

# **Studies in pre-existing heart disease and pregnancy**

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## **Abstract**

- Aims:** To study the effect of pre-existing maternal cardiac disease on cardiovascular function during pregnancy, and on obstetric and fetal/neonatal outcomes, and to investigate maternal risk factors for adverse events.
- Methods:** Retrospective case note review.
- Results:** Four hundred and eighty-nine pregnancies in 326 women were studied. Most pregnancies (50%) occurred in women with congenital heart disease. There were 4 maternal deaths, 6 stillbirths and 5 neonatal deaths. Cardiovascular events occurred in 7.4% of pregnancies, while obstetric and perinatal complications occurred in 34% and 30% of pregnancies respectively.
- Conclusions:** Pregnancy in women with pre-existing heart disease continues to be associated with high rates of maternal and neonatal mortality and morbidity. This work highlights the importance of effective pre-pregnancy counselling and meticulous surveillance during pregnancy, delivery and the puerperium by an experienced multidisciplinary team. Additionally there is an urgent need for well-designed randomised-controlled trials to determine best practice.

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## Abbreviations

|          |                                                            |
|----------|------------------------------------------------------------|
| AF:      | atrial fibrillation                                        |
| APH:     | antepartum haemorrhage                                     |
| AR:      | aortic regurgitation                                       |
| AS:      | aortic stenosis                                            |
| ASD:     | atrial septal defect                                       |
| AVNRT:   | atrioventricular nodal re-entry tachycardia                |
| BAV:     | bicuspid aortic valve                                      |
| BPV:     | bioprosthetic valve                                        |
| ccTGA:   | congenitally-corrected transposition of the great arteries |
| cGMP     | cyclic guanosine monophosphate                             |
| CARPREG: | CARdiac disease in PREGnancy                               |
| CMACE:   | Centre for Maternal and Child Enquiries                    |
| CMR:     | cardiac magnetic resonance                                 |
| COA:     | coarctation of the aorta                                   |
| DCM:     | dilated cardiomyopathy                                     |
| ESC:     | European Society of Cardiology                             |
| FGR:     | fetal growth restriction                                   |
| HCM:     | hypertrophic cardiomyopathy                                |
| ICD:     | implantable cardioverter-defibrillator                     |
| INR:     | international normalized ratio                             |
| LMWH:    | low molecular weight heparin                               |
| LHO:     | left heart obstruction                                     |
| LHR:     | left heart regurgitation                                   |

|           |                                                   |
|-----------|---------------------------------------------------|
| LVOT:     | left ventricular outflow tract                    |
| LVOTO:    | left ventricular outflow tract obstruction        |
| MFS:      | Marfan syndrome                                   |
| MI:       | myocardial infarction                             |
| MPV:      | mechanical prosthetic valve                       |
| MRI:      | magnetic resonance imaging                        |
| MS:       | mitral stenosis                                   |
| MWU-test: | Mann-Whitney U-test                               |
| NYHA:     | New York Heart Association                        |
| OAC:      | oral anticoagulants                               |
| PAP:      | pulmonary arterial pressure                       |
| PCI:      | percutaneous coronary intervention                |
| PDA:      | patent ductus arteriosus                          |
| PET:      | pre-eclampsia                                     |
| PH:       | pulmonary hypertension                            |
| PHV:      | prosthetic heart valve                            |
| PIH:      | pregnancy-induced hypertension                    |
| PPCM:     | peripartum cardiomyopathy                         |
| PPH:      | postpartum haemorrhage                            |
| PPROM:    | preterm pre-labour rupture of membranes           |
| PR:       | pulmonary regurgitation                           |
| RCOG:     | Royal College of Obstetricians and Gynaecologists |
| RHD:      | rheumatic heart disease                           |
| RHO:      | right heart obstruction                           |
| RHR:      | right heart regurgitation                         |

|         |                                                                                                     |
|---------|-----------------------------------------------------------------------------------------------------|
| RVOTO:  | right ventricular outflow tract obstruction                                                         |
| SADS:   | sudden adult death syndrome                                                                         |
| SGA:    | small for gestational age                                                                           |
| SVT:    | supraventricular tachycardia                                                                        |
| TGA:    | complete transposition of the great arteries                                                        |
| TR:     | tricuspid regurgitation                                                                             |
| UFH:    | unfractionated heparin                                                                              |
| VHD:    | valvular heart disease                                                                              |
| VSD:    | ventricular septal defect                                                                           |
| VT:     | ventricular tachycardia                                                                             |
| WHO:    | World Health Organisation                                                                           |
| ZAHARA: | Zwangerschap bij Aangeboren HARtAfwijkingen<br>(translation: pregnancy in congenital heart disease) |

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## **Declaration**

I declare that the work presented in this thesis was conducted by the author whilst in a registered post-graduate candidature unless otherwise acknowledged.

The copyright of this thesis rests with the author and is made available under a Creative Commons Attribution Non-Commercial No Derivatives licence. Researchers are free to copy, distribute or transmit the thesis on the condition that they attribute it, that they do not use it for commercial purposes and that they do not alter, transform or build upon it. For any reuse or redistribution, researchers must make clear to others the licence terms of this work.

## **Chapter 1:     Introduction**

## **1.1 Aims and hypotheses**

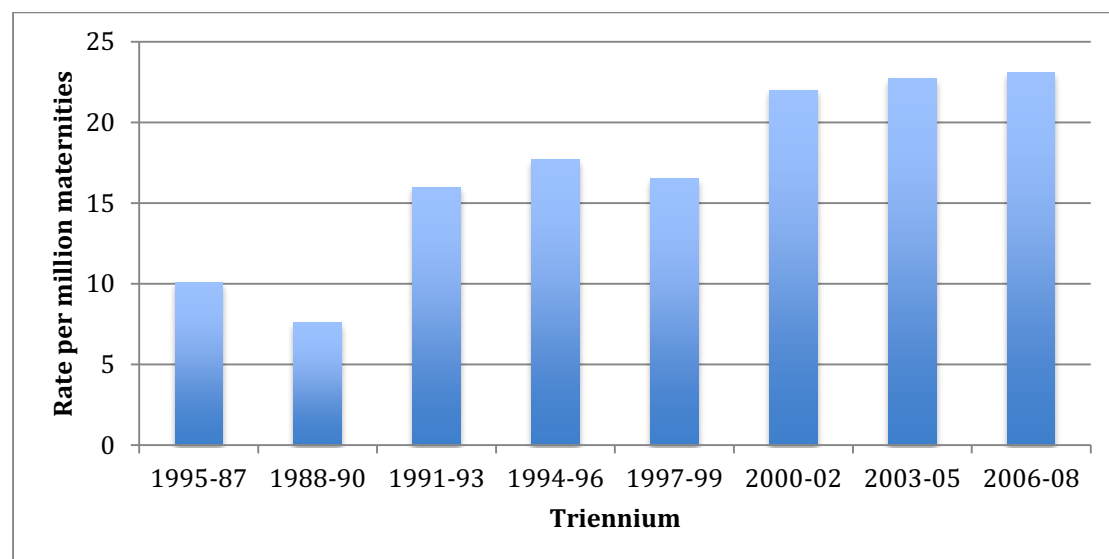
The aims of the work reported in this thesis are:

1. To study the effect of pre-existing maternal cardiac disease on cardiovascular function during pregnancy, and on obstetric and fetal/neonatal outcomes, and to investigate maternal risk factors for adverse events
2. Within the framework of a retrospective case note analysis to test the following hypotheses:
  - Maternal cardiovascular and obstetric outcomes are impaired in the presence of pre-existing maternal cardiac disease
  - Fetal/neonatal outcomes are impaired in women with pre-existing maternal cardiac disease
  - Fetal growth is impaired in women with cardiac disease who have a limited ability to increase their cardiac output in response to pregnancy
  - Adverse outcomes from pregnancy can be predicted at least in part by maternal factors

## 1.2 Epidemiology

It is estimated that 0.2 to 4% of all pregnancies in Western industrialized countries are complicated by cardiovascular disease.<sup>1</sup> In the UK the incidence of heart disease during pregnancy has remained relatively constant at 0.9% over several decades.<sup>2</sup>

*Figure 1: Rates of cardiac maternal deaths; UK: 1985-2008; data from Centre for Maternal & Child Enquiries (CMACE)<sup>3</sup>*



The most recent report of the Confidential Enquiries into Maternal Deaths (2006-2008) identified cardiac disease as the commonest single cause of maternal death with a maternal mortality rate of 23.1 per million maternities (up from 7.6 per million in the 1988-1990 enquiry).<sup>3</sup> Care was felt to be substandard in 51% of cardiac deaths. Current management is based upon limited clinical experience and an inadequate body of prospective research as the heterogeneity of disease has hindered the development of randomized controlled trials or appropriate pregnancy management protocols. Neither the latest European Society of Cardiology (ESC) guideline on the management of cardiovascular disease during pregnancy,<sup>4</sup> nor the Royal College of

Obstetricians and Gynaecologists (RCOG) good practice guidance on cardiac disease in pregnancy<sup>5</sup> reference a single randomized controlled trial involving pregnant women.

The increase in cardiac deaths in the UK is mainly attributable to a rise in deaths due to acquired heart disease (20.8 per million maternities in the last report), with the leading causes of death being sudden adult death syndrome (SADS), myocardial infarction (MI), dissection of the thoracic aorta and cardiomyopathy.

*Figure 2: Indirect maternal deaths from congenital and acquired heart disease; UK: 1985-2008; data from CMACE<sup>3</sup>*

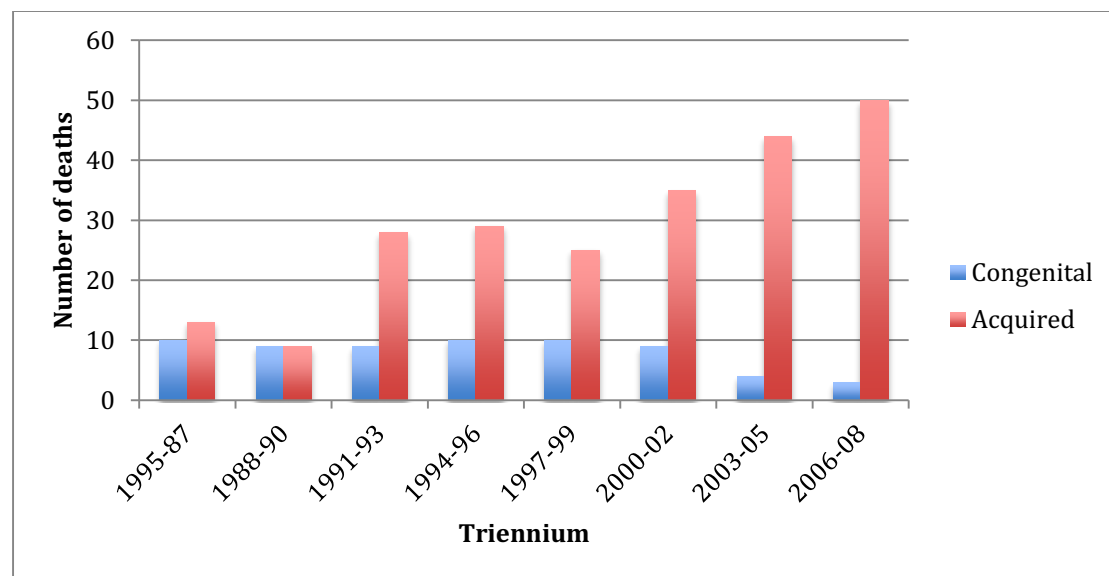
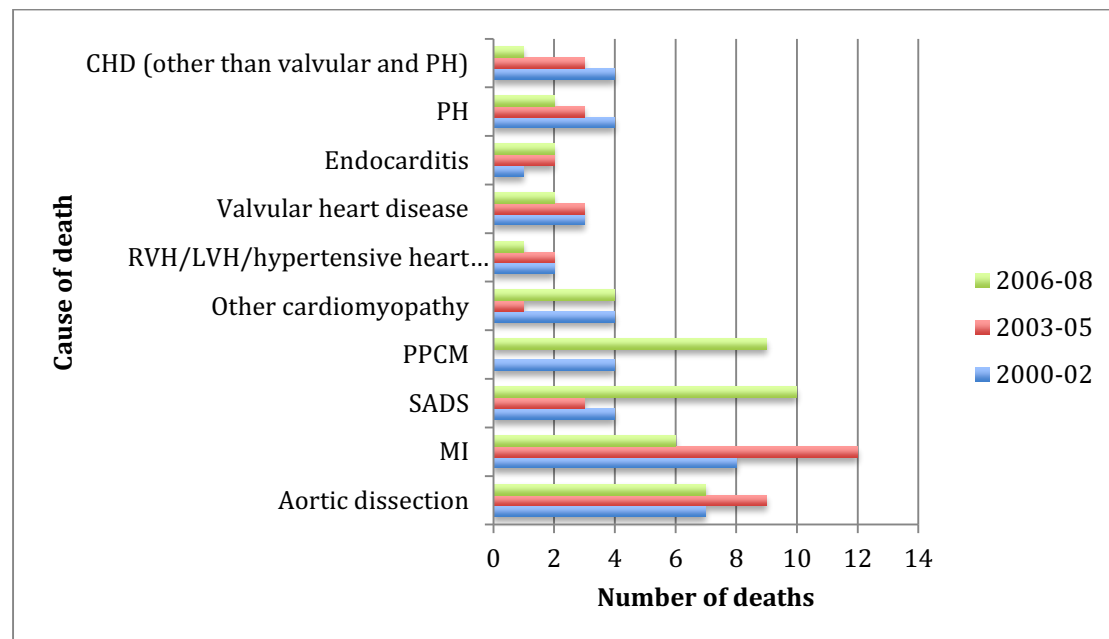


Figure 3: Causes of maternal death from cardiac disease: UK: 2000-2008; data from CMACE<sup>3</sup>



*MI – myocardial infarction; SADS – sudden adult death syndrome; PPCM – peripartum cardiomyopathy; RVH – right ventricular hypertrophy; LVH - left ventricular hypertrophy; PH – pulmonary hypertension; CHD – congenital heart disease*

This trend is likely to continue as more women delay pregnancy until later life and as rates of obesity and other chronic conditions such as hypertension and diabetes continue to rise. Moreover many women with acquired heart disease may be unaware of their condition, the diagnosis only being made when they become pregnant and develop symptoms.

Conversely, the majority of women with congenital heart disease will be aware of their diagnosis and known to cardiac services, with over 80% having some knowledge about their treatment, frequency of follow up, dental practices, occupational choices, appropriateness of oral contraceptives and the risks of pregnancy.<sup>6</sup> Although death

rates in women with congenital heart disease and pulmonary hypertension continue to fall, congenital heart disease has become the most frequent form of cardiovascular disease present during pregnancy in the western world (75-82%).<sup>4,7,8</sup> Over 85% of infants with congenital heart disease now survive into adulthood such that adults with congenital heart disease now outnumber children.<sup>9,10</sup> In particular, advances in diagnosis and treatment have led to an improvement in the survival of those with complex congenital heart disease.<sup>11</sup> Nevertheless, most interventions are not curative and many adults with congenital heart disease will face the prospect of re-intervention and, if managed inappropriately, premature death. The increasing complexity of congenital heart disease in the pregnant population is further reflected by a significant rise in severe complications during delivery and the high-risk postpartum period.<sup>12</sup> Approximately 1600 people with congenital heart disease requiring on-going follow-up enter adulthood per year in the UK.<sup>11</sup> Half of these are women, many of whom will wish to become pregnant and start a family.

