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Severe morbidity and mortality associated with cardiac disease during pregnancy in the Free State Public Health Service.

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To my wife Phydelia

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List of Abbreviations

ACE	Angiotensin converting enzyme
AI	Aortic incompetence (regurgitation)
ASD	Atrial septal defect
CO	Cardiac output
ECG	Electrocardiogram
ES	Eisenmenger syndrome
HCM	Hypertrophic cardiomyopathy
HCW	Health Care worker
HIV	Human immunodeficient virus
ICU	Intensive care unit
Kg	Kilogram
LA	Left atrium
LV	Left ventricle
LVEF	Left ventricular ejection fraction
Mg	Milligram
MI	Mitral incompetence (regurgitation)
MS	Mitral stenosis
NO	Nitric oxide
NYHA	New York Heart Association (functional grading)
PDA	Patent ductus arteriosis
PND	Paroxysmal nocturnal dyspnoea
Qp	Pulmonary flow
Qs	Systemic flow
RA	Right atrium
Rp	Resistance pulmonary
Rs	Resistance systemic
RV	Right ventricle
SD	Standard deviation
SLE	Systemic Lupus Erythematosis
TE	Thrombo-embolic
TI	Tricuspid incompetence (regurgitation)
VSD	Ventricular septal defect

Introduction

Many years of interest and experience in High Care Obstetrics and in particular pregnancies complicated by a diseased heart initiated the idea of this thesis. With the introduction of the Obstetric High Care Unit at the Pelonomi hospital in 1988, patients with complications were concentrated in a single ward and we were astonished by the numbers of ill women presenting at our institution. This led to a publication from our hospitals describing the disease profile of pregnancies complicated by a diseased heart. [1]

When a multi-center study on severe acute morbidity ("near-miss" study) was conducted (1997-1998) and detailed information of the complicated cases became available, we became acutely aware of the significance of this method of describing morbidity. I assessed all the case records and with the help of our research assistant, I was sure that all the complicated cases and deaths in the index population were reported. As assessor of maternal deaths in the Free State Province, I was also sure that we did not miss any deaths of possible cardiac disease.

Over the past 12 years, after the introduction of the Obstetric High Care Unit, the tradition developed at our institutions (Pelonomi and Universitas hospitals) that all pregnancy related medical complications were referred to the Obstetric High Care Unit. This institutional habit ensured that we could be reasonably sure that all cases referred to the specialist center, would be included in the study. However, isolated cases may have ended up elsewhere and general practitioners may have managed uncomplicated cases without referral. As

uncomplicated cases do not have an impact on the health care services, they are probably not that important. A thorough study of the women with severe acute morbidity and mortality may be helpful to identify those at risk.

The decision to compile the available data in a thesis was done because 1] No standardised method of evaluating morbidity was available in the literature 2] Data from the index population is the best yet available to give an idea of the occurrence of heart disease in our province and 3] The high prevalence of myocardial disease necessitates a reconsideration of this disease in our community.

A Literature review

1. General literature

The pregnant woman with a diseased heart often attracts the attention of medical practitioners because of the special problems of these patients. At the mortality and morbidity meetings, these patients are often discussed in detail. In this literature review I would like to highlight the aspects known in modern medicine which relate to the clinical diagnosis and management of women with cardiac disease in pregnancy. It is not my intention at this point to discuss all the possible mechanisms of normal cardiac function but rather to concentrate on the clinically relevant changes during pregnancy.

1.1 Physiology

Pregnancy is a state of altered physiology. Profound cardiovascular changes occur during pregnancy which are well tolerated by the healthy pregnant individual but may be hazardous in the person with an abnormality of the heart. During pregnancy symptoms and signs also develop which often are associated with cardiac disease. To understand the effect of heart disease in pregnant women, we need an in-depth knowledge of the normal physiological changes which occur during the pregnant state.[2] This should be seen in the context of the various abnormalities and how it affects the cardiovascular function.

Myocardial fibers have an interesting property in the sense that tension or pressure applied to the fiber has a relationship with the contractility properties. This is referred to as the Starling-effect.[3] If the muscle fibers are allowed to shorten, there is a direct proportional relationship with the extent and velocityof the contraction known as the force-length relationship.[4]

Two important physical properties have a significant impact on myocardial function:[5]

a. Pre-load

Pre-load is the force that stretches the resting myocardium and determines the length of the contractile fibres. In clinical practice there is a direct proportional relationship between the ventricular end-diastolic volume and the pre-load. It is however, difficult to measure the end-diastolic volume. Today this can be done with rapid computed computerised tomography or magnetic resonance with a great degree of accuracy. It can also be measured with trans-esophageal echocardiography. In practical clinical terms, the only bedside investigation is invasive and by means of measuring the capillary pulmonary wedge pressure.

b. After-load

After-load refers to the tension of muscle fibres during contractions, thus the force opposing shortening of fibres and ejection of blood during ventricular contractions. This opposing force depends on two important factors:

i. *Myocardial load* (instantaneous force within the ventricular wall) - This relates to both the chamber size and shape and the pressure within the chamber.

ii. *Arterial load* - which are the physical properties of the arterial system during the ejection period.

The arterial and ventricular pressures, peripheral vascular resistance, aortic input impedance, systolic wall stress and effective arterial elastinance represent the after-load.[6,7] A progressive decrease in myocardial afterload is demonstrated throughout pregnancy by a decrease of 40% in the systemic vascular resistance (SVR).[8] During pregnancy the after-load may be misinterpreted because the left ventricle remodels throughout pregnancy with actual hypertrophy.[9] End-systolic wall stress has been proposed as a sensitive index of after-load and decreases throughout pregnancy by 26-28%, not exactly parallel to the reduction in the SVR.[8]

The main purpose of the cardiovascular system is to deliver oxygen together with other nutrients to tissues of the body and, in return, to remove waste products.[10]

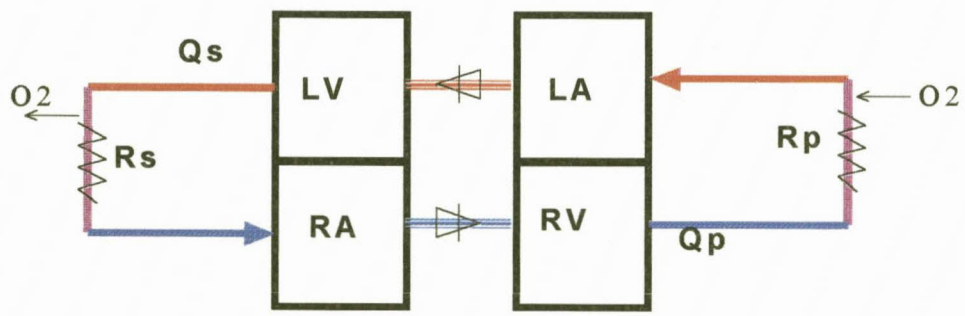
In the broader sense, we can look at the heart as a double pump system connected in series to a peripheral and pulmonary vascular bed. The right heart receives de-oxygenated blood from the peripheral system and pumps it to the pulmonary system for re-oxygenation. The left heart receives oxygenated blood from the pulmonary system and redistributes it to the peripheral tissue. The oxy-hemoglobin dissociation curve also affects the

pump properties. Other physical properties such as the compliance laws of Laplace[11] and properties relating to flow and serial connections also apply.

The formulas and equations can be calculated using invasive and non-invasive techniques. These parameters can then be used to compare differences in physiological conditions such as exercise and pregnancy and in pathological conditions.

The mainstay of cardiac function is to deliver oxygen. Oxygen delivery can be

Figure 1 Circulatory diagram



RA= Right atrium LA= Left atrium LV= Left ventricle RV=Right ventricle
Rs= Systemic resistance Rp=Pulmonary resistance
Qs = Systemic flow Qp=pulmonary flow

calculated according the following formula:-

Oxygen delivery = CaO_2*CO (cardiac output where cardiac output = (stroke volume)x(Pulse rate)).

During pregnancy and labour adjustments are required for the altered needs.[12]

These are addressed by an increase in maternal blood volume by approximately 2 liter, representing a 45% increase above the normal non-pregnant intravascular volume,[13,14] although central venous pressures[27] and pulmonary wedge pressures remain unchanged.[15]

The cardiovascular system has been investigated with various techniques since the turn of the century. Cardiac output was measured by dye dilution,[16,17] thermo-dilution,[18] electrical impedance,[19] ECG,[20] echocardiography[21] and Doppler.[22] There is general consensus of opinion that cardiac output increases by about 40% during pregnancy.

In normal pregnant women there is a small but progressive increase in oxygen consumption throughout pregnancy,[17] but during exercise the oxygen consumption increases less in women with heart disease than in normal women.

Mabie *et al.*[22] summarised the important cardiac output studies (Table 1 includes the current list of most recent values[23]).

Table 1 Summary of cardiac output during pregnancy and postpartum [22,23]

		Antepartum			*Postpartum*		
	Method	Cardiac output	Heart Rate	Stroke volume	Cardiac output	Heart Rate	Stroke volume
Ueland (1969)	Dye	5.7	83	69	5.0	70	71
Clark (1989)	Thermo-dilution	6.2	83	75	4.3	71	61
Atkins (1981)	Electr Impedance	5.8	76	79	5.4	57	93
Katz (1978)	M-Mode	8.6	88	97	5.4	69	79
Mashini (1987)	M-Mode	5.5	88	64	4.2	66	66
Easterling (1990)	Doppler	7.2	-	-	5.5	-	-
Robson (1987)	Doppler	7.6	88	88	5.4	67	78
Robson 1989	Doppler	7.2	87	84	4.9	75	66
Mabie (1994)	Doppler	8.7	88	99	5.7	69	84
Poppas (1997)	Doppler	7.9	80	99	6.0	66	87

In recent years non-invasive techniques became available to accurately determine cardiac output. There is a strong correlation of echocardiography with thermo-dilution and electrical impedance techniques although no data exist on the reliability of systolic time intervals.[17,18,19, 20,24]

Most studies reviewed were cross-sectional (33 studies) and most of the longitudinal studies did not have a value prior to pregnancy – the non-pregnant data were obtained in the puerperium. Only the study by Robson and co-workers[25] did commence pre-conception with an increase from 4.88 l/min before pregnancy to a maximum of 7.3 l/min by 34 weeks of pregnancy

Table 2 Changes in hemodynamic parameters in pregnancy [26]

	Early	Middle	Late	Postpartum
Heart rate (bpm)	75±1	83±1	82±2	67±2
Stroke volume (ml/beat)	66±2	69±2	70±2	62±2
Cardiac output (l/min)	5.0±.2	5.7±.2	5.8±.2	4.2±.1
Cardiac Index (l/min/m2)	3.1±.1	3.3±.1	3.3±.1	2.5±.1
MAP mmHg	59±1	58±1	62±1	64±1
Total peripheral resistance	1027±39	876±27	941±37	1356±69
LV diastolic dimension (cm)	4.52±.05	4.53±.04	4.52±.04	4.50±.04
LV Diastolic volume (ml)	95±2	98±2	99±3	89±2
Diameter/length	0.56±.001	0.55±.001	0.55±.001	0.55±.001
LV dias wall thickness (mm)	75±1	78±2	78±2	71±11
Radius/wall thickness	3.1±.06	3.0±.7	3.0±.7	3.2±.6
LV mass	129±3	131±3	135±2	129±3
LVEF %	70±1	70±1	71±1	70±1
Fractional shortening	44±1	45±1	45±1	44±1

representing a 50% increase in cardiac output. There is a general consensus of opinion that there is an increase in cardiac output during pregnancy, but a disagreement regarding the magnitude of the increase.

In 1997 Gilson[26] and co-workers published a longitudinal study (Table 2) with a wide range of parameters worth noting.

Doppler made an enormous impact on the ability to measure cardiac parameters in a non-invasive way. The results from wave and pulsed-Doppler measurements are similar. Cardiac output values of earlier studies vary from the later studies, and this is thought to be as a result of more reliable ultrasound techniques and different formulas.

Therefore it can be generally accepted that there is an increase in cardiac function in pregnancy and that most changes already occur in the first trimester of pregnancy. Moderately enhanced intrinsic myocardial contractility contributes to the overall increase in the cardiac output. Structural changes include an increase in the left ventricular end-diastolic diameter suggesting an increased pre-load during pregnancy.[27] We can thus accept that pregnancy is a chronic, natural volume overload state.[28] A reversible fall in contractility has also been observed.[29] The systolic function is preserved throughout pregnancy by a fall in the after-load, although this decreases near term and in the postpartum period because of decreased contractility and diminished pre-load.

Cardiovascular data during labour is not well reported. There is an increase in both cardiac output (in-between contractions and progressively during contractions as labour progresses[30,31]) and arterial pressure accompanied by a reflex bradycardia.[32] The cardiac output increases as much as 34% at full dilatation when compared to earlier stages in labour.[33] The increased cardiac output during labour is generally thought to be the result of anxiety and pain.

Labour and delivery represent a period of considerable hemodynamic demands.[34]

Symptoms and signs of heart disease in normal pregnancies

During a normal pregnancy some symptoms and signs usually associated with heart disorders may occur in normal women[35] (Table 3). Dyspnoea or

Table 3 Pregnancy related symptoms and signs

Symptoms		Signs	
Hyperventilation	Common	Hyperventilation	Common
Dyspnoea	Common	Lower limb edema	Common
Decreased exercise capacity	Common	Jugular venous distension	Common
Orthopnea	Occasional	Capillary pulsation	Common
Paroxysmal nocturnal dyspnoea	Occasional	Brisk and displaced left apex	Common
Lightheadedness	Occasional	Palpable pulmonary trunk	Common
Syncope	Occasional	Full/collapsing arterial pulse	Common
Chest discomfort	Occasional	Persistent 2nd heart sound -splitting	Common
		3rd heart sound	Common
		Mid systolic murmur parasternal	Common
		Continuous murmur	Common

shortness of breath is common during normal pregnancy.[36,37,38] In the first half of pregnancy almost half of women with no cardiopulmonary disease complain of dyspnoea increasing to 75% by 31 weeks of gestation.[39] Although dyspnoea is usually regarded as a single sensation, breathlessness may encompass multiple sensations.[40] From various clusters investigated, air hunger (I feel hunger for more air, I feel out of breath, I cannot get enough air)

is the only form of dyspnoea associated with pregnancy although it may also occur in women with cardiac disease or chronic obstructive airway disease.[41]

A third heart sound occurs in a large proportion of normal pregnant women without any evidence of heart disease.[42]

Table 4 ECG changes in pregnancy

Axis shift	Common
Sinus tachycardia	Common
ST segment and t-wave changes	Occasional
Atrial and ventricular premature beats	Common
Supraventricular tachycardia	Common
Ventricular tachycardia	Rare

The electrocardiogram (ECG) (Table 4) shows changes in rate, rhythm, intervals and axis. The increased heart rate causes decrease in the PR and QT intervals, but the QRS amplitude and duration on the ECG are unaffected.[43] No consensus exists as to the deviation of the axis, as some report it to be to the left while others report no shift, but usually to the right if it did occur.[44] It seems however, that the normal QRS axis is age dependant and that a left axis deviation should be considered accordingly.[45] During the third trimester a small q wave and inverted T wave are common and the exercise time to onset of the ST segment suppression significantly shorter.[46] ST segment suppression in women even with chest pain is usually not associated with myocardial ischemia.[47]

Pregnancy also has an effect on the appearance of the chest radiograph. Lordotic positioning of the patient during filming may mimic left atrial

enlargement with a straightening of the left heart border as well as prominence of the main pulmonary artery. In the lordotic position the clavicles appear parallel to the top of the radiograph. Right atrial enlargement have been reported as normal for pregnancy.[48] In 50% of cases with right atrial enlargement pulmonary hypertension can be diagnosed and this should be regarded as a normal variant requiring further investigation.[49] Doubling of the pulmonary blood flow is required before morphologic changes occur in pulmonary vessels on the chest radiograph. If pulmonary vascularity is increased, the patient should be investigated as non-pregnant women with increased pulmonary blood flow.

There are no characteristic radiographic changes during pregnancy and the same criteria for interpretation should be applied for non-pregnant and pregnant women.

Indicators of heart disease in pregnant women

Although similarities of symptoms and signs between normal pregnant individuals and those with heart disease exist, certain findings increase the suspicion that a pregnant woman has significant cardiovascular disease. Dyspnoea that limits activity and true orthopnea are unusual in normal pregnancy.[50] Syncope in the upright position also cannot be explained by pregnancy and should warrant further investigation. Hemoptysis is abnormal in pregnancy. Although chest discomfort is common in pregnancy, if it limits

Table 5 Indicators of heart disease

Symptoms	Signs
Severe dyspnoea	Cyanosis
Progressive orthopnoea	Clubbing
Paroxysmal nocturnal dyspnoea	Persistent neck vein distension
Hemoptysis	Systolic murmur > III/IV
Syncope with exertion	Diastolic murmur
Chest pain related to effort	Cardiomegaly
	Arrhythmia
	Criteria for pulmonary hypertension
	Left parasternal lift
	Loud 2nd heart sound

activity, worsens or is indistinguishable from angina, it must be further investigated.

Physical signs not normal in pregnancy include cyanosis, clubbing and diastolic heart murmurs. The indicators of possible heart disease in pregnant women are highlighted in Table 5.

1.2 General epidemiology

The prevalence of cardiac disease in pregnancy is unknown, but estimated between 0.1 and 3.7% of pregnancies.[51,52,53,54] Reports relating to heart disease are extrapolated usually from maternal mortality data or hospital based prevalence studies, which may be biased due to referral patterns or recognition of heart disease only when they become symptomatic or complicated. The disease pattern has changed during the past decades and there are also continental differences (Table 6).[55,56,57,58,59,60] Pregnancy *per se* does not have an effect on the progress of heart disease,[61,62,63] although symptoms may increase.[64] In perhaps one of the most remarkable long term

Table 6 Summary of prevalence, mortality and disease type

	Type	Continent	Prev	Deaths`	Congenital	Rheumatic	Other
Schoon 1990- 95	Hosp	Africa	0.4	3.4 %			
Szekely 1942-1969	Hosp	Europe	1.7	0.9 %			
Sugrue 1969-78	Hosp	Europe	0.5	0.67 %	14	83	3
Mc Faul 1970-83	Hosp	Europe	1.3	0.57%	31	60	9
Tan 1995-97	Hosp	Europe	0.4	0	69	12	19
Theron 1990-92	Deaths	Africa	?	10/138	0	60	40
Hibbard 1960-68	Deaths	America	0.22	77/1362	12	36	52
Sachs 1954 –85	Deaths	America	?	72/?	18	38	44
Walters 1953-67	Deaths	Australia	?	34/392	6	32	62
Shearman 70-72	Deaths	Australia	?	14/45		7	
Shearman 70-72	Deaths	Australia	?	18/168		33	
Howit 1964-66	Deaths	Europe	?	50/597	8	85	7

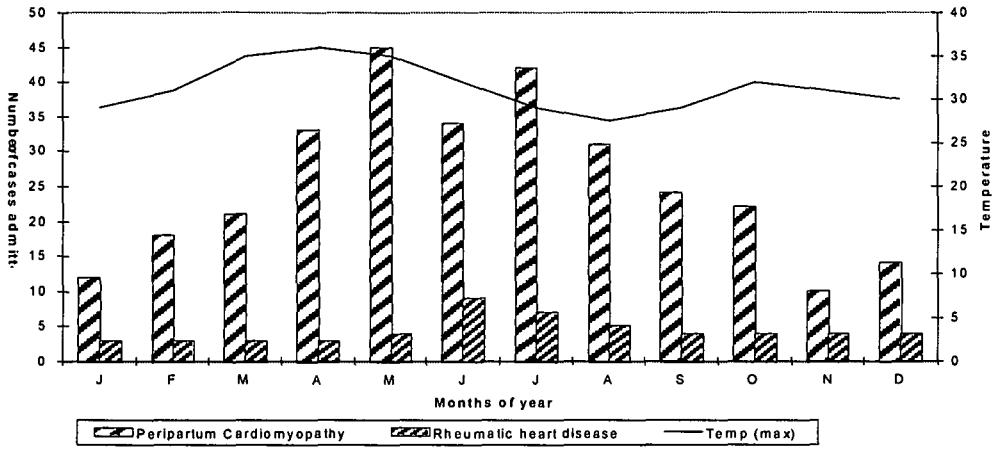
Type = Hospital based (Hosp) or Death report (Deaths) ?= prevalence not determined from data

follow-up studies Chesley[65] documented 25 - 30 year follow-up after pregnancy and found no clear evidence that pregnancy or decompensation in pregnancy increased remote mortality. Poor prognostic signs relating to long term outcome were the presence of atrial fibrillation and aortic valvular disease.

The seasonal occurrence of heart disease or its complications is poorly documented. There was one study from Nigeria[66] documenting a seasonal distribution of peripartum cardiomyopathy (Fig 2) and admissions with rheumatic heart disease. This indicates that there is a peak incidence just after the warmest months. A similar pattern is also seen for admissions of complicated rheumatic heart disease. They do not have a satisfactory explanation for this variation, but hypothesise that heat may have an effect on blood pressure leading to complications.

In most of the "first world" countries, heart disease is an important cause of maternal death.[67]

Figure 2 Seasonal variations in Nigeria[66]



There are only a few attempts to document morbidity, therefore maternal mortality rates are generally used to describe quality of care. This has been challenged recently as mortalities are becoming increasingly rare.[68] Despite the low maternal mortality, heart disease in pregnancy is associated with

Table 7 Pathological categories

Category	*Definition*
Shunt	Atrial or ventricular septal defect, or sinus of Valsalva fistula
Right heart obstruction (RHO)	Tricuspid valve area < 2 cm^2 or RV outflow peak gradient > 25 mm Hg
Left heart obstruction (LHO)	Aortic valve area < 1.5 cm2, Mitral valve area < 2 cm2 or left outflow tract peak gradient > 30 mm Hg
Right heart regurgitation	Moderate to severe regurgitation of the pulmonic or tricuspid valve
Left heart regurgitation	Moderate to severe regurgitation of the aortic or mitral valve
Arrhythmia	Sustained symptomatic tachy-/or bradyarrhythmia diagnosed before conception and requiring therapy.
Pulmonary hypertension	Systolic pulmonary artery pressure > 50 mm Hg

significant cardiac morbidity.[69] Unplanned admissions to the ICU are an accepted quality assurance indicator for gynecological patients[70] and should perhaps be used as a general indicator of maternal well-being.[71]

In view of the wide spectrum of disease, Siu[69] and co-workers attempted to define functional pathology (Table 7), but failed to bring this in context with maternal cardiac outcomes.

