STATE-OF-THE-ART PAPER

Rheumatic Heart Disease in Pregnancy

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Introduction

Rheumatic Heart Disease (RHD), although causing significant mortality and morbidity is given inadequate consideration. In developing countries, over half of the cardiovascular complications during pregnancy are caused by RHD [(1)]. It has been projected that more than 15 million people suffer from RHD worldwide, which is likely a significant underestimation, according to the increasing data on subclinical RHD[(2)]. RHD accounts for a major proportion of all cardiovascular disease (CVD) in children and young adults African countries and for 17–43% of all cardiovascular disease in sub-Saharan Africa (SSA) [(2)]. The disease causes 400, 000 deaths annually, mainly among children and young adults living in developing countries. [(3)]. In the recent REMEDY study (Global Rheumatic Heart Disease Registry) 3343 patients with RHD were enrolled from 12 African countries and also from Yemen and India. Among them 66.2% were female and almost 50% of total enrolled patients were female of Child bearing age and among these females only 3.6% are using contraceptives [(4)]. Bearing in mind the poor socioeconomic background, the need for long term medications (with the hazards of anticoagulant treatment), the scarcity of readily available higher cardiac centers and the high cost of interventional procedures, all these facts raise the problem of RHD (in general and during pregnancy in particular) as humanity, political and international rather than a local issue for these jeopardized communities.

The objective of this review is to give a concise road map for risk assessment, counseling and managing this group of patients.

As most of the efforts on RHD are directed at the primary health care (PHC) level i.e. towards prevention and control rather than towards tertiary care (due to the palliative nature of the interventional measures, the high cost and the need of technical expertise and quality service), this led to paucity of large scale interventions with randomized trials and subgroups studies to establish sound evidence based guidelines for management of such disease at the tertiary care level, so most data driven for meta analysis for such review are at level C of evidence or local policies.

Effect of pregnancy on hemodynamics

The Hemodynamic changes with Normal Pregnancy and during labor are summarized on Table 1and 2 respectively. Table 111 shows the Hemostatic changes during Normal Pregnancy. These changes are necessary adaptations required for adequate uterine and placental perfusion [(5)].

Table 1: Hemodynamic changes with Normal Pregnancy [1]

30–50% increase in blood volume
Reduction in systemic vascular resistance (low resistance placental circulation)
Tachycardia
Decreased systolic and diastolic BP
30% increase in COP (maximum between 5th and 8th months).

During first trimester as a result of human chorionic gonadotropin hormone activity and physiological hyperaldosteronism, there is sodium and water retention causing expanded intravascular volume and peripheral arteriolar dilatation causing decrease systemic vascular resistance. Final result is tachycardia and increased cardiac output [6]

Table 2: Hemodynamic changes during Delivery [2]

During Labor:
Increased O_2 consumption
Increased baseline COP
Increased BP and COP during uterine contractions
Post partum
Increased blood shift from placenta
Increased preload and COP

In the second trimester the same phenomenon continues resulting in more volume expansion and more preload to heart, but peripheral vasodilatation dominates that causes some fall in blood pressure. In third trimester volume expansion peaks but now vascular resistance started rising. Labor is accompanied by a further increase in cardiac output. Delivery has complex hemodynamic effects, including both blood loss and auto transfusion of blood from the contracted uterus. Furthermore postpartum anemia also contributes in cardiac workload [7].

Pregnancy creates a hypercoagulable state with accelerated rates of thrombus formation and fibrinolysis [8]. This adaptation is necessary for hemostasis of choriodecidual space of placenta and also to prevent loss of blood from placenta during delivery. This adaptation will increase the risk of thrombotic events in susceptible individuals.

Table 3: Hemostatic changes during Normal Pregnancy [3]

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- Increased platelets adhesiveness
- Increased concentration of coagulation factors and fibrinogen
- Impaired fibrinolysis
- Hypercoagulable state

In summary, the cardiac consequences of pregnancy are those of increased preload, reduced afterload, and increased heart rate, stroke volume and cardiac output in a hypercoagulable circulation subject to progressive change throughout pregnancy but also confronted by acutely increased demands during labor and immediately after delivery [9].