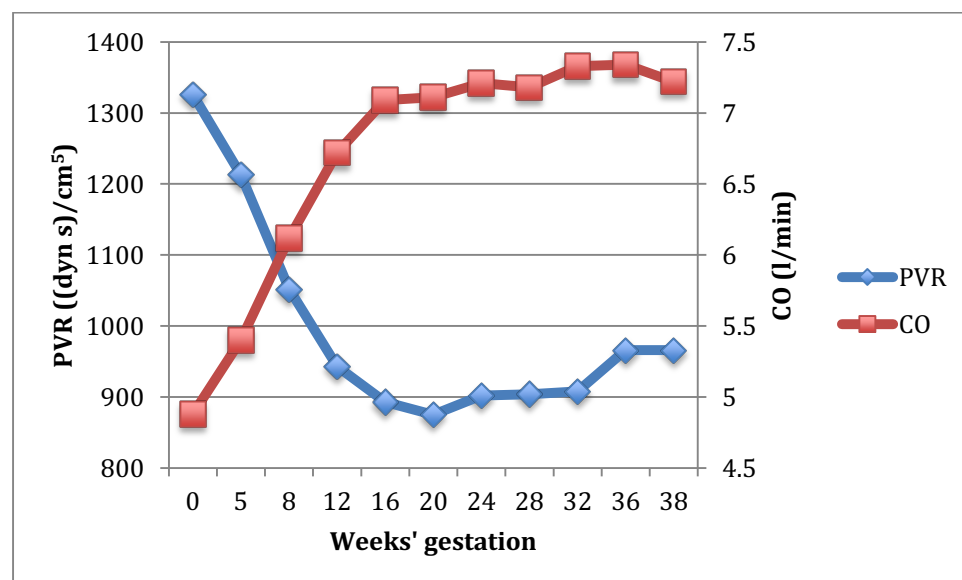
There are few data describing either the spectrum or outcomes of cardiovascular disease related to pregnancy in developing nations. Patterns of disease appear to be markedly different from those seen in the developed world and are often complicated by HIV/AIDS as a co-morbidity. Rheumatic heart disease (RHD) is the commonest abnormality, although cardiomyopathies and undiagnosed or un-operated CHD are also major problems.<sup>13</sup>

## 1.3 Normal cardiovascular adaptation to pregnancy

### 1.3.1 Changes in the cardiovascular system

Pregnancy is associated with substantial physiological changes in the cardiovascular system. They are essential for successful pregnancy. The key elements – changes in peripheral vascular resistance, cardiac output and blood volume – have been well documented in normal pregnancy.<sup>14,15</sup>

*Figure 4: Changes in peripheral vascular resistance and cardiac output in pregnancy; data from Robson et al<sup>15</sup>*



The ‘unifying hypothesis’ suggests that body fluid regulation in pregnancy is principally determined by peripheral vasodilatation which triggers the haemodynamic and subsequent hormonal responses that result in sodium and water retention via activation of the renin-angiotensin-aldosterone system.<sup>16</sup> Systemic vascular resistance falls to 70% of non-pregnant levels by 8 weeks of gestation, secondary to a marked peripheral dilatation induced by both endocrine and local factors.<sup>17,18</sup> This state of

relative vascular under-fill is thought to lead to increases in blood volume and cardiac output. It is also associated with a fall in mean arterial blood pressure (predominantly due to a reduction in diastolic blood pressure) that occurs in the first trimester and continues until the third trimester when both systolic and diastolic blood pressure rise gradually towards pre-pregnancy values.<sup>15,19</sup> Both high and low diastolic blood pressures during pregnancy have been shown to be associated with small babies and increased perinatal mortality.<sup>19</sup> Similar haemodynamic changes (arterial vasodilatation, reduced mean arterial pressure and increased cardiac output) have been described during the luteal phase of the menstrual cycle and are suggested to be the result of an oestrogen-induced increase in prostacyclin levels.<sup>20</sup> This suggests that the changes seen in early pregnancy occur independently of the placenta and may be dependent on the corpus luteum, as oestrogen is predominantly ovarian in origin at this stage of pregnancy. Other hormones, (such as relaxin and hCG), and vasodilatory peptides, such as calcitonin gene-related peptide and nitric oxide, may also play a role.<sup>14</sup>

As a result of fluid retention plasma volume increases by 50%. There is a relatively smaller increase in total red cell mass, which results in an overall fall in haemoglobin concentration (haemodilution). Inadequate plasma volume expansion has been shown to be associated with fetal growth restriction.<sup>21</sup> Cardiac output increases by 30-60%<sup>15,22,23,24</sup> with a rapid rise in the first trimester, reaching a peak at 20-24 weeks after which it plateaus or falls slightly. The rise in cardiac output is disproportionately greater than the increase in heart rate and is therefore attributable to augmentation in stroke volume. However, as pregnancy advances heart rate increases further, becoming the predominant factor in increasing cardiac output. The resultant increase

in pulmonary blood flow is balanced by a reduction in pulmonary vascular resistance, thereby preventing a rise in pulmonary artery pressure.<sup>15</sup> During pregnancy, resting cardiac output fluctuates markedly, particularly with changes in maternal position, with compression of the inferior vena cava by the enlarging gravid uterus resulting in decreased venous return and a fall in cardiac output.

### 1.3.2 Ventricular structure and function

Pregnancy leads to structural and functional changes in the heart. Data regarding systolic and diastolic cardiac function in pregnancy are scarce, however, serial echocardiography during pregnancy has demonstrated an increase in left ventricular mass and dimensions, ejection fraction and fibre shortening.<sup>15,22</sup> Thus normal pregnancy appears to be associated with a physiological left ventricular hypertrophy, similar to that seen in athletes.

### 1.3.3 Labour and delivery

Labour and delivery substantially alter the maternal haemodynamic state secondary to pain, anxiety and uterine contractions. Contractions increase venous return by up to 500ml as uterine blood returns to the circulating pool.<sup>25</sup> This results in an increase in stroke volume and subsequently cardiac output. Basal cardiac output has been reported to increase by about 12% during labour with a further rise during contractions of up to 20%.<sup>26</sup> The magnitude of the increase in cardiac output during contractions increases as labour progresses.<sup>27</sup> Pain and anxiety have a significant effect on both heart rate and blood pressure during labour. Both systolic and diastolic blood pressure rise during labour, peaking during the second stage. The pain of labour and delivery can be effectively interrupted by blocking the T10 to L1 nerve roots

before their entrance into the spinal cord (caudal, low epidural or low subarachnoid blocks). Reduction of pain by epidural anaesthesia may limit the haemodynamic changes and the progressive rise in cardiac output seen between contractions.<sup>28</sup> Carefully administered, regional anaesthesia is probably safe in patients with severe cardiac disease, although the optimum management is yet to be determined.

In spite of the blood loss associated with delivery there is reported to be a 60-80% rise in cardiac output immediately after delivery.<sup>25</sup> This occurs because of the increase in venous return due to relief of aorto-caval compression, and from additional blood moving from the contracting uterus back into the systemic circulation. It can result in a substantial rise in ventricular filling pressures and stroke volume, and may lead to clinical deterioration in women with severe cardiac disease. However, within 2 weeks of delivery, cardiac output falls considerably, returning to the non-pregnant state by six months post-partum.<sup>29</sup>

#### 1.3.4 Other considerations

Of note, the physiological changes that occur during pregnancy can dramatically alter the pharmacokinetics of any drugs administered. The increase in plasma volume has a dilutional effect on many drugs while drug clearance is enhanced by the raised glomerular filtration rate and enhanced hepatic metabolism. Higher doses may be required to achieve therapeutic plasma concentrations.

## 1.4 Maternal and Fetal Risks

The risk of adverse events (both maternal and fetal) during pregnancy for women with pre-existing heart disease is determined by the ability of their cardiovascular system to adapt to the associated physiological changes. This is dependent on the specific cardiac condition, the current haemodynamic status and functional capacity of the patient, and a prior history of adverse cardiac events.<sup>8,30,31,32</sup> It may range from a risk of maternal death of up to 50% for women with pulmonary hypertension (PH), such that pregnancy is deemed to be inadvisable, to the same as the general population for women with minor lesions such as a successfully repaired ventricular septal defect (VSD).

### 1.4.1 Maternal Cardiovascular Complications

Previous studies have sought to develop scores to aid risk stratification. Assessing disease-specific risk is difficult as reports focusing on outcomes in women with particular types of heart disease are usually retrospective and tend to be too small to identify reliable predictors of poor outcome. Other investigators have included larger populations with a wide variety of forms of heart disease including congenital heart disease, ischaemic heart disease, cardiomyopathies, acquired valvular heart disease (VHD) and arrhythmias in women with structurally normal hearts. The CARPREG (CARDiac disease in PREGnancy) investigators led the way in identifying predictors of adverse pregnancy outcome in women with pre-existing heart disease<sup>30</sup> and were the first to design a risk score<sup>8</sup> which has subsequently been validated in several studies.<sup>33</sup> Prior cardiac events (heart failure, transient ischaemic attack, stroke prior to pregnancy, arrhythmia), poor maternal functional capacity (New York Heart

Association (NYHA) class > II),<sup>34</sup> presence of cyanosis, left heart obstruction and myocardial dysfunction (ejection fraction <40%) were identified as predictors of maternal cardiovascular events during pregnancy.<sup>8,30</sup> However, it has been suggested that because the CARPREG cohort includes women with primary electrical and acquired heart disease, as well as congenital heart disease (some types of which, in particular complex congenital heart disease, are under-represented), it may overestimate risk in women with congenital heart disease<sup>35,36</sup> Other investigators have identified additional predictors in this population including the presence of mechanical valve prostheses (MPVs), moderate/severe systemic and sub-pulmonary atrioventricular valve regurgitation, use of cardiac medication pre-pregnancy and maternal cigarette smoking,<sup>35,36</sup> but these have not been validated in other studies. Current guidance<sup>4</sup> advises use of the modified World Health Organization (WHO) risk classification to conduct maternal risk assessment.<sup>37</sup> This includes all known maternal cardiovascular risk factors: the underlying disease and other co-morbidities, as well as contra-indications for pregnancy (such as PH and aortic dilatation) that are not incorporated in either the CARPREG<sup>8</sup> or ZAHARA<sup>36</sup> predictors and correlates well with cardiac, obstetric and fetal outcomes.<sup>38</sup> Pregnancy related risks are additive and generally increase with increasing disease complexity.<sup>8,30,37,39</sup>

There is also a suggestion that pregnancy may have an irreversible detrimental effect on cardiac function in women with certain types of congenital heart disease<sup>40</sup> (Tetralogy of Fallot<sup>41</sup>, transposition of the great arteries (TGA) corrected by atrial switch procedure (Mustard or Senning operation<sup>42</sup>). Larger studies are required to investigate this issue further.

*Table 1: New York Heart Association (NYHA) functional classification<sup>34</sup>*

| <b>NYHA Class</b> | <b>Functional Capacity</b>                                                                                                                                                                                                                                |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>I</b>          | Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or angina pain                                                                        |
| <b>II</b>         | Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pain                                                      |
| <b>III</b>        | Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnoea or angina pain                                                         |
| <b>IV</b>         | Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. |

*Table 2: Modified WHO classification of maternal cardiovascular risk: principles<sup>4,37</sup>*

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

Table 3: Modified WHO classification of maternal cardiovascular risk: application<sup>4,37</sup>

|                                                                                                                                                                                                                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Conditions in which pregnancy is WHO I</b>                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>• Uncomplicated, small or mild <ul style="list-style-type: none"> <li>- pulmonary stenosis</li> <li>- patent ductus arteriosus</li> <li>- mitral valve prolapse</li> </ul> </li> </ul> |
| <ul style="list-style-type: none"> <li>• Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage)</li> </ul>                                 |
| <ul style="list-style-type: none"> <li>• Atrial or ventricular ectopic beats, isolated</li> </ul>                                                                                                                             |
| <b>Conditions in which pregnancy is WHO II or III</b>                                                                                                                                                                         |
| <i>WHO II (if otherwise well and uncomplicated)</i>                                                                                                                                                                           |
| <ul style="list-style-type: none"> <li>• Unoperated atrial or ventricular septal defect</li> </ul>                                                                                                                            |
| <ul style="list-style-type: none"> <li>• Repaired tetralogy of Fallot</li> </ul>                                                                                                                                              |
| <ul style="list-style-type: none"> <li>• Most arrhythmias</li> </ul>                                                                                                                                                          |
| <i>WHO II-III (depending on individual)</i>                                                                                                                                                                                   |
| <ul style="list-style-type: none"> <li>• Mild left ventricular impairment</li> </ul>                                                                                                                                          |
| <ul style="list-style-type: none"> <li>• Hypertrophic cardiomyopathy</li> </ul>                                                                                                                                               |
| <ul style="list-style-type: none"> <li>• Native or tissue valvular heart disease not considered WHO I or IV</li> </ul>                                                                                                        |
| <ul style="list-style-type: none"> <li>• Marfan syndrome without aortic dilatation</li> </ul>                                                                                                                                 |
| <ul style="list-style-type: none"> <li>• Aorta &lt;45mm in aortic disease associated with bicuspid aortic valve</li> </ul>                                                                                                    |
| <ul style="list-style-type: none"> <li>• Repaired coarctation</li> </ul>                                                                                                                                                      |
| <i>WHO III</i>                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>• Mechanical valve</li> </ul>                                                                                                                                                          |
| <ul style="list-style-type: none"> <li>• Systemic right ventricle</li> </ul>                                                                                                                                                  |
| <ul style="list-style-type: none"> <li>• Fontan circulation</li> </ul>                                                                                                                                                        |
| <ul style="list-style-type: none"> <li>• Cyanotic heart disease</li> </ul>                                                                                                                                                    |
| <ul style="list-style-type: none"> <li>• Other complex congenital heart disease</li> </ul>                                                                                                                                    |
| <ul style="list-style-type: none"> <li>• Aortic dilatation 40-45mm in Marfan syndrome</li> </ul>                                                                                                                              |
| <ul style="list-style-type: none"> <li>• Aortic dilatation 45-50mm in aortic disease associated with bicuspid aortic valve</li> </ul>                                                                                         |
| <b>Conditions in which pregnancy is WHO IV (pregnancy contraindicated)</b>                                                                                                                                                    |
| <ul style="list-style-type: none"> <li>• Pulmonary arterial hypertension of any cause</li> </ul>                                                                                                                              |
| <ul style="list-style-type: none"> <li>• Severe systemic ventricular dysfunction (LVEF &lt;30%, NYHA III-IV)</li> </ul>                                                                                                       |
| <ul style="list-style-type: none"> <li>• Previous peripartum cardiomyopathy with any residual impairment of left ventricular function</li> </ul>                                                                              |
| <ul style="list-style-type: none"> <li>• Severe mitral stenosis, severe symptomatic aortic stenosis</li> </ul>                                                                                                                |
| <ul style="list-style-type: none"> <li>• Marfan syndrome with aorta dilated &gt;45mm</li> </ul>                                                                                                                               |
| <ul style="list-style-type: none"> <li>• Aortic dilatation &gt;50mm in aortic disease associated with bicuspid aortic valve</li> </ul>                                                                                        |
| <ul style="list-style-type: none"> <li>• Native severe coarctation</li> </ul>                                                                                                                                                 |