1.3 Valvular disease

Most heart disease involving heart valves is acquired and rheumatic of origin. With the decline in rheumatic fever, it becomes apparent that many valve lesions previously thought to be rheumatic of origin are in fact due to other pathologies.[72] Although the basic underlying pathology may differ, the valvular lesions will be discussed together as the hemodynamic effects are related to the integrity and properties of the different valves.

Management of patients with valvular lesions should ideally start before pregnancy when decisions regarding surgery can be made.[72,73] Echocardiography provides helpful information confirming structural abnormalities.[74]

Mitral valve

One of the most important valves of the heart is the mitral valve, not only because of common involvement, but also because of the hemodynamic effects across this valve. Stenosis of the valve is usually because of rheumatic fever (post streptococcal inflammatory reaction), but can also more rarely, be due to auto-immune diseases such as systemic lupus, rheumatoid arthritis and amiloidosis. Tumors such as atrial myxomas may simulate functional stenosis. Regurgitation of the mitral valve is also commonly caused

by rheumatic fever. Mitral valve prolapse is the most common congenital abnormality and affects 4% of the general population.[75,76]

A mitral valve surface area of > 2 cm^2 is usually not associated with symptoms of congestion and > 1.5 cm^2 not associated with symptoms at rest.[77] First symptoms are usually precipitated by factors that either increase cardiac output or decrease the diastolic filling period – such as exercise, pregnancy, infection or dysrhythmias.

Pulmonary hypertension frequently complicates mitral stenosis. This may be due to passive hypertension because of increased left atrial pressure, or pulmonary vasoconstriction mediated by neuro-hormonal factors, or medial hypertrophy causing an increase in pulmonary artery resistance. This may be a protective mechanism to protect the lungs from severe congestion. Pulmonary hypertension leads to tricuspid regurgitation and right-sided heart failure.

Symptoms of mitral stenosis include dyspnoea, paroxysmal nocturnal dyspnoea (suggesting congestion), fatigue (usually because of a decreased cardiac output), palpitations and hemoptysis. In 15% of cases chest pains, not distinguishable from angina, may be present and in 10% of cases might have signs of systemic embolisation. A holodiastolic rumble is indicative of severe disease.

Mitral stenosis is a mechanical disorder and the treatment is surgical. The surgical methods could be by opening the valve surface area with valvuloplasty or by replacing the valve with a prosthetic valve. Medical therapy is only to ameliorate symptoms.

It is recommended that surgical relief should be obtained before conception. Most patients who are symptom free will go through the pregnancy with minimal problems. During pregnancy heart failure usually develops towards the end of the second trimester and during the third trimester. Although surgery during pregnancy has been performed safely,[78,79] it is recommended that the resting heart rate should be kept as low as possible[80] during pregnancy and labour. Women should be treated with selective beta1-blockers if a relative tachycardia develops[81] and low dose diuretics for symptoms of congestion.[77] Some authors[82] feel that prophylactic use of beta-blockers will prevent acute lung edema during pregnancy and labour. Surgery should be reserved during pregnancy for those failing on medical amelioration. Valvotomy offers a good outcome[83] and should be the procedure of choice in women still having to complete their pregnancy. Percutaneous balloon valvotomy is safe and offers an excellent alternative to open surgery.[84,] (See discussion on page 25).

Valve replacement surgery intrapartum or early postpartum may be associated with severe peri-operative uterine hemorrhage.[85]

Mitral regurgitation lesions are usually very well tolerated during pregnancy and labour.[80,81,86] Pregnancy induced hypertension may predisposed to lung edema in the presence of mitral regurgitation. A significant risk for the development of complications is regurgitation causing atrial enlargement and/ or atrial fibrillation.

The outcome of women with mitral valve prolapse is excellent,[75] but a small percentage may develop angina-like chest pain relieved effectively by beta-blockers.[81]

Tricuspid and pulmonary valves

Isolated right-sided lesions of rheumatic origin are uncommon, although it may develop secondary to valvular endocarditis.[87] Although tricuspid regurgitation may develop as a complication[77] of secondary pulmonary hypertension, lesions from these valves are well tolerated throughout pregnancy and do not result in lung edema. Pulmonary stenosis in children is of congenital origin and they rarely survive to adulthood.[88] Survivors may develop obstructive cardiomyopathy.[89] Congestive heart failure occurs in only 2.8% of women with pulmonary stenosis.[90] Cautious fluid administration during labour and delivery is advised.

Aortic valves

Fortunately significant aortic stenosis during pregnancy is rare.[91] Although the quoted maternal mortality of aortic stenosis is 30%, more recent reviews of published cases indicate a much lower mortality of < 7%.[92] The fixed cardiac output in severe disease may be inadequate to maintain coronary artery or cerebral perfusion and may lead to sudden death.[81]

Women who are asymptomatic prior to pregnancy with a good left ventricular function, normal ECG and who can achieve at least 7 mets on the treadmill

without angina, will not be affected by a fall in blood pressure. During pregnancy the Doppler outflow velocity should increase if there is good left ventricle function. Clinical onset of tachycardia, dyspnoea or angina are danger signals in women with aortic stenosis. In these cases bed rest combined with a beta-blocker to improve diastolic time for coronary flow and left ventricular filling is needed. If possible, the pregnancy should be managed expectantly until the fetus is viable with delivery by caesarean section under general anesthesia before dealing with the mother's valve.[93] More recently, the use of epidural blocks have been reported as an alternative.[94] Echocardiographic evaluation of the valve during pregnancy is a better indication of disease severity than pressure gradient alone because of the high outflow state of pregnancy. Aortic stenosis combined with an incompetence can yield a pseudocritical stenosis.[95] Once the stenosis progresses to cardiac decompensation, surgery is indicated,[96] preferably in the mid-trimester.[97] Treatment of severe symptomatic aortic stenosis with percutaneous balloon valvotomy is without significant fetal effects and offers an excellent therapeutic alternative during pregnancy.[98]

Acute onset aortic regurgitation may cause a decreased forward stroke volume with resulting pulmonary edema and cardiogenic shock due to inability of the left ventricle to dilate. Chronic insufficiency with compensatory hypertrophy on the other hand allows normal ejection, but eventually decompensates due to systolic left ventricular dysfunction (decreased left ventricular ejection fraction at rest) leading to pulmonary congestion.[86]

If they become symptomatic during pregnancy, the symptoms are treated with vasodilators (such as hydralazine or nifedipine). The presence of left ventricular systolic dysfunction (even in the absence of symptoms) is an indication for corrective surgery.

1.4 Prosthetic valves and valvular surgery

Corrective surgery should be done prior to conception.[72,73] Successful pregnancies have been described after single,[108] double[360] and triple valve[99]

Table 8 Thrombo-embolic risk

	Risk of thrombosis
Mitral prosthesis	
Any thrombi	37%/patient/year
Prosthesis thrombosis only	20%/patient/year
Heparin therapy*	46%/patient/year
Warfarin therapy**	10%/patient/year

(26 patient-years heparin* and 29 patient-years warfarin** experience)[106]

replacements. Although the hearts of women with artificial valves are capable of tolerating the physiological adaptations of the maternal cardiovascular load of pregnancy, it is fraught with problems for both mother and fetus.[100,101] Prosthetic thrombosis[102] and systemic thrombo-embolism[103,104] are the most important maternal complications after prosthetic valve replacement. The available series published are summarised in Table 9.[1,100,105,106,107,108,109,110,111,112] Although there are numerous incidental reports of thrombosis in patients with metallic valve prosthesis[113,114,115,116,117,118] and because of the thrombotic risk in pregnancy, anticoagulation therapy is indicated during pregnancy.[119] The optimal anticoagulation therapy in

pregnant women is a subject of controversial debate.[120,121] Warfarin crosses the placenta and is associated with fetal abnormalities[122,123,124] (even after the first trimester),[125] and losses[126] although there is some indication that fewer fetal abnormalities occur if the maternal dose is less than 5 mg.[127] Some, however, believe that the occurrence of warfarin embryopathy is overrated.[128,129] Heparin does not cross the placenta and it was suggested as an alternative to coumarin during the first trimester, but might be associated with an increased incidence of valvular thrombosis, both on low dose subcutaneous[130] and intravenous[131,107] routes as an even anticoagulant effect is often very difficult to achieve.[132] Valvular thrombosis was also described with the use of calcium heparin.[133] The use of heparin is also associated with

Table 9 Thrombosis and deaths in metallic valve prosthesis

	N	Thrombosis	TE on heparin	Deaths
Sbarouni (1994)	141	13	10	6
Hanania G (1994)	108	10	6	3
Wang (1983)	14	5	5	0
Pavankumar (1988)	37	2	0	0
Vidne (1973)	10	1	1	1
Ibarra-Perez(1976)	25	2	0	0
Vallejo (1990)	7	1	1	0
Salazar (1984)	160	27	1	4
Lecuru (1996)	54	1	1	2
Schoon(1997)	31	10	1	5
Guidozzi(1984)	33	6	?	2
n	587	72	26	21
		12.2%#	36.1%*	3.6%# (29.1%*)

Percentage of all cases with metalic valves
*Percentage of all cases with thrombosis

increased risk of bleeding. It is also of concern that pregnancy losses are similar in patients on warfarin and heparin.[134] The experience with low molecular weight heparins is limited to incidental case reports,[135] all with a good outcome. A recent multi-center trial assessing fractionated heparin was stopped because of two maternal deaths on injection (unpublished data). The parenteral route may affect patients' compliance and increase the

hospitalisation although a case was described using high dose intravenous heparin at home.[136] She did, however, use an electronic infusion pump. Concern has been expressed with long-term high dose heparin use because of a high occurrence of asymptomatic bone loss.[137] The type and position of the valve also affects the risk of thrombosis.[120] Transfer from oral anticoagulants to heparin has been advocated but no published series justifies this practice.[138] The use of antiplatelet drugs has been reported,[139] but without great acceptance. There is thus clear evidence that metallic valve prosthesis is not without a significant risk to the mother and the fetus.

The ideal prosthetic valve should be functionally durable, nonthrombogenic and hemodynamically satisfactory.[140] Bioprosthetic valves offer an alternative and of all available cardiac prostheses, perhaps come the closest in all these respects. Because of the biologic nature of porcine biografts, anticoagulation therapy is not required,[141] but there is a problem with durability.[142,143] Normal pregnancies without maternal thrombo-embolic sequela have been reported[144,145,146,147] with perinatal morbidity and mortality within normal limits.[148] While there are reports of a need for replacement of bioprosthesis during or soon after the pregnancy,[105] pregnancy *per se* did not affect the structural deterioration of biografts[149] compared to non-pregnant biografts.

Although the biografts offer an alternative to pregnant women, the life span is short and a permanent prosthesis needs to be placed. Both warfarin and heparin anticoagulation carry hazards, but whereas warfarin brings a small risk to the fetus, heparin jeopardises the mother whose long-term safety is paramount.[150] Tiede[120] and co-workers recommends warfarin throughout

pregnancy as the preferred method if the patient will accept the risk (especially if the INR can be maintained at a dose of 5 mg or less) with full intravenous heparinisation during the last two weeks of pregnancy until onset of labour. The heparin during labour should be discontinued as briefly as possible. The European Society of Cardiology recommends[151] either [a] the use of heparin until 13th week of pregnancy, then oral anticoagulants to 37 weeks. The therapy is then switched to intravenous heparin until delivery; or [b] oral coumarin use throughout pregnancy (with INR 2.0-2.5) to 37 weeks, then to be switched to intravenous heparin until delivery. *Switching from oral therapy to heparin should occur in hospital.* The patient should make the decision of anticoagulation method with full informed consent. The Committee[152] more recently re-emphasised that the heparin switch should occur in hospital and that "*the decision whether to use heparin during the first trimester or to continue oral anticoagulant treatment throughout should be made after full discussion with the patient and her partner and if she chooses to change to heparin for the first trimester, she should be made aware that heparin is less safe for her with a higher risk of both thrombosis and bleeding and that any risk to the mother jeopardizes the baby.*"

Valvular thrombosis is the most important complication of women with prosthetic valves and requires urgent surgery to avoid death. This may occur even with thromboprophylaxis.[153] Some cases have been reported where cardiac surgery followed caesarean section without major problems. An alternative is the use of thrombolytics. Some case reports are becoming available supporting the use of thrombolytic drugs. The initial case report

using streptokinase reported[154] a uterine hemorrhage 12 hours after initiation of treatment which was followed by an uneventful treatment of a thrombus at 28 weeks gestation.[155] Streptokinase has a short half-life and placental passage is minimal.[156] Successful treatment with plasminogen activator has also been reported in the mid-trimester of pregnancy.[133]

Although valve replacement surgery improves cardiac function in pregnancy, it does not remove the mortality and morbidity risk to the patient.[1] It might not be too outrageous to suggest no further pregnancies with a permanent form of contraception, such as sterilisation even in young women.[157,158]

Progressive heart failure during pregnancy not responding to medical therapy could necessitate open-heart surgery during the pregnancy.[79] While balloon valvotomy offers a relatively safe alternative for management of stenotic lesions,[159] open mitral commisurotomy or valve replacement surgery might be indicated. If possible the surgery should be restricted to the middle trimester to decrease the high pregnancy losses, associated especially with open valvotomy or aortic and mitral valve replacement surgery.[80] High flow, high pressure normothermic perfusion is probably the safest for the fetus.[79] New advances with aortic bypass techniques allowing pulsatile perfusion prevents placental vasoconstriction seen with the traditional techniques.[160]

Caesarean section while on cardiac bypass could be associated with neonatal hypoxia.[161] Valve replacement surgery on bypass during labour or the early puerperium carries a significant risk of uterine hemorrhaging because of anticoagulation medication,[97] although successful operations have been decribed using aprotinin.[162]

1.5 Myocardial disease

Intrinsic abnormalities of the heart muscle during pregnancy, because of different pathophysiology and treatment approaches, can be divided into two main categories: cardiomyopathy and ischemic heart disease.

Cardiomyopathy

Pregnant women, like all other women, can develop cardiomyopathy. In addition, however, a relationship between pregnancy and cardiomyopathy has been recognised since the middle to late 1800's when described by Virchow, Ritchie and Poark,[163,164] although the first significant reports came from Gouley[165] and co-workers. Cardiomyopathy was the term used to describe primary heart muscle disease of unknown etiology.[166,167] This implies that the term cardiomyopathy will disappear when all the etiologies are discovered,[168] although others would embrace the linguistic roots of the word and use it to refer to disorders affecting one or both ventricles in a diffuse manner producing heart failure in at least some patients.[169] The cardiomyopathies are classified as: *congestive* characterised by poor systolic function, *hypertrophic* characterised by impaired diastolic compliance and *obliterative* characterised by obliteration of the ventricle cavities.[170] The association of cardiomyopathy with pregnancy relates to congestive cardiomyopathy,[171] as it shares common anatomical pathology features.[172,173]

Definitions of the cardiomyopathy relating to pregnancy were vague and the terminology confusing. The terms peripartum and postpartum cardiomyopathies were used interchangeably, as well as terms such as toxic

peripartal disease, postpartum heart disease, postpartum miocardosis and Meadows syndrome.[164] Demakis[174] *et al.* reported on the natural course of the disease by using a standard definition. More recently, the definition was modified to include newer diagnostic methods[175] (Table 10).

The prevalence of peripartum cardiomyopathy varies from as many as 1/100 to as few as 1/15000 deliveries.[176,177] Although there is an association with older multigravid women,[178,179] obesity and hypertension,[180,181] none is as strong as the predilection of black women,[182,183,184] although the association with mortality rather reflects socio-economic status.[185] A possible interaction between nutritional factors and genetic events are important in at least some

Table 10 Diagnostic criteria for peripartum cardiomyopathy

Demakis *et al.* (1971)	Hibbard *et al.* (1999)
Development of heart failure in last month of pregnancy or within 5 months of delivery	Heart failure within last month of pregnancy or within 5 months of delivery
Absence of determinable etiology for the cardiac failure	No determinable cause
Absence of demonstrable heart disease prior to the last month of pregnancy	Absence of prior heart disease
	Strict evidence of LV dysfunction: Left ventricular ejection fraction < 45% OR Fractional shortening < 30% and LV end diastolic diameter < 0.27cm/m^2

of the cases. The disease sometimes occurs in a familial pattern.[186,187,188]

Histology ranges from fibrosis and fiber disarray[189,190,191] suggesting terminal disease no different from other forms of cardiomyopathy,[192] to inflammatory processes.[193] Although many factors have been implicated as etiological agents, including toxoplasmosis,[194] viruses,[195,196] drugs[197] and factors associated with dilated cariomyopathy, myocarditis[198] is likely to occur. There is no direct proof that viruses cause myocarditis, but they may trigger an autoimmune reaction of the myocardium. However, no humoral autoimmune

processes could be demonstrated in women with cardiomyopathy.[199] More recently, impaired contractility and dilatation are blamed on nitric oxide and inducible nitric oxide synthetase activity has been demonstrated both in myocarditis and cardiomyopathy.[200]

There do not appear to be any predictive signs or symptoms identifying these patients before development of peripartum cardiomyopathy.[181] The disease is clinically recognised by symptoms and signs of congested heart failure[164, 201] such as coughing, dyspnoea, paroxysmal nocturnal dyspnoea, orthopnoea, crackles in the lower lung lobes, tenderness over the liver and pedal edema often presenting in a non-uniform way.[202]

As the cardiac diagnostic skills and technology improve and our understanding of the basic sciences of the heart function expands, we are able to understand more of this entity and the possible relationship with pregnancy.[188,203,204]

A chest radiograph will reveal a dilated heart with signs of pulmonary congestion, but in modern medicine, an echocardiogram forms part of the diagnostic criteria demonstrating clear evidence of systolic ventricular dysfunction (Table 10). Cardiomyopathy of pregnancy is rarely associated with cerebral damage, including strokes which could end in death.[205]

Unlike the common dilated cardiomyopathy, the hemodynamic pattern of peripartum cardiomyopathy is not homogeneous, varying from high output heart failure to near-normal ventricular function.[206,207] Endomyocardial biopsies suggest myocarditis, at least in some cases.[208] The cause of the

myocarditis is unknown, but it is suggested to be secondary to an abnormal immunologic reaction. Some cases have been described where the offspring also contracted cardiomyopathy.[209]

Management of cardiomyopathy is supportive. Treatment of the failing heart is important in the acute phase. Diuretics is probably the single most effective aspect of therapy.[169,210] Oral[211,212,213] and intravenous digoxin[214] are beneficial as well as vasodilators, especially if more than a moderate dose of diuretics is needed to treat the heart failure.[215,216,217,218] Although ACE-inhibitors are more effective,[219,220,221] and normalises the LVEF,[222] it's use in pregnancy is limited because of fetal effects.[223,224,225,226] In a recent publication Steffensen[227] *et al.* questioned the seriousness of the ACE-inhibitor related problem. Beta-blocking agents were generally regarded as contra-indicated in women with cardiac failure, but long-term use of a low dose of the beta-adrenergic blocker, carvedilol,[228, 229] seems to be beneficial in the long-term[230,231] treatment of women with dilated cardiomyopathy, especially in circumstances where ACE-inhibitors are contraindicated. No publications could be found relating to effects of this drug on pregnancy and the fetus, but theoretically it should be similar to other beta-blocking agents.

In the acute phase of the disease mechanical ventilation and an intra-aortic balloon pump may be required to support cardiac output.[232] Inotropic support with adrenaline and dobutamine[233,234] have been used with success in the acute phase. More recently, successful use of enoximone, a phosphodiesterase inhibitor acting intracellularly, was described in a case where the other receptor-dependent inotropes failed.[235] The use of steroids

has not been proven to be beneficial and may make the failure worse if it is caused by a viral myocarditis.[236] The left ventricular dysfunction can still exist in patients who completely improved clinically.[237]

Traditionally pregnancy has been discouraged and sterilisation advocated to avoid the risk of deterioration of left ventricular function, although the effects of subsequent pregnancies on ventricular function have never been systematically examined.[174] Major teaching institutions in the United States do not have significant numbers of patients with this condition to provide specific recommendations relating to future pregnancies.[238] In as many as 50% of cases the ventricular dysfunction normalises within six months.[239,240] In a small prospective study of only four cases, the poor ventricular function did not re-emerge in subsequent pregnancies.[241]

More recently, Lampert[242] *et al.* described a decreased contractile reserve in women with peripartum cardiomyopathy where the left ventricular size and performance normalised. This could be determined with the dobutamine stress test using dobutamine 5μg/kg/min.

Cardiomyopathy may also appear in patients with other structural heart disease and should be considered as a cause of peripartum cardiac failure even in the presence of other more obvious conditions.[243.244] These cases are particularly at risk if cardiomyopathy coincides with left sided obstructive lesions, pulmonary hypertension, valve prosthesis, cyanosis and cases with poor ventricular function.[93]

The other forms of cardiomyopathy are rare in pregnancy. Hypertrophic cardiomyopathy (HCM) is a genetically transmitted cardiac disease with a broad clinical and morphologic spectrum which is now recognised with increasing frequency.[245] It is clinically recognised because of episodes of syncope or chest pain[246] and is usually well tolerated during pregnancy and delivery,[247,248] although sudden deaths have been described.[249,250] Acute angina may develop requiring beta-blockade.[251] The main difference from dilated cardiomyopathy is that hypertrophic cardiomyopathy causes diastolic dysfunction compared to systolic dysfunction,[252] although a case with systolic dysfunction induced by pregnancy has recently been described.[253] Treatment is as in the non-pregnant population. Surgery is usually not required during pregnancy.

Idiopathic dilated cardiomyopathy may rarely present in early pregnancy.[254] It is almost identical to the peripartum cardiomyopathy except that it may occur earlier than the last month of pregnancy.