All these physiological changes during pregnancy are tolerated well by a normal heart but in the presence of RHD, depending upon the type and severity of valvular involvement (Generally speaking Stenotic lesions are poorly tolerated than regurgitant valvular lesions which may benefit from the decreased afterload) [10] may lead to life threatening scenarios for both mother and fetus (like Pulmonary Edema, Decompensated Heart Failure, Cardiogenic Shock, new onset arrhythmias, peripheral thromboembolism, Fetal compromise and Death). In addition, medications necessary for managing patients with RHD can lead to severe Fetal Malformations. Moreover if Cardiac Surgery is required it can lead to 30% of fetal loss table 4 [1].

Table 4: Fetal Hazards [4]

- Placental insufficiency from CCF (The rates of prematurity are 20% to 30%, fetal growth restriction 5% to 20%, and stillbirth (1% to 3%).
- The risks of anticoagulation during pregnancy and fetal malformation
- Thromboembolism and fetal miscarriage

Cardiac surgery may lead to 30% fetal loss

Rheumatic Heart Disease

The clinical picture, morbidity and mortality, frequency and speed of development of an established valve disease differ geographically and are affected primarily by the socioeconomic and medical background of the patients [11]. In developing countries the course is more violent with severe pathological valvular lesions necessitating surgery in young age [12].

Studies from Ethiopia, Nigeria, India and Sudan showed that the mitral valve was the commonest valve involved in RHD (about

60 -75%), followed by combined mitral valve and aortic valve involvement (25%). Isolated aortic valve disease was rare (7%, mainly aortic regurgitation (AR) or AR+ aortic stenosis (AS) as isolated AS is very rare) [13, 14,15and 16].

In this review RHD valvular lesions may be grouped according to the pattern of involvement and hemodynamic significance as follows (see table 5)

Table 5: Pattern of valvular lesions according to hemodynamic significance

Group	pattern of lesion	Management
End stage (Contra indicate pregnancy)	severe LV dysfunction i.e. with LVEF<35% severe Pulmonary Hypertension >60% of Systemic pressure	
Predominantly Stenotic lesions (may need early intervention)	MS or MS with mild MR or AR and with favorable criteria for PTMC	PTMC
	MS or MS with mild MR or AR and with favorable criteria for PTMC but persistent LA thrombus	Open commissurotomy
	- MS not suitable for PTMC - Multi valvular involvement MS + MR ± (AR ± AS)	Valve replacement
Predominantly regurgitant lesions (Usually pregnancy is tolerated with medical treatment)	Isolated Mitral regurgitation (MR) with Carpentiers	Valve repair
	MR, AR, combined MR+AR or Multi valvular involvement	Valve replacement
Prosthetic valves should be assessed on the same lines as native valves but carries the morbidity of Redo		

1- **End stage RHD** (contra indicate pregnancy)
   a- Any lesion with severe LV dysfunction (with LVEF<35%) [1]
   b- Severe Pulmonary HTN (pulmonary pressure is >60% of systemic pressure) [1]
2- **Predominantly Stenotic lesions** (pregnancy is not well tolerated and may need intervention at an early stage)
   a- Isolated mitral stenosis (MS) or MS +mild mitral regurgitation (MR) or AR suitable for percutaneous Transvalvular mitral commissurotomy (PTMC)
   b- MS not suitable for PTMC ± MR ± (AR ± AS)

3- **Predominantly regurgitant lesion**
(usually tolerate pregnancy and intervention is not needed early)
   a- Isolated MR with Carpentiers criteria favorable for valve repair
   b- MR not suitable for repair, AR or combined MR+AR or Multi valvular involvement.