*LVEF: left ventricular ejection fraction*

#### 1.4.2 Obstetric Complications

Women with pre-existing heart disease appear to be at increased risk of adverse obstetric outcomes, although reliable cardiac predictors for these have not been identified.<sup>36,39,43</sup> Several studies have described an increased preterm birth rate in these women compared with the general population.<sup>7,8,30,32,33,39,43</sup> While iatrogenic preterm delivery may result from concerns about maternal decompensation, it has been reported that preterm delivery rates remain high even after the exclusion of such patients, and that the risk of preterm delivery was higher in those with an intermediate CARPREG score.<sup>33</sup> This concurs with the CARPREG investigators who found an association between cardiac complications and the onset of preterm labour.<sup>8,30,32</sup> Increased rates of preterm labour appear to be particularly marked in women with more complex congenital heart disease including Ebstein's anomaly, TGA, cyanotic congenital heart disease, Eisenmenger syndrome, Fontan circulation and pulmonary atresia with VSD.<sup>39</sup> A higher incidence of spontaneous preterm labour secondary to preterm premature rupture of membranes (PPROM) has also been reported in women with congenital heart disease (approximately 1.5 times that in the general population),<sup>43</sup> especially in women with TGA or a Fontan circulation.<sup>38</sup> The reason for this is unclear. Increases in amniotic fluid matrix metalloprotease (MMP) 1,8 and 9 and a decrease in tissue inhibitors of MMP 1 and 2 leading to reduced membrane collagen content are thought to be an important factor in developing PPRM. Similar changes have also been implicated in aortic aneurysm formation and congenital valvular disease. Oxidative stress may also play a role.<sup>43</sup>

Rates of post-partum haemorrhage (PPH) two to four times higher than that seen in the general population have been reported.<sup>33,43</sup> This has been attributed both to a

prolonged second stage of labour (and subsequent uterine atony), and to the increased use of elective assisted vaginal delivery (with an increased risk of trauma, in particular with forceps) in an attempt to avoid repeated Valsalva manoeuvres which may increase cardiac stress. Use of anticoagulants and antiplatelet agents may also be a factor but the evidence for this is conflicting.<sup>33,43</sup>

Overall, pre-existing heart disease does not appear to be associated with an increased risk of developing a hypertensive disorder of pregnancy (pregnancy-induced hypertension (PIH), pre-eclampsia (PET) and eclampsia). However, an increased incidence has been documented with certain types of congenital heart disease. Specifically, patients with aortic coarctation (COA) and TGA seem to be at increased risk, and a twofold higher incidence than that seen in the general population has been reported.<sup>39</sup>

#### 1.4.3 Fetal and Neonatal Complications

Maternal cardiac disease is associated with increased fetal and neonatal complications including fetal loss, fetal growth restriction (FGR), preterm birth and intra-cranial haemorrhage. This risk is again highest in women with cyanosis and poor functional class (NYHA functional class III or IV) or left heart obstruction.<sup>30</sup> It is further increased in the presence of maternal age <20 and >35 years, multiple pregnancy, maternal cigarette smoking and treatment with anticoagulants.<sup>8,32</sup>

Normal fetal growth is regulated at multiple levels and is determined by the interaction between the genetically determined growth potential and various maternal, fetal and placental factors. FGR is defined as failure to realize this potential. It is not

only an important cause of perinatal morbidity and mortality, but epidemiological studies report an association between poor growth in utero and development of the metabolic syndrome in adulthood.<sup>44</sup>

The fact that the risk of FGR is highest in women with poor functional class (NYHA functional class III or IV), cyanosis or left heart obstruction suggests two possible mechanisms for FGR in these pregnancies: hypoxia, and reduced placental perfusion as a consequence of restriction in cardiac output. Cyanotic congenital heart disease has been shown to be associated with a higher incidence of low birth weight infants compared to acyanotic congenital heart disease.<sup>31,45,46</sup> Maternal oxygen saturations below 85% are predictive of poor pregnancy outcome with a livebirth rate of only 12%.<sup>47</sup> As a result of this hypoxaemia there is a compensatory polycythaemia which is independently related to lower birth weight.<sup>47</sup> The effect of cyanosis may be exacerbated further by reduced cardiac output in, for example, single ventricle circulations, or the inability of the right heart to adapt to requirements for an increase in cardiac output, as seen in PH. Even after surgical repair fetal growth may continue to be affected, again presumably secondary to reduced cardiac output.<sup>48</sup> In conditions with fixed outflow tract resistance (valvular aortic/sub-aortic stenosis, COA) there may be an inability to accommodate the increased cardiac output of pregnancy, which can lead to heart failure with a rise in left ventricular pressures but low cardiac output and subsequent restriction of fetal growth.

Additionally, in pregnant women with congenital heart disease the risk of a congenital cardiac anomaly in the fetus is increased to 3-5% (dependent on the maternal lesion) compared with a background risk of 0.8% in the general population.<sup>49</sup>

## **1.5 Risks related to specific cardiac conditions**

In general, conditions associated with volume overload are better tolerated than those associated with pressure overload.<sup>8,30,32</sup>

### **1.5.1 Pulmonary hypertension & Eisenmenger Syndrome**

Although pregnancy in women with pulmonary vascular disease is rare (estimated incidence of 1.1 per million maternities) it continues to be associated with a high maternal mortality. Women with pulmonary hypertension (PH) with an already pressure-overloaded right ventricle may struggle to cope with the additional cardiovascular demands of pregnancy. The fall in systemic vascular resistance may worsen the right to left shunt seen in Eisenmenger syndrome.<sup>50,51</sup> Deterioration generally occurs during the second trimester with most deaths seen within the first month post-partum, usually from right heart failure as the acute increase in right ventricular preload at delivery leads to volume overload and an acute rise in pulmonary vascular resistance. The majority of complications occur at the end of pregnancy and during the first postpartum week. Current guidelines continue to advise against pregnancy.<sup>4,37</sup>

### **1.5.2 Cardiomyopathies**

In the 2006-2008 triennium,<sup>3</sup> cardiomyopathy was the commonest cardiac cause of maternal death, with 13 deaths (two of which were late ie. more than 42 days after the pregnancy had ended) attributed to this condition. The aetiology of cardiomyopathies occurring in pregnant women is diverse, including both inherited and acquired forms of the disease. Cardiomyopathy is a significant predictor for the development of heart

failure during pregnancy, which is associated with high rates of adverse maternal and fetal outcomes.<sup>52</sup> Labour, delivery and the early post-partum period are times of particular risk as a result of the acute changes in cardiac output caused by pain, anxiety and exertion, uterine contractions, bleeding, autotransfusion from the involuting uterus and resorption of oedema.<sup>25-28</sup>

Peripartum cardiomyopathy (PPCM) and dilated cardiomyopathy (DCM) share similar clinical and diagnostic criteria (with the notable exception that PPCM has a temporal relationship to pregnancy), although their pathophysiologies are different. Death is usually from intractable heart failure, arrhythmia, or systemic or pulmonary embolism from mural thrombus.

Hypertrophic cardiomyopathy (HCM) is the commonest inherited cardiac disease<sup>53</sup> and is generally well tolerated in pregnancy. Complications generally arise as a result of diastolic dysfunction due to the hypertrophic, non-compliant myocardium, severe left ventricular outflow tract obstruction (LVOTO) and arrhythmias.

### 1.5.3 Obstructive left heart disease

Obstructive left heart lesions (aortic and mitral stenosis, HCM, and unrepaired COA) may reduce the ability of the heart to increase cardiac output during pregnancy. The resultant limited increase in cardiac output may also restrict uteroplacental perfusion and fetal growth. In the developed world, aortic stenosis (AS) is usually congenital, and mitral stenosis (MS) rheumatic in origin.

Congenital bicuspid aortic valve (BAV) is the most common cause of AS complicating pregnancy and is generally well tolerated in those with mild to moderate disease and normal ventricular systolic function. In pregnant women with moderate to severe AS, (even in the absence of symptoms), their limited ability to increase cardiac output through a fixed obstructive lesion may result in excessive elevation of left ventricular diastolic filling pressures, which may precipitate or exacerbate heart failure or ischaemia, thus increasing the need for intervention – both cardiac and obstetric.<sup>8,35</sup> Severe AS has been associated with high rates of both maternal (17%) and fetal (30%) mortality,<sup>54</sup> although recent series report more encouraging data.<sup>55</sup>

MS is particularly poorly tolerated in pregnancy. It is often diagnosed during pregnancy, as the inability to adapt to the cardiovascular changes of pregnancy precipitates symptoms for the first time. A combination of restricted flow through the stenotic mitral valve and the increase in stroke volume and heart rate lead to an increase in left atrial pressure. This may subsequently progress to pulmonary venous hypertension and right ventricular failure. Women with MS are especially vulnerable during the peripartum period, when the large fluid shifts seen during labour and immediately after delivery may precipitate pulmonary oedema.<sup>56</sup>

#### 1.5.4 Aortopathies

Aortic dissection is now one of the commonest causes of maternal death from cardiac disease<sup>3</sup>. Normal pregnancy is associated with structural and functional changes in the aorta (dilatation, increased compliance and a reduction in mucopolysaccharides in the aortic wall<sup>57,58,59</sup>), which help to optimize cardiac function: reduction in vascular resistance and increased aortic compliance assist left ventricular ejection. However,

these factors may also contribute to the increased risk of dissection, which is most common in the third trimester or early postpartum period. A wide range of pathologies, both congenital (Marfan syndrome (MFS) and other connective tissue disorders such as Ehlers-Danlos syndrome, COA, BAV disease, Tetralogy of Fallot, Turner syndrome) and acquired (trauma, severe hypertension, atherosclerosis, infection, crack cocaine use) may predispose to aortopathy and dissection. Pregnant women with MFS carry an increased risk for spontaneous aortic dissection during pregnancy and the puerperium, even in the absence of aortic root dilatation.<sup>60,61</sup>

Congenital BAV is present in 1-2% of the general population.<sup>62</sup> It is associated with a proximal aortopathy and increased risk of aneurysm formation, aortic regurgitation (AR) and aortic dissection. Dilatation of the ascending aorta occurs in 30-50% of patients<sup>62</sup> and is often maximal in the distal region, which is difficult to visualize adequately with echocardiography. Pre-pregnancy assessment with magnetic resonance imaging (MRI) is therefore important. The risk of adverse pregnancy outcomes in women with a bicuspid aortic valve is not known although many centres advise pre-pregnancy surgery in the setting of aortic diameters >5cm.<sup>4,62</sup>

COA accounts for 5-8% of congenital heart disease<sup>63</sup> and is commonly found in association with other cardiovascular abnormalities. Most women will have had previous surgical intervention, but nonetheless the risks of hypertension, re-coarctation and aneurysm formation remain. Significant coarctation may lead to severe maternal hypertension which may be refractory to drug therapy, while hypotension in the lower body results in hypoperfusion of the placenta and an increased risk of fetal mortality and morbidity. However, pregnancy in women with

repaired coarctation is generally well tolerated provided there is no aneurysm at the site of repair.

#### 1.5.5 Cyanotic heart disease

Cyanotic heart disease is associated with a high risk of maternal and fetal adverse outcomes. Maternal complications (such as heart failure, pulmonary or systemic thrombosis, supraventricular arrhythmias and infective endocarditis) occur in 30% of cyanotic women during pregnancy<sup>4</sup> while the fetus is more likely to be affected by FGR.<sup>31,45,46</sup> Maternal oxygen saturations below 85% are particularly predictive of poor outcomes.<sup>47</sup>

#### 1.5.6 Valvular heart disease (VHD)

VHD may be congenital or acquired and is an important cause of maternal and fetal morbidity and mortality. Stenotic lesions are generally tolerated less well than regurgitant lesions, due to an inability to accommodate the significant increase in blood volume and cardiac output associated with pregnancy. Left-sided valve disease has a higher complication rate than right-sided valve disease.<sup>8,36,39</sup> It is not uncommon for VHD to present for the first time in pregnancy, especially in unscreened immigrants, as the increasing demands on the heart lead to decompensation and the development of symptoms.

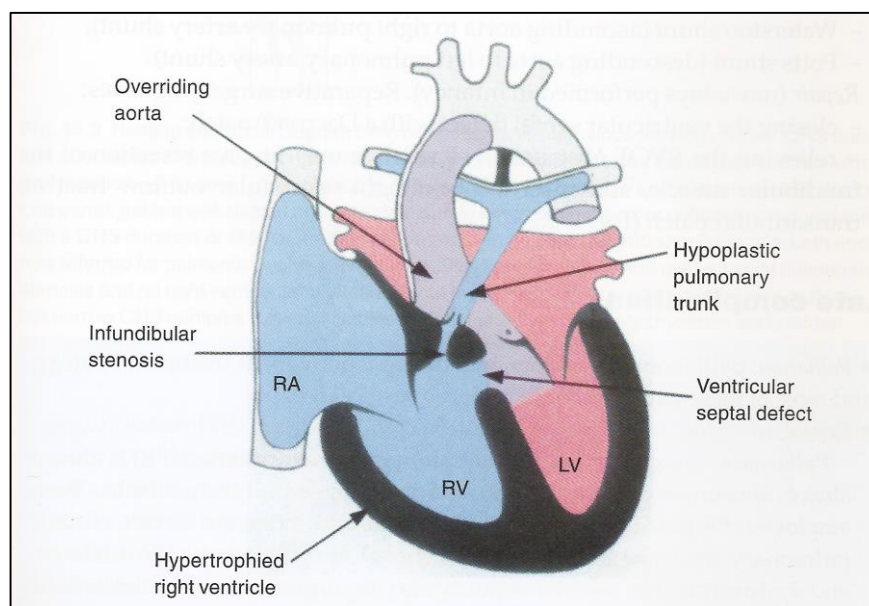
Prosthetic heart valves (PHVs) continue to represent a particular challenge in pregnancy with both mechanical and bioprosthetic valves (BPVs) carrying specific risks. Although bioprostheses avoid the risks of valve thrombosis and the need for anticoagulation, these patients will almost certainly require reoperation in the future:

it is unclear whether pregnancy accelerates this deterioration. The debate in patients with MPVs relates to the type of anticoagulation and the need to balance the risk to the mother with the risk to the fetus.