Myocardial infarction

Myocardial infarct is a serious but fortunately rare condition in pregnancy. The incidence is estimated to be 1:10000 deliveries[255,256] with a mortality of 20 - 40%.[257] A systematic review of acute myocardial infarction associated with pregnancy was possible from 125 well-documented cases.[258] The highest incidence is in the third trimester of pregnancy in older women. They often present suddenly without prodromal angina.[259] Diagnosis can be problematic

in labour and puerperium as the MB-isoenzyme of creatinine kinase is also released from the postpartum myometrium.[260] Cardiac troponin-T (cTnT) is currently one of the most sensitive and specific markers of myocardial ischemia and remains within physiological range in healthy pregnant women.[261]

Myocardial infarcts can be caused by coronary spasm. It is also associated with the use of intravenous tocolytics,[261] bromocryptine,[262] thrombosis[263,264] and phaeochromocytoma.[265, 266]

The size of the infarct can be reduced by giving beta-blockers and ACE-inhibitors (even with its effect on the fetus) as soon as possible after the diagnosis was made.[258] Some may require support with an intra-aortic balloon pump[267] in combination with surgery[268] as part of an aggressive management protocol. The 20% mortality rate is associated with infarction within two weeks of labour or delivery. In an acute myocardial infarction in labour, early caesarean section may reduce the necrosis and lead to a prompt improvement of congestive heart failure.[269, 270 271] Hankins[256] and co-workers however, reported a maternal mortality of 23% for women delivered by caesarean section compared to 14% for those delivered vaginally. Oxytocic drugs constrict the coronary arteries and should be avoided. [259]

Women who have good left ventricular function and no evidence of critical stenosis should be counselled to continue with the pregnancy. If not, termination of pregnancy should be advised or if non-pregnant, then pregnancy should be avoided.[272] Coronary angioplasty[273] and coronary artery

bypass surgery[274,275] during pregnancy with successful outcome have been described.

Irrespective of the cause of heart failure, those with low left ventricular ejection fractions (LVEF) of less than 40% represent a distinct clinical subgroup characterised by higher in-hospital resource utilisation, need for a greater number of cardiac medications and more re-admissions within 30 days.[276]

1.6 Other acquired disease

Other acquired heart diseases in pregnant women are fortunately rare.

Endocarditis

Endocarditis is a rare but potentially fatal complication in pregnancy which usually involves a heart valve previously injured by rheumatic heart disease,[277] although single case reports were published of patients with normal valves.[278] The outcome of endocarditis is similar in pregnant and non-pregnant women with a mortality of 15-20% with appropriate therapy. If the endocarditis is complicated with moderate to severe congestive heart failure, the mortality rate increases to 50-90%.[279] Early valve replacement is associated with a 75% 5-year survival rate.[280] Surgery is generally indicated at the first sign of hemodynamic deterioration.

Gonococcal endocarditis is also a rare event since the discovery of penicillin.[281] Disseminated gonococcal infection is associated with pregnancy and immunocompromised conditions.[282] The most common presenting symptoms of gonococcal endocarditis are arthritis, fever, generalised rash, nephritis and chest pain.[283] The majority of cases have no history of heart disease antedating the onset of endocarditis.[284] Aortic valve destruction is common with gonococcal infection,[285] often requiring valve replacement.

Because of the rarity of endocarditis post delivery, intrapartum antibiotics are no longer required in the prevention of bacterial endocarditis.[286]

Auto-immune disease

Systemic lupus erythematosus (SLE) is not uncommon in women of child-bearing age. Cardiac involvement in women with SLE could be 18%[287] to 38%.[288] Lupus cardiac manifestations include pericarditis, myocarditis, non-infective endocarditis as well as coronary artery disease.[289] Cardiac involvement should be suspected if there are ST segment or T-wave abnormalities on ECG. High-grade heart block and life-threatening arrhythmias are very uncommon in patients with SLE.[290] Congenital heart block has been described, but is also uncommon.[291]

Pericarditis and pericardial effusions

Pericarditis can be involved in almost every kind of disease.[292] Tuberculous pericarditis requires special consideration because of a tendency to cause

pericardial constriction even with appropriate chemotherapy and disseminated or pulmonary involvement in more than half of the cases.[293] Patients usually present with an acute stabbing chest pain. This is characteristically relieved by leaning forward and ascerbated by lying supine. Dyspnoea is usually present with a moderate to large pericardial effusion.[292] The equalisation of pressures within the pericardial space and cardiac chambers can cause cardiac tamponade.[294]

Pericardial effusions can be secondary to pericarditis and may cause a tamponade effect. Cardiac tamponade is rare in cases with viral pericarditis, but common when due to meningococcal infection.[295] In some cases effusions can develop *de novo* without an apparent etiology. These idiopathic effusions occur late in pregnancy and may be more common than expected. In about 40% of women a silent effusion of variable degree may be found with echocardiography.[296] Symptomatic pericarditis during the second trimester is rare.[297] Relief will be experienced after pericardiocentesis, although in acute forms pericardiostomy with or without pericardectomy may be required. Pericardectomy is usually indicated in cases with constricted pericarditis.[298,299,368]

Human Immunodeficiency virus (HIV) and the heart

With increasing numbers of HIV infected pregnant women, it is important to briefly review the effect of the human immunodeficiency virus on the heart. The association with pericardial effusion is well known and has a prevalence

of 5-10% in the United States.[300] Although infective etiology can be proved in some, 45-63% is idiopathic and probably relates to HIV infection. The development of pericardial effusion indicates a poor prognosis.[301] Echocardiographic evaluation should be included in symptomatic HIV infected patients.[302]

Dilated cardiomyopathy has also been documented by echocardiographic studies in 11-22% of HIV infected persons.[303] Focal lymphocytic and histiocytic infiltrates and myocardial necrosis can be seen in post-mortem studies.[304] There is also an increased frequency of circulating cardiac specific auto-antibodies in HIV positive women, particularly in those with heart muscle disease. Development of anti-α myocin auto-antibodies may be a marker of left ventricular dysfunction.[305] Drug induced cardiomyopathies due to zidovudine and characterised by mitochondrial abnormalities have been described.[303] Myocardial damage is associated with low CD4 counts, duration of the HIV infection[306] and selenium deficiency.[307] Myocardial damage was also found among cocaine users, even in HIV negative persons.[308]

Cases with myocardial infarction associated with protease inhibitor treatment have also been described.[309]

1.7 Congenital disease

Congenital heart disease reflects those abnormalities a baby is born with. Towards the end of the previous century, with improved diagnostic and treatment regimens, more women with congenital defects reached

reproductive age and there has been an apparent increase in the prevalence of congenital heart disease. Although some valvular lesions originate from birth, the most common congenital abnormalities are the septal defects. In this section we will review the septal defects with or without shunting along with pulmonary hypertension and the Marfan syndrome.

Atrial Septal Defects

Atrial septal defects (ASD) are the most common congenital lesions seen in pregnancy, usually asymptomatic[310,381] and often first diagnosed during pregnancy.[311] The increased volume during pregnancy may cause a left-to-right shunt with a significant burden on the right ventricle leading to congestive heart failure and arrhythmias in some,[87] although the lesion is well tolerated during pregnancy by most. It is characterised by high pulmonary blood flow with normal pulmonary artery pressures. The risk associated with ASD includes emboli from lower limb veins to the systemic circulation, infective endocarditis and rarely pulmonary hypertension.[312] It is suggested that fluid overload should be avoided during labour. Additional oxygen, lateral recumbent position, epidural anesthesia and prophylaxis against infective endocarditis should be considered. The risk of congenital heart abnormality in the fetus is 3-11%.[311,312]

Ventricular Septal Defect

Ventricular septal defect (VSD) may occur as a single lesion or be part of other congenital abnormalities (i.e. Tetralogy of Fallot, transposition of the

great vessels, or coarctation of the aorta).[87] Small defects are tolerated well, but the larger lesions are associated with complications. In contrast to the high flow / low pressure state seen in ASD, ventricular septal defects are characterised by a high pressure / high flow state leading to pulmonary hypertension (Eisenmenger syndrome is defined as pulmonary hypertension approximating systemic arterial pressures).[313] Intrapartum considerations for the uncomplicated VSD are similar to that of ASD. The fetal risk for congenital heart disease is 19-23%.[90] Management of VSD complicated by pulmonary hypertension will be discussed under Eisenmenger syndrome.

Patent Ductus Arteriosis

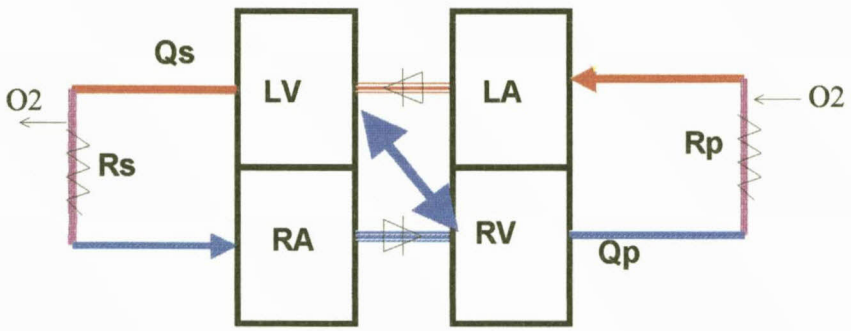
Patent ductus arteriosis (PDA) is usually detected and corrected in early childhood and therefore its occurrence during pregnancy is uncommon.[314] Uncomplicated cases are similar to ASD and uncomplicated VSD, but large lesions also have a high pressure / high flow left-to-right shunt leading to pulmonary hypertension.

Eisenmenger syndrome / Severe pulmonary hypertension

The Eisenmenger syndrome (ES) is defined as pulmonary hypertension secondary to an uncorrected left-to-right shunt secondary to a VSD, ASD or PDA.[311] Other causes of severe pulmonary hypertension include an autosomal familial pulmonary hypertension,[315] connective tissue disorders, portal hypertension,[316] HIV infection,[317,318] hypothyroidism,[319] and drug use,

especially 5-hydroxytryptamine inhibitors[320] and appetite suppressants.[321] There has been no improvement in the mortality of this syndrome over the past 50 years and even in the 1990's the overall mortality was still 40% in the

Figure 3 Right-to-left shunting in Eisenmenger syndrome



United Kingdom.[322] Pregnancy mortality rates of between 26%[323] and 30%[330] have been reported. Most patients die in the puerperium because of a falling PaO_2 with an associated decrease in cardiac output.[324] In a large VSD blood is freely mixed in the right and left ventricles. The ratio of blood flow in the pulmonary circuit (Qp) and systemic circulation (Qs) is inversely proportional to the pulmonary (Rp) and systemic (Rs) resistance (i.e. $Qp/Qs \propto Rs/Rp$) . Pulmonary blood flow is also proportional to the cardiac output: $Qp \propto CO.Qs.Rs/Rp$. In any situation where the Rs/Rp decreases, there would be a drop in pulmonary blood flow causing a deterioration of the syndrome.

If the patient becomes hypotensive with increasing cyanosis, high doses of oxygen will decrease pulmonary vascular resistance, increase the Qp/Qs and increase peripheral oxygen saturation.[325] Alpha-mimetic drugs such as phenylephrine and nor-adrenaline will increase Rs, resulting in increased

pulmonary blood flow.[326] Dopamine and beta-mimetic drugs given to increase cardiac output will decrease the systemic resistance, and if the systemic resistance decreases more than the increase in cardiac output, the pulmonary blood flow will decrease. The management of deteriorating Eisenmenger therefore depends on giving oxygen, calcium channel blockers[327] and alpha-sympathomimetic amines.[324] More recently, nitric oxide (NO) has been used successfully to lower pulmonary pressures during delivery.[328]

Considering the hemodynamic events associated with pulmonary hypertension, abortion appears to be the only rational option to offer women with Eisenmenger syndrome.[329] Induction of labour should not be offered unless there are good obstetric indications, as it may result in a higher incidence of caesarean section, which is associated with a high mortality rate of 75% compared to a mortality of 35% with vaginal delivery.[330] Mortality is usually due to sudden deaths, thought to be due to sudden changes in the Rs, producing changes in the degree of right-to-left shunting resulting in fatal syncope.[331] In the presence of a right-to-left shunt it is also imperative that no air bubbles inadvertently be infused as it may result in cerebral injury.[332]

Adverse pregnancy outcome is generally associated with a poor maternal functional class and the presence of cyanosis.[333] A multi-disciplinary team approach is essential to improve the outcome.[334]

Tetralogy of Fallot

Tetralogy of Fallot is the complex of VSD, overriding of the aorta, right ventricular hypertrophy and pulmonary stenosis. Most lesions are corrected in infancy and corrected lesions have an excellent pregnancy outcome.[90,311] Uncorrected tetralogy is associated with a high mortality in the mid-twenties and subfertility in the remainder.[335] Poor prognostic factors include right ventricular pressure exceeding 120 mmHg, hematocrit greater than 60% and the presence of repeated syncope attacks.[336] It is also associated with intra-uterine growth retardation and perinatal losses.[337]

Polycythemia should only be corrected if thrombo-embolism or intra-uterine growth retardation is evident.[271] The use of oxygen supplementation, especially during the evening, may be helpful.[338] During delivery, management should be aimed at keeping the blood pressure stable by optimising the pre-load and ensuring adequate pain relief. Diuresis should be reserved for frank pulmonary edema.[311]

Coarctation of the Aorta

Coarctation of the aorta is rare and usually asymptomatic.[339] Diagnosis is usually made in work-up for hypertension. The presence of aortic disease or aneurysms (aortic or cerebral) significantly increases the mortality risk to 15%, in which case therapeutic abortion should be considered. Uncomplicated coarctation probably has a mortality risk of 3-4%.[340]

Marfan syndrome

The Marfan syndrome is an autosomal dominant generalised connective tissue disorder causing mitral valve prolapse and aortic root weakening. This appears to be located on the Marfan gene on chromosome 15.[341] Prognosis is individualised. An aortic root diameter of < 40 mm has a mortality of less than 5%.[342] Aortic valve involvement or aortic dilatation will increase the mortality risk to 50%. Routine use of beta-blocking agents have been suggested to reduce the pulsatile pressure on the aortic wall.[343,344] Aortic dissection is more likely if the valve is biscuspid[345] and pregnancy related increases in the diameter of the aorta[346] suggest that pregnancy is a risk factor for aortic dissection.[347] Currently it is recommended that elective cardiac surgery be considered for aortic root replacement once the aortic root dilatation exceeds 50 mm.[348]

2. *South African literature*

During the past 25 years, there have been only 40 publications referring to pregnancy and cardiac or heart conditions in pregnancy. Some articles just referred to pregnancy as an aspect of their discussion and others discussed pregnancy in more detail (Table 11).

Table 11 Summary of Southern African publications

Author	Year	Type	Relationship to pregnancy	Topic	Comment
Beyers BG[349]	1975	Discussion	Indirect	Air transport	
Divanovic E[350]	1999	Series	Direct	Antenatal care	
Kort HI[351]	1981	Series	Direct	Anticoagulation	
Schoon MG [1]	1997	Series	Direct	Cardiac morbitity	
Rossouw GJ [389]	1993	Series	Direct	Cardiac surgery	
Stevens JE[352]	1997	Discussion	Direct	Cardiology	
Ikeme AC[353]	1976	Review	Indirect	Cardiomegaly	
Reid JV[354]	1970	Discussion	Indirect	Cardiomyopathy	
Seftel HC[355]	1972	Discussion	Indirect	Cardiomyopathy	
Desai D[356]	1995	Series	Direct	Cardiomyopathy	
Bada JL[357]	1973	Series	Indirect	Cardiomyopathy	Non RSA
Reid JV[358]	1973	Series	Indirect	Cardiomyopathy	
Edmunds AWB[359]	1979	Series	Indirect	Cardiomyopathy	Non RSA
O'Donnell D[360]	1983	Case	Direct	Endocarditis	
Dommisse J[361]	1988	Case	Direct	Endocarditis	
Swift PJ[362]	1984	Case	Indirect	Endocarditis	
Bhoola RL[363]	1979	Letter	Direct	Endocarditis	
Rush RW[364]	1983	Series	Direct	Induction of labour	
Van C De Groot HA[365]	1986	Series	Indirect	Maternal mortality	
Chrighton D [375]	1973	Series	Indirect	Maternal mortality	
Van C De Groot HA [377]	1979	Series	Indirect	Maternal mortality	
Melrose EB [376]	1984	Series	Indirect	Maternal mortality	
Spies CA [378]	1995	Series	Indirect	Maternal mortality	
Cooreman BF [379]	1989	Series	Indirect	Maternal mortality	
Rush RW[366]	1982	Review	Direct	Obstetrics	
Dommisse J [367]	1993	Review	Direct	Obstetrics	
Richardson PM[368]	1970	Case	Direct	Pericardectomy	
Rush RW [381]	1979	Series	Direct	Prevalence	
Desai DK[369]	1996	Series	Indirect	Pulmonary edema	
Kallichurum S[370]	1969	Series	Indirect	Thrombosis	
Barnard PM [385]	1969	Case	Direct	Valve prosthesis	
Kanarek KS [383]	1973	Case	Direct	Valve prosthesis	
Diab F [382]	1975	Case	Direct	Valve prosthesis	
Kingston HGG [384]	1977	Case	Direct	Valve prosthesis	
Antunes M De J[371]	1985	Discussion	Indirect	Valve prosthesis	
Mayosi BM[372]	1996	Letter	Direct	Valve prosthesis	
Dalby AJ[373]	1980	Review	Indirect	Valve prosthesis	
Guidozzi F [386]	1984	Series	Direct	Valve prosthesis	
Dommisse J [388]	1996	Series	Direct	Valvotomy	
Commorford PJ [387]	1982	Series	Indirect	Valvotomy	
Desai DK[374]	2000	Series	Direct	Mitral stenosis	

2.1 Overview and prevalence

Most references to the prevalence of heart disease in pregnancy were derived from maternal mortality studies commenting on the importance of heart disease in maternal mortality.[375,376,377,378,379] In the first interim report of the Confidential Enquiries into Maternal Deaths in South Africa,[380] 14 (5%) of all deaths were due to cardiac disease. This indicates no change to the previously reported mortality of 3.5%[375] - 7%.[378] Only two studies attempted to address the prevalence of heart disease in a pregnant population.[1,381] Both of these studies were descriptive studies and hospital based. The study in the Cape Peninsula did include all hospitals in the Peninsula Maternity Services and is probably the best reference to prevalence of heart disease in South Africa to date.[381]

In the Free State Province the prevalence was confined to the specialist referral hospitals in Bloemfontein, although the author did stratify for the Bloemfontein population. Patients with heart disease comprised 0.2% of deliveries in the Bloemfontein academic hospitals. In this study Schoon *et al.*[1] subdivided the cardiac lesions into valvular stenotic lesions, regurgitation lesions, prosthetic heart valves, cardiomyopathy and other lesions. The maternal mortality rates in this study were extremely high (3.5% for the local women with heart disease in pregnancy and 9% for the referred group).

2.2 Valvular lesions

Prosthetic valves

Except for one series, the published literature directly related to this category comprised four incidental case reports and one letter. [353,365,366,367,368,369] The earlier publications referred to successful pregnancy after the insertion of prosthetic valves[382,383] or complications of valve prostheses[384] including the use of anticoagulants.[385]

In a descriptive study of pregnancy outcome in women with prosthetic valves, Guidozzi[386] subdivided the 33 cases into those with good maternal and fetal outcome, fetal wastage and maternal complications. There were two maternal deaths (6%) including one of the six patients that required re-operation during the pregnancy. The other death occurred in the postpartum period due to valve thrombosis after an uncomplicated pregnancy.

These cases emphasise that patients with cardiac valves can withstand the hemodynamic changes of pregnancy[386] but highlight the problems associated with anticoagulation therapy.[372]

The adverse effects of coumarin were highlighted in a retrospective analysis of pregnancy outcome demonstrating a direct fetal loss of 7% associated with warfarin.[351] The practice of withholding warfarin in the first trimester of pregnancy and for two to three weeks before delivery was supported. Although only an indirect reference to pregnancy, the post-mortem study of Kallichurum[370] highlighted an association of venous thrombosis (in 50-65% of post-mortems) with cardiac abnormalities or cardiac failure.

There were also two publications discussing prosthetic valves in general and they only referred to pregnancy indirectly. Dalby[373] and co-authors discussed the working mechanisms of the different valves and mentioned in a paragraph that women should be hospitalised during the first trimester of pregnancy for intravenous heparin as well as two weeks prior to delivery. Oral anticoagulants were proposed for the rest of the pregnancy. Antunes[371] discussed the choice of prostheses in young women and suggested bioprosthesis in women of child-bearing age. He highlighted failure of tissue valves of 11% per patient year with a mortality of 28.7%. These results demonstrated that valve substitution often replaced one disease with another. Although he did not elaborate in detail on the technique or outcome of valvuloplasty, he proposed it as an alternative method used at Baragwanath hospital in Johannesburg since early 1981.

Other valve lesions / valvular surgery

Commerford[387] and co-workers analysed all patients who had received a closed valvotomy at Grootte Schuur hospital. In a sub-analysis of 32 patients who had surgery during pregnancy, valve function lasted significantly longer than those who had surgery when not pregnant.

Another clinical trial relating to valvular disease comprised of 11 cases reported from Grootte Schuur hospital in Cape Town who had uncomplicated pregnancies after a closed balloon valvotomy for mitral stenosis that did not

respond to medical therapy.[388] From the same institution seven cases were reported where intra-cardiac surgery was done during pregnancy.[389]

Desai (2000) published their experience with mitral stenosis in King Edward VIII hospital.[374] The strongest predictors for lung edema were the severity of the lesion, late presentation and moderate-to-severe symptoms present before the pregnancy. They found that symptoms persisted in spite of medical treatment in 29% of their 128 cases. Balloon valvuloplasty was highly effective in treating those with moderate to severe stenosis.

There was also one case-report of a pericardectomy performed during pregnancy.[368]

2.3 Myocardial disease

Cardiomyopathy

Cardiomyopathy certainly drew the attention of many authors although almost all publications were only indirectly related to pregnancy. In the early 1970's both Seftel[355] and Reid[354] published on the aetiology of idiopathic cardiomyopathy in the Bantu and specifically referred to the syndrome of postpartal myocardial failure. At that time they believed this syndrome was not a specific entity related to pregnancy, but a variant of some form of cardiomyopathy, especially idioapthic cardiomyopathy.[355,357] This syndrome was postulated to result from the interaction of the physiological stress of pregnancy and the postpartal period with an underlying myocardial disease.[359]

A dietary etiology was suggested, while Reid[358] suggested dietary adjustments as part of the therapeutic strategy.

Although myocardial failure has been reported from all over the world, there is clear evidence of its preponderance in Africans and a high prevalence among underprivileged sociocultural groups.[353,390] Seftel and Susser[391] found the disease to occur predominantly in multiparous older women with an association between adverse outcome and increasing maternal age and parity.

The only noteworthy studies relating to cardiomyopathy and pregnancy came from Durban. Desai[356] and co-workers reported an incidence of peripartum cardiomyopathy in 1:1000 deliveries. They reported on 97 women (all black Africans except one) with peripartum cardiomyopathy. Their mean age and parity were 29 years and three respectively, compared to 25 years and two for the controls. In 48% of cases the women were older than 30 years compared to the 25% of the controls. The cases were subdivided in those with a good outcome (NYHA I and II) and those with a poor outcome. In 53% of those with a good outcome, the women presented early, compared to 30% of those with a bad outcome, but there was no statistical difference in the age or parity between the groups. None of those who presented prior to delivery had a bad outcome.