Patients with defective prosthetic valves should be assessed on the same lines as the native valves but carries more morbidity of Redo(see blew)

Severity of the lesion is assessed clinically (symptoms and signs) and by Echocardiography which is the fundamental tool for objective assessment (Table 6) [1]

Table 6: Echo criteria for valve lesion severity

lesion	Severity to indicate intervention
MS	Valve area (cm^2) <1.0 Mean gradient (mmHg) >10 (At heart rates between 60 and 80 bpm and in sinus rhythm)
AS	Valve area (cm^2) <1 Mean gradient (mmHg) >40
MR	Vena contracta width ≥ 0.7cm with large central MR jet (area< 40% of LA) or with a wall-impinging jet of any size, swirling in LA Large flow convergence[5] Systolic reversal in pulmonary veins Prominent flail MV leaflet or ruptured papillary muscle
AR	Central Jet, width ≥ 65% of LVOT Vena contracta > 0.6cm[5] Pressure half-time < 200 ms

Maternal risk

WHO classification of risk of pregnancy by medical conditions [1] is shown on table 7. Table 8 shows the Carpreg study risk stratification [10]. According to this WHO classification the groups suggested for valvular involvement in RHD may be arranged as follows:

Table 7: WHO classification of risk of pregnancy by medical condition

Risk class	Risk of pregnancy by medical condition
I	No detectable increased risk of maternal mortality and no/mild increase in morbidity.
II	Small increased risk of maternal mortality or moderate increase in morbidity.
III	Significantly increased risk of maternal mortality or severe morbidity. Expert counselling required. If pregnancy is decided upon, intensive specialist cardiac and obstetric monitoring needed throughout pregnancy, childbirth, and the puerperium.
IV	Extremely high risk of maternal mortality or severe morbidity; pregnancy contraindicated. If pregnancy occurs termination should be discussed. If pregnancy continues, care as for class III.

1- Class IV:

a- End stage valvular lesion with severe LV dysfunction (caused more by regurgitant lesions) or severe Pulmonary Hypertension (caused more by Stenotic lesions), such patients are advised against pregnancy i.e. absolute contraindication.

b- Severe MS or severe Multi valvular involvement with predominant Stenotic lesions, such lesions contraindicate pregnancy unless intervention is done.

2- Class III:

a- Symptomatic Patients with predominant regurgitant lesions with Echo criteria of severity to mandate surgical intervention. These patients are advised strongly for intervention before pregnancy.

b- Asymptomatic patients with predominant regurgitant lesions with Echo criteria of severity to mandate surgical intervention with poor exercise tolerance

c- Symptomatic patients with moderate Echo criteria of severity with poor exercise tolerance

Patients of these subtypes (b and c) are advised for Exercise testing which is useful for objective assessment of the functional capacity, the hemodynamic response and possible presence of exercise-induced arrhythmias [1].

Patients with poor exercise tolerance are regarded as class 111 and should be advised for intervention before pregnancy

d- Mechanical prosthetic valve (see blew)

Table 8: Carpreg study Risk Stratification

Four predictors, one score for each:

- 1-Prior event e.g. CCF, embolic phenomenon, referral for intervention…
- Baseline NYHA >11
- significant LV obstruction; MS or AS
- 4-LV dysfunction EF<40%

1- Zero point=5% !point=27% and >1 point=75%

2-

Class II and I (according to the severity):

a- Patients with mild to moderate lesions by Echo criteria

b- Patients with good response to exercise tolerance

Patients of these classes are classified as low risk and are allowed to proceed for pregnancy under medical treatment and follow up.

Medical Treatment during pregnancy [1]

Strict medical treatment should be continued and surgical intervention should be thought of only on failure to control patient condition despite maximal medical treatment.

- With regurgitant valves, Diuretics, Hydralazine and Nitrates may be used safely to control symptoms (tachycardia is a common side effect) (Class1 B).
- Diuretics, beta blockers and Digoxin may be used to control symptoms, in patients with mild to moderate MS (Class1 B).
- Anticoagulation should be continued as in patients with prosthetic valves (see blew)
- Prophylaxis for ARF should be continued during pregnancy.
- For prophylaxis for Endocarditis, the same measures apply as in non pregnant patients
- Antibiotic prophylaxis is not recommended during vaginal or Cesareans delivery (Class111 C)
- Angiotensin receptor blockers (ARB) and ACE inhibitors are contraindicated during pregnancy (Class111 C)
- Reversible factors that predispose to cardiac de-compensation like hypertension, arrhythmias, infection, anemia and hyperthyroidism should be monitored and treated.
- Compliance with medications can't be over emphasized.