#### 1.5.7 Right-sided heart disease

##### Tetralogy of Fallot

*Figure 5: Tetralogy of Fallot<sup>64</sup>*

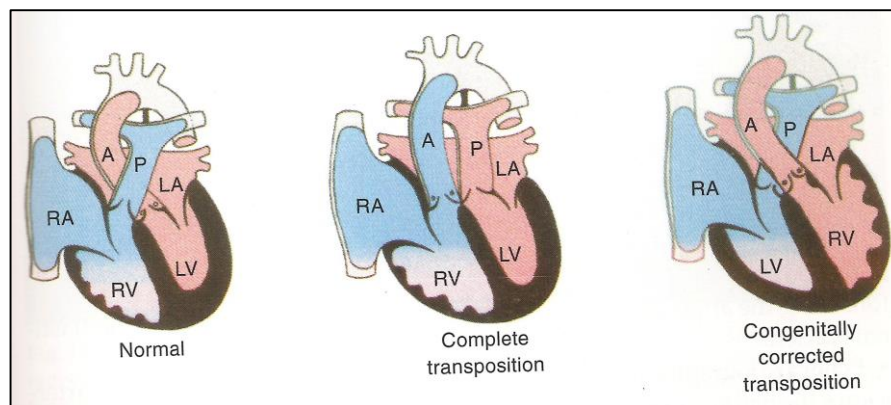


Tetralogy of Fallot is the most common congenital heart defect associated with systemic cyanosis. It is characterized by a nonrestrictive VSD, overriding aorta, right ventricular outflow tract obstruction (RVOTO) and right ventricular hypertrophy. Women with repaired tetralogy of Fallot and little residual haemodynamic impairment generally tolerate pregnancy well. Residual shunts, right ventricular outflow tract obstruction (RVOTO), moderate to severe pulmonary regurgitation (PR) and right ventricular dysfunction are all risk factors for cardiovascular complications (including arrhythmias and heart failure) and obstetric complications.<sup>65</sup> Repaired tetralogy of Fallot is also associated with low birth weight, particularly in women

with moderate to severe pulmonary insufficiency.<sup>66</sup> Additionally there are some data to suggest that pregnancy has an irreversible detrimental effect on right ventricular function.<sup>41</sup>

### Complete and congenitally corrected transposition of the great arteries

*Figure 6: Transposition of the great arteries<sup>64</sup>*



In complete TGA there is atrioventricular concordance but ventriculoarterial discordance, resulting in the pulmonary and systemic circulations running in parallel, rather than in series as normally occurs. Survival prior to surgical repair is dependent upon mixing of the circulations, either naturally (via a VSD, atrial septal defect (ASD) or patent ductus arteriosus (PDA)) or by intervention (septostomy). Surgical management aims to redirect blood either at the atrial level using a baffle (Mustard and Senning operations, atrial switch) such that the morphologic right ventricle supports the systemic circulation, or at the arterial level by switching the aorta and pulmonary arteries such that the morphologic left ventricle becomes the subaortic ventricle and supports the systemic circulation (arterial switch). In congenitally corrected transposition of the great arteries (ccTGA) the connections of both the atria to the ventricles and the ventricles to the great vessels are discordant so that the

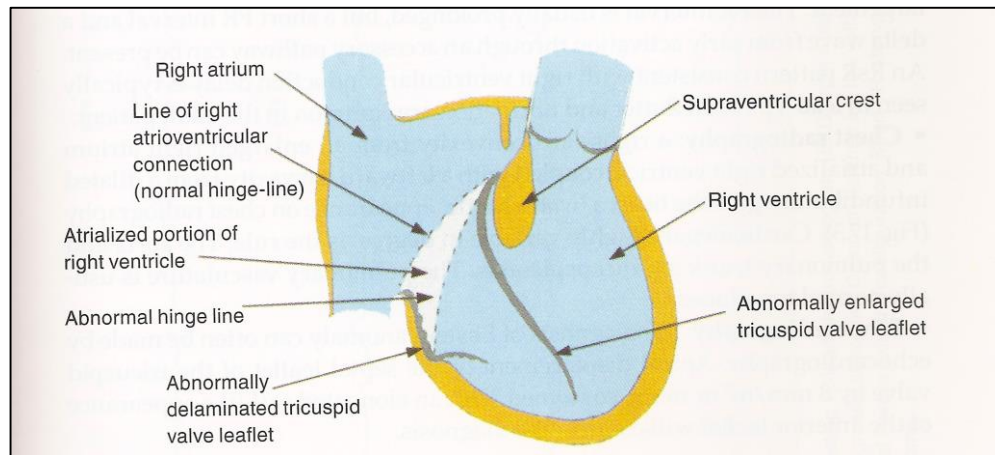
morphologic right ventricle supports the systemic circulation. It is usually associated with other anomalies including VSD (75%), pulmonary or subpulmonary stenosis (75%), left-sided valve anomalies (>75%) and complete atrioventricular block (2% per year).<sup>64</sup> Surgical repair in patients with a VSD and RVOTO is either a classic repair (VSD patch closure and relief of RVOTO, leaving the morphologic right ventricle supporting the systemic circulation) or double switch (atrial and arterial switch, achieving 'anatomic' correction, with flow from the morphologic left ventricle being directed into the systemic circulation).

During pregnancy, a systemic right ventricle may not be able to withstand the increased haemodynamic demands placed upon it, and such women have an increased risk of developing complications such as arrhythmias (including atrioventricular block) and heart failure.<sup>4</sup> There is also an increased risk of thrombotic complications due to impaired blood flow through the atrial baffle in women who have undergone the Mustard procedure.<sup>64</sup> Pregnancy following a Mustard operation, however well tolerated, may result in right ventricular dysfunction which is sometimes irreversible.<sup>42</sup> PET has been reported to be more common in this group of patients,<sup>39</sup> and neonatal adverse events such as low birth weight and preterm delivery are also more frequent.<sup>67</sup>

Only small series of women who have undergone the arterial switch have been described, but in those with good functional capacity pre-pregnancy the risk of adverse outcomes appears to be low.<sup>68</sup>

### Ebstein's anomaly

Figure 7: Ebstein's anomaly<sup>64</sup>



Ebstein's anomaly is a malformation of the tricuspid valve which is displaced apically, resulting in enlargement of the right atrium, a smaller 'functional' right ventricle and tricuspid regurgitation (TR) with subsequent reduced cardiac output. It is commonly associated with an ASD (which allows right-to-left shunting, thereby leading to cyanosis when the right-sided pressures exceed the left) and with atrial re-entry tachycardias. The ability to tolerate the haemodynamic demands of pregnancy is dependent on the severity of TR and the functional capacity of the right ventricle. Women without cyanosis or heart failure usually cope well.<sup>69,70</sup>

### Fontan circulation

The Fontan operation is a palliative procedure performed when a two-ventricle repair is not feasible (for example in tricuspid atresia, pulmonary atresia with an intact ventricular septum and univentricular hearts). Several operations exist, connecting either the right atrium or the caval veins to the pulmonary arteries and directing the systemic venous return directly to the pulmonary circulation. Blood flow to the lungs is driven by systemic venous pressure only and the systemic circulation is supported

by the single ventricle with subsequent low cardiac output. All women who have undergone a Fontan-type operation should be considered high risk in pregnancy (WHO class III or IV) and should be carefully assessed and counselled prior to becoming pregnant. Adverse maternal and fetal outcomes are directly related to the effect of pregnancy on ventricular function, a prothrombotic circulation, the degree of cyanosis (a result of right-to-left shunting across persistent systemic venous to left-sided bypass tracts) and a tendency to atrial arrhythmias which may cause significant haemodynamic deterioration.<sup>71,72,73</sup>

#### 1.5.8 Ischaemic heart disease

In the last triennium eleven women died as a result of acute MI or chronic ischaemic heart disease, a rate of 0.48 per 100,000 maternities.<sup>3</sup> While pregnancy increases the risk of acute MI three to four times (and this is further increased 30-fold in women over the age of 40 compared with those less than 20 years of age), a high incidence of identifiable risk factors is consistently reported in these women.<sup>74</sup> Pregnancy-related risk factors include PET and eclampsia, post-partum infection, thrombophilia and blood transfusion. The majority of cases of acute MI in pregnancy are associated with atherosclerosis; other causes are coronary dissection (the primary cause of infarction before and after delivery) and coronary artery thrombosis.<sup>3,74,75</sup> Prompt diagnosis and treatment are crucial to reduce morbidity and mortality in both the mother and the fetus.<sup>76</sup> Diagnostic criteria and principles of management are the same as in non-pregnant patients with percutaneous coronary intervention (PCI) being the treatment of choice. Diagnosis is often delayed as a result of the presenting symptoms and signs being attributed to the normal manifestations of pregnancy and the physiologic

changes of pregnancy affecting ECG interpretation. Close liaison between obstetricians, cardiologists and anaesthetists is required.

#### 1.5.9 Arrhythmia

Arrhythmias are common in pregnancy, in both women with structurally normal hearts and those with congenital heart disease. Premature extra beats and sustained tachyarrhythmias may present for the first time in pregnancy, or become more frequent. Most palpitations are benign, but new onset ventricular tachycardia (VT) in pregnancy should prompt investigation to rule out structural heart disease. All anti-arrhythmics cross the placenta and no major controlled studies have been conducted during pregnancy. Beta-blockers and digoxin should be the first choice for tachyarrhythmias. Beta-blockers are relatively safe during pregnancy, although they are associated with a small but significant reduction in birth weight<sup>77,78</sup> Higher doses of digoxin may be required to counteract the increased renal clearance and increased blood volume seen in pregnancy. Atrial flutter and atrial fibrillation (AF) are rare during pregnancy. However, they are associated with an increased risk of thrombo-embolic events and therefore thromboprophylaxis is recommended.<sup>4</sup> Indeed anticoagulation is mandatory for women undergoing electrical cardioversion for atrial flutter or AF in pregnancy. Electrical cardioversion is safe during pregnancy, however the defibrillator pads should be placed in such a way that the exposure of the fetus to the electrical discharge is minimized, as there is a theoretical risk of fetal ventricular arrhythmias.<sup>73</sup> Some women have an implantable cardioverter-defibrillator (ICD) *in situ* at conception, although so far there are minimal data regarding outcomes.<sup>40</sup> In cases where the arrhythmia is refractory to drugs, catheter ablation may be necessary.

Due to the high radiation exposure this should ideally be deferred until the second trimester, or other imaging modalities such as MRI should be utilized.

SADS was identified in the most recent report of the Confidential Enquiries into Maternal Deaths as the leading cause of cardiac maternal death.<sup>3</sup> It is a pathological diagnosis and is defined as sudden death in an adult for which no cause can be found. There may be an association with obesity and cardiac hypertrophy leading to arrhythmias and sudden cardiac death.<sup>79</sup> High circulating non-esterified fatty acid concentrations and genetic causes have also been linked to SADS.<sup>80,81</sup>

#### 1.5.10 Septal defects

##### Atrial Septal Defect (ASD)

An ASD is a direct communication between the two atrial chambers which permits shunting of blood. Associated malformations are present in 30% of cases.<sup>64</sup> Pregnancy is generally well tolerated unless PH or Eisenmenger syndrome are present. Haemodynamically significant ASDs should be closed prior to pregnancy. Thrombo-embolic complications and arrhythmias may occur, and in women in whom the ASD is unrepaired there is an increased risk of PET and of the fetus being small for gestational age (SGA) at birth.<sup>4</sup>

##### Ventricular Septal Defect (VSD)

A VSD is a direct communication between the two ventricles and is one of the most common congenital heart defects. A restrictive VSD produces a significant pressure gradient between the left and right ventricles but is usually accompanied by a small shunt with minimal haemodynamic effect. A large or non-restrictive VSD results in

left ventricular volume overload and subsequent rise in pulmonary artery pressure in childhood. As with ASDs, if the defect is haemodynamically insignificant or has been repaired, and there is no pulmonary hypertension, VSDs have a good prognosis in pregnancy.<sup>4</sup>

#### *Atrioventricular septal defect (AVSD)*

AVSDs are caused by abnormal development of the endocardial cushions and are particularly common in patients with trisomy 21. Where there is minimal residual atrioventricular valve regurgitation and good ventricular function following repair, pregnancy is usually well tolerated (WHO risk class II). As with other septal defects haemodynamically significant lesions may be associated with pulmonary hypertension, so an assessment of pulmonary arterial pressures is indicated as part of the pre-pregnancy work-up. Arrhythmias and worsening atrioventricular valve regurgitation during pregnancy have been reported but the risk of heart failure is low.<sup>4</sup>

## 1.6 Principles of management

### 1.6.1 Pre-pregnancy counselling and contraception

All women with heart disease should have access to specialist counselling regarding reproductive issues such as future pregnancy, family planning and contraception.<sup>4</sup>

Ideally this should begin in adolescence for those with congenital heart disease and at the time of diagnosis for women with acquired heart disease and be conducted by a multidisciplinary team of appropriately trained family planning specialists, cardiologists and obstetricians.<sup>4,10,37</sup> In addition to identifying and quantifying the risks of pregnancy for both mother and fetus, thus allowing the woman to make an informed choice, it should also allow the woman to come to terms with the impact of her disease on her childbearing potential. Unfortunately many women fail to receive timely and competent family planning advice, thereby causing unnecessary risk to both mother and child.<sup>82</sup>

Women should be given information on:<sup>10,37</sup>

- maternal and fetal morbidity and mortality associated with pregnancy
- the risk of recurrence of congenital heart disease in offspring
- maternal life expectancy and the effect of pregnancy on this
- timing of pregnancy – for example, in women with a systemic right ventricle or Fontan circulation maternal risk will increase with age, and therefore such women should be advised against delaying pregnancy until their late 30s
- the need for an up-to-date assessment prior to conception – this should review functional status and current medications

- the possible need for pre-pregnancy interventions to reduce the risk of pregnancy
- the level of surveillance, need for treatment and potential hospitalization required during pregnancy
- contraception

The ideal contraceptive should combine acceptability to the woman with a high degree of cardiovascular safety (this will vary according to the cardiac condition in question) and efficacy.

*Table 4: WHO classification of maternal cardiovascular risk from contraceptive use<sup>37</sup>*

| <b>Risk Class</b>            | <b>Risk for contraceptive method by cardiac condition</b>                                                                                                                                                                                                          |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>I</b><br>Always useable   | Risk no higher than the general population                                                                                                                                                                                                                         |
| <b>II</b><br>Broadly useable | Small increased risk, advantages of method generally outweigh risks                                                                                                                                                                                                |
| <b>III</b><br>Caution in use | Risks usually outweigh advantages of method. Other methods preferable. Exceptions if: <ol style="list-style-type: none"> <li>1. Patient accepts risks and rejects alternatives</li> <li>2. Risk of pregnancy very high and other methods less effective</li> </ol> |
| <b>IV</b><br>Do not use      | Method contraindicated: represents unacceptable health risk                                                                                                                                                                                                        |

Contraceptives containing oestrogen are contraindicated (WHO IV) in women at high risk of thrombosis. This includes women with older MPVs (for example the single leaflet tilting disc mitral valve), with actual or potential right-to-left shunts, cyanosis, PH or a Fontan circulation.<sup>37</sup> The levonogestrel-releasing intrauterine device is the safest and most effective contraceptive available that can be used in women with high risk conditions such as these, with a contraceptive efficacy that is superior to sterilization.<sup>4,37</sup> It should be noted that up to 5% of women experience a vasovagal reaction during insertion, which could prove to be fatal in those with a Fontan circulation or pulmonary vascular disease. For this reason it should only be used in such women if progesterone-only pills or subdermal implants cause unacceptable vaginal bleeding, and it should be inserted by an experienced operator in a hospital environment.<sup>4,37</sup>

For women requesting sterilization, hysteroscopically-inserted intratubal stents (Essure™) may be inserted under local anaesthesia and have a very low failure rate. This avoids the need for the pneumoperitoneum, head-down tilt and positive-pressure ventilation required for laparoscopic tubal ligation, which may cause haemodynamic instability in women with a Fontan circulation or pulmonary vascular disease.<sup>4,37,73</sup>

Termination of pregnancy should be discussed if pregnancy occurs in women for whom it would represent a major maternal and/or fetal risk (WHO IV). Ideally this should be performed as soon as possible as the risks increase with advancing gestation. Suction termination is the safest method of termination in the first and second trimesters and should be carried out in a unit with appropriate expertise and on-site cardiac surgery. Medical termination using prostaglandins E1 or E2 may be

considered in both the first and second trimesters. However, systemic absorption may lead to a fall in systemic vascular resistance and hypotension, such that high risk women should be closely monitored.<sup>4,10,37</sup>

### 1.6.2 Antenatal care

It is important that antenatal and intrapartum care is individualized according to the woman's cardiac condition and functional status. However, guidelines regarding the frequency of review and the personnel who should be involved are based on clinical experience rather than prospective studies or randomized controlled trials, and rely largely on Class C evidence (small studies, retrospective studies, registries and/or consensus of opinion of experts).<sup>4,5,10,73</sup>

Risk assessment should be carried out early in pregnancy by an experienced multidisciplinary team consisting of an obstetrician, cardiologist and anaesthetist. Low risk women can be returned to routine care, while moderate to high-risk patients should be cared for in a tertiary centre with appropriate expertise. These women should be seen regularly (weekly in the third trimester), with cardiovascular assessment (including measurement of blood pressure and pulse rate/rhythm, and oxygen saturations in cyanotic women) performed carefully at each visit as changes may be suggestive of early signs of decompensation. Women with structural congenital heart disease should be offered fetal echocardiography at 18-22 weeks' gestation and serial growth scans may be appropriate in pregnancies at high risk of fetal growth restriction.