In 10 of the 14 deaths there were thrombo-embolic events, as well as a further nine cases with adverse outcome. This lead the authors to conclude that anticoagulant therapy should be given until the myocardial function improves.

In the 19 cases with adequate antenatal records, hypertension was recorded in 15 cases and was severe (> 160/110 mm Hg) in nine cases. They concluded that the role of hypertension was probably over-estimated, as the largest proportion of patients with pre-eclampsia did not develop peripartum cardiomyopathy.

In a more recent study Desai[369] *et al.* took the issue of hypertension further by investigating cardiac abnormalities in women who develop pulmonary edema associated with a hypertensive crisis in pregnancy. They compared hypertensive women who developed acute lung edema with hypertensives without lung edema and normotensive controls. Of the 16 cases with lung edema, four (25%) had systolic dysfunction with left ventricular ejection fractions remaining low on follow-up. In 11 (69%) of the patients the diastolic blood pressure recordings were 120 mm Hg or more. In eight women, the pulmonary edema was present on admission while the remainder (seven) had steroid therapy to enhance fetal lung maturity. They noted that in the cases with normal systolic function, diastolic filling abnormalities might have played a significant role in the pathogenesis of pulmonary edema. Cardiomegaly was difficult to assess in pregnancy and with no simple clinical markers echocardiography is extremely useful in quantifying systolic dysfunction.

2.4 Other acquired disease

Infective endocarditis

Although endocaritis in pregnancy is rare, a small number of cases have been described in the South African literature. A case was reported where an aortic and mitral valve replacement were necessary due to infective endocarditis during pregnancy.[360] In a letter, Bhoola and Rajmohamed[363] reported a case that developed infective endocarditis soon after an evacuation following an unsafe abortion. In this case a β-hemolytic streptococcus was cultured and a mitral valve was replaced for intractable cardiac failure. Although not related to pregnancy, Swift[362] reported cases who developed staphylococcal endocarditis after gynecological procedures. In perhaps the most important South African publication related to endocarditis, Dommisse[361] described three cases from Cape Town with infective endocarditis. In all three cases hematuria, which resolved after medical therapy, was present. The hematuria was probably due to circulating immune complexes. Appropriate investigations for infective endocarditis should be included in women with known valvular lesions who develop hematuria.

They also indicated that, because of the rarity of infective endocarditis, antibiotics were not to be routinely administered to all women with valvular lesions at delivery. They would however, give penicillin and amikin during labour to high risk cases - that is those who have prolonged labour, ruptured membranes for > 12 hours, traumatic vaginal deliveries, manual removal of placenta, caesarean section and patients with prosthetic heart valves.[361]

2.5 Other publications

Obstetric management

Two publications reviewed the management of heart disease in pregnancy. Rush[366] and co-workers highlighted the risk of anticoagulant use in pregnancy, the dangers of ergot containing preparations and the consequences of infective endocarditis. Dommisse also emphasised the importance of pre-pregnancy evaluation and counselling.[367,392] Both authors emphasised the importance of assessing the functional status, making an appropriate diagnosis, prevention and management of obstetric complications which increase the workload of the heart (such as anaemia, infection, hypertension) as well as the importance of tachycardia. Although both agreed that caesarean section should be avoided because of anaesthetic risk, hemorrhage and infection, Dommisse[367] advised that induction of labour should be avoided. However, Rush[364] *et al.* published a series of 37 women with heart disease who were induced using prostaglandin-E_2 tablets *per vagina*. Thirty-one women went into labour and delivered within 24 hours. None developed prostaglandin side effects or any deterioration of their cardiac condition. They concluded that natural prostaglandin E_2 is a simple and safe method of achieving elective delivery. Both publications concluded that contraceptive advice is important and that progesterones, either parental or oral preparations, are acceptable. Where Rush[366] and co-workers advised against the use of combined pills in the early eighties, Dommisse in the mid-nineties reported that low dose combined pills are acceptable.[367]

Divanovic and Buchmann[350] challenged the routine use of heart and lung auscultation as part of the complete physical examination in pregnancy. They reviewed the records of 3191 mothers. Twenty-two mothers with pre-existing

heart disease were recorded by history taken at the first visit. A further six cases, referred by midwives for possible heart disease because of clinical findings, were asymptomatic. Aortic disease was confirmed in one case. They concluded that almost all cardio-respiratory disease is detected at antenatal history taking and that the physical examination plays an almost insignificant role.

Transport

In an article on transportation by air,[349] it is advised that pregnant women should be transported with their backs to the pilot to diminish the tension of the safety belt on the pregnant uterus. Severe valvular stenosis, diminished cardiac reserve, cyanosis, congestive heart failure and shock could be aggravated by air transport.

Morbidity and mortality

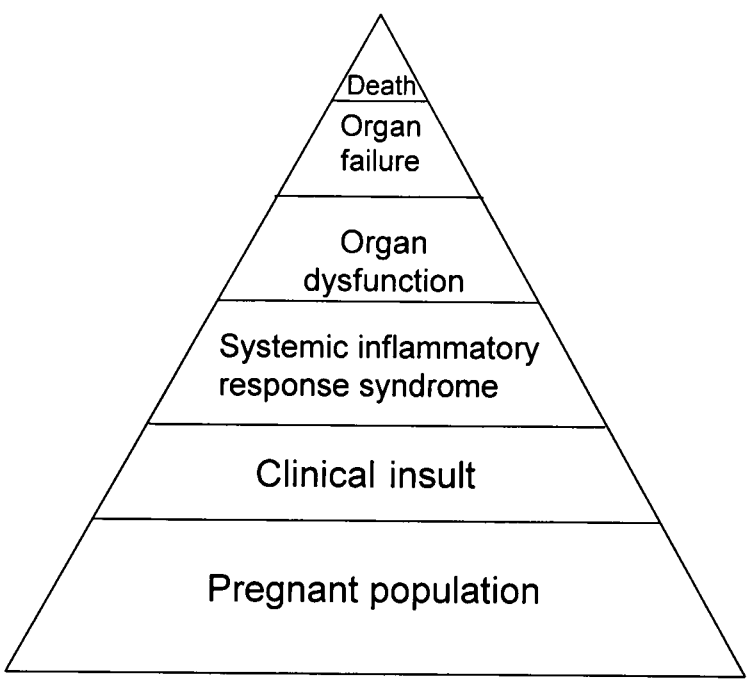
Morbidity and mortality, although important, are often only addressed in a subsection of publications dealing with other aspects of heart disease. Only one article dealt with morbidity and mortality as the main theme. [1]

In this publication, Schoon[1] and co-workers tried to give an overview of the disease profile prevalent in their pregnant population. Rheumatic related valvular disease, mechanical valve prostheses and cardiomyopathy were the important contributors to heart disease in the pregnant women. The weakness of this descriptive study was that it only included patients from the academic referral hospitals, creating somewhat of a bias. Unfortunately the definition of

morbidity was vague. In their study the overall morbidity was 70% with a 9% maternal mortality. As in other studies, cardiomyopathy was common and predominantly in black Africans.

One of the difficulties in interpreting some of the data in the literature is the lack of an adequate description of morbidity. Although maternal mortality has been accurately defined before,[393] several definitions exist, but the definitions are not always referred to in articles. Unfortunately the same cannot be said for morbidity. To date no standardised definition exists for acute maternal morbidity. The best attempt to define morbidity was the "near-miss" concept introduced by Mantel[394] and co-workers with a definition of severe acute morbidity. This concept was introduced as a possible method to evaluate

Figure 4 Disease cascade in pregnancy[394]



causes of maternal deaths. This is probably a valuable definition of serious morbidity as it reflects cases with either organ dysfunction or organ failure which could lead to death without appropriate intervention. As this definition reflects the upper portion of the disease cascade (Figure 4), it would be an appropriate choice whereby to evaluate cardiac disease, as this would reflect the cases with clinical significance.

B Research

1. Objectives

Aim 1.

To accurately document all deaths and acute severe morbidity relating to heart disease in pregnant women in the Free State Province (complicated cardiac disease).

Aim 2.

To accurately describe the demographic profile of women with complicated cardiac disease.

Aim 3.

To document the quality of care and avoidable factors associated with the women with complicated cardiac disease.

Aim 4.

To describe the type of disease in patients with complicated cardiac disease.

Aim 5

To compare the impact of complicated cardiac disease with uncomplicated cardiac disease on health care in terms of human resources, hospitalisation time and intensive care admissions.

2. Methodology

2.1 Definitions

A serious attempt was made to standardise terminology, so it would be appropriate to start with some definitions. The definition of cardiac disease was problematic to apply in some cases of maternal death, as a specific diagnosis of heart disease or lesion had not been made, while the history was highly suggestive of heart disease.

Maternal death: Any death during pregnancy of any duration or within 42 days of termination of a pregnancy.[393]

"Near-miss": Acute severe morbidity during pregnancy of any duration or within 42 days of termination of pregnancy (Table 12).

Cardiac disease: Women with a confirmed abnormality of the heart.

Complicated cardiac disease: All maternal deaths and "near-miss" in women with heart disease.

Index population: The pregnant population resident in the geographical area of Health Regions A and B. (See map of Free State Province on page 74)

Index sample: Pregnant women with cardiac disease resident in Health Regions A and B known to the Public Health sector.

Referred sample: Pregnant women with cardiac disease resident outside Health Regions A and B but who were referred for management at the specialist hospitals in Region A and B.

Table 12 Clinical criteria for "near-miss"

Organ system based	
1. Cardiac dysfunction	Pulmonary edema -clinical diagnosis requiring furosemide or intubation
	Cardiac arrest
2. Vascular dysfunction	Hypovolaemia requiring 5 or more units of whole blood or packed cells
3. Immunologic dysfunction	Intensive care admission for sepsis
	Emergency hysterectomy for sepsis
4. Respiratory dysfunction	Intubation/ventilation > 60 min after anaesthesia (for any reason)
	Oxygen saturation on pulse oximetry < 90% lasting > 60 min
	$PaO_2/FiO_2 < 3$
5. Renal dysfunction	Oliguria, (< 400 ml/24 hrs not responding to fluid challenges or attempts to induce diuresis with furosemide or dopamine)
	Acute deterioration of urea to > 15 mmol or creatinine > 400 mmol
6. Liver dysfunction	Jaundice in association with proteinuric hypertension
7. Metabolic dysfunction	Diabetic ketoacidosis
	Thyroid crisis
8. Coagulation dysfunction	Acute thrombocytopaenia requiring platelet transfusion
9. Cerebral dysfunction	Coma lasting > 12 hrs
	Sub-arachnoid/intracerebral hemorrhage
	Cerebral infarct
Management based	
1. Intensive care admission	For any reason
2. Emergency hysterectomy	For any reason
3. Anaesthetic accidents	Severe hypotension (associated with spinal or epidural block)
	Failed tracheal intubation

Quality of care:

Grade 1: Optimal care

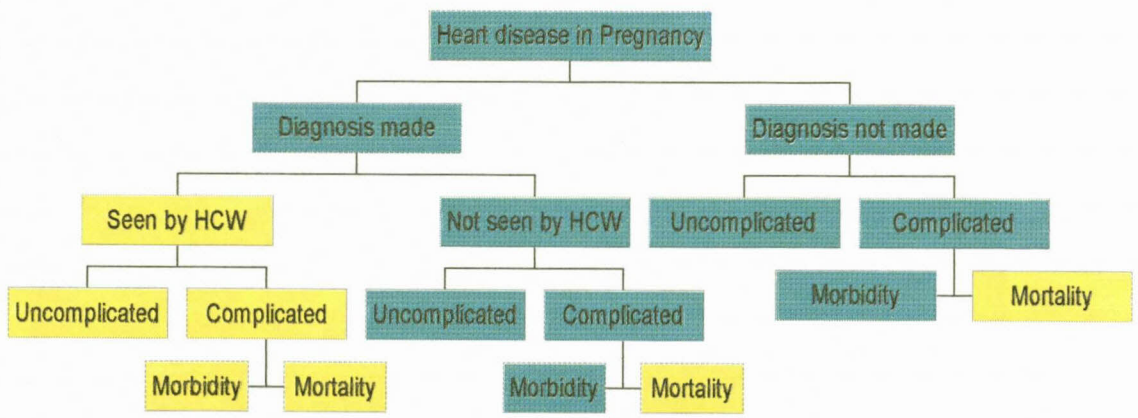
Grade 2: Sub-optimal care, but other management would have made no difference in the outcome.

Grade 3: Sub-optimal care and other management would probably have made a difference in the outcome.

Grade 4: Sub-optimal care and other management would definitely have made a difference in the outcome.

It is also important to recognise that a realistic study of all cardiac cases is, to say the least, impossible. It is not within realistic clinical practice to diagnose all women with cardiac disease in a certain population. Many women with mild

Figure 5 Diagnostic outlay of pregnant women with heart disease



HCW = Health care worker
Yellow-bar areas are the cases likely to be included in a report

heart disease without clinical signs and symptoms will pass unnoticed, although it is reasonable to accept that most women with complicated cardiac disease will have been identified (Figure 5). At least the end-point (deaths) will be identified, although the diagnosis of cardiac disease may have been missed in some cases. It was therefore important for us to collect all possible cases with cardiac disease ending in death as well as all cases with severe acute morbidity as they will have an impact on medical services. We did however, make an attempt to also document all cases with uncomplicated cardiac disease although we recognise that some cases may have been missed.

To ensure the best possible results, all cases admitted to the specialist hospitals of the Province's Health Regions A and B were documented. We selected the Province's Health Regions A and B as the study population because this was also the study population for all cases with acute severe morbidity in the Maternal Health Study. This region included both a secondary care hospital (Pelonomi hospital) and the tertiary care hospital (Universitas hospital). The level of care in these hospitals was mixed, but during the study period most cases with severe heart problems were referred to the Universitas hospital, although the Obstetrical High Care Unit in the province was still located at Pelonomi hospital. To assure that accurate data of all patients with complicated heart disease and all deaths were documented, all the cases managed in a defined geographical population were documented. It would be reasonable to accept that all cases within Health Region A and Region B that became complicated would have been admitted to either of the

specialist hospitals. It would also be reasonable to accept that almost all cases with known or suspected heart disease in this geographical region would have been managed by either one of the institutions. Therefore the pregnant population in these Regions were defined as the index population and the women with heart disease the index sample. There are however, district hospitals (primary health care level) within this region that may not have referred some of the uncomplicated cases. To ensure that all possible cases were included in the study, a professional nurse was employed to document all complicated cases on a daily basis and to build a good network with primary health care workers throughout Region A and B (as well as the other Health Regions). To establish this, we had several meetings with health care managers throughout the province. She also made contact with health care workers, the patients and relatives of the deceased to obtain more information whenever the information was incomplete. The data for all deaths and "near-miss" were collected prospectively. To determine the prevalence of pregnancies with abnormalities of the heart as previously estimated by Schoon[1] and co-workers in Bloemfontein, would require a sample size of several thousand pregnancies requiring good cardiac assessment, a costly exercise with very limited practical application. It was therefore decided that an attempt would be made to document the known uncomplicated cases and compare their profile with those of complicated heart disease. During early 1999, the research assistant also screened all registers in the labour wards, antenatal wards and high care unit to pick up cases with uncomplicated heart disease seen at the specialist hospitals from 1 January 1997 to 31 December

1998. She also screened all the echocardiograms for the corresponding period for ultrasounds done from the maternity section for cases with significant abnormalities.

Cases with complicated cardiac disease were selected from the "near-miss" database for the sample period 1 January 1997 - 31 December 1998. This included all cases from the index population (Region A and Region B) as well as cases referred to the tertiary hospital in the study area from other regions in the province. All "near-miss" and maternal deaths were prospectively collected and the completed files evaluated by the investigator. (Maternal Health Trial, ETOVS 171/96).

All uncomplicated cases for the same period were collected retrospectively from ward registers in the maternity section and the files were reviewed in the same fashion.

The complete records of all cases with cardiac disease in the sample period were reviewed. Data was entered on a data collection sheet and entered on a Microsoft Access Database designed for collecting the data.

2.2. Data management

The data was stratified for women residing in the Health Regions A and B (index population) and cases living outside the index population's geographical area. The sample of pregnant women with known cardiac disease from the index population was classified as the ***index sample*** and

the sample of pregnant women with known cardiac disease from the referred population living outside the geographical area of Health Regions A and B as the ***referred sample***. In all the cases a sub-stratification was made in terms of maternal outcome (morbidity or death).

The prevalence of pregnancies complicated by heart disease was calculated for Health Regions A and B based on the female population for the region according to the 1996 census.[395]

The mean and median of age, gravidity, parity, and income as well as the percentages of race distribution and educational grade were documented in all cases.

In all cases (where possible) the quality of care was graded. Avoidable factors as related to the disease complications or death were stratified in terms of patient, administrative and medical categories.

The disease profile was classified in terms of congenital or acquired as well as disease type (valvular, prosthetic, cardiomyopathy, dysrhythmia or other).

The impact on health care was evaluated in terms of hospitalisation time, intensive care admissions and expertise required by health care professionals.

All data was entered on a Microsoft Access database and analysed utilising descriptive statistics (percentages, median, mean and standard deviation where appropriate).

3. Results

3.1 Population distribution

During the study period there were 67 women with heart disease managed at the referral hospitals or reported as a maternal death. A total of 42 women had a residential address in Region A and B and was defined as the index sample. The rest were referred from the other health regions in the Free State Province (20 women) and from outside the province (5 women), predominantly from Lesotho. They were defined as the referred sample. Of the women in the index sample, 31 were complicated and 11 were uncomplicated. The referred sample was predominantly complicated (22 women), and 3 uncomplicated cases were referred for opinion. Residential districts for index and referred cases with heart disease are stratified in Appendix 1, Table R1. All documented cases were managed in the specialist hospitals of Region A and B, except for 4 women, defined as complicated cases, who were included because they died elsewhere (Appendix 1, Table R2).

3.2 Age, gravidity, parity and racial distribution

The mean age of the women in the index sample with complicated heart disease was 27.0 years (Standard Deviation [SD] 7.3, median 25 years) and those with uncomplicated heart disease was 28.9 years (SD 5.7, median 31 years). For the referred cases, the mean age was 32.7 years (SD 8.6, median 31.5 years) for complicated cases and 28.3 years (SD 8.1, median 32 years) for uncomplicated cases. The stratification of different age groups is included

in Appendix 1, Table R3 and age stratification for the various disease categories in Appendix 1, Table R25.

The median gravidity and parity for the index sample with complicated heart disease were 2 and 1 compared to the 2 and 2 of the uncomplicated cases. For the referred sample it was 3 and 2.8 and 3 and 2.6 for complicated and uncomplicated cases, respectively (Appendix 1, Table R4 and R5 for stratified analysis). Of the women with complicated heart disease, 10 (32%) of the index sample of pregnant women with known cardiac disease and 7 (32%) of the referred sample were primigravidae and 3 (9%) of the index sample and 7 (32%) of the referred sample had 4 or more pregnancies prior to the current pregnancy. None of the uncomplicated cases were grande multiparas. Gravidity and parity stratified for disease categories are tabulated in Appendix 1, Table R26 and R27.

The race distribution of women with heart disease in this study showed that they were predominantly African. Only 2 women with complicated heart disease in the index sample were of mixed origin. One uncomplicated case in the index sample and 1 complicated referred case were Caucasian of origin (Appendix 1, Table R6).

3.3 Antenatal clinic and risk factors

The mean gestational age of the women at their first antenatal contact was 16.7 weeks (SD 6.4, median 16 weeks) for the complicated women in the index sample compared to 20.9 weeks (SD 7.3, median 19 weeks) for the uncomplicated cases. For the referred sample the means were 20.2 and 16,

respectively (Appendix 1, Table R7). Only 4 women (all in the complicated index sample) were seen in the first trimester.

On average, complicated cases in the index sample were seen 4.3 (SD 2.6, median 4) times at antenatal clinics compared to the 4.9 (SD 2.7, median 4) times in the referred sample. The mean number of clinic visits of women with uncomplicated heart disease in the index sample was 5.3 (SD 3.5, median 5) (Appendix 1, Table R8).

The mean number of specialist visits, however, for complicated cases in the index sample was 0.1 (SD 0.3, median 0) and 1.3 (SD 2.4, median 0) visits in the referred sample. The mean number of specialist visits of women with uncomplicated heart disease in the index sample was 2.6 (SD 2.1, median 2) (Appendix 1, Table R9).

Risk factors extracted from the medical history were detected in only 6 (19.4%) of the index sample and 5 (22.7%) of the referred sample with complicated cardiac disease and in none of the uncomplicated cases (Appendix 1, Table R10). Hypertension was present in 13 (41.9%) of complicated cases and 5 (45.5%) of the uncomplicated cases in the index sample and 5 (22.7%) of the complicated cases in the referred sample.

Only 3 complicated cases (9.7%) in the index sample and 1 complicated case (4.5%) in the referred sample were anaemic. Three complicated cases (9.7%) in the index sample and 1 complicated case (4.5%) in the referred sample were HIV positive. One of the 3 uncomplicated cases referred for opinion was HIV positive as well.

3.4 Symptoms and signs

The most common symptom or sign that lead to a diagnosis or referral (Appendix 1, Table R11) was dyspnoea, present in 27 (87.1%) of women with complicated heart disease in the index sample and 19 (86.4%) of women with complicated heart disease in the referred sample. It was also present in 4 (36.4%) women with uncomplicated heart disease in the index sample. This was followed by paroxysmal nocturnal dyspnoea (PND) present in 12 (38.7%) women with complicated heart disease in the index sample and 1 (9.1%) woman with uncomplicated heart disease. In the referred sample 11 (50.0%) women with complicated heart disease had PND. Hemoptysis was present in 4 (12.9%) of the index sample and 6 (27.3%) of the referred sample with complicated heart disease. A heart murmur was the diagnostic sign in 2 (6.5%) women with complicated and 5 (45.5%) women with uncomplicated heart disease in the index sample. In the referred sample 4 (18.2%) women with complicated heart disease and 1 (33.3%) woman with uncomplicated heart disease was referred because of a murmur. Only three women (1 uncomplicated and 2 complicated cases) complained of excessive tiredness and 2 women (1 complicated and 1 uncomplicated case) of chest pain. None presented with cyanosis.