Types of intervention

Although intervention for RHD is still palliative but it is not widely available for a large proportion of patients living in the developing countries who need it.

Symptomatic patients with MS, which is the most common acquired valvular lesion in pregnant women (25%) and the most common cause of maternal death from cardiac causes worldwide [17] if they have pure MS or MS with mild MR or mild AR and have favorable valve criteria should go for PTMC [18] or for open commissurotomy (if there is an LA thrombus not resolving with anticoagulant treatment) [19]. Open commissurotomy during pregnancy doesn't increase risk for the mother but it increases fetal mortality (by 6% to 33%). In contrast, PTMC has been reported without fetal loss and may be the preferred modality of treatment in this subset of patients [19].

MV repair may be tried in few selected patients with MR however, even after successful valve repair, long term follow up of patients showed that late mortality was 15%, and the reoperation rate was 27% , mainly related to the ongoing inflammation[20]

Apart from the afro mentioned types, any other type of involvement needs valve replacement (see blew) but this should be done as early as possible to allow pregnancy at a younger maternal age and a less advanced pathological heart.

Management of Individual patients

- *Any female patient with RHD seen earlier at childhood or adolescence should be followed up regularly to intervene at the right time before end stage heart disease. Counseling should be started earlier at the time of marriage, at the time of surgery or for follow up patients to avoid the problem of coming already pregnant. Also the awareness of female patients with RHD at the age of marriage should be raised about problems of pregnancy.*

Counseling before pregnancy

Counseling for patients with RHD or prosthetic valves, is important and should be done by team work including the cardiac team, obstetric team and the family in addition, social worker, religious and traditional leaders may be integral part of the team (Class I C) [1]

- Parameters to be taken into account during counseling for maternal and fetal welfare in addition to the outlined general frame of risk assessment and type of treatment according to pattern and severity of valvular involvement, include Obstetric history which is an objective way of assessing the cardiac risk and expected problems during pregnancy and labor as well as socio medical and family parameters (e.g. the number of the live babies she has, the expected number of pregnancies allowed, feasibility of intervention, reliability for anticoagulation…ect) tables 9 and 10 [21].
- From cardiology perspective, emphasis should be put on mother safety, accepting small family, completing the family as early as possible before valve surgery and types of valves and their problems if valve replacement is necessary before pregnancy.
- **Class IV** patients with absolute contraindication for pregnancy may be advised for permanent contraception (Class 1 C) [1].

Operable **Class IV and Class III**

Patients are advised for intervention before pregnancy but if that is not feasible, patients are advised strongly to use contraceptive measures. Intervention is recommended as early as feasible, as lesion progression and advanced maternal age increase the maternal and fetal risk tables 9 and 10 [21].

Table 9: Risk factors for maternal mortality during cardiac surgery [9]

- Maternal functional class >2
- The use of vasoactive drugs
- Maternal age >35 yr
- Type of surgery
- Reoperation.

Classes I and II patients are allowed for pregnancy under strict medical treatment and follow up but should also be advised to complete their family before advanced age and lesion progression [1]

Class I: Patients with severe valve dysfunction (including prosthetic valves who already came pregnant

Mother safety takes priority over fetal safety and intervention may be at any time if mother safety is compromised. Medical treatment should be continued and intensified on the same lines as for patients with mild to moderate disease with follow up by cardiologist at least twice monthly [1].