Delivery planning should take place in the early third trimester, again in the setting of

the multidisciplinary team. Factors such as mode and place of delivery, analgesia/anaesthesia, personnel to be present, appropriate prophylaxis against postpartum haemorrhage and postpartum management (including monitoring and length of stay in hospital after delivery, and timing of postnatal review) should be discussed and agreed with the woman and recorded in the maternity notes.<sup>5,10</sup>

### 1.6.3 Labour and delivery

#### Timing and mode of delivery

In the majority of cases the preferred mode of delivery is vaginal, with Caesarean section for the usual obstetric reasons.<sup>4</sup> Vaginal delivery is generally associated with smaller haemodynamic changes and less risk of haemorrhage, infection and venous thromboembolism than delivery by caesarean section.<sup>83</sup> However, Caesarean section may become necessary for a variety of reasons, both fetal (there is a high risk of FGR in many women with cardiac disease, and the growth-restricted fetus may be less able to tolerate the stresses of labour) and maternal (signs of cardiac decompensation), and when performed in labour may be associated with increased blood loss and rates of infection.<sup>83</sup> It is often suggested that women with borderline cardiac dysfunction should avoid a prolonged active second stage of labour with a low threshold for assisted delivery aimed at reducing the cardiac work-load. There are however, no data to support this approach.<sup>78</sup> Adequate pain relief with epidural anaesthesia is thought to attenuate the haemodynamic changes associated with labour and delivery.<sup>28</sup> If a trial of vaginal delivery is considered appropriate labour should not be induced unless there are specific obstetric reasons or signs of cardiovascular decompensation. In particular preterm induction of labour is often prolonged and is associated with a higher rate of emergency Caesarean delivery than induction of labour at term.

Elective Caesarean section offers the advantage of timing the delivery to ensure optimal conditions, in particular, for high-risk conditions, the presence of senior and experienced staff. Caesarean section should also be considered in women on oral anticoagulants in preterm labour, patients with MFS and an aortic root >45mm, women with acute or chronic aortic dissection and those with acute heart failure.<sup>4</sup>

### Management of the third stage

In normal pregnancy uterotonics have been shown to significantly reduce the risk of PPH by up to 50%.<sup>84</sup> However, they have significant haemodynamic effects which may make them unsuitable in women with cardiac disease. It is well established that ergometrine causes vasoconstriction (especially in the coronary arteries) and hypertension.<sup>78</sup> Bolus doses of oxytocin cause an increase in pulmonary vascular resistance and a reduction in systemic vascular resistance causing hypotension and tachycardia.<sup>85</sup> Two recent randomized controlled trials have reported ECG changes suggestive of myocardial ischaemia associated with oxytocin administration in healthy women undergoing elective caesarean section with regional anaesthesia.<sup>86,87</sup> Recent advice from the RCOG<sup>5</sup> and ESC<sup>4</sup> recommends a low dose (<2U/min) syntocinon infusion, and consideration of the use of uterine compression sutures at Caesarean section.<sup>5</sup>

## **1.7 Summary**

Cardiac disease in pregnancy continues to be of growing importance both in terms of the number of women affected and maternal and neonatal morbidity and mortality.

Although ischaemic heart disease, cardiomyopathy and aortic dissection are now the leading cardiac causes of maternal death, rheumatic heart disease is again becoming common due to increasing immigration from countries where rheumatic fever is endemic. Although considerable progress has been made in the management of congenital heart disease in pregnancy and maternal mortality rates in such women continue to fall, it remains the commonest type of cardiac disease seen in pregnancy, and women with increasingly complex disease are now becoming pregnant. Despite this care remains largely empirical; guidelines are based on evidence from case series and experience rather than randomised controlled trials.

## **Chapter 2: Methods**

## **2.1 Study design**

This study is a retrospective analysis of the effect of maternal cardiac disease on maternal and fetal/neonatal outcomes in a tertiary referral academic cardiac and obstetric unit. It was carried out at the Chelsea and Westminster and Royal Brompton Hospitals in London, UK, between April 2008 and October 2011.

## **2.2 Data collection**

Women with cardiac disease cared for by the Joint Cardiac and Obstetric Service of the Chelsea and Westminster and Royal Brompton Hospitals were identified from a database commenced in 1994.

Data were collected from a detailed review of case notes supplemented with data from the Circonia Maternity Information System (CMIS<sup>®</sup>, HD Clinical Ltd, Bishops Stortford, Herts, UK), used for routine maternity data collection at the Chelsea and Westminster Hospital. Demographic data including age at booking, parity, co-morbidities, regular medication, tobacco smoking and use of illicit drugs, previous cardiac surgery and functional, echocardiographic and/or cardiac magnetic resonance (CMR) assessment were recorded in a spreadsheet, with appropriate safeguards regarding confidentiality. Information on cardiovascular, obstetric and anaesthetic management during pregnancy and labour, and maternal and neonatal outcomes was gathered and also entered into the spreadsheet.

Control data, where required, were obtained about the women who delivered immediately before and immediately after the index case, thus allowing comparison with the overall obstetric population at the Chelsea and Westminster Hospital. If the

date of delivery was prior to 1998 then women who delivered on the same date in 1999 were used as controls, as routine CMIS<sup>®</sup> data were not available before this time.

Customised birth weight centiles, adjusted for gestational age, parity, maternal body mass index (BMI) and ethnic origin, were calculated using computer-generated charts.<sup>88,89</sup>

Cardiac, obstetric and fetal/neonatal complications and intrapartum events were noted, according to the following definitions:

#### 2.2.1 Cardiac complications

- cardiomyopathy (new onset in pregnancy) – structural and functional abnormalities of the ventricular myocardium that are unexplained by flow-limiting coronary artery disease or abnormal loading conditions<sup>90</sup>
- myocardial infarction
- heart failure – decline in NYHA functional class and/or evidence of pulmonary oedema on clinical examination or chest x-ray, and/or deterioration of ventricular function on echocardiography
- sustained arrhythmia requiring treatment
- aortic dissection
- endocarditis
- cardiac death

### 2.2.2 Obstetric complications

- pregnancy-induced hypertension (PIH) - raised blood pressure  $>140/90$  mmHg on two occasions at least two hours apart after 20 weeks of gestation
- pre-eclampsia (PET) - PIH plus proteinuria of  $\geq 300$ mg/L in a 24-hour urine collection, or persistent ++ proteinuria on dipstick
- eclampsia - PET with major convulsive seizures
- antepartum haemorrhage (APH) - bleeding from the genital tract after 24 weeks of gestation
- gestational diabetes
- preterm pre-labour rupture of membranes (PPROM) - spontaneous rupture of membranes prior to 37 weeks' gestation
- spontaneous preterm labour - labour prior to 37 weeks' gestation
- post-partum haemorrhage (PPH) - blood loss of greater than 500ml at vaginal delivery or 1000ml at caesarean section
- venous thromboembolism

### 2.2.3 Intrapartum events

- mode of delivery
- use of regional and general anaesthesia
- length of second stage of labour in vaginal deliveries

### 2.2.4 Fetal/neonatal complications

- preterm birth - delivery after 24 and before 37 completed weeks' gestation

- small for gestational age (SGA) - birth weight less than the fifth customized centile
- perinatal mortality - stillbirth after 24 completed weeks of pregnancy and neonatal death up to 1 week after birth
- neonatal mortality - up to 1 month of life
- recurrence of congenital heart disease in the offspring (diagnosed either pre-or postnatally)

### **2.3 Data analysis**

Data were analysed using SPSS 22 for Windows and GraphPad Prism version 6.0d.

Descriptive statistics are reported as frequency and median and range, or mean and standard deviation, as appropriate. Continuous variables were compared with the students t-test if the data were normally distributed and with the Mann-Whitney U-test if they were not. The chi-square test or Fisher's exact test with cell numbers of <5 were used to test differences between relative frequencies of occurrence. All tests were two-tailed and  $p < 0.05$  was considered statistically significant.

Where relevant, binary logistic regression was performed to identify patient characteristics associated with adverse pregnancy outcomes divided into the 3 composite endpoints (as defined above): cardiac, obstetrics and fetal/neonatal complications. Multiple pregnancies were excluded because they pose special risks and the numbers were too small for meaningful analysis. Women with isolated mitral valve prolapse (ie. with no haemodynamic consequences) were also excluded.

Univariable analysis was performed initially. Variables associated with an increased

incidence of the studied endpoints ( $p < 0.1$ ) were then brought forward to multivariable analysis, with sequential backward deletion of the least significant characteristic until all remaining variables were significantly ( $p < 0.05$ ) associated with the endpoint.

Univariable analysis alone is limited by the fact that the independent variables in a series of univariable regressions may be correlated; if such correlated variables are treated as if they are independent this may lead to an overestimation of the likelihood of the outcome event. Subsequent multivariable analysis tests for interaction between variables, and thus adjusts for confounding.

## **2.4 Ethical Approval**

This study received approval from the Brompton, Harefield and NHLI Research Ethics Committee (ref. no. 06/Q0404/37).

## **Chapter 3:      Pregnancy outcomes in women with pre-existing heart disease**

### 3.1 Abstract

#### 3.1.1 Aims:

To assess cardiac, obstetric and fetal/neonatal outcomes in pregnant women with heart disease and to investigate maternal risk factors for adverse events

#### 3.1.2 Methods:

Retrospective review of case records

#### 3.1.3 Results:

There were 489 pregnancies in 326 women. Congenital heart disease was the largest group (50%), followed by valvular heart disease (28%). Two hundred and eighty-two pregnancies (58%) were in nulliparous women. There were 4 maternal deaths. Significant cardiac complications occurred in 7.4% of pregnancies: the most frequently encountered complication was arrhythmia (4.3%), followed by heart failure (2.0%). A history of arrhythmia prior to pregnancy ( $p<0.0001$ ) and presence of a mechanical heart valve ( $p=0.003$ ) independently predicted cardiac events. Obstetric complications occurred in 34% of pregnancies, most commonly postpartum haemorrhage (21.9%), which was independently associated with delivery by emergency caesarean section ( $p<0.001$ ) and use of dose-adjusted low molecular weight heparin ( $p=0.001$ ). Delivery was by caesarean section in 39% of cases and regional anaesthesia was used in 73.6% of deliveries. There were 6 stillbirths and 5 neonatal deaths. Adverse perinatal outcomes occurred in 30.3% of pregnancies. Twenty percent of babies were small for gestational age, while 11.7% were born before 37 completed weeks of gestation. Factors independently associated with fetal/neonatal complications were poor maternal functional class pre-

pregnancy ( $p=0.001$ ), use of any cardiac medication ( $p=0.022$ ), the presence of a mechanical prosthetic heart valve ( $p=0.024$ ) and the presence of a systemic right ventricle ( $p=0.007$ ).

#### 3.1.4 Conclusions:

Pregnancy in women with pre-existing heart disease is associated with significant rates of maternal and perinatal complications. Predictors previously described as being associated with adverse outcomes were confirmed and the presence of a systemic right ventricle was reported as a new association with fetal/neonatal events.

## 3.2 Introduction

Up to 4% of pregnancies in developed countries are complicated by maternal cardiovascular disease. It is the commonest single cause of maternal death in the United Kingdom, and death rates are continuing to rise.<sup>3</sup> Despite congenital heart disease being the most frequent form of cardiovascular disease present during pregnancy in the western world (75-82%),<sup>4,7,8</sup> most deaths now occur in women with acquired heart disease, the leading causes being sudden adult death syndrome (SADS), myocardial infarction (MI), dissection of the thoracic aorta and cardiomyopathy.<sup>3</sup> This trend may be attributable to rising rates of obesity, chronic conditions such as hypertension and diabetes, and the tendency for women to delay pregnancy until later in life. Furthermore, deaths in women with rheumatic heart disease are rising again due to increasing immigration from countries where rheumatic fever is endemic.

Pregnancy in women with pre-existing heart disease is known to be associated with increased risks of cardiac events, and obstetric and perinatal complications.

The risk of adverse events is dependent on the ability of the woman to adapt to the profound physiological and haemodynamic changes associated with pregnancy and delivery. Assessment of disease-specific risk is difficult. Current guidance<sup>4</sup> recommends use of the modified WHO risk classification (which includes all known maternal cardiovascular risk factors)<sup>37</sup> to conduct maternal risk assessment, although other risk scores have also been developed.<sup>8,36</sup> Conditions associated with volume overload are usually better tolerated than those associated with pressure overload.<sup>8,30,32</sup> Previous cardiac events, poor functional class (NYHA III or IV) prior

to pregnancy, presence of central cyanosis, left heart obstruction, myocardial dysfunction and mechanical valve prostheses have all been identified as independent predictors of adverse maternal and fetal/neonatal outcomes.<sup>8,30,31,32,33,35,36,38,39</sup>

Although significant improvements have been made in the management of pregnancy in women with pre-existing heart disease, care was felt to be substandard in half of the cardiac deaths reported to the 2006-2008 Confidential Enquiry,<sup>3</sup> with current guidelines being based upon evidence from case series rather than randomised controlled trials.<sup>4,5</sup>

### **3.3 Aims**

To assess cardiac obstetric and fetal/neonatal outcomes in pregnant women with heart disease and to investigate maternal risk factors for adverse events.

### 3.4 Methods

Women with cardiac disease cared for by the Joint Cardiac and Obstetric Service of the Chelsea and Westminster and Royal Brompton Hospitals were identified from a database commenced in 1994.

