polycystic ovary syndrome: An individual participant data meta-analysis. *Human Reproduction Update*, *25*(6), 717–732. https://doi.org/10.1093/humupd/dmz029

Whicher, C. A., O'Neill, S., & Holt, R. I. G. (2020). Diabetes in the UK: 2019. *Diabetic Medicine: A Journal of the British Diabetic Association*, *37*(2), 242–247. https://doi.org/10.1111/dme.14225

WHO CVD Risk Chart Working Group. (2019). World Health Organization cardiovascular disease risk charts: Revised models to estimate risk in 21 global regions. *The Lancet. Global Health, 7*(10), e1332–e1345. https://doi.org/10.1016/S2214-109X(19)30318-3

Witz, C. A., Daftary, G. S., Doody, K. J., Park, J. K., Seifu, Y., Yankov, V. I., & Heiser, P. W. (2020). Randomized, assessor-blinded trial comparing highly purified human menotropin and recombinant follicle-stimulating hormone in high responders undergoing intracytoplasmic sperm injection. *Fertility and Sterility*, *114*(2), 321–330. https://doi.org/10.1016/j.fertnstert.2020.03.029

Yinon, Y., Pauzner, R., Dulitzky, M., Elizur, S. E., Dor, J., & Shulman, A. (2006). Safety of IVF under anticoagulant therapy in patients at risk for thrombo-embolic events. *Reproductive Biomedicine Online*, *12*(3), 354–358. https://doi.org/10.1016/s1472-6483(10)61009-7

Youssef, M. A., Van der Veen, F., Al-Inany, H. G., Mochtar, M. H., Griesinger, G., Nagi Mohesen, M., Aboulfoutouh, I., & van Wely, M. (2014). Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. *The Cochrane Database of Systematic Reviews*, *2014*(10), CD008046. https://doi.org/10.1002/14651858.CD008046.pub4

Table of recommendations.