Table10: Predictors of neonatal complications

Independent predictors of neonatal complications include:

- maternal New York Heart Association heart failure classification >2
- anticoagulation use during pregnancy
- multiple gestation
- left heart obstruction
- maternal age >35 yrs
- reoperation, emergency surgery
- type of myocardial protection, and anoxic time
- smoking,

Class IV

a- Patients with absolute contra indication for pregnancy (severe LV dysfunction or severe Pulmonary Hypertension) should be advised for immediate termination. A high maternal mortality risk is reported (30–50% in older series and 17–33% in more recent papers) [1]

b- Symptomatic patients with severe MS ± mild MR or AR and favorable valve criteria should go for PTMC at the end of 2nd or beginning of 3rd trimesters (Class11a C) [22 and23].

c- Patients with severe MS (not suitable for PTMC) or multi valvular with dominant Stenotic lesions with refractory NYHA class IV HF symptoms that are not responsive to medical therapy, early surgery is advisable, However, valve operation during pregnancy is high risk, with a 30% to 40% fetal mortality rate and up to 9% maternal mortality rate [17 and 24].

There is no ideal time during pregnancy to perform open heart surgery, so timing is based on the combination of the clinical status of the mother and the fetus. The period between the 20th and 28th weeks of pregnancy appears to be safest for the fetus in terms of risk of malformation and premature

delivery. If the mother can carry the fetus to full maturity, a combined cesarean section followed by cardiac surgery can be planned [24].

If surgery is not feasible such patients may be advised for early termination (during the first trimester).

Class III

RHD with predominantly Regurgitant valves carries a lower risk for poor maternal and fetal outcomes than Stenotic lesions. Maternal risk is dependent on the severity of the regurgitation symptoms and left ventricular function. Close follow up on a monthly basis is recommended and Medical therapy is usually sufficient [17]. Valve operations should not be performed in pregnant patients with valve regurgitation in the absence of severe intractable HF symptoms. (CLASS III - C) [24]

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However patients with refractory NYHA class IV HF symptoms that are not responsive to medical therapy, early surgery may be encountered but usually the patient may be stabilized with medical therapy and surgery may be delayed to be combined with Cesarean section [24].

Predictors of increased risk of maternal mortality and neonatal complications during cardiac surgery are summarized on tables 9&10

Delivery

Vaginal delivery is the preferred method of delivery, and in those patients who become symptomatic, epidural anesthesia and a shortened second stage is advisable [1and 24]. Indications for Cesarean section are summarized in table 11

Table11: Indications for Cesarean section [1]

- Severe heart failure
- Pre term labor in patients on OAC
- Severe Ms with Class III or IV symptoms, or who have pulmonary hypertension despite medical therapy, in whom percutaneous mitral valvuloplasty cannot be performed, or has failed.
- Severe AS (11aC)

Valve replacement

for this special group of young females at child bearing age, valve replacement is a great issue even if the question of the logistics and cost is sorted out, it needs careful decision making between mechanical prosthetic valves (with durability but increased risk of Thromboembolism, valve thrombosis and the hazard of long term use of anticoagulant) and bioprosthetic valve with safety (no need for anticoagulation) but less durable and valve dysfunction may be accelerated with pregnancy[1,25 and 26]. Overall, about 50% of women of childbearing age will require valve replacement owing to valve dysfunction 10 years after the original operation [27]

Putting in mind bioprosthetic valves with more present safety (classify the patient as Class1 or11) and expected future problem and the mechanical valve with potentially current problems (classify the patient by default as Class111) but expected future durability in addition to the socioeconomic background, the availability, quality and cost of anticoagulant service it was found that in general women with mechanical valves have a higher complication rate, including the increase of both maternal and fetal events, compared with women with bioprostheses [25 and 26]

Prosthetic Valves

Mechanical prosthetic valves carry high maternal and fetal complications during pregnancy. On one hand procoagulant effect of pregnancy needs adequate anticoagulation and on the other hand adequate anticoagulation increases the chance of fetal malformation and may cause excessive hemorrhage.

Anticoagulation

Anticoagulation treatment is special problem in the developing countries due to paucity of readily available and affordable quality service with reliable INR monitoring. However, without any anticoagulation, maternal mortality is high (up to 5%), and there is a high risk of thromboembolic events (up to 24%) and valve thrombosis. Because of the physiological effects of pregnancy, there are constantly changing requirements for antithrombotic regimens. Effective anticoagulation with frequent monitoring of its effect is critical throughout pregnancy [24]

There is no uniform opinion about the use of different anticoagulants during pregnancy.