Data were collected from a detailed review of the case notes, supplemented by the Circonia Maternity Information System (CMIS<sup>®</sup>, HD Clinical Ltd, Bishops Stortford, Herts, UK). Only singleton pregnancies progressing beyond 24 weeks of gestation were included. In all women, demographic data and information on obstetric and anaesthetic management during pregnancy and labour, and maternal and neonatal outcomes was obtained, noting cardiac, obstetric and fetal/neonatal complications and intra-partum events as previously described in chapter 2.

Data were analysed using SPSS 23 and GraphPad Prism version 6.0d. Descriptive statistics for nominal data are expressed in absolute numbers and percentages. Mean value and standard deviations are presented for normally distributed continuous variables, and for non-normally distributed continuous variables, median and range. Binary logistic regression was performed to identify patient characteristics associated with adverse pregnancy outcomes divided into the 3 composite endpoints: cardiac, obstetrics and fetal/neonatal complications (as defined previously in chapter 2).

Women with isolated mitral valve prolapse (ie. with no haemodynamic consequences) were also excluded. The following baseline variables and cardiac diagnoses were assessed: history of arrhythmias, the presence of pre-existing myocardial dysfunction (ejection fraction <40% prior to pregnancy), maternal NYHA class prior to pregnancy, the presence of central cyanosis, previous cardiac surgery, previous

cardiac events (heart failure, cerebrovascular accident, transient ischaemic attack, myocardial infarction, endocarditis), pre-existing hypertension, use of cardiovascular medication during pregnancy, use of anticoagulants, use of beta blockers, maternal cigarette smoking during pregnancy, presence of PH (pulmonary artery pressure >25mmHg at rest pre-pregnancy), coarctation of the aorta, Marfan syndrome, complex cyanotic congenital heart disease (pulmonary atresia, Fontan circulation), Ebstein's anomaly, valvular heart disease, presence of a metallic prosthetic heart valve, tetralogy of Fallot (repaired), presence of a systemic right ventricle, presence of a patent shunt in the absence of pulmonary hypertension (atrial septal defect, ventricular septal defect, patent ductus arteriosus), left heart obstruction (aortic stenosis, mitral stenosis, coarctation of the aorta, hypertrophic cardiomyopathy), left heart regurgitation (aortic regurgitation, mitral regurgitation), right heart obstruction (pulmonary stenosis) and right heart regurgitation (pulmonary regurgitation, tricuspid regurgitation). Univariable analysis was performed initially. Variables that were associated with an increased incidence of the studied endpoints ( $p < 0.1$ ) were then brought forward to multivariable analysis, thus testing for interaction between them and adjusting for confounding.

## 3.5 Results

### 3.5.1 Baseline characteristics and maternal cardiac diagnoses

There were 489 pregnancies in 326 women. The distribution of the primary cardiac diagnoses is shown in table 1. Most occurred in women with congenital heart disease (50%), while valvular heart disease was the next most common diagnosis (28%).

Fifty-eight percent of pregnancies (282) were in nulliparous women.

Baseline characteristics are shown in table 2. Mean age at booking was 30 years (SD 6.0). Fifty percent of pregnancies occurred in women who had undergone previous cardiac surgery, including repair of COA (10.4%), Fontan palliation (0.8%), repair of tetralogy of Fallot (10.9%), Mustard palliation for transposition of the great arteries (TGA) (3.5%) and closure of shunt lesions (6.3%). Six percent were in women who had previously suffered a cardiac event (heart failure, cerebrovascular accident, transient ischaemic attack, myocardial infarction, endocarditis). NYHA functional class was I in 449 (91.8%) pregnancies; 37 (7.6%) pregnancies occurred in women in NYHA functional class II and 3 (0.6%) were in women in NYHA functional class III.

### 3.5.2 Maternal and fetal/neonatal outcomes

Cardiac, obstetric, intrapartum and neonatal outcomes are detailed in tables 3, 4 and 5.

#### *Cardiac outcomes*

There were 36 (7.4%) pregnancies with at least one cardiac complication. The most frequent event was arrhythmia (4.3%), followed by heart failure (2.0%). There were 4 maternal deaths: the 2 deaths in women with PH (one died as a result of a PH crisis

after developing PET at 26 weeks, and the other following a sustained arrhythmia at the time of delivery which led to profound hypotension and unrecoverable asystolic cardiac arrest) and that of another woman who suffered thrombosis of a mechanical aortic valve are described elsewhere in this thesis. A fourth woman with dilated cardiomyopathy (DCM) died unexpectedly in the postnatal period, presumably from an arrhythmia.

### *Obstetric outcomes*

Caesarean section was performed in 39% of pregnancies (electively in 16.1% of cases), but there is limited data in most cases as to the reason for performing the Caesarean. Labour was induced in 21% of cases. Thirty-five percent of the vaginal deliveries were spontaneous, the remainder being assisted by use of ventouse or forceps. Regional anaesthesia was used in 73.6% of deliveries overall.

There were 166 (34.0%) pregnancies with at least one obstetric complication, the most common being postpartum haemorrhage (PPH) which occurred in 21.9% of cases. Hypertensive disorders occurred in 8.2% of pregnancies. Spontaneous preterm labour (before 37 completed weeks of gestation) occurred in 4.9% of cases.

### *Fetal/Neonatal outcomes*

Adverse perinatal outcomes occurred in 30.3% of pregnancies. Median gestational age at delivery was 39 weeks (range 25 to 42). The preterm delivery rate was 11.7% and in 58% of these, early delivery was undertaken for medical reasons. Median birth weight and customized birth weight centile were 3165g (range 420g to 5130g) and 34<sup>th</sup> centile (range 0 to 98) respectively. The most frequently encountered

complication was being small for gestational age (birth weight less than the 5<sup>th</sup> customized centile) (20.9%). There were 6 stillbirths and 5 neonatal deaths (3 as a result of complications of prematurity in babies delivered iatrogenically preterm).

### *Logistic regression*

Tables 6-9 illustrate the results of the univariable and multivariable logistic regression analyses. A history of arrhythmia and presence of an MPV were independently predictive of cardiac complications ( $p < 0.0001$  and  $0.003$  respectively). Known myocardial dysfunction was associated with development of heart failure during the pregnancy (OR 15.40, 95% CI 2.09-113.39,  $p = 0.007$ ). Use of cardiac medications was independently associated with obstetric complications ( $p = 0.001$ ); presence of pre-existing hypertension was predictive of development of PIH (OR 4.14, 95% CI 1.54-11.14,  $p = 0.005$ ) while use of dose-adjusted LMWH and delivery by emergency caesarean section were both independently associated with PPH ( $p = 0.001$  and  $p < 0.001$  respectively). Maternal NYHA functional class  $\geq 2$  was predictive of neonatal complications ( $p = 0.007$ ) as was use of any cardiac medication ( $p = 0.022$ ), presence of an MPV ( $p = 0.024$ ) and the presence of a systemic right ventricle ( $p = 0.007$ ). Maternal NYHA functional class  $\geq 2$  was also independently associated with iatrogenic preterm delivery ( $p = 0.033$ ), as was use of any cardiac medication and the presence of left heart obstruction ( $p = 0.018$  and  $0.029$  respectively). Birth weight less than the 5<sup>th</sup> customised centile (SGA) was predicted by use of beta blockers ( $p = 0.006$ ), presence of a systemic right ventricle ( $p = 0.001$ ) and complex cyanotic congenital heart disease ( $p = 0.016$ ).

Table 1: Primary cardiac diagnoses

| Primary cardiac diagnosis                        | Number of pregnancies (%) |                   |                   |                 |                 |
|--------------------------------------------------|---------------------------|-------------------|-------------------|-----------------|-----------------|
|                                                  | Total                     | P0                | P1                | P2              | P>2             |
|                                                  | <b>489 (100.0)</b>        | <b>282 (57.7)</b> | <b>149 (30.4)</b> | <b>42 (8.6)</b> | <b>16 (3.3)</b> |
| <b>Pulmonary hypertension</b>                    | <b>9 (1.8)</b>            | <b>5</b>          | <b>2</b>          | <b>2</b>        | <b>0</b>        |
| <b>Cardiomyopathy</b>                            | <b>23 (4.7)</b>           | <b>10</b>         | <b>10</b>         | <b>1</b>        | <b>2</b>        |
| - DCM                                            | 8                         | 5                 | 3                 | 0               | 0               |
| - PPCM                                           | 5                         | 0                 | 3                 | 0               | 2               |
| - HCM                                            | 9                         | 5                 | 3                 | 1               | 0               |
| - ARVC                                           | 1                         | 0                 | 1                 | 0               | 0               |
| <b>Coarctation of the aorta</b>                  | <b>57 (11.7)</b>          | <b>30</b>         | <b>15</b>         | <b>6</b>        | <b>6</b>        |
| - unrepaired                                     | 6                         | 2                 | 1                 | 1               | 2               |
| - repaired                                       | 51                        | 28                | 14                | 5               | 4               |
| <b>Marfan syndrome</b>                           | <b>30 (6.2)</b>           | <b>21</b>         | <b>8</b>          | <b>1</b>        | <b>0</b>        |
| <b>Complex cyanotic congenital heart disease</b> | <b>12 (2.5)</b>           | <b>9</b>          | <b>3</b>          | <b>0</b>        | <b>0</b>        |
| - pulmonary atresia with VSD                     | 7                         | 5                 | 1                 | 0               | 0               |
| - Fontan circulation                             | 5                         | 4                 | 2                 | 0               | 0               |
| <b>Valvular heart disease</b>                    | <b>138 (28.2)</b>         | <b>77</b>         | <b>48</b>         | <b>11</b>       | <b>2</b>        |
| - AS                                             | 20                        | 12                | 7                 | 1               | 0               |
| - AR                                             | 15                        | 7                 | 5                 | 2               | 1               |
| - mixed AVD                                      | 9                         | 5                 | 3                 | 1               | 0               |
| - MS                                             | 16                        | 8                 | 5                 | 2               | 1               |
| - MR                                             | 21                        | 13                | 8                 | 0               | 0               |
| - mixed MVD                                      | 4                         | 1                 | 1                 | 2               | 0               |
| - Mixed AVD/MVD                                  | 1                         | 1                 | 0                 | 0               | 0               |
| - bioprosthetic valve                            | 10                        | 5                 | 4                 | 1               | 0               |
| - mechanical valve                               | 8                         | 4                 | 3                 | 1               | 0               |
| - BAV – no AS/AR                                 | 6                         | 3                 | 3                 | 0               | 0               |
| - PS                                             | 21                        | 12                | 8                 | 1               | 0               |
| - PR                                             | 5                         | 4                 | 1                 | 0               | 0               |
| - TR                                             | 2                         | 2                 | 0                 | 0               | 0               |
| <b>Tetralogy of Fallot (repaired)</b>            | <b>53 (10.9)</b>          | <b>35</b>         | <b>12</b>         | <b>4</b>        | <b>2</b>        |
| - Tetralogy of Fallot (repaired) with severe PR  | 13                        | 9                 | 2                 | 2               | 0               |
| <b>Complete TGA (repaired)</b>                   | <b>17 (3.5)</b>           | <b>12</b>         | <b>4</b>          | <b>1</b>        | <b>0</b>        |
| - Atrial switch                                  | 17                        | 12                | 4                 | 1               | 0               |
| - Arterial switch                                | 0                         | 0                 | 0                 | 0               | 0               |
| <b>Cc TGA (unrepaired)</b>                       | <b>6 (1.2)</b>            | <b>4</b>          | <b>2</b>          | <b>0</b>        | <b>0</b>        |
| <b>Ebstein's anomaly</b>                         | <b>4 (0.8)</b>            | <b>3</b>          | <b>1</b>          | <b>0</b>        | <b>0</b>        |
| <b>Ischaemic heart disease</b>                   | <b>1 (0.2)</b>            | <b>0</b>          | <b>0</b>          | <b>1</b>        | <b>0</b>        |
| <b>Arrhythmia</b>                                | <b>63 (12.9)</b>          | <b>34</b>         | <b>20</b>         | <b>8</b>        | <b>1</b>        |
| - AF                                             | 12                        | 7                 | 4                 | 0               | 1               |
| - CCHB                                           | 5                         | 3                 | 1                 | 1               | 0               |
| - L-L-G                                          | 6                         | 3                 | 2                 | 1               | 0               |
| - Long QT syndrome                               | 5                         | 1                 | 3                 | 1               | 0               |
| - SVT                                            | 19                        | 10                | 6                 | 3               | 0               |
| - VT                                             | 1                         | 1                 | 0                 | 0               | 0               |
| - WPW syndrome                                   | 13                        | 7                 | 4                 | 2               | 0               |
| - sinoatrial disease                             | 1                         | 1                 | 0                 | 0               | 0               |
| - malignant vasovagal syndrome                   | 1                         | 1                 | 0                 | 0               | 0               |
| <b>Shunt lesions (no PH)</b>                     | <b>66 (13.6)</b>          | <b>37</b>         | <b>21</b>         | <b>6</b>        | <b>2</b>        |
| - unrepaired                                     | 35                        | 19                | 12                | 4               | 0               |
| - repaired                                       | 31                        | 18                | 9                 | 2               | 2               |
| <b>Other</b>                                     | <b>9 (1.8)</b>            | <b>4</b>          | <b>3</b>          | <b>1</b>        | <b>1</b>        |
| - cardiac sarcoidosis                            | 1                         | 0                 | 0                 | 0               | 1               |
| - Cardiac syndrome X                             | 1                         | 0                 | 0                 | 1               | 0               |
| - DCRV                                           | 4                         | 2                 | 2                 | 0               | 0               |
| - LA isomerism                                   | 2                         | 1                 | 1                 | 0               | 0               |
| - repaired TAPVD                                 | 1                         | 1                 | 0                 | 0               | 0               |

DCM: dilated cardiomyopathy; PPCM: peripartum cardiomyopathy; HCM: hypertrophic cardiomyopathy; ARVC: arrhythmogenic right ventricular cardiomyopathy; AS: aortic stenosis; AR: aortic regurgitation; AVD: aortic valve disease; MS: mitral stenosis; MR: mitral regurgitation; MVD: mitral valve disease; BAV: bicuspid aortic valve; MVP: mitral valve prolapse; PS: pulmonary stenosis; PR: pulmonary regurgitation; TGA: transposition of the great arteries; ccTGA: congenitally corrected transposition of the great arteries; AF: atrial fibrillation; CCHB: congenital complete heartblock; SVT: supraventricular tachycardia; VT: ventricular tachycardia; WPW syndrome: Wolff-Parkinson White syndrome; DCRV: double-chambered right ventricle; LA isomerism: left atrial isomerism; TAPVD: total anomalous pulmonary venous drainage