The first onset of symptoms predominantly occurred either in the third trimester or in the early (within 10 days) postpartum period (Appendix 1, Table R12). In women with complicated heart disease in the index sample, symptoms started in the second trimester in 3 (9.7%) cases, the third trimester in 11 (35.5%) cases, during labour in 1 (3.2%) case, early

postpartum in 15 (48.4%) cases and late postpartum in 1 (3.2%) of the cases. In the referred sample the onset of symptoms occurred in the second trimester in 1 case (4.5%), the third trimester in 7 (31.8%) cases, during labour in 3 (13.6%) cases, early postpartum period in 10 (45.5%) cases and late postpartum in 1 (4.5%) of the complicated cases. In the uncomplicated cases of the index sample the initial symptom or sign occurred in the first trimester in 1 (9.1%) case, the second trimester in 3 (27.3%) cases and the third trimester in 6 (54.5%) cases. After the third trimester the initial diagnosis was made in only 1 patient (9.1%) (in the late postpartum period).

3.5 Delivery outcome

The mean gestational age at onset of symptoms (or delivery in case of postpartum onset of symptoms) was 33.6 weeks (SD 6.9, median 36 weeks) for women with complicated and 29.6 weeks (SD 6.9, median 32 weeks) for women with uncomplicated heart disease in the index sample. In the referred sample it was 34.3 weeks (SD 5.7, median 36 weeks) and 33.5 weeks (SD 9.2, median 33.5 weeks) respectively for complicated and uncomplicated cases (Appendix 1, Table R17).

In cases where the complication occurred for the first time in the postpartum period, it occurred within the first two weeks in 9 of 11 cases (81.8%) in the index sample and 3 of 9 cases (33.3%) in the referred sample (Appendix 1, Table R18).

The mean gestational age at time of delivery of the fetus (or death if death occurred prior to delivery of the fetus) (Appendix 1, Table R14) was 33.9

weeks (SD 6.6, median 36 weeks) in complicated and 35.6 weeks (SD 6.8, median 38 weeks) in uncomplicated cases of heart disease in the index sample in Region A and B compared to 34.3 weeks (SD 5.6, median 36 weeks) for complicated and 33.5 weeks (SD 9.1, median 33.5 weeks) for uncomplicated referred cases. Accurate gestational ages at time of delivery were unknown in 5 (16.1%) complicated and 3 (27.3%) uncomplicated cases in the index sample, 3 (13.6%) and 1 (33.3%), respectively for the referred sample. The mean birth weight was 2241.3 g (SD 984.7, median 2380 g) and 2349.4 g (SD 1102.1, median 2790 g) for complicated and uncomplicated cases in the index sample and 2286.0 g (SD 1102, median 2220 g) for complicated referred cases. The birth weight was known in only 1 of the 3 uncomplicated referred cases (Appendix 1, Table R13 for stratification of birth weights).

The caesarean section rates for complicated and uncomplicated cases were 48.4% and 27.3% in the index sample and 22.7% and 33.3% in the referred sample. Babies were delivered vaginally without instrumental assistance in 11 (35.5%) complicated and 4 (36.4%) uncomplicated cases in the index sample and 15 (68.2%) complicated and 1 (33.3%) uncomplicated referred cases (see the methods of delivery in Appendix 1, Table R15). Twenty-one women (67.7%) in the index sample with complicated heart disease and 13 women (59.1%) in the complicated referred sample had babies that were alive, which compared well to the respective 8 (72.7%) and 2 (66.7%) for women with uncomplicated heart disease. The perinatal mortality rates for pregnancies with complicated heart disease in the index and referred samples

were 193/1000 and 409/1000 deliveries, respectively. There were no perinatal deaths in pregnancies with uncomplicated heart disease, but the pregnancy outcome was unknown in 3 pregnancies (Appendix 1, Table R16).

3.6 Morbidity and mortality

The severe acute morbidity ("near-miss") in complicated cases was due to cardiac dysfunction in 27 cases (87.1%), circulatory dysfunction in 2 (6.5%), respiratory dysfunction in 1 (3.2%) and 1 home death (3.2%) in the index sample and cardiac dysfunction in 17 cases (77.3%), circulatory dysfunction in 2 (9.1%), renal dysfunction in 1 (4.5%) and 2 home deaths (9.1%) in the referred sample. Three women (9.7%) with complicated heart disease in the index sample died compared to 8 (36.4%) of the women referred with complications (Appendix 1, Table R19). In the index sample 1 death was associated with respiratory dysfunction and the "near-miss" events were unknown in 2, because these deaths occurred outside the specialist institutions. In the referred sample deaths were associated with cardiac dysfunction in 5 cases, circulatory dysfunction in 1 case and the "near-miss" events unknown in 2 (Appendix 1, Table R20).

3.7 Heart lesions

The heart lesion was diagnosed to be valvular in 20 (29.8%) cases, prosthetic valve in 5 (7.5%), myocardial disease in 35 (52.2%), dysrhythmia in 3 (4.5%), pulmonary hypertension in 1 (1.5%) and other lesions in 3 (4.5%) (Appendix 1, Table R23). In the index sample with complications there were 22 (71.0%) with myocardial disease, 6 (19.4%) with valvular lesions and 1 (3.2%) each of

prosthetic valve, dysrhythmia and pulmonary hypertension, respectively. Those in the index sample without complications were valvular lesions in 6 (54.5%), dysrhythmias in 2 (18.2%) and 1 each (9.1%) of valve prosthesis, myocardial disease and other lesions, respectively. The referred complicated sample consisted of 12 (54.6%) women with myocardial disease, 7 (31.8%) with valvular disease, 1 (4.5%) with a valve prosthesis and 2 classified as other. The uncomplicated referred cases were 1 valvular disease and 2 prosthetic valves.

3.8 Causes of dysfunction

Apart from the diseased heart *per se*, the primary factor leading to organ dysfunction in women with cardiac disease included hypertension, anesthesia and hemorrhage (Appendix 1, Table R22). In the index sample with complications, the primary cause for organ dysfunction was cardiac in 23 (74.2%), hypertensive disease in 6 (19.4%), anaesthesia in 1 (3.2%) and obstetric hemorrhage in 1 (3.2%). In the uncomplicated cases it was either cardiac disease 8 (72.7%) or hypertensive disease 3 (27.3%). The referred complicated cases were cardiac disease in 17 (77.3%), hypertension in 2 (9.1%), infection in 2 (9.1%) and an ectopic pregnancy in 1 (4.5%). Of the 3 referred with uncomplicated heart disease, 1 (33.3%) was hypertensive and the other 2 were related to the heart condition.

The primary reasons for referral to the specialist centers, or why the patient was investigated for cardiac disease in the index sample was cardiac failure in 24 (77.4%), known cardiac disease in 4 (13%), dysrhythmia in 1 (3.2%), murmur in 1 (3.2%) and other in 1 (3.2%) in complicated heart disease. In

uncomplicated heart disease it was a murmur in 5 (45.4%), known cardiac disease in 3 (27.3%), dysrhythmias in 2 (18.2%) and 1 case (9.1%) suggestive of congestion. In the referred sample the reason for referral in complicated cases was cardiac failure in 18 (81.8%), known cardiac disease in 2 (9.1%) and a heart murmur in 1 (4.55%). In 1 case the referral was co-incidental for another reason (see stratification in Appendix 1, Table R24).

3.9 Quality of care

It was not possible to grade the quality of care in 11 (16.4%) pregnancies because of lack of detailed information. Sub-optimal care, where other management by health care workers probably or definitely would have made a difference in outcome, was present in 26 (83.9%) of the index sample and 19 (86.3%) of the referred sample with complicated heart disease. In the uncomplicated cases there was only 1 (9.1%) in the index sample and none in the referred sample (Appendix 1, Table R21).

Maternal deaths in the index sample occurred in 2 (8.7%) with myocardial disease, 1 (33.3%) with dysrhythmias and 1 (100%) of cases with pulmonary hypertension. In the referred sample mortality occurred in 1 (12.5%) with valvular disease, 1 (33.3%) with prosthetic valves, 5 (41.7%) with myocardial disease and 1 (33.5%) other lesions (Appendix 1, Table R28).

3.10 Hospitalisation

Of the index sample with valvular disease, 2 (16.7 5) were admitted to the Intensive Care Unit (ICU) with a median stay of 1.5 days compared to 3 (37.5%) in the referred sample with a median stay of 1 day. None of the

women with valvular prosthesis in the index sample was admitted to the ICU, but 1 (33.3%) of the referred cases was admitted for 7 days. In women with myocardial disease, 7 (30.4%) of the index sample was admitted for a median of 6.5 days and 4 (33.3%) of the referred sample was admitted for a median of 2 days. The only case of pulmonary hypertension (in the index sample) was admitted for 2 days (Appendix 1, Table R29 and R30).

The mean and median hospital stay for the various lesions are stratified in Appendix 1, Table R31. The median duration of hospitalisation for complicated valvular lesions were 10 days for the index sample and 9 days for the referred sample. Hospitalisation for the uncomplicated cases were 4.5 and 14 days, respectively. The median hospitalisation for women with complicated valvular prosthesis were 7 days and 22 days for the index and referred samples and those with uncomplicated lesions 5 and 1 day, respectively. Complicated myocardial disease were 9.5 days for the index sample and 11.5 days for the referred sample. In the index sample, complicated dysrhythmias were hospitalised for 12 days compared to 5 days in the uncomplicated cases. The woman with pulmonary hypertension was hospitalised for 8 days.

Symptoms and signs in the different lesions are stratified in Appendix 1, Table R32.

3.11 Echocardiography

The available echocardiographic data are tabled in Appendix 2, (Table RE1 to RE8). Although the data was collected prospectively, the echocardiographic data depended on the institution and the technologist for completeness. In

some cases there were one or more missing values. The means and medians were calculated ignoring the missing values.

The mean and median aortic valve opening diameter for the index sample was 18 mm. The median aortic diameter for the complicated referred cases was also 18 mm, although the 3 uncomplicated cases had a median of 20 mm.

The mean and median mitral valve surface area was 3.4 cm^2 for the complicated and 2.5 cm^2 for the uncomplicated index sample. The median mitral surface area was 3.5 cm^2 for the complicated and 2.6 cm^2 for the uncomplicated referred sample although the mean area for the complicated cases was 2.7 cm^2. The mean and median diameter of the left atrium was 3.9 and 3.8 cm for the complicated index sample and 3.8 and 3.5 cm for the uncomplicated cases. For the complicated referred sample the mean and median values were 4 and in the 3 uncomplicated referred cases the mean and median values were 5.1 and 4.7 cm, respectively. The left ventricular diameter at the end of diastole had a median of 5.7 cm for the complicated index sample and 4.8 cm for the uncomplicated cases. Among the complicated cases there were 13 women (43.3%) with a diameter of more than 5.7 cm compared to none of the uncomplicated cases. The median diameter for the complicated referred sample was 5.5 cm with 6 (37.5%) dilated more than 5.7 cm.

The median left ventricular wall thickness at the end of diastole was 9 mm for both the complicated and uncomplicated index sample and 11 mm and 13 mm respectively for the systolic thickness. The corresponding diastolic values

for the referred sample were 9.6 and 10 mm and for the systolic values 11.8 and 12 mm (Appendix 2, Table RE5 and RE6).

The median left ventricular ejection fraction (expressed as percentage) for the complicated index sample was 45% compared to 62% for the uncomplicated cases and 46% for the referred complicated cases compared to 60% for the uncomplicated cases (Appendix 2, Table RE7).

Significant regurgitation was seen with Doppler at the aortic valve in 3.4% of echocardiograms of the complicated index sample and 25% of the complicated referred sample. Aortic valve regurgitation was not seen in uncomplicated cases with heart disease. Significant regurgitation of the mitral valve was seen in 27.6% of complicated and 18.2% of uncomplicated echocardiograms in the index sample and in 31.1% of complicated and 33.3% of uncomplicated referred cases. Significant regurgitation was also reported in 10.3% of complicated and 18.2% of uncomplicated cases of the index sample and 18.3% of complicated and 33.3% of uncomplicated referred cases. In only 6.9% of the complicated index sample was regurgitation seen in the area of the pulmonary valve.

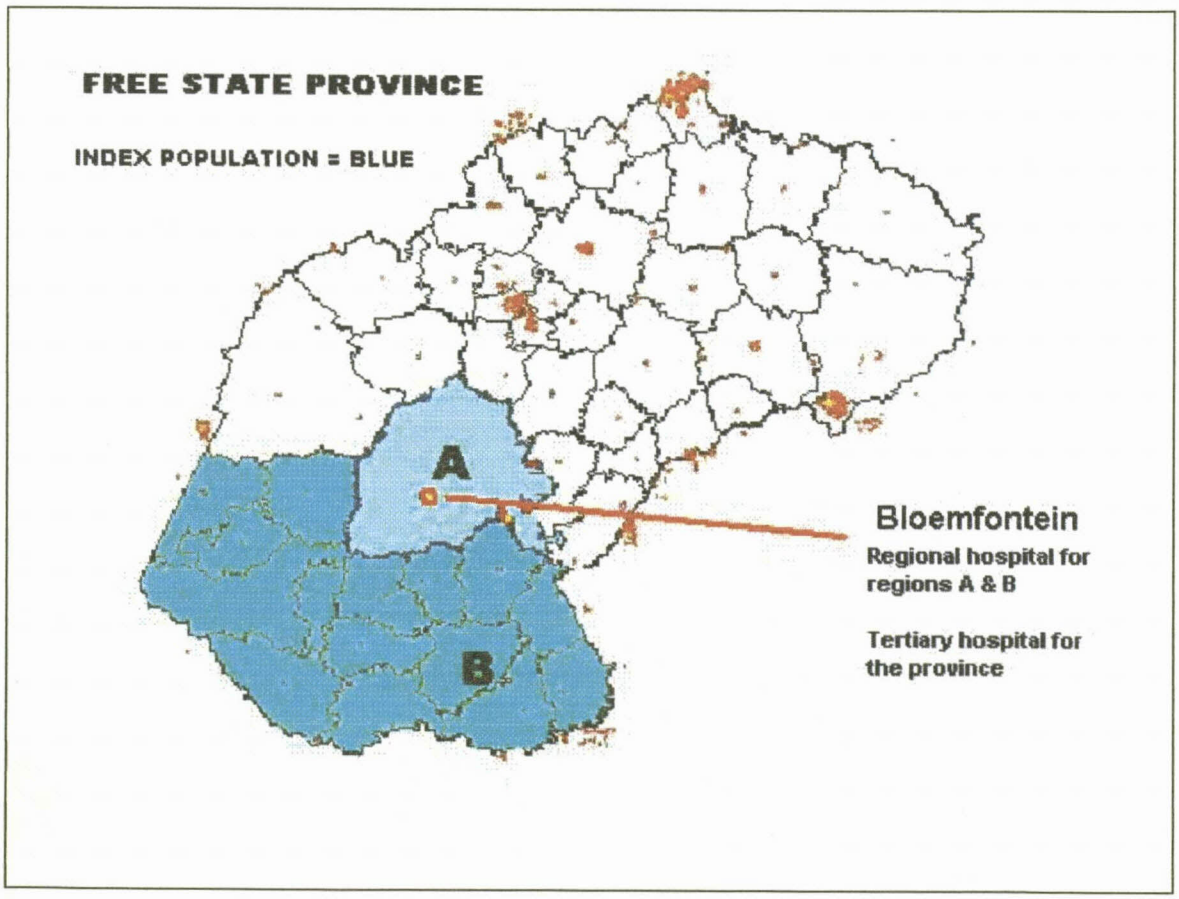
C Discussion and conclusion

1. Comparison of current findings with those reported in the literature

1.1 Demographic data

Incidence

During the study period there were 67 women with complicated heart disease. In the demographic area with adequate population data, defined as the index population (see map of the Free State Province) there were 42 cases, 31 complicated and 11 uncomplicated. The corresponding number of deliveries



in that geographic area was 34100, giving an incidence for heart disease during pregnancy of 0.12% or 1:812 deliveries in the index population. The incidence of complicated cardiac disease was 0.09% (1:1100 deliveries) and uncomplicated cardiac cases was 0.03% (1:3100 deliveries). As only the tertiary referrals from the rest of the province were known, no comment can be made on the incidence in the rest of the province. Since the actual number of deliveries in the index population corresponded well with the estimated number of deliveries calculated from the 1996 population census,[395] the denominator could be regarded as valid. By using the 1996 census figures, the prevalence of complicated cardiac referrals from the rest of the province was 0.07% (1:1500 deliveries), lower than expected if the nature of complicated cardiac disease is considered. It may, however, be that women with serious cardiac problems move nearer to the tertiary institution leading to an abnormal high incidence surrounding the institution. The incidence of 0.12% falls within the estimates previously made ranging from 0.1 to 3.7% of pregnancies.[51,52,53,54] These results are similar as those published from our institution for the Bloemfontein area (0.2%) in the first half of the 1990's.[1]

The lower prevalence in our study probably represents the true nature of a population based prevalence study. Some of the other publications were biased with hospital based statistics and confounded with referrals to tertiary centers.

Disease profile

In our index sample 14 women (33%) suffered from disease related to rheumatic fever. The uncomplicated cases were more prone to rheumatic fever related disease (64%) than the complicated cases (22.5%). The complicated cases did not have an increase in congenital heart disease as seen in Europe,[52] but they did have more myocardial disease (cardiomyopathies) as seen elsewhere in Africa.[66] This is different from data previously reported from our institution,[1] where myocardial disease was reported as 18% compared to the current 54%.

Maternal Age

Although an increased maternal age and parity is cited by some as a risk factor for complicated heart disease, very few studies refer to maternal age. In this study the mean age for the index sample was 27.5 ± 6.9 years (median 25.5) with 7 (16.6%) < 18 or > 35 years. In a cohort of 252 pregnancies with cardiac disease in Canada, the mean age was 29 ± 5 years with 15% being <18 or > 35 years.[69] The median age of the complicated index sample in our current study was 25 years compared to the 31 years of the complicated referred cases. Of the complicated cases 35.5% were 30 years or more and 19.4% less than 20 years, compared to the 54.5% of 30 years or older and no teenagers in the uncomplicated group.

In the National Confidential Enquiry into Maternal Deaths report,[380] 5 of the 7 women who died of cardiac disease were 35 years or older with a median parity of 3.

Gravidity and parity

Data relating to gravidity and parity in women with cardiac disease is as scarce as data relating to age. In the Canadian study[69] the majority (54%) never had a completed pregnancy compared to only 1% with a parity of greater than 5. In our study 14% had never had a viable baby, but there were no grande multiparas with > 5 viable pregnancies (although 1 (2.4%) had 5 previous babies). The mean parity for the index sample was 1.8 ± 0.2 completed pregnancies (with a median of 1.5). This is lower than previously reported from our institution.[1] There was a steady decline in parity in the local population over the past 5 years that can explain this decline in parity.

Racial distribution

In our index sample the racial distribution were African 39 (92.8%), Caucasian 1 (2.3%) and mixed in 2 (4.6%). In the 1996 population census the corresponding proportions for females in the index population were African 81.0%, Caucasian 11.7%, mixed 7.2% and Asian 0.1%.[395] This distribution is disproportionate towards more black Africans and less Caucasians. This could partly be explained by the observation that more black Africans are inclined to develop cardiomyopathy. It is also true that in the Free State Province, black Africans are more likely to be of a very low socio-economic background and that this disproportion may relate to socio-economic status rather than ethnicity.

Mortality

In the current study there were a total of 4 deaths in the index sample. This comprised 9.5% of the women known with heart disease in pregnancy in the index population or 11.7 deaths per 100 000 of all deliveries in Region A and B. Of the referred sample 8 died. This represents 32% of the referred cases or an estimated 8.7/100 000 of all deliveries in the rest of the Free State (1996 census). In the previous publication from our institution the mortality for the local population was 3.7% and for the referred sample 11.8%. This indicates a trend that the mortality relating to heart disease in pregnancy is rising significantly.

Two important differences must be considered: 1.] In the previous study the local population was defined as those with a Bloemfontein address. This was a population group with easy access to medical care since both the specialist hospitals are located in Bloemfontein. The current study included both Regions A and B, so chosen because of the rural nature of the area and the availability of both a regional and tertiary hospital within the area. 2.] A mortality survey was done in the province during the study period and a research assistant built an extensive network with health care workers and community leaders to ensure that all deaths were included in the maternal death notifications. This may have resulted in the inclusion of deaths which were omitted in the previous study. In the current study deaths reported from other centers or home deaths were included under "complicated" cardiac cases. It is somehow disturbing that the death rate of the index sample with the best medical facilities was higher when compared to the rest of the

province. In the Free State Province during the same period, there were 188 maternal deaths (publication in press). The deaths due to cardiac disease were 12 (6.4%) of all the documented maternal deaths. This is lower than the 10.5% reported by the National Enquiry into Maternal Deaths[380] and the 8.7% and 7.2% previously reported for our institution[378] and the Cape Province,[59] but higher than the 3.8% previously reported in Durban.[375]

Death rates of less than 1% for women with heart disease in Europe are significantly less than our 9.5%.[51,54] However, if cardiac deaths are compared to all maternal deaths, the proportion of 5.6% in America[56] is similar to our proportion of deaths, although the 8-10% in Europe[55] and Australia[60,58] is slightly higher.

The main reasons why an increased mortality is experienced includes the following: late diagnosis and referrals; poor compliance; low socio-economic populations and the rural nature of our province.

1.2 Valvular disease

Rheumatic disease

Rheumatic heart disease is regarded as the dominant lesion in developing populations. Almost all valvular lesions in our population were of rheumatic origin. Of all the cardiac cases in this study, 25 (37.3%) were probably due to post rheumatic fever complications. There were 14 (33%) in the index sample and 11 (44%) in the referred sample. In our previous report,[1] 77% were due to rheumatic fever related lesions. This dramatic change in the profile could

have resulted from two important factors: 1.] An aggressive attempt to decrease the number of pregnancies in women with artificial heart valve prostheses because of our previously reported poor maternal outcome. 2.] A greater awareness of cardiomyopathy.

With the morbidity study, all cases with heart failure in pregnancy and the puerperium were reported to the investigating team. This also included cases from the Department of Internal Medicine that may have been omitted in the previous publication. Although there is a trend in European and American literature of a decrease in rheumatic related lesions with an increase in congenital lesions,[52,56,57] our results indicated a decrease of rheumatic related lesions and an increase in cardiomyopathy. This may be a true increase, but it is more likely to be an apparent increase because of previous underreporting of cardiomyopathies in our population.