1	**Recommendation:** All reproductive medicine units should develop strong links with one or more local cardiology teams, regional obstetric physicians and pregnancy heart teams to help ensure the safe care of patients with, or at high risk of, cardiovascular disease.	IIb, C
2	**Recommendation:** All patients should have an assessment of their cardiovascular risk before starting MAR	IIb, C
3	**Recommendation:** Alternative options to family formation should be discussed, including no treatment, use of donor gametes, surrogacy or adoption.	IIb, C
4	**Recommendation:** The risks of poor neonatal outcomes are increased both in patients with known cardiovascular disease, and in MAR-conceived pregnancies, so the increased neonatal risks should be considered in pre-treatment assessment and counselling.	IIa, B
5	**Recommendation:** Patients with cardiovascular disease requesting MAR should not be turned down for treatment on the basis of assumed cardiovascular risk, until the case has been discussed in an MDT involving the pregnancy heart team and the reproductive medicine unit.	IIa, C
6	**Recommendation:** Women with known cardiovascular disease or at high risk of cardiovascular disease seeking cross border MAR should be provided with clear information about benefits vs risks of MAR, including the risks of becoming unwell while abroad, and the importance of single embryo transfer to help them make an informed decision.	IIb, C
7	**Recommendation:** Pre-implantation Genetic Testing should be offered to men and women with an inheritable cardiac condition where the pathogenic gene variant is known and who meet local and national eligibility criteria for PGT. (Class IIa, C)	IIa, C
8	**Recommendation:** Patients with known cardiovascular disease in mWHO Class I should have a minimum of a local cardiology assessment *including specific pre-pregnancy counselling* in the 2 years prior to embarking on MAR. If no concerns are raised by the cardiologist, no specific precautions need to be taken by the reproductive medicine or anaesthetic teams.	IIa, C
9	**Recommendation:** Patients with known cardiovascular disease in mWHO Class II should have had a cardiology assessment *including specific pre-pregnancy counselling* by a pregnancy heart team in the 12 months prior to embarking on MAR. If there are haemodynamically significant cardiovascular lesions which are treatable, treatment should be undertaken before embarking on an assisted conception pathway. A multi-disciplinary team discussion including the pregnancy heart team and reproductive medicine team should be undertaken before the patient starts treatment. Alterations to medical treatment or assisted reproduction pathways may be considered.	IIa, C
10	**Recommendation:** Patients with known cardiovascular disease in mWHO Class II-III, should have had a cardiology assessment *including specific pre-pregnancy counselling* by a pregnancy heart team in the 12 months prior to embarking on MAR. If there are haemodynamically significant cardiac lesions or issues (such as poorly controlled hypertension) which are treatable, this should be undertaken before starting MAR. A multidisciplinary team discussion including the pregnancy heart team and reproductive medicine team is recommended before the patient starts treatment. Alterations to medical treatment or assisted reproduction pathways should be considered.	IIa, C
11	**Recommendation:** It is recommended that patients with known cardiovascular disease in mWHO Class III have a cardiology assessment *including specific pre-pregnancy counselling* by a pregnancy heart team in the 6 months prior to starting MAR. If there are haemodynamically significant cardiac lesions which are treatable, this should be undertaken before starting MAR. A multidisciplinary team discussion including the pregnancy heart team and reproductive medicine team is recommended before the patient starts treatment. Alterations to the standard pathways of care should be implemented.	I, C
12	**Recommendation**. It is recommended that patients with known cardiovascular disease in mWHO Class IV seeking MAR should have had an up-to-date cardiology assessment with a pregnancy heart team and a multidisciplinary team discussion including the pregnancy heart team and the assisted reproduction team. If there are haemodynamically significant cardiac lesions which are treatable, this may be undertaken, and may reduce their risk category. However, in many patients in this group, there will be no treatment options which will sufficiently modify their risk profile to reduce their risk category. While pregnancy risk to mother or baby is likely to be prohibitively high, ovarian stimulation, oocyte retrieval and embryo formation for use in a surrogate may occasionally be possible and these options should be considered and discussed. In this instance, it is expected that alterations to the standard pathways will be required.	I, C
13	**Recommendation:** It is recommended that all patients are assessed for cardiovascular risk factors before commencing MAR.	I, C
14	**Recommendation:** It is recommended that patients with increased risk for atherosclerotic cardiovascular disease[@] are referred for review by a physician with expertise in the management of medical disorders[+] in pregnancy prior to starting MAR.	I, C
15	**Recommendation:** All women with known diabetes should be referred for assessment with a physician expert in the management of diabetes in pregnancy prior to starting MAR. MAR should only be commenced in patients with diabetes once satisfactory glycaemic control has been achieved.	I, C
16	**Recommendation:** An HbA1c is recommended in all patients aged over 35 years, those with obesity (BMI of 30 kg/m^2 or greater), those with a family history of diabetes in first degree relatives, previous history of gestational diabetes, and all patients of an ethnicity other that White Caucasian before starting MAR.	I, C
17	**Recommendation:** It is recommended that all patients who continue to smoke should be advised to stop and offered smoking cessation support	I, A
18	**Recommendation:** All patients should have a blood pressure measurement within the year prior to commencing MAR. If hypertension is identified according to thresholds in the National Institute for Clinical Excellence (NICE) Hypertension in Pregnancy guideline (NICE, 2019) treatment should be started with pregnancy-appropriate antihypertensive agents and screening for secondary causes considered. MAR should only be commenced in patients with hypertension once blood pressure control is satisfactory.	I, C
19	**Recommendation:** All patients with known non-familial hypercholesterolaemia should be advised about the importance of a cardio-protective diet, and other appropriate lifestyle changes, and statins should usually be stopped prior to starting MAR.	IIb, C
20	**Recommendation**: Patients known to have familial hyperlipidaemia, hypertriglyceridaemia, or on lipid-lowering agents other than a statin, should be referred for medical review by a metabolic medicine team, prior to starting MAR.	IIb, C
21	**Recommendation:** Obese women should be given advice on weight management and lifestyle changes, and should be encouraged to lose weight before starting MAR.	IIb, C
22	**Recommendation:** It is recommended that a thorough assessment of family history of cardiovascular disease is obtained prior to commencing MAR, to assess the likelihood of inherited heart disease.	I, C
23	**Recommendation:** It is recommended that patients at high risk for inherited cardiac conditions are discussed with the local pregnancy heart team or local inherited Cardiac Conditions (ICC) team prior to starting MAR.	I, C
24	**Recommendation:** Ovulation induction may be used in patients with cardiac disease following satisfactory cardiac review (see section 4), but it is recommended to monitor closely for development of multiple follicles, to avoid the risk of multiple pregnancy.	I, B

(*continued*)

Continued.