Table 2: Baseline characteristics

|                                                              | mean (SD)    |
|--------------------------------------------------------------|--------------|
| <b>Maternal age at booking (years)</b>                       | 30 (6.0)     |
|                                                              | <b>n (%)</b> |
| <b>Previous cardiac surgery</b>                              | 246 (50.3)   |
| <b>Previous cardiac event</b>                                | 28 (5.7)     |
| <b>NYHA</b>                                                  |              |
| - I                                                          | 449 (91.8)   |
| - II                                                         | 37 (7.6)     |
| - III                                                        | 3 (0.6)      |
| <b>Cardiac medications</b>                                   |              |
| - $\beta$ -blocker*                                          | 58 (11.9)    |
| - calcium channel blocker*                                   | 6 (1.2)      |
| - diuretic*                                                  | 6 (1.2)      |
| - antiarrhythmic*                                            | 7 (1.4)      |
| - any anticoagulant*                                         | 40 (8.2)     |
| - Warfarin*                                                  | 1 (1.2)      |
| - dose-adjusted low molecular weight heparin*                | 25 (5.1)     |
| - unfractionated heparin*                                    | 1 (1.2)      |
| - aspirin*                                                   | 37 (7.6)     |
| - sildenafil*                                                | 7 (1.4)      |
| - iloprost*                                                  | 2 (0.4)      |
| - taking more than 1 medication                              | 37 (7.6)     |
| <b>Haemodynamics</b>                                         |              |
| - left heart obstruction                                     | 135 (27.6)   |
| - left heart regurgitation                                   | 80 (16.4)    |
| - right heart obstruction                                    | 38 (7.8)     |
| - right heart regurgitation                                  | 58 (11.9)    |
| <b>Central cyanosis</b>                                      | 17 (3.5)     |
| <b>Previous sustained arrhythmia (not primary diagnosis)</b> | 110 (22.5)   |
| <b>Pre-existing myocardial dysfunction</b>                   | 31 (6.3)     |
| <b>Pre-existing hypertension</b>                             | 38 (7.8)     |
| <b>Smoking</b>                                               | 37 (7.6)     |

\* not mutually exclusive as some women were receiving more than one type of medication

n = number of pregnancies

Table 3: Event rate in absolute numbers (percentages) in 489 pregnancies

|                                                   | n (%)      |
|---------------------------------------------------|------------|
| <b>Maternal cardiac complications</b>             |            |
| - Cardiomyopathy (new diagnosis during pregnancy) | 4 (0.8)    |
| - Myocardial infarction                           | 3 (0.6)    |
| - Heart failure                                   | 10 (2.0)   |
| - Arrhythmia                                      | 21 (4.3)   |
| - Endocarditis                                    | 4 (0.8)    |
| - Aortic dissection                               | 1 (0.2)    |
| - Cardiac surgery during pregnancy                | 1 (0.2)    |
| - Death                                           | 4 (0.8)    |
| <b>Maternal obstetric complications</b>           |            |
| - Pregnancy-induced hypertension                  | 24 (4.9)   |
| - Pre-eclampsia                                   | 16 (3.3)   |
| - Antepartum haemorrhage                          | 13 (2.7)   |
| - Post-partum haemorrhage                         | 107 (21.9) |
| - Gestational diabetes mellitus                   | 5 (1.0)    |
| - Preterm pre-labour rupture of membranes         | 2 (0.4)    |
| - Preterm labour                                  | 24 (4.9)   |
| - Venous thromboembolism                          | 4 (0.8)    |
| <b>Fetal/neonatal complications</b>               |            |
| - Preterm delivery                                | 57 (11.7)  |
| <i>Iatrogenic preterm delivery</i>                | 33 (6.7)   |
| - Small for gestational age                       | 102 (20.9) |
| - Stillbirth                                      | 6 (1.2)    |
| - Neonatal death                                  | 5 (1.0)    |

Table 4: Overview of pregnancies with adverse events, organized by primary cardiac diagnosis (n=number of affected pregnancies)

| Primary cardiac diagnosis                     | Total number of pregnancies | Pregnancies affected by $\geq 1$ adverse event: n (%) |                   |                      |
|-----------------------------------------------|-----------------------------|-------------------------------------------------------|-------------------|----------------------|
|                                               |                             | Cardiac event                                         | Obstetric event   | Fetal/neonatal event |
| Pulmonary hypertension                        | 9                           | 3 (33.3)                                              | 7 (77.8)          | 7 (77.8)             |
| Cardiomyopathy                                | 23                          | 4 (17.4)                                              | 9 (39.1)          | 7 (30.4)             |
| Coarctation of the aorta                      | 57                          | 3 (5.3)                                               | 16 (28.1)         | 14 (24.6)            |
| Marfan syndrome                               | 30                          | 2 (6.7)                                               | 9 (30.0)          | 13 (43.3)            |
| Pulmonary atresia with VSD                    | 7                           | 0 (0.0)                                               | 3 (42.8)          | 6 (85.7)             |
| Fontan circulation                            | 5                           | 1 (25.0)                                              | 4 (80.0)          | 5 (100.0)            |
| Valvular heart disease                        | 138                         | 9 (6.5)                                               | 45 (32.6)         | 40 (29.0)            |
| Tetralogy of Fallot (repaired)                | 53                          | 4 (7.5)                                               | 20 (37.7)         | 13 (24.5)            |
| Complete TGA (repaired)                       | 17                          | 3 (17.6)                                              | 7 (41.2)          | 11 (64.7)            |
| ccTGA                                         | 6                           | 0 (0.0)                                               | 2 (33.3)          | 1 (16.7)             |
| Ebstein's anomaly                             | 4                           | 0 (0.0)                                               | 3 (75.0)          | 4 (100.0)            |
| Ischaemic heart disease                       | 1                           | 1 (100.0)                                             | 1 (100.0)         | 0 (0.0)              |
| Arrhythmia                                    | 63                          | 9 (14.3)                                              | 19 (30.2)         | 13 (20.6)            |
| Shunt lesion (without pulmonary hypertension) | 66                          | 0 (0.0)                                               | 17 (25.8)         | 12 (18.2)            |
| Other                                         | 9                           | 0 (0.0)                                               | 4 (44.4)          | 2 (22.2)             |
| <b>Overall</b>                                | <b>489</b>                  | <b>36 (7.4)</b>                                       | <b>166 (34.0)</b> | <b>148 (30.3)</b>    |

Table 5: Intrapartum outcomes

|                                            | n (%)                 |
|--------------------------------------------|-----------------------|
| <b>Mode of delivery</b>                    |                       |
| SVD                                        | 171 (35.0)            |
| assisted vaginal delivery                  | 127 (26.0)            |
| Elective CS                                | 79 (16.1)             |
| Emergency CS                               | 112 (22.9)            |
| <b>Anaesthesia</b>                         |                       |
| regional                                   | 360 (73.6)            |
| general                                    | 34 (7.0)              |
| neither                                    | 95 (19.4)             |
|                                            | <b>median (range)</b> |
| <b>Gestational age at delivery (weeks)</b> | 39 (25 – 42)          |
| <b>Birth weight (g)</b>                    | 3165 (420 - 5130)     |
| <b>Customised birth weight centile</b>     | 35 (0 – 98)           |

SVD: spontaneous vaginal delivery; CS: Caesarean section

Table 6: Univariable analysis for predictors of complications during pregnancy in women with pre-existing heart disease

| Complications         | Predictor                                   | Odds Ratio   | 95% CI            | p                |
|-----------------------|---------------------------------------------|--------------|-------------------|------------------|
| <b>Cardiac</b>        | History of arrhythmia                       | 3.68         | 1.74-7.81         | 0.001            |
|                       | Myocardial dysfunction (prior to pregnancy) | 3.22         | 1.14-9.09         | 0.028            |
|                       | Mechanical valve                            | 7.93         | 1.39-45.16        | 0.020            |
|                       |                                             |              |                   |                  |
| <b>Obstetric</b>      | Previous cardiac surgery                    | 1.53         | 1.05-2.24         | 0.028            |
|                       | Any cardiac medication                      | 2.84         | 1.86-4.32         | <0.0001          |
|                       | Dose-adjusted LMWH                          | 5.57         | 2.01-16.05        | 0.001            |
|                       | Pulmonary hypertension                      | 5.89         | 1.57-22.05        | 0.009            |
|                       | Mechanical valve                            | 9.69         | 1.12-83.68        | 0.039            |
| <b>PPH</b>            | <i>Delivery by emergency CS</i>             | <i>3.34</i>  | <i>2.06-5.40</i>  | <i>&lt;0.001</i> |
|                       | <i>Central cyanosis</i>                     | <i>2.72</i>  | <i>0.99-7.49</i>  | <i>0.050</i>     |
|                       | <i>Dose-adjusted LMWH</i>                   | <i>10.78</i> | <i>3.79-30.69</i> | <i>&lt;0.001</i> |
|                       | <i>Mechanical valve</i>                     | <i>17.75</i> | <i>2.05-153.6</i> | <i>0.009</i>     |
|                       |                                             |              |                   |                  |
| <b>Fetal/Neonatal</b> | NYHA $\geq 2$                               | 7.34         | 3.54-15.23        | <0.0001          |
|                       | Previous cardiac surgery                    | 1.68         | 1.13-2.51         | 0.011            |
|                       | Central cyanosis                            | 3.53         | 1.32-9.48         | 0.012            |
|                       | Any cardiac medications                     | 3.21         | 2.09-4.93         | <0.0001          |
|                       | Dose-adjusted LMWH                          | 2.34         | 1.24-4.45         | 0.009            |
|                       | Beta blocker                                | 2.97         | 1.71-5.16         | <0.0001          |
|                       | Pulmonary hypertension                      | 4.95         | 1.47-16.71        | 0.010            |
|                       | Mechanical valve                            | 12.28        | 1.42-106.08       | 0.007            |
|                       | Systemic right ventricle                    | 6.14         | 2.12-17.77        | 0.001            |
|                       | Complex cyanotic CHD                        | 4.92         | 1.21-19.95        | 0.026            |
| <b>Iatrogenic PTD</b> | NYHA $\geq 2$                               | 10.08        | 4.63-21.93        | <0.001           |
|                       | Central cyanosis                            | 5.53         | 1.84-16.68        | 0.002            |
|                       | Any cardiac medication                      | 5.38         | 2.67-10.83        | <0.001           |
|                       | Dose-adjusted LMWH                          | 20.31        | 7.73-53.34        | <0.001           |
|                       | Pulmonary hypertension                      | 9.64         | 2.90-32.10        | <0.001           |
|                       | Mechanical valve                            | 26.61        | 4.70-150.66       | <0.001           |
|                       | Complex cyanotic CHD                        | 12.54        | 1.72-91.76        | 0.013            |
|                       | Left heart obstruction                      | 2.06         | 1.04-4.07         | 0.039            |
| <b>SGA</b>            | NYHA $\geq 2$                               | 3.50         | 1.76-6.97         | <0.001           |
|                       | Central cyanosis                            | 4.32         | 1.53-12.21        | 0.006            |
|                       | Any cardiac medications                     | 2.33         | 1.46-3.72         | <0.001           |
|                       | Dose-adjusted LMWH                          | 3.03         | 1.16-7.89         | 0.023            |
|                       | Beta blocker                                | 2.59         | 1.46-4.60         | 0.001            |
|                       | Mechanical valve                            | 7.43         | 1.34-41.15        | 0.022            |
|                       | Systemic right ventricle                    | 5.58         | 2.07-15.04        | 0.001            |
|                       | Complex cyanotic CHD                        | 9.38         | 1.79-49.10        | 0.008            |

95%CI: 95% confidence interval; LMWH: low molecular weight heparin; PPH: post partum haemorrhage; CS: caesarean section; PTD: pre-term delivery; SGA: small for gestational age; CHD: congenital heart disease

*Table 7: Multivariable analysis for predictors of complications during pregnancy in women with pre-existing heart disease*

| <b>Complications</b>  | <b>Predictor</b>                | <b>Odds Ratio</b> | <b>95% CI</b> | <b>p</b> |
|-----------------------|---------------------------------|-------------------|---------------|----------|
| <b>Cardiac</b>        | History of arrhythmia           | 4.43              | 2.02-9.72     | <0.0001  |
|                       | Mechanical valve                | 15.56             | 2.58-93.9     | 0.003    |
|                       |                                 |                   |               |          |
| <b>Obstetric</b>      | Any cardiac medication          | 2.33              | 1.43-3.79     | 0.001    |
| <b>PPH</b>            | <i>Delivery by emergency CS</i> | 3.25              | 1.98-5.35     | <0.001   |
|                       | <i>Dose-adjusted LMWH</i>       | 7.96              | 2.31-27.40    | 0.001    |
|                       |                                 |                   |               |          |
| <b>Fetal/Neonatal</b> | NYHA $\geq 2$                   | 4.66              | 1.86-11.89    | 0.001    |
|                       | Any cardiac medication          | 2.88              | 1.16-7.12     | 0.022    |
|                       | Mechanical valve                | 8.68              | 1.32-57.09    | 0.024    |
|                       | Systemic right ventricle        | 5.73              | 1.62-20.28    | 0.007    |
| <b>Iatrogenic PTD</b> | NYHA $\geq 2$                   | 3.34              | 1.11-10.10    | 0.033    |
|                       | Any cardiac medication          | 2.70              | 1.19-6.18     | 0.018    |
|                       | Left heart obstruction          | 2.57              | 1.10-5.99     | 0.029    |
| <b>SGA</b>            | Beta blocker                    | 3.56              | 1.42-8.86     | 0.006    |
|                       | Systemic right ventricle        | 6.88              | 2.27-20.86    | 0.001    |
|                       | Complex CHD                     | 16.58             | 1.70-102.33   | 0.016    |

*95% CI: 95% confidence interval; LMWH: low molecular weight heparin; PPH: post partum haemorrhage; CS: Caesarean section; PTD: pre-term delivery; SGA: small for gestational age; CHD: congenital heart disease*

## 3.6 Discussion

Pregnancy in women with pre-existing cardiac disease continues to be associated with a high frequency of adverse cardiac events, and obstetric and fetal/neonatal complications.

### 3.6.1 Baseline characteristics and cardiac diagnoses

Congenital heart disease was the largest subgroup in this series (50%) followed by valvular heart disease (28%). This is a similar distribution to that described in the data from the ROPAC registry.<sup>38</sup> Women with cardiomyopathy (4.7%) and ischaemic heart disease (1 pregnancy only) were encountered less frequently. Despite the increase in cardiac deaths in the UK being attributed to an increase in rates of acquired heart disease, congenital heart disease remains the most frequent form of cardiovascular disease seen during pregnancy in the western world.<sup>4,7,8</sup>

Most pregnancies occurred in mothers who were in NYHA functional class I prior to pregnancy (91.8%); 7.6% were in women in NYHA functional class II, and 0.6% in women who were in functional class III.<sup>8,9,33,43</sup> The risk of adverse events during pregnancy for women with pre-existing heart disease is strongly associated with the functional capacity of the patient.<sup>8,30,31,32</sup> The cohort of women with heart disease described in this study have comparable functional status to those reported elsewhere in the literature.<sup>8,9,33</sup>

### 3.6.2 Maternal outcomes

#### *Cardiac complications*

Cardiovascular complications occurred in 7.4% of pregnancies, consistent with the findings of the ZAHARA investigators.<sup>36</sup> Maternal mortality was 0.8%, and was highest among women with cardiomyopathy. High rates of heart failure (20%) and ventricular arrhythmias (20%) were also seen in this group of women, which is consistent with the ROPAC data.<sup>38</sup> Cardiomyopathy was the commonest cardiac cause of maternal death in the 2006-2008 CMACE report.<sup>3</sup> In women with DCM poor functional capacity prior to pregnancy and/or moderate to severe left ventricular systolic dysfunction are predictive of adverse maternal and fetal outcomes and also of further cardiac events in the 16 months following delivery.<sup>91</sup>

Clinically significant arrhythmias (4.3%) and heart failure (2.0%) were the most frequent adverse cardiac events overall. This is a lower rate of heart failure than that reported in many series<sup>8,35,38,39</sup> but is comparable with the ZAHARA data.<sup>36</sup> Several of the symptoms of early heart failure (such as increasing shortness of breath on exertion) are seen in healthy pregnancy. A strict definition of heart failure was applied to the patients in this study: a decline in NYHA functional class and/or evidence of pulmonary oedema on clinical examination or chest x-ray, and/or deterioration of ventricular function on echocardiography; this may account for the lower rate observed in the study. Myocardial dysfunction prior to pregnancy strongly predicted the development of heart failure (OR 15.40, 95% CI 2.09-113.39, p=0.007).