Valvular lesions

The dominant valvular lesion involved the mitral valve. There were 9 cases with mitral regurgitation (incompetence) (MI). In 2 of these cases the mitral

Table 13 Valvular lesions

	Index sample		Referred sample		Total
	C	U	C	U	
MI	3	0	1	0	4
MI/AI	2	0	0	1	3
MI/MS	1	3	1	0	5
MS	0	1	5	0	6
Prolapse	0	1	0	0	1
TI	0	1	0	0	1

c=complicated u=uncomplicated

incompetence was associated with a significant aortic regurgitation (AI) and in 4 cases with a significant mitral stenosis (MS). In only 1 case the mitral stenosis was not associated with other significant lesions. The others were a mitral valve prolapse diagnosed after investigation for persistent tachycardia in a woman with pre-eclampsia, and 1 case with a significant tricuspid regurgitation.

This distribution of lesions is similar to that previously reported by our institution,[1] but the number of cases with mitral stenosis are more than that previously reported for the United States.[51]

There was 1 woman referred in a moribund condition from a neighbouring country 13 days after onset of heart failure. A clinical diagnosis of deep vein thrombosis with a critical mitral stenosis was made. She died within hours of admission to our institution. All but 1 of the women with a mitral surface area $\leq$ 1 cm^2 were admitted in heart failure. The single case without failure was seen by a specialist and treated prophylacticly with a beta-blocking agent. One of the other cases seen regularly by a specialist during the antenatal period was admitted with tachycardia, but was managed without any beta-blockers by one of the junior doctors. She subsequently developed lung edema in the early puerperium. This highlights the importance of recommendations in the literature to use beta-blockers to control tachycardia in women with mitral stenosis.[82,81]

One woman with a mitral valve area of 2.3 cm^2 combined with a mitral regurgitation was admitted with lung edema at 34 weeks gestation. Her left ventricular ejection fraction (LVEF) was 40% with a dilated left ventricle. After

six months her LVEF was still unchanged (41%) and she was selected for mitral valve replacement. Interpretation of this situation is difficult. It is known that peripartum cardiomyopathy can occur in patients with other lesions and have been described with aortic stenosis.[243,244] In this case heart failure was unlikely due to mitral stenosis because a surface area of > 2 cm^2 is usually not associated with symptomatic congestion.[77] The cause of the tricuspid regurgitation could not be established. Her right heart was within normal limits and no other lesions could be seen on echocardiography. The pregnancy and puerperium was uneventful.

Although mitral valve prolapse is reported as the most common abnormality in the general population,[75,76] it is not a common diagnosis in our population and is probably grossly underreported. The only case included in this study was diagnosed during an investigation for intractable tachycardia in a woman with hypertension. She was on beta-blockers for the hypertension and the pregnancy ended in an early mid-trimester miscarriage. She did not have any cardiac morbidity.

As previously reported, mitral regurgutation lesions (MI) are more prevalent than the stenotic lesions. In the current study only the complicated cases were documented for the index sample. This condition is probably underreported.

It is also interesting to note that the women with mitral stenosis in the index sample were usually uncomplicated when compared to the usually complicated cases referred from elsewhere in the province. This could be explained by the aggressive prophylactic use of beta-blocking agents by specialists in the regional and tertiary hospitals serving the index population.

The referred cases were usually referred in heart failure. From these results we can recommend the routine use of beta-blocking agents in pregnant women with MS. Early assessment and follow-up by a specialist may also play an important role in preventing morbidity.

Prosthetic valves

Unlike the previous report from our institution[1] where almost 20% of women with heart lesions had a previous valve prosthesis with an astronomic mortality of 16%, in the current study only 5 cases with prostheses (7% of all cases with heart disease) were reported. One of them died (20%). Four valves were metalic prostheses in the mitral area and 1 was an aortic homograft. One woman (while on warfarin) developed a massive postoperative hemorrhage after a tubal ligation requiring re-operation. Another patient died three days after a tubal ligation. She was admitted for heparinisation at 38 weeks and a urinary tract infection was confirmed and treated prior to delivery. Progressive shock developed on the second day after surgery which did not respond to supportive treatment. A final diagnosis could not be made because the family refused a request for a post-mortem.

It is important to note that 2 women did not attend any antenatal care at all and 1 only presented to the antenatal clinic at 32 weeks. Although the numbers are small, the mortality in this study group is similar to that previously reported.[1] The decline in numbers could be attributed to an aggressive attempt since the previous report to reduce pregnancies in women with a valve prosthesis.

Anticoagulation therapy is known to be associated with hemorrhage morbidity.[131,132] Although successful pregnancies have been described where anticoagualtion therapy was not taken,[385] this practice is not advisable.[151,120] No ideal prosthesis exists[140] and mechanical prostheses are associated with significant morbidity and mortality. Because of the high maternal mortality (16-20%) and the relatively high but serious morbidity, pregnancy should not be advised in women with a valve prosthesis.

Heart surgery

No patient underwent heart surgery during the pregnancy or puerperium in the study period, but some cases were identified by the cardiologists for surgery after the puerperium. In our previous report of heart disease only one case had a mitral valvotomy[1]. Compared to some other centers in South Africa, [388,389] we are conservative with surgical treatment. This may be because most of the studies describing surgery during pregnancy were involved in a trial investigating a surgical technique and were biased in terms of entry criteria.

All women with heart failure in our population responded well to medical treatment once admitted to hospital. Although open-heart surgery is not contraindicated during pregnancy,[396] it poses a risk to both mother and fetus.[397] Closed balloon valvotomy is regarded as safe during pregnancy[84,159] and offers excellent long-term results.[387] However, this technique is not favoured by our cardiologists and therefore in our setting not an ideal method of treatment.

1.3 Myocardial disease

The incidence of cardiomyopathy in South Africa (Durban)[356] is 1:1000 deliveries. That includes early (up to six weeks postpartum) and late (up to six months postpartum) cardiomyopathies. In our current study only the early onset cardiomyopathies were included and not those who presented to the Department of Internal Medicine after six weeks postpartum. The incidence of the early onset cardiomyopathy in the index population is 1:1400 deliveries. In Durban the comparative calculation was 1:3000 deliveries.[356]

Patients with cardiomyopathy are predominantly African as shown in our study as well as several other studies from all over the world.[182,183,184,353] The mean age of cases in the index sample was 26±7.1 years (median 24 years with 7 (30%) aged 30 years or more) and the median parity was 1.6±0.3 (median 1 with only 1 para 5 or more). In the literature cardiomyopathy is documented as a disease of women older than 30 years[174,177] who are usually multiparous (although some reported it in primiparas in up to 57% of cases[239,398]). In some studies,[239,391,399] increasing age and parity were associated as a risk for adverse outcome, but similar to the study in Durban,[356] we did not find age and parity as predictive of adverse outcome, and our patient profile was somewhat younger with a lower parity.

There were 2 deaths in the index population. Neither died at a specialist center. One was a 27-year-old woman with an anaesthetic related death during caesarean section at term for severe pre-eclampsia. Post-mortem findings were consistent with restrictive cardiomyopathy. The other died within hours of admission to a district hospital with a four day history of severe

dyspnoea, coughing and hemoptysis. She did attend a primary health care clinic at the onset of symptoms soon after delivery, but failed to go to the district hospital until moribund.

Hypertension of varying degree was found in 11 (47.8%) of the index sample with cardiomyopathy. Pre-existing hypertension or pregnancy related hypertension has been implicated in the etiology, [174,176,400] although in some the effect appears to be quite small.[391,401] A similar proportion of hypertension was also found in Durban, which they related to the higher prevalence of hypertension in their obstetric population.[356] We agree with their opinion that the role of hypertension in the pathogenesis is probably overrated since most patients with pre-eclampsia do not develop cardiomyopathy. Hypertension as precipitating factor antenatally has been suggested because 75% of cardiomyopathies presenting in the antenatal period for the first time had hypertension prior to the onset of symptoms. In our index sample there were 5 women with antenatal onset of symptoms and 4 (80%) had pre-eclampsia. This effect could be explained on the basis that if there was an underlying heart with poor contractility, any increase in the peripheral resistance would precipitate acute heart failure leading to diagnosis.

In our study of early onset cardiomyopathy, in 5 (21.7%) patients symptoms started prior to onset of labour, in 5 (21,7%) during labour, in 10 (43.4%) within the first two weeks postpartum and the remainder after two weeks. This is somehow different to the data reported by Desai[356] and co-workers where only 4% presented antenatally. In contrast, O'Connell *et al.* reported antenatal onset in as much as 57%.[239]

As expected, the left ventricular ejection fraction (LVEF) in this group was low with a mean of 42.7±6.5% (median 43% with 11 (48%), 40% or less). The mean left ventricle and left atrium diameter was within the upper normal limit at 5.6±0.68 cm (median 5.7 with 10 (43.5%) dilated more than 5.7 cm) and 3.7±0.37 cm (median 3.7 cm with 7 (30%) greater than 4 cm) respectively. These results are similar to data published from Sao Paulo,[206] but unlike their study, we only used heart failure and subnormal left ventricular ejection fractions as diagnostic criteria. They concluded that peripartum cardiomyopathy can have near normal left ventricular function. This highlights the problems related to diagnosis.[175] The use of the left ventricular ejection fraction makes sense[276] as it measures systolic dysfunction. We can accept that systolic dysfunction plays a central role in the heart failure in cardiomyopathy and measuring the systolic dysfunction can place patients in comparable categories.

Clinical features of congestive heart failure can, however, occur in women with normal left ventricular ejection fractions. Historically, diastolic dysfunction was not researched in the context of heart failure and congestive heart failure was described with normal systolic dysfunction.[402] The pathological processes are different. The main processes are decreased compliance due to increased ventricular wall thickness occurring in hypertension and impaired myocyte relaxation during ischemia and stress (tachycardia leading to a decreased diastolic filling period). This subgroup is a new concept described during the mid 1990's and has not been researched in pregnancy.

1.4 Congenital abnormalities

There was only 1 case with a congenital abnormality. A history was obtained of a previous VSD repair and she was referred for a specialist opinion when pulmonary hypertension was diagnosed. She had a massively enlarged right atrium. She unfortunately arrived in labour at the hospital, delivered vaginally and was discharged by an intern the next morning without notifying either the cardiologist or obstetrician. She was re-admitted six days later to the coronary care unit in cardiogenic shock, but succumbed 48 hours later.

This was probably an Eisenmenger syndrome[311,313] and although she was not treated at the appropriate level of care, the prognosis of this condition is poor[330] and they usually die in the early postpartum period as in this case.[324]

We should prevent this type of sub-optimal care, as in this condition it is especially important to have a multidiciplinary specialist approach to improve outcome.[334]

1.5 Other

There were 2 cases with pericarditis. One patient was critically ill with cardiac failure, premature labour and a human immunodeficience virus infection with a very low CD-4 count regarded as pre-terminal AIDS. A tuberculous pericarditis was confirmed with aspiration of the pericardial effusion because of a tamponade effect. Tuberculosis treatment was initiated and she was returned to her referring hospital in a neighbouring country. The other patient with pericarditis also had confirmed tuberculosis. She was a 16-year old HIV-

negative primigravida who presented with heart failure at her family practitioner. The diagnosis of heart failure was made and he started digoxin. She subsequently returned twice without improvement before he referred her 10 days later in a moribund condition to the nearest secondary hospital where the diagnosis of pericarditis was confirmed, but she subsequently died.

Pericarditis can be involved in almost every kind of disease.[292] Tuberculous pericarditis requires special consideration because of a tendency to cause pericardial constriction even with appropriate chemotherapy and disseminated or pulmonary involvement in more than half of the cases.[293] Patients usually present with an acute stabbing chest pain. It is characteristically relieved by leaning forward and acerbated by lying supine. Dyspnoea is usually present with a moderate to large pericardial effusion.[292]

1.6 Presenting symptoms and signs

In the women with complications, the most common presenting symptom was dyspnoea (87%) followed by paroxysmal nocturnal dyspnoea (PND) in 39% of cases and hemoptysis in 13%. Other symptoms and signs included murmurs

Table 14 Presenting symptoms and signs in index sample

	Complicated		Uncomplicated	
	N	%	N	%
Dyspnoea	27	***87.1***	4	***36.4***
PND	12	***38.7***	1	***9.1***
Hemoptysis	4	***12.9***	0	***0.0***
Murmur	2	***6.5***	5	***45.5***
Palpitations	1	***3.2***	2	***18.2***
Tiredness	0	***0.0***	1	***9.1***
Chest pain	0	***0.0***	1	***9.1***
Cyanosis	0	***0.0***	0	***0.0***

PND = Paroxysmal Nocturnal Dyspnoea

in 6.5% and palpitations in 3%. In the uncomplicated cases the initial sign was a murmur (45%) followed by dyspnoea (36%), palpitations (18%), PND (9%) and chest pain (9%) (Table 14). It is interesting that dyspnoea in our cases was more frequent than PND, as it is suggested that PND should be the most common when congestion develops. This could be explained by late presentation to health care workers. In many circumstances where there was overt dyspnoea the order in which the symptoms developed could not be ascertained from the history. These findings illustrate the late referral pattern in our patients.

Of more importance is the reason why she was referred as either a cardiac case or for further investigations to a specialist center. In the index sample with complications most (77.4%) were referred because of overt cardiac failure or symptoms of pulmonary congestion, followed by known cardiac disease (13%) and murmurs, dysrhythmias and for other reasons in the remainder (3% each). For the uncomplicated population however, the majority were referred because of a murmur heard by the health care worker (45%), followed by prior knowledge of cardiac disease (27%), palpitations (18%) and signs of lung congestion (9%). This is in sharp contrast to some other studies.[50]

Tan and De Swiet[52] suggested that heart disease diagnosed *de novo* during pregnancy is uncommon since most have been diagnosed prior to pregnancy. Although they said that this finding could have a significant impact on nurse delivered maternity care, they failed to make a final recommendation and advised that this finding in West London should be confirmed in a larger group

in other parts of the United Kingdom. Divanovic and Buchmann,[350] on the other hand, recently published their findings of a study in South Africa looking at first diagnosis of cardiorespiratory abnormalities. They concluded that routine clinical examination of the heart is of very little value in perinatal care since all the cases were identified by cardiologists prior to pregnancy. Although this might be true for the more affluent African population in the greater Soweto, our data suggest that the same is not true in the more rural Free State where a low socio-economic population and large distances make the situation different. In our uncomplicated cases almost half were referred during the pregnancy because of abnormal heart murmurs. It is somewhat worrying that so many women with complications were only diagnosed once in heart failure.

2. Evaluation of morbidity in cardiac disease: The "near-miss" concept

In general terms, the quality of maternity care has been monitored by using maternal mortality statistics. Since the maternal mortality was extremely high during the first half of the previous century, maternal mortality provided a good reflection of quality of care. As the quality of medicine improved in the developed countries, mortality rates decreased. The proportion of deaths due to cardiac disease however, did not change.[393] As the mortality rate as end-point decreased, the question arose if the decreasing number of deaths were not replaced by serious morbidity.

One of the major problems with maternal morbidity is that no standard exists for assessing morbidity. It has been suggested that acute admissions to intensive care units could be taken as a method of evaluating quality of care in gynaecological patients. Although this seems to be a logical method, the variables are enormous. The availability of ICU beds is not evenly distributed and the entry criteria for admission vary significantly. Furthermore, the difference between those at private institutions seeking profits and those in state institutions aiming at saving expenditure contributes to inconsistent standards regarding ICU admissions.

Morbidity also varies in it's impact on health and health expenditure. For example, transient fever morbidity is not comparable with a post-operative hemorrhage of 1.5 liters as there is a vast difference in health related morbidity and the potential of death. Patients with the latter condition would probably have died in the early part of the previous century because of lack of treatment modalities - this would be mortality replaced by morbidity - although preventing the hemorrhage would also prevent the morbidity.

Pediatricians have been using the term "near-miss" to describe near-fatal events. To date the best example of an attempt to describe severe acute morbidity was published by Mantel[394] and co-workers. They defined acute severe morbidity as "near-miss" events by describing various organ dysfunction and -failures as endpoints (Table 12).

The "near-miss" concept is new and the only publication relating to it is the preliminary data published by Mantel and co-workers. The "near-miss" Study Group in South Africa assessed the validity of the "near-miss" definitions as

defined by Mantel (unpublished data). In this study we used the proposed criteria to assess the patients and cases were classified as complicated or uncomplicated, based on the presence or absence of severe acute morbidity described as a "near-miss".

Since the definition of "near-miss" includes the definitions of organ dysfunction and organ failure which, if untreated are likely to end in death, this would be a valid method to evaluate serious complications in women with heart disease.

Although various forms of maternal morbidity exist, the "near-miss" concept would most likely be the conditions which would have an impact on health care resources. By monitoring this type of morbidity, one could assess the efficiency of the health care services to prevent serious complications in women with heart disease. The clear definitions would also have allowed reproducibility and comparison of data, which in terms of this thesis is difficult to assess because of the lack of standardised definitions.

The attempt by Siu[69] *et al.* to define functional pathology was remarkable, but he failed to bring this in context with maternal outcome. It was impossible to apply the criteria (Table 7) to our data, except for the left heart obstruction and shunt as our echocardiography data did not include the tricuspid valve surface

Table 15 Primary "near-miss" event

	Index sample	Referred sample
Cardiac	27	17
Circulatory	2	2
Respiratory	1	0
Renal	0	1
Death at home	1	2

area and the systolic pulmonary artery pressures could not be measured. There were also combination lesions, for example both left heart obstruction

and left heart regurgitation, making application of Siu's criteria impossible. This definition also did not allow for myocardial dysfunction. By using the left heart obstruction on echocardiograms, it also did not correlate with complicated heart disease. Therefore, the criteria as defined by Siu[69] *et al.* are unpractical for defining heart disease in pregnancy.

In our study only 10 (32%) women with complicated heart disease (defined as women with "near-miss" events) were admitted to an intensive care unit. Because "near-miss" events are acute morbidity with significant organ failure or dysfunction, this highlights the problem with ICU admissions as criterium. A further 15 cases were admitted to our Obstetric High Care Unit at Pelonomi, since there was no high care unit at Universitas hospital and cases in this hospital were only admitted to the ICU once there were clear respiratory problems requiring ventilatory support.

Not surprising for women with primary heart conditions, the majority (87%) of women in the index sample and 77% of the referred sample had "near-miss" events relating to cardiac dysfunction (Table 15).

[a] Cardiac related "near-miss" events

These were either cardiac arrest or pulmonary edema necessitating either furosemide or intubation. This definition could also be criticised. The clinical diagnosis of pulmonary edema may vary from practitioner to practitioner, although we could accept that dyspnoea with the presence of basal crepitations would be accepted by most as diagnostic. The issue arises when

to begin administering furosemide. Some of the medical schools accept furosemide as the first line of therapy for left heart failure or pulmonary edema. In others, the aggressive use of nitrates such as TNT obviate the need for additional furosemide in many cases. The problem is where to draw the line between heart congestion and failure. Most practitioners would start with furosemide even if there was congestion. Even though this might be a point of difference, one can accept that even if severe congestion does develop, the risk is great for potential life threatening lung edema and that management by a specialist center is appropriate.

Therefore, this definition helps to define the population that needs to be at a specialist center, although prevention of the congestion is actually the priority. In the index sample 1 patient and in the referred sample 5 of the women with a "near-miss" event relating to cardiac dysfunction died. Therefore, although there might be some differences in interpreting the diagnostic criteria of cardiac dysfunction, this definition for morbidity is appropriate in this regard.

[b] Circulatory "near-miss" events

In the index sample there were 2 cases with circulatory dysfunction, and in the referred sample 2 cases of whom 1 died. The circulatory dysfunction in the index sample was caused by shock, 1 due to abruptio placentae (although she later had a cardiac arrest before the diagnosis of cardiomyopathy was confirmed with a echocardiogram) and the other one due to operative

hemorrhage after sterilisation in a woman with a valve prosthesis on anticoagulation therapy.

In the referred sample a woman was referred in shock due to a hemorrhaging extra-uterine pregnancy. She later developed cardiomyopathy with a LVEF of 32%, but was discharged from hospital on cardiac failure treatment. The other one with a prosthetic valve died after she developed shock three days after a sterilisation procedure. Although a post-mortem could not be done because her family did not consent to the procedure, the final diagnosis was considered to be septic shock following an urinary tract infection.

[c] Respiratory dysfunction

The only case presenting with respiratory dysfunction in the index sample died. She was a woman with known HIV infection and was admitted to a district hospital for pneumonia. She was transferred because of deteriorating blood gases. On admission she was intubated, but her respiratory function deteriorated progressively. Echocardiography confirmed cardiomyopathy with a LVEF of 38%, as well as collapse of the right atrium due to a pericardial effusion. She died within hours of admission.

[d] Renal dysfunction

One of the referred cases was classified as a "near-miss" because of oliguria (due to eclampsia) that did not respond to fluid challenges. Later

cardiomyopathy was diagnosed on echocardiography when a persistent tachycardia was investigated.

Some of the complicated patients (with "near-miss" events) presented with more than one life-threatening event (Table 16). In the index sample 13 (42%) had more than one "near-miss" incident and 2 (6.5%) had three "near-miss" incidents. Although only one initial "near-miss" event was due to respiratory dysfunction, 10 of the 13 with more than one "near-miss" events had respiratory dysfunction. This indicates that besides cardiac dysfunction, respiratory dysfunction is important in 32% of the population presenting with complicated heart disease.

No methodology has been published to assess morbidity in pregnant women with cardiac disease in a rational way. We believe that the "near-miss" concept is a rational way to document women with heart disease since it has clear definitions relating to organ dysfunction or failure.

Table 16 Multiple "near-miss" events

	2nd event		3rd event	
	Study population	Referred sample	Study population	Referred sample
Cardiac	3	1	0	3
Respiratory	8	4	2	0
Renal	1	1	0	0
ICU admission	1	0	0	0
Coma	0	0	0	1

3. Cardiomyopathy: a disease entity or common pathway in end stage cardiac disease?

The issue of cardiomyopathy relating to pregnancy has been debated in maternal medicine and cardiac circles since early in the previous century. Literally the term "cardiomyopathy" can be translated as *cardio* = *heart* and *myopathy* = *pathology of muscle.* Therefore, we can accept that cardiomyopathy literally means a sick heart muscle.

In our population cardiomyopathy in the last month of pregnancy and within the first six weeks after delivery (early onset cardiomyopathy) was 1:1500 deliveries. This suggests a high prevalence in the Free State Province.

Currently, cardiomyopathy is the term referring to primary heart disease of unknown origin[166,167] - implying that when all the etiologies are discovered, the term peripartum cardiomyopathy would disappear.