The risk of embryopathy, abortion and fetal loss in the first trimester, is increased with any anticoagulant regimen. For warfarin it is dose dependent, with a low risk (<3%) if the dose is up to 5 mg per day. Long term UFH has a lower fetal risk but may cause heparin induced thrombocytopenia and osteoporosis also continuous infusion is required which is a source of infection. LMWH has less chance of these complications but monitoring of Factor Xa activity is required [1 and 24].

Despite of the fetal risk, warfarin is the most effective and reliable anticoagulation available to be used and Continuation of warfarin during the first trimester is reasonable if the dose of warfarin to achieve a therapeutic INR is 5 mg per day or less after full discussion with the patient about risks and benefits (Class 11a –B). However, if warfarin dose needed is >5mg /day during the first trimester, dose-adjusted LMWH appears to be the safest choice in terms of prevention of thromboembolic events but peering in mind the cost and lack of available factor Xa monitoring facilities, UFH may be an alternative . Dose of warfarin is not a matter for the 2nd and 3rd trimesters but after 36 weeks of gestation UFH is recommended.

Valve thrombosis

There is lack of large scale data but one series of Thrombolysis as the initial therapy for valve thrombosis during pregnancy for 24 women showed successful Thrombolysis, with no maternal mortality and five fetal deaths (20%) [28]. so it may be rational to treat as for non pregnant ladies with Thrombolysis and surgery if Thrombolysis failed.

Endocarditis

All patients with prosthetic heart valves (bioprosthetic or mechanical) are at risk of Endocarditis [29]. For all types of Endocarditis during pregnancy (valvular and non valvular), the maternal mortality rate can reach 33%, with most deaths related to

heart failure or an embolic event. The rate of fetal mortality can reach 29% [30]. Raising awareness and implementing prevention measures are important [29]. Although the use of antibiotic prophylaxis during delivery is controversial (29) it may be empirically advisable.

Need for Redo for defective prosthetic valves

Redo operation carries a higher maternal and fetal risk [31]. Most data are case reports or very small groups but empirically defective prosthetic valves may be assessed and managed on the same lines as native valves with the accepted more hazard of Redo operation if surgery deemed necessary.

Conclusion

RHD is still the common heart disease in females at child bearing age in the developing countries. Although current intervention is palliative it is not widely available. As many patients attend medical care before marriage, every possible care should be done to conserve the native valve (regular prophylaxis for RF and Endocarditis, controlling symptoms and precipitating factors) and the patient should be advised to complete her family at a younger age and to accept small family.

RHD may be classified into 4 groups; predominantly Stenotic, predominantly regurgitant, end stage valvular disease with poor LV function or severe Pulmonary HTN and operated patients with prosthetic valves.

If intervention deemed necessary (Class 1V or Class 111) this should be done as early as possible. Apart from PTMC (or open commissurotomy if persistent LA thrombus), MV repair for selected cases, any other intervention needs valve replacement which should be tailored for the individual patient but taking into consideration the poor socioeconomic background and limited facilities, tissue valves may have less maternal and fetal complications than mechanical ones. If intervention is not feasible, contraception is strongly advised.

For those who already came pregnant, mother safety takes priority over fetal safety. Patients with end stage heart disease should be advised for termination. Predominantly Stenotic lesions usually tolerate pregnancy less well than regurgitant lesions. Surgical intervention should be delayed to be with or after delivery by Caesarean section, but if symptoms failed to be controlled with medical therapy, intervention may be needed at earlier stage despite the high rate of complications. PTMC may be done safely but preferably at 7th month.

For mechanical valves Warfarin is safe during the 2nd and 3rd trimesters, but is needed to be substituted with LMWH or UH in the first trimester if the dose is>5mg/day and on the 36th week. Anticoagulation treatment should be monitored carefully with PTT for UH and anti Xa level for LMWH. Low dose Thrombolysis may be used for prosthetic valve thrombosis.

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