1	**Recommendation:** All reproductive medicine units should develop strong links with one or more local cardiology teams, regional obstetric physicians and pregnancy heart teams to help ensure the safe care of patients with, or at high risk of, cardiovascular disease.	IIb, C
25	**Recommendation:** When undertaking IVF in patients with cardiovascular disease or risk factors for cardiovascular disease, specific steps to avoid OHSS are recommended.	I, B
26	**Recommendation:** Steps should be taken to minimise the risk of OHSS 1. GnRH antagonist protocol is preferred for pituitary desensitization as it offers an option to avoid the hCG trigger. 2. Controlled ovarian stimulation should aim to use standard or lower dose of FSH to avoid OHSS. 3. In predicted high responders the use of highly purified hMG is probably preferable to recombinant FSH. 4. Controlled ovarian stimulation cycles should be intensely monitored with frequent blood tests for oestradiol and ultrasound monitoring of the follicles. 5. Cryopreservation of viable oocytes/embryos (FAE) with segmentation of treatment cycle allows the maternal hyper-oestrogenaemic state to recover prior to a potential pregnancy. 6. Natural cycle frozen embryo transfer is preferable over medicated cycle in women with regular periods to minimise the risk of hypertensive disorder in subsequent pregnancy.	I, B
27	**Recommendation:** In patients with known cardiovascular disease, or risk factors for cardiovascular disease specific consideration of measures to minimise the risk of VTE and arterial thrombosis should be considered in pre-treatment multi-disciplinary discussion including a haematologist. In patients at high risk, segmentation of the treatment cycle should be considered.	I, C
28	**Recommendation:** In patients with known cardiovascular disease who are fully anticoagulated, the high risks of egg collection must be considered by the whole multi-disciplinary team (including a haematologist) and the patient before starting treatment. If IVF is undertaken, ovarian stimulation should be minimised, and a detailed protocol for management of anticoagulation at the time of egg collection put in place. This is of particular concern in patients with mechanical heart valves.	I, C
29	**Recommendation:** In all patients with cardiovascular disease or risk factors for cardiovascular disease, single embryo transfer is recommended.	I, B
30	**Recommendation:** Should MAR result in a multiple pregnancy in a high-risk patient, MDT discussion regarding risk and management options should be undertaken.	IIa, C
31	**Recommendation:** Pregnancies resulting from MAR should be managed in accordance with the recommendations for their mWHO risk category. Caregivers should be aware of the increased pregnancy risks associated with MAR pregnancy.	IIb, C
32	**Recommendation:** It is recommended that an obstetric anaesthetist is an integral part of the Pregnancy Heart team providing pre-pregnancy counselling, and should include a discussion around appropriate anaesthesia and analgesia at the time of delivery.	IIa, C
33	**Recommendation:** It is recommended that in mWHO Class III or IV patients who are being considered for MAR, anaesthetic assessment of the safety and feasibility of planned procedures including laparoscopy and trans-vaginal oocyte recovery under sedation/GA, should be part of the pre-treatment multi-disciplinary discussion and planning.	I, C
34	**Recommendation:** The co-location of support services including critical care facilities should be considered when planning MAR in patients with known cardiovascular disease, or at high risk of cardiovascular disease. An agreed escalation plan should be documented in high-risk patients to facilitate rapid assessment and treatment in the event of a complication.	IIa, C
35	**Recommendation:** Published guidance including the 2013 Academy of Medical Royal Colleges (AoMRC) multi-disciplinary guidelines on sedation practice, updated in 2021 (www.aomrc.org.uk/2021), Guidelines on Day Case Surgery 2019 (Bailey et al., 2019); Standards of Monitoring during Anaesthesia and Recovery in 2021 (Klein et al., 2021); and Immediate Post-Anaesthesia Recovery in 2013 (Membership of the Working Party, Whitaker et al., 2013), should all be adhered to during MAR. (Class 1, C)	I, C