Strict criteria are needed for diagnosis of cardiomyopathy. The suggested criteria by Hibbard[175] and co-authors are most certainly a great improvement compared to previous definitions, since it also includes echocardiographic criteria. Although the ultrasound criteria suggest myocardial dysfunction in a previously normal heart, the occurrence of heart failure within the last month of pregnancy or within five months following pregnancy[170,171,172] may be criticised. Women may have myocardial dysfunction in the absence of heart failure. Heart failure disappears rapidly with supportive treatment, although the left ventricular ejection fraction remains abnormal. We have seen a woman who became pregnant soon after the diagnosis of cardiomyopathy

was made and although her left ventricular dysfunction remained 25% throughout the next pregnancy (on supportive treatment) she did not develop any signs of heart failure.

In theory the physiological changes in pregnancy are of such a nature that if systolic dysfunction is present, it would eventually lead to heart failure.

An identical scenario may develop where a woman develops heart failure prior to "the last month of pregnancy", but meets all other criteria. In this case the diagnosis can be none other than idiopathic "dilated" cardiomyopathy although echocardiographic criteria for a dilated heart may not be found.

In our study there were 35 women with myocardial involvement. In the index sample there were 23 women, of whom 22 had "near-miss" events and 1 in whom pulmonary congestion was diagnosed.

Peripartum cardiomyopathy was diagnosed in 20 patients in the index sample, HIV related in 1, restrictive cardiomyopathy in 1 and secondary to sepsis in 1. In the referred group peripartum cardiomyopathy was diagnosed in 11 and cardiomyopathy secondary to an antiphospholipid syndrome in 1.

The gestational age at time of delivery is tabulated in Table 17. Of the cases in the index sample who developed lung edema or congestion either intrapartum or antenatally, 2 were 36 weeks gestation or more; 2 were 31-32 weeks and 2 were < 30 weeks. Of the women who developed heart failure after delivery, another 5 were less than 36 weeks gestation. If the new criteria of Hibbard[175] and co-workers were to be taken in consideration, 10 women with the diagnosis of cardiomyopathy were not "in the last month of

pregnancy". If the definition only includes those in the last month of pregnancy only when they developed symptoms prior to delivery, then 5 cases would not

Table 17 Relationship between gestational age at delivery and period of onset of heart failure

	Gestational age at delivery	
	Index sample	Referred sample
< 28 weeks	2	2
28-36 w	8	3
> 36 weeks	13	7
	Gestational period at onset of heart failure	
	Index sample	Referred sample
Antenatal	4	2
Intrapartum	2	1
1-7 days pp	5	2
8-14 days pp	6	1
14-21 days pp	2	0
> 21 days	0	3
Unsure pp	4	2

pp=postpartum

have been included in the diagnosis and would probably have been classified as idiopathic (but not dilated) cardiomyopathy. If cardiac failure occurred in pregnancies ending before 37 weeks, but where symptoms only developed after the delivery could be included, the criterium of "the last month of pregnancy" can be criticised unless the authors mean heart failure in the four weeks before the end of the pregnancy irrespective of the gestational age when the pregnancy ended.

The criterium of systolic dysfunction can also be criticised. Our cardiac echocardiography gives the normal ejection fraction as 52-75%. In our index sample 17 women (77%) met the criteria of LVEF $\leq$ 45%, but the remainder were in the borderline subnormal area in spite of "near-miss" events. In only 10 cases (45%) the left ventricle was enlarged and in 7 (33%) the left atrium was dilated. Heart failure has been described in women with normal systolic

dysfunction, but then it was caused by longstanding hypertension with remodelling of the heart.[402] In 1 woman the cardiomyopathy developed after a hysterectomy for sepsis and was probably due to sepsis. In 2 cases hypertension was present, but symptoms developed later on and could not be attributed to the hypertension. There was 1 woman who developed heart failure three days after an abruptio placentae, but in the remainder there was no contributing risk factor.

Although strict criteria are needed for documentation and comparison purposes, gaps exist in practical application. Even the criterium of no previous heart disease can be questioned. Oakley[244] suggested that peripartum cardiomyopathy may occur even in women with congenital abnormalities, and if that be considered true, it may even co-exist with rheumatic heart disease making it extremely difficult to distinguish between diseases.

Systolic dysfunction, defined as a decreased left ventricular ejection fraction, indicates a diseased heart muscle which will end in cardiac failure and this end point remains the same irrespective of etiology. Treatment and support of systolic dysfunction is also similar.[220,222,230,403] Mechanical obstructions seldom cause systolic dysfunction unless there is damage to the underlying muscle.

In the obstetric patient it is therefore important to be able to distinguish between the women developing pulmonary edema due to capillary leak, over-hydration or mechanical obstruction with a normal systolic function and those with heart failure due to a myocardial cause.

The term cardiomyopathy in pregnancy should be reserved for women with systolic dysfunction. In that respect echocardiograms should be an essential part of assessing women with heart failure in pregnancy. Because hypertension can be associated with episodes of acute pulmonary edema in women with pre-eclampsia, they should be investigated if cardiac failure persists or re-occurs.

Cardiomyopathy in pregnant women is probably an end stage disease. The ability of the heart to recover from the insult determines the long-term outcome and should be assessed before a patient contemplates a further pregnancy.

We therefore conclude that with the modern criteria of peripartum cardiomyopathy, the last month of pregnancy is probably not that important. The diagnosis of cardiomyopathy, however, indicates the need for a specific treatment regimen and follow-up.

4. The impact of cardiac disease on the health services in the Free State Province.

The prevalence of cardiac disease in the province is unsure. Known cases have a significant proportion of potential life threatening complications. In our index sample 31 (74%) of the 42 cases diagnosed with cardiac disease had either "near-miss" events or deaths. The majority of these women were living in Region A. It may be that Region A, being home to the tertiary care unit, could be more congested with people with cardiac disease.

Of the 31 women with complicated heart disease in the study area, 12 were admitted to a critical care unit. There were 3 deaths.

Determining the cost of care of the women with heart disease was difficult. To simplify calculations, the cost of care did not include medication costs and was calculated by assigning R450.00 per day for hospitalisation in a low care bed, R1500 in a high care or ICU bed and an additional R250.00 if a cardiac echogram was performed. Assigning cost to death was also difficult. The cost of death was calculated by using loss of income up to the age of 55 based on a probable active economic income of R30 000.00 per annum.

Of the 42 cases in the index sample, 12 were admitted to an ICU for a total of 119 days (mean 9.9 days, median 3 days; range 1-32). The hospital stay and direct cost for the index sample are summarised in Table 18.

Table 18 Direct hospitalisation cost of women in the index sample

	ICU admission	No ICU Admission
n	12	30
Mean hospital stay	18.58 (1-66 days)	8.23 (1-29 days)
Median hospital stay	11 (3 ICU)	7
Mean hospital cost*	R26,462.00	R4,050.00
Median hospital cost*	R 9,700.00	R3,400.00

* costs exclude death-costs in women with heart disease.

Although the direct hospital cost indicated that women admitted to an ICU was more expensive than those not admitted to an ICU, cost of death was not taken in consideration and could reflect cost-effective management. The cost of deaths was added to the direct hospital costs. As medications were not documented in detail, the cost of medicines was excluded in the calculations. Including the above calculations for maternal deaths, the median cost for

women admitted to an ICU was R45 690.00 compared to R4 290.00 for women not admitted to an ICU.

The impact of the cost of heart disease is probably better illustrated in Table 19 highlighting the complication profile. The median cost of uncomplicated heart disease was significantly lower than those with complications. It was

Table 19 Cost of complication profile (including maternal death cost)

	Complicated			Uncomplicated		
	n	Mean	Median	n	Mean	Median
Population based (total)	31	R 89,394	R 6,315	11	R2,640	R2,490
Referred sample (total)	22	R326,433	R17,115	3	R2,640	R1,140
Population based						
Not attending clinics	2	R421,695	R421,695	4	R2,152	R2,265
Sub-optimal care	7	R 58,547	R 6,990	0	-	-
Optimal care	20	R 70,203	R 5,190	6	R3,090	R2,490
Not assessed	2	-	-	1	-	-

also much more expensive to refer a patient with complicated heart disease than to refer a patient with uncomplicated disease for opinion. Non-attendance of antenatal care was costly if complications developed. The median cost in the absence of complications was similar in those who did not attend clinics and those who had optimal care at clinics. This probably illustrates the significant savings which can be obtained by optimal clinic care if complications can be prevented. During the period of this study, myocardial disease was the most expensive category of heart disease. This highlights the significant impact of cardiomyopathy in our population.

The direct hospital costs (excluding calculations for deaths) for the diseases and categories referred to the specialist hospitals are highlighted in Table 20 and Table 21. The hospital costs were significantly more if cases were

referred in cardiac failure than when they were referred for assessment of a murmur.

Table 20 Cost per disease (Index sample)

	Mean	Median
Dysrhythmia	R 5,340	R 2,490
Myocardial disease	R103,067	R 6,315
Valve prosthesis	R 2,940	R 2,940
Valvular disease	R 4,270	R 3,615
Pulmonary hypertension	R367,440	R367,440
Other	R 2,490	R 2,490

No publications could be found to compare the costing. From these results, although only rough estimates and probably grossly underestimated, the following becomes evident:

Table 21 Direct cost of problem recognition

	Mean	**Median**
Cardiac failure	R15,361	R5,190
Known cardiac	R 4,804	R3,390
Dysrhythmia	R 5,040	R2,490
Murmur	R 2,130	R2,040

- Heart disease with life-threatening complications ("near-miss") is three times more expensive than uncomplicated heart disease in the index sample and in those requiring emergency referral to the tertiary institution, eight times more expensive.
- Treatment cost of women who do not attend clinics and who develop complications is almost 200 times more than that of those who do not develop complications. They are also 80 times more expensive to treat than those who attended clinics and then developed complications.

- Pulmonary hypertension, cardiomyopathy and valvular disease are the most expensive categories of heart disease in pregnancy in our population.
- The most expensive group to treat are the patients in whom the diagnosis is made only after she presents with heart failure.

5 Conclusions and recommendations

Mortality

The population based mortality in women with heart disease during pregnancy is 9.5%. Compared to previous figures from our institutions,[1] this represented a rise in the prevalence.

In the index population myocardial disease (cardiomyopathy) and pulmonary hypertension were the diseases resulting in death. Patients referred to the tertiary institution died predominantly because of cardiomyopathy and valvular disease, including valve prosthesis.

The shift towards cardiomyopathy related deaths indicate a change in our profile. Factors contributing to the cardiomyopathy related deaths include late diagnosis and referral. Practitioners need to be made aware of the disease entity and the symptoms and signs indicating possible myocardial disease.

An important difference to our previous report[1] is the decreased number of deaths due to complications of valve prostheses. During the study period only a limited number of women was seen with a prosthetic valve. This change

could be due to an aggressive awareness program launched after the previous publication, especially under cardiothoracic surgeons. Prevention of pregnancy in these women had the effect hoped for. During the study period there was 1 death amongst the few with prosthetic valves, indicating that the condition is still dangerous in our population. A further difference was the decreased number of deaths in women with mitral stenosis. This is probably due to the aggressive approach at the specialist hospitals to prevent tachycardia in these women by giving prophylactic beta-blockade.

The death of the woman with pulmonary hypertension also highlights the importance of this condition in pregnancy. Obstetricians need to be made more aware of this problem.

It is impossible to assign a monetary value to a death. This is always a sad event in young women. It is evident that the mortality of heart disease is lower in women managed routinely at a tertiary referral center. Emergency referrals to the tertiary center are associated with a very high mortality.

Early referral to and assessment by maternal-medicine specialists seem to make a difference in survival. Mechanisms should be found to decentralise the maternal-medicine expertise.

Morbidity

No comparative data exist to evaluate cardiac morbidity. The "near-miss" concept does, however, offers a method to document severe acute morbidity in pregnancy and establishes a standardised method to document morbidity.

This method to document morbidity is probably reliable. There is also a good correlation between the definition of life-threatening events and hospitalisation cost, indicating that it can identify the women with a need for specialist support and a risk of dying during pregnancy and childbirth.

This study also highlighted the difficulties in documenting the prevalence of uncomplicated heart disease. Because the women with "near-miss" events have an impact on the health care providers, they are an important group to identify. The prevalence of complicated heart disease (with "near-miss" events) was 31 in 34 100 deliveries, a rate of 90/100 000 deliveries.

This is probably an important rate, since it could be used as a norm to document cardiac morbidity in a population. Unfortunately, no figures or rates to this effect have been published before. If we can eliminate non-attendance of antenatal clinics and sub-optimal care then we should be able to achieve a rate of 58/100 000 deliveries and with improved treatment techniques a rate of <50/100 000 deliveries could be possible.

Cardiac dysfunction, in particular pulmonary edema, was the most common "near-miss" event. In many circumstances the diagnosis was missed initially, often thought to be a mild bronchitis with treatment only initiated at a late stage of cardiac failure. Awareness of subtle signs and symptoms of cardiac failure or pulmonary edema need to be promoted among health care workers, especially at primary care level. Late referrals to specialist centers are associated with an increased cost in management of patients. In the referred sample, pulmonary edema in women with mitral stenosis was prominent. This could be decreased with more aggressive use of beta-blocking agents in

these women. Late diagnosis and lack of facilities to investigate heart abnormalities are the most important contributing factors. In many cases, the women are referred with heart failure that does not respond to treatment without any attempt to investigate the cause, usually because of a lack of diagnostic skills or means. This highlights the importance of early recognition of symptoms and signs and referral to appropriate specialist centers for assessment. The problem is also that some designated specialist centers do not have specialists or special equipment.

Impact on health care services

Complicated heart disease requires expert management and if not managed correctly, has an increased risk for intensive care support. Delayed diagnosis and referral contribute to the high cost of management in women with heart disease in pregnancy. Unfortunately this condition requires expert opinion for optimal management. Not only are the skills of a cardiologist needed, but also a specialist familiar with the effects of pregnancy on the cardiovascular system. Specialists with this expertise are rare, since most physicians are unfamiliar with the physiological effects of pregnancy on the cardiovascular system and most obstetricians are ignorant as far as heart disease is concerned. As this high level of specialist expertise is uncommon and expensive, the evaluation and management of these women are restricted to tertiary care levels. The general physician is not trained to assess and treat pregnant women with heart disease. To decentralise the experts to regional institutions is unpractical. It may be possible to have an expert team moving to

the rural areas to advise and treat these women. The medical faculty should ensure that newly qualified specialist physicians are proficient in assessing pregnant women as well.

Guidelines for Health Services in the Free State Province

- Prosthetic valve replacement poses a specific risk to pregnant women. Currently the anticoagulation therapy regimen is unsatisfactory and women with prosthetic valves are at an increased risk for either death or severe morbidity. Cardiologists and cardiothoracic surgeons should be advised to insist on permanent forms of contraception prior to valve replacement surgery. If patients do become pregnant, midwives and general practitioners should refer these patients timely for expert advice and follow-up.

- The routine use of beta-blocking agents in women with mitral stenosis significantly reduces the risk of acute pulmonary edema and should be encouraged in women with mitral stenosis.

- The HIV related effects on myocardial disease should not be under-estimated. With the increased number of women with the disease, an increase in heart failure due to cardiomyopathy should be expected in future. Women with unexplained cardiac failure should be screened for the HI virus. An increase in complications due to cardiomyopathy and pulmonary hypertension should be expected in this group of patients. Practitioners in regional hospitals should be advised on how to assess and manage these women.

- The most costly category of women with heart disease are those referred for intensive care treatment. ICU admissions should be reduced if an early assessment can be made by appropriate specialists. Practitioners should be advised and trained to identify the possible cases at risk for early assessment. These should include the following:
    - Murmurs of the heart - especially diastolic murmurs or murmurs associated with congestive symptoms.
    - Tachycardia in any woman with heart murmurs.
    - Disproportionate dyspnoea.
    - Any prosthetic heart valve.
    - Lung edema of unknown cause.
    - Persistent postpartum tachycardia.
    - Known heart disease.

In many institutions the diagnostic means are lacking – doctors should be encouraged to refer women with murmurs or symptoms as soon as possible for proper assessment at an institution with adequate means of evaluating the heart and cardiac function. Regional hospitals with appropriately trained specialists should be equipped with echocardiography equipment.

Both health care professionals and the general population should be informed to consult appropriately trained professionals for pre-pregnancy counselling prior to onset of a pregnancy. Too many cases in our province do not receive any form of advice prior to the pregnancy.

In summary we can conclude that women with heart disease in pregnancy require specialist advice. In most circumstances, adequate assessment and advice prior to a pregnancy can make a huge difference in outcome and may even mean the difference between life and death.

Appendix 1

Table R1 Residential districts

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
A	29	93.5	9	81.8	38					
B	2	6.5	2	18.2	4					
C						4	18.2	2	66.7	4
D						2	9.1	0	0.0	2
E						7	31.8		0.0	7
F						5	22.7		0.0	5
Outside						4	18.2	1	33.3	5
Total	31		11		42	22		3		25

Table R2 District where the event occurred

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
A	31		11		42	18	81.8	3		21
B						0	0.0			0
C						1	4.5			1
D						1	4.5			1
E						1	4.5			1
F						1	4.5			1
Total	31		11		42	22		3		25

Table R3 Maternal Age (years)

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
10- 19	6	19.4	0	0.0	6	2	9.1	1	33.3	3
20-29	14	45.2	5	45.5	19	7	31.8	0	0.0	7
30-39	9	29.0	6	54.5	15	5	22.7	2	66.7	7
40-50	2	6.5	0	0.0	2	6	27.3	0	0.0	6
Unknown	0	0.0	0	0.0	0	2	9.1	0	0.0	2
Mean	27		28.9			32.7		28.3		
Std Dev	7.3		5.7			8.6		8.1		
Median	25		31			31.5		32		

Table R4 Maternal Gravidity

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
1	10	32.3	1	9.1	11	7	31.8	1	33.3	8
2-4	18	58.1	10	90.9	28	6	27.3	2	66.7	8
5+	3	9.7	0	0.0	3	7	31.8	0	0.0	7
Unknown	0	0.0	0	0.0	0	2	9.1	0	0.0	2
Mean	2.4		2.7			3.2		2.6		
Std Dev	1.8		1.1			2.4		1.5		
Median	2		2			3		3		

Table R5 Maternal Parity

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
0	6	19.4	0	0.0	11	1	4.5	0	0.0	8
1	13	41.9	2	18.2	28	5	22.7	1	33.3	8
2-4	11	35.5	9	81.8	3	6	27.3	2	66.7	7
5+	1	3.2	0	0.0	0	7	31.8	0	0.0	2
Unknown	0	0.0	0	0.0		2	9.1	0	0.0	
Mean	1.5		2.6			2.8		2.6		
Std Dev	1.2		1.2			2.3		1.5		
Median	1		2			2		3		

Table R6 Racial distribution

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
African	29	93.5	10	90.9	39	21	95.5	3	100.0	24
Coloured	2	6.5	0	0.0	2	0	0.0	0	0.0	0
White	0	0.0	1	9.1	1	1	4.5	0	0.0	1
Asian	0	0.0	0	0.0	0	0	0.0	0	0.0	0

Table R7 Gestational age at time of first visit

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
< 12	4	12.9	0	0.0	4	0	0.0	0	0.0	0
12-17	10	32.3	5	45.5	15	6	19.4	1	33.3	1
18-23	3	9.7	2	18.2	5	2	6.5	0	0.0	2
24 -29	7	22.6	2	18.2	0	3	9.7	0	0.0	2
30-35	0	0.0	2	18.2	2	0	0.0	0	0.0	0
> 35	0	0.0	0	0.0	0	1	3.2	0	0.0	1
NA/?	7	22.6	0	0.0	7	10	32.3	2	66.7	12
Mean	16.7		20.9			20.2		16		
Std Dev	6.4		7.3			7.8		0		
Median	16		19			17.5		16		

Table R8 Number of Antenatal clinic visits (all levels of care)

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
0	2	6.5	0	0.0	2	5	22.7	1	33.3	6
1	6	19.4	1	9.1	7	2	9.1	0	0.0	3
2	3	9.7	3	27.3	6	1	4.5	1	33.3	2
3	3	9.7	0	0.0	3	0	0.0	0	0.0	0
4-6	12	38.7	3	27.3	15	7	31.8	0	0.0	7
> 6	5	16.1	4	36.4	9	4	18.2	0	0.0	4
Unknown	0	0.0	0	0.0	0	3	13.6	1	33.3	4
Mean	4.3		5.3			4.9		2		
Std Dev	2.6		3.5			2.7		0		
Median	4		5			4		2		

Table R9 Number of Antenatal clinic visits (specialist clinics)

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
0	26	89.7	2	18.2	28	9	40.9	0	0.0	9
1	3	10.3	1	9.1	4	0	0.0	0	0.0	0
2	0	0.0	4	36.4	4	0	0.0	1	33.3	1
3	0	0.0	0	0.0	0	0	0.0	0	0.0	0
4-6	0	0.0	4	36.4	4	2	9.1	0	0.0	2
> 6	0	0.0	0	0.0	0	1	4.5	0	0.0	1
Unknown										
Mean	0.1		2.6			1.3		2		
Std Dev	0.3		2.1			2.4		0		
Median	0		2			0		2		

Table R10 Risk factors present

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
History	6	19.4	0	0.0	6	5	22.7	0	0.0	5
Hypertension	13	41.9	5	45.5	18	5	22.7	1	33.3	6
Anemia	3	9.7	0	0.0	3	1	4.5	0	0.0	1
Previous CS	1	3.2	0	0.0	1	0	0.0	0	0.0	0
HIV Positive	3	9.7	0	0.0	3	1	4.5	1	33.3	2
HIV Unknown	4	12.9	1	9.1	5	4	18.2	1	33.3	5

Table R11 Symptoms / signs leading to diagnosis / referral

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
Tiredness	0	0.0	1	9.1	1	2	9.1	0	0.0	2
Dyspneoa	27	87.1	4	36.4	31	19	86.4	0	0.0	19
PND	12	38.7	1	9.1	13	11	50.0	0	0.0	11
Chest pain	0	0.0	1	9.1	1	1	4.5	0	0.0	1
Palpitations	1	3.2	2	18.2	3	2	9.1	0	0.0	2
Hemoptysis	4	12.9	0	0.0	4	6	27.3	0	0.0	6
Murmur	2	6.5	5	45.5	7	4	18.2	1	33.3	5
Cyanosis	0	0.0	0	0.0	0	0	0.0	0	0.0	0

Table R12 Gestational period at onset of first symptoms

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
Trimester 1	0	0.0	1	9.1	1	0	0.0	0	0.0	0
Trimester 2	3	9.7	3	27.3	6	1	4.5	2	66.7	3
Trimester 3	11	35.5	6	54.5	17	7	31.8	0	0.0	7
Intrapartum	1	3.2	0	0.0	1	3	13.6	0	0.0	3
Early postpartum	15	48.4	0	0.0	15	10	45.5	1	33.3	11
Late postpartum	1	3.2	1	9.1	2	1	4.5	0	0.0	1

Table R13 Birthweight of baby

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
0-499	1	3.2	1	9.1	2	0	0.0	0	0.0	0
500- 999	4	12.9	0	0.0	4	2	9.1	0	0.0	2
1000 – 1499	0	0.0	2	18.2	2	2	9.1	1	33.3	3
1500 – 1999	5	16.1	0	0.0	5	2	9.1	0	0.0	2
2000 – 2499	1	3.2	0	0.0	1	2	9.1	0	0.0	2
2500 – 2999	5	16.1	4	36.4	9	0	0.0	0	0.0	0
3000 – 2499	4	12.9	2	18.2	6	5	22.7	0	0.0	6
3500 – 3999	2	6.5	0	0.0	2	0	0.0	0	0.0	0
4000 – 4499	0	0.0	0	0.0	0	1	4.5	0	0.0	1
Undelivered	1	3.2	0	0.0	1	0	0.0	0	0.0	0
Unknown	8	25.8	2	18.2	10	8	36.4	2	66.7	10
Mean	2241.3		2349.4			2286		1050		
Std Dev	984.7		1102.1			1102		0		
Median	2380		2790			2220		1050		

Table R14 Gestational age at time of delivery (or death in case undelivered)

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
< 12	0	0.0	0	0.0	0	0	0.0	0	0.0	0
12-17	2	6.5	0	0.0	2	0	0.0	0	0.0	0
18-23	0	0.0	1	9.1	1	0	0.0	0	0.0	0
24 -29	3	9.7	0	0.0	3	4	18.2	1	33.3	5
30-35	7	22.6	2	18.2	9	4	18.2	0	0.0	4
> 35	14	45.2	5	45.5	19	11	50.0	1	33.3	12
Unknown	5	16.1	3	27.3	8	3	13.6	1	33.3	4
Mean	33.9		35.6			34.3		33.5		
Std Dev	6.6		6.8			5.6		9.1		
Median	36		38			36		33.5		

Table R15 Delivery method

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
Undelivered	1	3.2	0	0.0	1	0	0.0	0	0.0	0
Miscarriage	3	9.7	1	9.1	4	0	0.0	0	0.0	0
Laparotomy	0	0.0	0	0.0	0	1	4.5	0	0.0	1
N vaginal delivery	11	35.5	4	36.4	15	15	68.2	1	33.3	16
Assisted vaginal	1	3.2	1	9.1	2	1	4.5	0	0.0	1
Caesarean delivery	15	48.4	3	27.3	18	5	22.7	1	33.3	6

Table R16 Delivery method

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
Undelivered	1	3.2	0	0.0	1	0	0.0	0	0.0	0
Early loss	3	9.7	1	9.1	4	0	0.0	0	0.0	0
Perinatal death	5	16.1	0	0.0	5	9	40.9	0	0.0	9
Alive	21	67.7	8	72.7	29	13	59.1	2	66.7	15
Outcome unknown	1	3.2	2	18.2	3	0	0.0	1	33.3	1

Table R17 Gestational age at time of event/first symptoms (or delivery in case of postpartum event)

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
< 12	1	3.2	0	0.0	1	0	0.0	0	0.0	0
12-17	0	0.0	0	0.0	0	0	0.0	0	0.0	0
18-23	2	6.5	2	18.2	4	0	0.0	0	0.0	0
24 -29	3	9.7	1	9.1	4	4	18.2	1	33.3	5
30-35	9	29.0	4	36.4	13	5	22.7	0	0.0	5
> 35	16	51.6	1	9.1	17	12	54.5	1	33.3	13
Unknown	0	0.0	3	27.3	3	1	4.5	1	33.3	2
Mean	33.6		29.6			34.3		33.5		
Std Dev	6.9		6.9			5.7		9.2		
Median	36		32			36		33.5		

Table R18 Day postpartum "near-miss" event occurred (where first event occurred after delivery)

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
0-6	2	18.2				1	11.1			
7-13	7	63.6				2	22.2			
14-20	0	0.0				2	22.2			
21-27	2	18.2				1	11.1			
28-34	0	0.0				1	11.1			
> 34	0	0.0				1	11.1			
Unknown	0					1	11.1			

Table R19 "Near-miss" events / organ dysfunction

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
Cardiac	27	87.1				17	77.3			
Circulatory	2	6.5				2	9.1			
Respiratory	1	3.2				0	0.0			
Renal	0	0.0				1	4.5			
Death at home	1	3.2				2	9.1			
Maternal deaths										
Died	3	9.7				8	36.4			
survived	28	90.3				14	63.6			

Table R20 "near-miss" events in relation to maternal survival

	Index sample		Referred sample	
	Death	Survivor	Death	Survivor
Cardiac dysfunction		26	5	12
Circulatory dysfunction		2	1	1
Respiratory dysfunction	1	0	0	0
Renal dysfunction		0	0	1
Death at home/unknown	2	0	2	0

Table R21 Worst grade quality of care

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
Grade 1	2	6.5	1	9.1	3	2	9.1	1	33.3	3
Grade 2	1	3.2	2	18.2	3	0	0.0	0	0.0	0
Grade 3	10	32.3	1	9.1	11	5	22.7	0	0.0	5
Grade 4	16	51.6	0	0.0	16	14	63.6	0	0.0	14
Not graded	2	6.5	7	63.6	9	0	0.0	2	66.7	2

Table R22 Primary cause of organ dysfunction

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
Cardiac disease	23	74.2	8	72.7	31	17	77.3	2	66.7	19
Anesthesia	1	3.2	0	0.0	1	0	0.0	0	0.0	0
Ectopic pregnancy	0	0.0	0	0.0	0	1	4.5	0	0.0	1
Hemorrhage	1	3.2	0	0.0	1	0	0.0	0	0.0	0
Hypertension	6	19.4	3	27.3	9	2	9.1	1	33.3	3
Infection	0	0.0	0	0.0	0	2	9.1	0	0.0	2
Median										

Table R23 Heart lesions

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
Valvular	6	19.4	6	54.5	12	7	31.8	1	33.3	8
Valve prosthesis	1	3.2	1	9.1	2	1	4.5	2	66.7	3
Myocardial	22	71.0	1	9.1	13	12	54.6	0	0.0	12
Dysrhythmias	1	3.2	2	18.2	3	0	0.0	0	0.0	0
Pulm.hypertension	1	3.2	0	0.0	1	0	0.0	0	0.0	0
Other	0	0.0	1	9.1	1	2	9.1	0	0.0	2
Median										

Table R24 Reason for referral/investigation for heart disease

	Index sample					Referred sample				
	Complicated		Uncomplicated			Complicated		Uncomplicated		
	n	%	n	%	Total	n	%	n	%	Total
Cardiac congestion	24	77.4	1	9.1	25	18	81.8	1	33.3	19
Dysrhythmias	1	3.2	2	18.2	3	0	0.0	0	0.0	0
Known cardiac disease	4	12.9	3	27.3	7	2	9.1	2	66.7	4
Heart murmur	1	3.2	5	45.5	6	1	4.5	1	33.3	2
Other	1	3.2	0	0.0	1	1	4.5	0	0.0	1

Basic data stratified by cardiac disease categories

R25 Maternal Age (years)

	Index sample				Referred sample			
	Complicated		Uncomplicated		Complicated		Uncomplicated	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Valvular	26.8	24.5	30.0	31.5	32.5	30.0	32.0	32.0
Valve prosthesis	25.0	25.0	32.0	32.0	48.0	48.0	26.0	26.5
Myocardial	26.1	24.5	24.0	24.0	32.6	31.0		
Dysrhythmias	33.0	33.0	28.0	28.0				
Pulmonary hypertension	43.0	43.0						
Other			26.0	26.0	26.5	26.5		

R26 Gravida

	Index sample				Referred sample			
	Complicated		Uncomplicated		Complicated		Uncomplicated	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Valvular	3.5	2.0	2.8	2.5	3.2	3.0	4.0	4.0
Valve prosthesis	2.0	2.0	4.0	4.0	7.0	7.0	2.0	2.0
Myocardial	2.1	2.0	4.0	4.0	2.7	2.0		
Dysrhythmias	2.0	2.0	1.5	1.5				
Pulmonary hypertension	3.0	3.0						
Other			2.0	2.0	4.0	4.0		

R27 Para

	Index sample				Referred sample			
	Complicated		Uncomplicated		Complicated		Uncomplicated	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Valvular	1.3	1.0	2.6	2.5	2.8	3.0	4.0	4.0
Valve prosthesis	0.0	0.0	4.0	4.0	7.0	7.0	2.0	2.0
Myocardial	1.6	1.0	4.0	4.0	2.3	2.0		
Dysrhythmias	2.0	2.0	1.5	1.5				
Pulmonary hypertension	3.0	3.0						
Other			2.0	2.0	3.5	3.5		

R28 Maternal deaths

	Index sample				Referred sample			
	Complicated		Uncomplicated		Complicated		Uncomplicated	
	Died	Survived	Died	Survived	Died	Survived	Died	Survived
Valvular	0.0	6.0	0.0	6.0	1.0	6.0		1.0
Valve prosthesis	0.0	1.0	0.0	1.0	1.0	0.0		2.0
Myocardial	2.0	20.0	0.0	1.0	5.0	7.0		
Dysrhythmias	0.0	1.0	0.0	2.0	0.0	0.0		
Pulmonary hypertension	1.0	0.0	0.0	0.0	0.0	0.0		
Other	0.0	0.0	0.0	1.0	1.0	1.0		

R29 Maternal admissions to Intensive Care Unit

	Index sample				Referred sample			
	Complicated		Uncomplicated		Complicated		Uncomplicated	
	Yes	No	Yes	No	Yes	No	Yes	No
Valvular	2.0	4.0	0.0	6.0	3.0	4.0	0.0	1.0
Valve prosthesis	0.0	1.0	0.0	1.0	1.0	0.0	0.0	2.0
Myocardial	7.0	15.0	0.0	1.0	4.0	8.0		
Dysrhythmias	0.0	1.0	0.0	2.0	0.0	0.0		
Pulmonary hypertension	1.0	0.0	0.0	0.0	0.0	0.0		
Other	0.0	0.0	0.0	1.0	0.0	2.0		

R30 Hospital stay (days in Intensive Care Unit)

	Index sample				Referred sample			
	Complicated		Uncomplicated		Complicated		Uncomplicated	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Valvular	1.5	1.5			4.3	1.0		
Valve prosthesis					7.0	7.0		
Myocardial	13.8	6.5			3.3	2.0		
Dysrhythmias	3.0	3.0						
Pulmonary hypertension	2.0	2.0						
Other								

R31 Hospital stay (total days in hospital any ward)

	Index sample				Referred sample			
	Complicated		Uncomplicated		Complicated		Uncomplicated	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Valvular	11.5	10.0	4.5	4.5	18.8	9.0	14.0	14.0
Valve prosthesis	7.0	7.0	5.0	5.0	22.0	22.0	1.0	1.0
Myocardial	14.3	9.5	11.0	11.0	14.3	11.5		
Dysrhythmias	12.0	12.0	5.0	5.0				
Pulmonary hypertension	8.0	8.0						
Other			5.0	5.0	2.0	2.5		

R32 Symptoms and signs

	Dyspnoea		PND		Hemoptysis		Chest pain		Palpitations		Tiredness	
	n	% (of all cases with disease)	n	% (of all cases with disease	n	% (of all cases with disease	n	% (of all cases with disease	n	% (of all cases with disease	n	% (of all cases with disease
Valvular	14	70.0	8	40	4	20.0	1	5.0	2	10.0	1	5.0
Valve prosthesis	1	20.0	0	0	0	0	0	0	0	0	0	0
Myocardial	32	91.4	15	42.9	5	14.3	1	2.9	0	0	2	5.7
Dysrhythmias	0	0	0	0	0	0	0	0	2	66.7	0	0
Pulmonary hypertension	1	100	0	0	0	0	0	0	0	0	0	0
Other	2	66.7	1	33.3	1	33.3	0	0	0	0	0	0

Appendix 2

Echocardiogram results

RE1 Aorta valve opening (mm)				
	Index sample		Referred sample	
	Complicated	Uncomplicated	Complicated	Uncomplicated
< 15	0	0	1	
15-26	28	11	15	2
> 26	0	0	0	1
Mean	18.1	18	17.6	21.6
Std dev	2.1	1.9	2.2	4.7
Median	18	18	18	20

RE2 Mitral valve surface area (cm2)				
	Index sample		Referred sample	
	Complicated	Uncomplicated	Complicated	Uncomplicated
< 15	0	0	3	0
15-26	2	4	3	1
> 26	25	5	10	1
Mean	3.4	2.7	2.7	2.6
Std dev	0.4	0.9	1.3	1.2
Median	3.4	2.7	3.5	2.6

RE3 Left atrium (cm)				
	Index sample		Referred sample	
	Complicated	Uncomplicated	Complicated	Uncomplicated
<1.9	0	0	0	0
1.9-4.0	26	9	13	2
> 4	3	2	3	1
Mean	3.9	3.8	4	5.1
Std dev	0.7	0.9	0.8	1.1
Median	3.8	3.5	4	4.7

RE4 Left ventricle diameter (end diastolic) (cm)				
	Index sample		Referred sample	
	Complicated	Uncomplicated	Complicated	Uncomplicated
< 3.5	1	0	0	0
3.5 -5.7	16	11	10	2
> 5.7	13	0	6	1
Mean	5.5	4.9	5.4	5.5
Std dev	0.8	0.3	0.9	0.7
Median	5.7	4.8	5.5	5.6

RE5 Left ventricle muscle thickness (end diastolic) (mm)				
	Index sample		Referred sample	
	Complicated	Uncomplicated	Complicated	Uncomplicated
<8	3	2	1	1
8-10	20	6	9	1
>10	4	3	3	1
Mean	9.2	9.1	9.6	9
Std dev	1.4	1.8	1.4	2
Median	9	9	10	9

RE6 Left ventricle muscle thickness (end systolic) (mm)				
	Index sample		Referred sample	
	Complicated	Uncomplicated	Complicated	Uncomplicated
<11	9	0	2	0
11-13	18	8	9	2
> 13	2	3	2	1
Mean	11	12.9	11.8	13
Std dev	1.7	1.7	1.9	1
Median	11	13	12	13

RE7 Left ventricle ejection fraction (%)				
	Index sample		Referred sample	
	Complicated	Uncomplicated	Complicated	Uncomplicated
< 52%	20	1	9	0
52-75%	6	10	6	3
> 75%	0	0	0	0
Mean	45.2	62	45.6	59.6
Std dev	10.8	7.5	16.7	4
Median	45	62	46	60

RE8 Doppler regurgitation lesions > grade2 (% of echocardiograms)				
	Index sample		Referred sample	
	Complicated	Uncomplicated	Complicated	Uncomplicated
Aorta valve	3.4	0	25	0
Mitral valve	27.6	18.2	31.1	33.3
Tricuspid valve	10.3	18.2	18.8	33.3
Pulmonary valve	6.9	0	0	0
Aorta and mitral valve	3.4	0	0	0

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Opsomming

Hartsiekte in swangerskap vorm 'n belangrike deel van moederlike sterfes. Daar is egter geen goeie populasiestudies wat die omvang van hartsiekte in swanger vroue beskryf nie. 'n Vorige studie aan hierdie inrigting het 'n poging aangewend om die morbiditeit en mortaliteit van hartsiekte in swangerskap te beskryf. Daar bestaan egter geen goeie riglyne oor hoe om morbiditeit te beskryf nie. Die beste model is in 1999 deur Mantel en medewerkers gepubliseer met 'n beskrywing van akute morbiditeit as orgaandisfunksie of –versaking wat tot sterfte sal lei indien daar geen behandeling toegepas word nie.

Die doel van hierdie studie was om hartsiekte te beskryf in 'n gegewe populasie na aanleiding van hierdie model en 'n poging aan te wend om die impak van die siekte op gesondheidsorg te bepaal.

Vanaf 1 Januarie 1997 tot 31 Desember 1998 is alle beskikbare inligting oor pasiënte wat presenteer met hartsiektes gedokumenteer. 'n Navorsingsassistent het verseker dat alle moontlike gevalle wat in die Vrystaat Provinsie se Gesondheidsstreke A en B behandel was, se volledige hospitaalrekords vir beoordeling beskikbaar was. Die saalregisters en hartsonarverslae in die streekshospitaal en tersiêre hospitaal (Pelonomi en Universitas) is ook nagegaan om te verseker dat alle moontlike gevalle ingesluit is.

Alle gevalle met erge akute morbiditeit volgens die Mantel kriteria is as gekompliseerd geklassifiseer. Die inligting van die pasiënte is ook gestratifiseer as deel van die indekspopulasie indien hul woonagtig was in Streke A of B (die populasie wat spesifiek ondersoek is) of as die verwysde populasie indien hulle

buite Streke A of B woonagtig was en na een van die twee hospitale verwys is. Gedurende die twee jaar is 67 pasiënte met hartsiekte behandel.

In die studiepopulasie was daar 42 gevalle (prevalensie van 0.12% van alle geboortes in Streke A en B) waarvan 31 (74%) gevalle gekompliseerd en 11 (26%) ongekompliseerd was. Rumatiese hartsiekte het in 14 (33%) van die gevalle voorgekom terwyl kardiomiopatie verantwoordelik was vir die meerderheid (23, 54%) van die gevalle. Daar was vier moederlike sterftes (9%) wat 11.7 / 100 000 van die bevallings in Streke A en B uitmaak.

Pasiënte met klepsiekte het hoofsaaklik mitraalklepaantasting gehad. Mitraalinkompetensie was die mees algemene letsel beide alleen of in kombinasie met ander letsels. Pasiënte met mitraalstenose op betablokkers het minder longedeem ontwikkel. Daar was slegs vyf pasiënte wat voorheen 'n klepvervanging gehad het, waarvan een (20%) gesterf het. Hierdie is 'n dramatiese verlaging sedert die vorige studie en waarskynlik te wyte aan 'n aggressiewe poging om swangerskappe in hierdie groep te voorkom.

Soos elders in Afrika was kardiomiopatie die mees algemene afwyking. Die voorkoms was 1:4000 bevallings in Streke A en B. Hipertensie was teenwoordig in 48% van hierdie pasiënte. Daar was slegs een geval met 'n kongenitale hartafwyking en twee wat perikarditis ontwikkel het.

Die groep pasiënte wat volgens die toegepaste model as gekompliseerde hartsiekte gedefinieer is, was duidelik die groep wie se behandeling die meeste gekos het. Hulle het ook aansienlik minder spesialisbesoeke gehad.

Die voorgestelde model van akute morbiditeit is baie nuttig om hartsiekte in swangerskap te evalueer en om die behandeling van pasiënte te monitor.

Spesialisbesoeke verminder die voorkoms van komplikasies en moet aangemoedig word. Pasiënte met hartsiekte wat nie voorgeboortesorg kry nie, kos die staat baie geld en gemeenskappe moet ingelig word oor die voordele van kliniekbywoning.

Vroue met hartsiekte in swangerskap benodig spesialiskundigheid en moet verkieslik reeds voor aanvang van die swangerskap volledig evalueer word en voldoende berading ontvang.

Summary

Cardiac disease in pregnancy is an important component of maternal mortality. No good population based study on the extent of cardiac disease in pregnancy has, as yet, been published. A previous study conducted at this institution aimed to describe the morbidity and mortality of cardiac disease in pregnancy, but no guidelines to define morbidity in these cases were available. In 1999 a model was published by Mantel and co-workers to define acute morbidity as organ dysfunction or failure that will lead to death without treatment.

The aim of this study was to describe cardiac disease in a specific population by utilising this model and to try to determine the impact of the disease on the health system.

From 1 January 1997 to 31 December 1998 all the available information of patients who presented with cardiac disease was documented. A research assistant was responsible to ensure that the completed hospital records of all the patients who were managed in Health Regions A and B of the Free State Province was available for evaluation. Ward registers and cardiac sonar reports in the regional and tertiary care hospitals (Pelonomi and Universitas) were also scrutinised to ensure that al possible cases were included.

All cases with severe acute morbidity according to the Mantel criteria were classified as complicated. The information of the patients was also stratified as either part of the index population if they resided in Regions A or B (the population that was specifically targeted) or as the referred population if they lived in one of the other Regions and were referred to one of the two hospitals. During the 2-year study period 67 patients with cardiac disease were treated.

In the study population there were 42 cases (prevalence of 0.12% of all deliveries in Regions A and B) and 31 (74%) were complicated and 11 (26%) uncomplicated. Rheumatic heart disease occurred in 14 (33%) of the cases whilst the majority (23, 54%) of the cases had cardiomyopathy. Four maternal deaths (9%) occurred which comprised 11.7 / 100 000 deliveries in Regions A and B.

Patients with valvular disease had predominantly mitral valve disease. Mitral regurgitation was the most common lesion, single or in combination with other lesions. Patients with mitral stenosis who were managed with beta-blockers developed less lung oedema. There were only five patients who had prosthetic valves of whom one (20%) died. This dramatic decrease in numbers compared to our previous report is probably due to an aggressive attempt to prevent pregnancies in this group of patients.

As reported in the rest of Africa, cardiomyopathy was the most common lesion. It occurred in 1:4000 deliveries that took place in Regions A and B. Hypertension was present in 48% of these women. Only one case with a congenital abnormality and two cases with pericarditis were reported.

The most expensive group to treat were those cases who were categorised according to the applied model as complicated cardiac disease. They also had significantly less specialist visits compared to the uncomplicated cases.

The proposed model of acute morbidity is useful to evaluate cardiac disease in pregnancy and to monitor progress in the management of these patients. Specialist visits decrease the number of complications and should be encouraged. Management of patients with cardiac disease who did not receive antenatal care is

expensive and communities should be informed of the advantages of antenatal care.

Women with cardiac disease in pregnancy need specialist expertise and should preferably be evaluated and counselled prior to the onset of pregnancy.

Key Words:

Heart disease, Pregnancy, Near-miss, Morbidity, Mortality, Mitral valve, Cardiomyopathy, Valve prosthesis, Pulmonary hypertension, Lung oedema, Cardiac output

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