A history of arrhythmias and the presence of an MPV were identified on multivariable logistic regression analysis as being independently associated with adverse

cardiovascular events, consistent with the observations of other investigators.<sup>8,30,33,36</sup> In women with pre-existing arrhythmias, exacerbation during pregnancy is common.<sup>92</sup> Cardiac complications arose in 2 of the 8 pregnancies in women with MPVs (25%), a similar rate to that reported elsewhere in the literature.<sup>93</sup> Valve thrombosis occurred in both and resulted in the death of one woman. The optimal anticoagulant regimen during pregnancy for such women remains contentious.<sup>78</sup> In contrast to the findings of the CARPREG and ZAHARA investigators, NYHA functional class > II and the presence of central cyanosis were not identified as independent predictors of cardiovascular events and may be explained by the low numbers of such women in this series.

### *Obstetric complications*

Obstetric complications were observed in 34% of pregnancies. PPH was the most frequent, occurring in 21.9% of pregnancies. There was an association with delivery by emergency Caesarean section (OR 3.25, 95% CI 1.98-5.35,  $p < 0.001$ ) which is generally associated with higher rates of haemorrhage compared with both elective Caesarean section and vaginal delivery.<sup>83</sup> Use of anticoagulants (specifically dose-adjusted low molecular weight heparin) was unsurprisingly an independent predictor for PPH (OR 7.96, 95% CI 2.31-27.40,  $p = 0.001$ ), although the evidence from other studies is conflicting.<sup>33,38,43</sup> The presence of central cyanosis was associated with PPH in the univariable, but not the multivariable analysis. Many patients with cyanotic heart disease have haemostatic defects<sup>8</sup>, and additionally in this series there was an association between use of anticoagulant medication and presence of central cyanosis ( $r = 0.241$ ,  $p < 0.001$ ), both of which may explain this trend.

Rates of hypertensive disease were similar to those seen in the general population.<sup>94</sup> Women with COA were most likely to develop PIH (OR 4.56, 95% CI 1.66-12.57,  $p = 0.005$ ); however, there was a strong association with pre-existing hypertension in these women ( $r=0.512$ ,  $p < 0.001$ ), which was an independent predictor for developing hypertensive disease during pregnancy ( $p=0.005$ ).

Delivery was by Caesarean section in 39% of pregnancies. Although this is higher than the national average (and that recommended by the World Health Organisation), many high-risk obstetric units in London teaching hospitals (including Chelsea and Westminster Hospital) have Caesarean section rates of around 30% of deliveries, and this is not significantly different to the rate in this cohort of women with heart disease ( $p=0.23$ ).

#### 3.6.4 Fetal/Neonatal Outcomes

Fetal/neonatal complications occurred in 30.3% of pregnancies. There were 6 stillbirths and 5 neonatal deaths: higher than stillbirth and neonatal death rates in England and Wales in 2012, as reported by the Office for National Statistics,<sup>95,96</sup> but similar to rates reported by the ZAHARA investigators.<sup>39</sup>

Birth weight below the fifth customized centile was the commonest adverse outcome, occurring in 20% of pregnancies, and was independently predicted by use of beta blockers ( $p=0.006$ ), a systemic right ventricle ( $p=0.001$ ) and complex cyanotic congenital heart disease ( $p=0.016$ ). The association between reduced cardiac output and lower birth weight has been well documented in healthy pregnancies and those in women with cardiac disease.<sup>30,77,97</sup> Ventricular function and degree of cyanosis are the

major determinants of fetal outcome in women with cyanotic congenital heart disease.<sup>31</sup> Use of beta-blockers (which have a negative inotropic effect),<sup>43,77,78,98</sup> and the presence of a systemic right ventricle<sup>67</sup> have also been shown to be associated with lower birth weight.

Preterm delivery (before 37 completed weeks of gestation) occurred in 11.7% of pregnancies, similar to that generally reported in developed countries,<sup>39</sup> and consistent with the preterm birth rate reported in the CARPREG<sup>8,30</sup> and ZAHARA<sup>36</sup> studies. In 58% of these, early delivery was undertaken for medical reasons. Independent predictors of iatrogenic preterm delivery were NYHA functional class  $\geq$  II (OR 3.34, 95% CI 1.11-10.10,  $p=0.033$ ), use of any cardiac medication (OR 2.70, 95% CI 1.19-6.18,  $p=0.018$ ) and presence of left heart obstruction (OR 2.57, 95% CI 1.10-5.99,  $p=0.029$ ). Spontaneous preterm labour occurred in 4.9% of pregnancies, (which is lower than that reported in other series<sup>30,32</sup>). Although an association between cardiac events during pregnancy and the onset of preterm labour has been described<sup>30,32</sup>, it is likely that improvements in the survival of preterm infants over the past decade have led to an increased willingness among obstetricians to undertake preterm delivery when there are signs of maternal and/or fetal decompensation.

NYHA functional class  $\geq$  II was an independent predictor for perinatal complications (OR 4.66, 95% CI 1.86-11.89,  $p=0.001$ ), which is consistent with the CARPREG study.<sup>8,30</sup> In common with the findings of the ZAHARA investigators<sup>36</sup> there was also an association with use of any cardiac medication (OR 2.88, 95% CI 1.16-7.12,  $p=0.022$ ) and the presence of an MPV (OR 8.68, 95% CI 1.32-57.09,  $p=0.024$ ). The presence of a systemic right ventricle (OR 5.73, 95% CI 1.62-20.28,  $p=0.007$ ) as a

predictor for adverse perinatal outcomes is a new finding. A systemic right ventricle may be unable to support the additional haemodynamic demands of pregnancy, (indeed pregnancy may result in irreversible right ventricular dysfunction<sup>4,42</sup>), and neonatal complications including low birth weight and preterm delivery have been reported as more frequent in this group of women than in normal pregnancy.<sup>67</sup>

### 3.7 Conclusions

Adverse cardiovascular, obstetric and fetal/neonatal outcomes occur frequently in pregnant women with pre-existing heart disease. A history of arrhythmias prior to pregnancy, myocardial dysfunction and presence of an MPV predicted cardiac events. Use of cardiac medications was independently associated with obstetric complications, mainly due to a significant association of use of anticoagulants with PPH. NYHA functional class  $\geq$  II, the use of cardiac medications and the presence of an MPV were predictive of poor perinatal outcomes and a new association of a systemic right ventricle with fetal/neonatal complications is reported.

## **Chapter 4: Pulmonary hypertension**

## **4.1 Abstract**

### **4.1.1 Aims:**

To investigate maternal and neonatal outcomes in a series of pregnancies in women with pulmonary hypertension

### **4.1.2 Methods:**

Multidisciplinary review of case records

### **4.1.3 Results**

There were twelve pregnancies in nine women. There were two maternal deaths (in 1995 and 1998), one related to pre-eclampsia and one to arrhythmia. Maternal morbidity included postpartum haemorrhage (three cases), and one post-Caesarean evacuation of a wound haematoma. There were three first-trimester miscarriages, nine live births and no perinatal deaths. Mean birth weight was 2197g, mean gestational age was 34 weeks (range 26 - 39), and mean birth weight centile was 36 (range 5 - 60). Five babies required admission to the neonatal intensive care unit but all were eventually discharged home. All women were delivered by Caesarean section (seven elective and two emergency deliveries) and all under general anaesthetic, except for one emergency and one elective Caesarean performed under regional block.

### **4.1.4 Conclusions**

Maternal and fetal outcomes for women with pulmonary hypertension may be improving. However, the risk of maternal mortality remains significant, so that early and effective counselling about contraceptive options and pregnancy

risks should continue to play a major role in the management of such women when they reach reproductive maturity.

## 4.2 Introduction

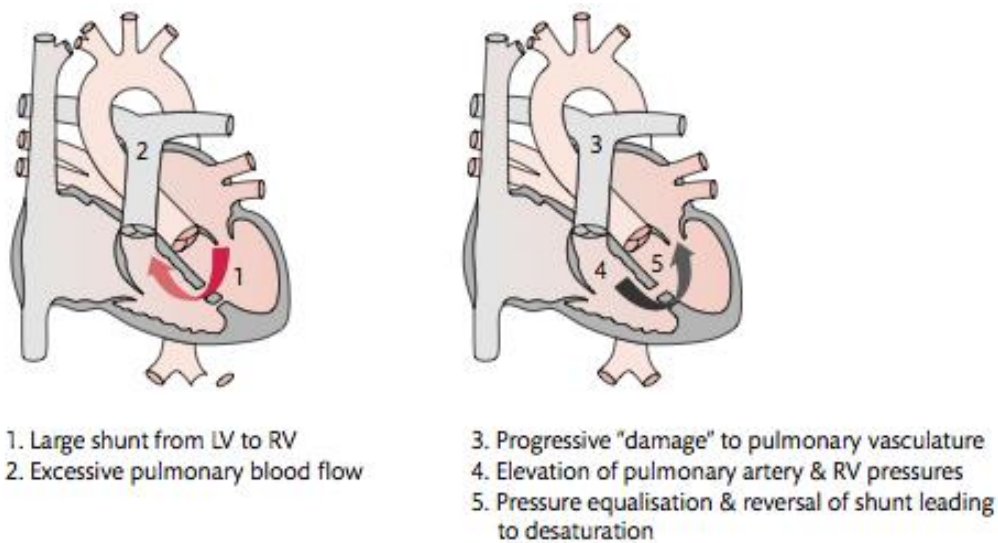
Pulmonary hypertension (PH) is defined at cardiac catheterization as a mean pulmonary artery pressure (PAP) of greater than 25mmHg at rest.<sup>89</sup> The causes are multifactorial (*table 1*).<sup>90</sup>

*Table 1: Updated classification of pulmonary hypertension; from Simmoneau et al<sup>90</sup>*

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>1 Pulmonary Arterial Hypertension (PAH)</b> <ul style="list-style-type: none"><li>• Idiopathic (IPAH)</li><li>• Heritable (HPAH)</li><li>• Drug and toxin induced</li><li>• Associated with connective tissue disorder (eg. scleroderma), congenital heart disease (including Eisenmenger physiology), portal hypertension, HIV infection, schistosomiasis</li><li>• unknown</li></ul> 1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis<br>1'' Persistent pulmonary hypertension of the newborn (PPHN) |
| <b>2 Pulmonary hypertension due to left heart disease</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>3 Pulmonary hypertension due to lung diseases and/or hypoxia</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>4 Chronic thromboembolic pulmonary hypertension (CTEPH)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>5 Pulmonary hypertension with unclear multifactorial mechanisms</b> <ul style="list-style-type: none"><li>• haematologic disorders: eg. chronic haemolytic anaemia, splenectomy</li><li>• systemic disorders: eg. sarcoidosis</li><li>• metabolic disorders: eg. glycogen storage disease</li></ul>                                                                                                                                                                                                                                  |

In its extreme form pulmonary pressures equal or even exceed systemic pressures (as seen with Eisenmenger physiology where a reversed central shunt leads to a progressive rise in pulmonary vascular resistance) and may subsequently have a detrimental effect on right ventricular function.

*Figure 1. Diagram illustrating the progressive reversal of a left-to-right shunt and development of Eisenmenger syndrome<sup>101</sup>*



The severity of PH is determined by the WHO functional class, a modification of the NYHA functional classification system recognising the importance of pre-syncope or syncope as a poor prognostic sign in patients with PH.<sup>102</sup>

Table 2: WHO functional classification of PH<sup>102</sup>

| WHO Class  | Definition                                                                                                                                                                                                                                                 |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>I</b>   | Patients with PH but without resulting limitation of physical activity.<br>Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope                                                                                 |
| <b>II</b>  | Patients with PH resulting in slight limitation of physical activity.<br>They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope                                                             |
| <b>III</b> | Patients with PH resulting in marked limitation of physical activity.<br>They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope                                                            |
| <b>IV</b>  | Patients with PH resulting in inability to carry on any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnoea and/or fatigue may even be present at rest.<br>Discomfort is increased by any physical activity |

Women with PH tolerate pregnancy poorly, with the rate of functional deterioration increasing from the second trimester onwards and the majority of deaths occurring within the first postnatal month, usually as a result of right heart failure.<sup>104</sup> Series from the 1990s reported a maternal mortality of 30-56%,<sup>51</sup> probably due to the limited ability of women with PH to adapt to the cardiovascular demands of pregnancy. However, more recent data from a systematic review<sup>103</sup> and two case series<sup>104,105</sup> suggest that maternal mortality may in fact be lower, with reported rates of 10-25%. Poor fetal outcomes have been well documented with high rates of preterm delivery

(85-100%), fetal growth restriction (FGR) (3-33%) and fetal/neonatal loss (7-13%).<sup>51,103,106</sup> Current guidelines continue to recommend discouraging pregnancy, with use of maximally effective contraception and early termination should pregnancy occur.<sup>4,37</sup> However, despite the risks, some women with PH still choose to become pregnant or to continue with an unplanned pregnancy.

### **4.3 Aims**

To investigate maternal and neonatal outcomes in a series of pregnancies in women with PH.

## **4.4 Methods**

Women with a diagnosis of PH (defined by a mean pulmonary artery pressure of > 25 mmHg at rest) cared for by the Joint Cardiac and Obstetric Service of the Chelsea and Westminster and Royal Brompton Hospitals were identified from a database started in 1994. Data were collected from a detailed review of case notes supplemented by the Circonia Maternity Information System (CMIS<sup>®</sup> HD Clinical Ltd, Bishops Stortford, Herts, UK). Information on patient characteristics, functional and echocardiographic assessment, cardiological, obstetric and anaesthetic management during pregnancy and labour and follow-up postnatal assessment was obtained.

## 4.5 Results

There were twelve pregnancies in nine women. Their baseline characteristics, together with maternal and neonatal outcomes, are recorded in Table 3. Their mean age at the initial clinic visit was 27 years (median 25 years, range 19-38). There were seven primigravidas. In four women (A, B, D and E) the diagnosis of PH was made using echocardiography during the index pregnancy. The remaining women were diagnosed before pregnancy at cardiac catheterization, with the exception of patient I who was diagnosed by echocardiography but not referred to tertiary care until she became pregnant. The PH aetiologies were varied – one each for idiopathic, HIV, left heart disease and primary lung disease, and five congenital heart disease.

### 4.5.1 Maternal mortality and morbidity

There were two maternal deaths, both before 1999. Patient A (1995) died on postnatal day 15 following a PH crisis, having been delivered at 26 weeks' gestation for fulminating pre-eclampsia (PET). Patient B (1998) died at Caesarean section having developed intractable supraventricular tachycardia (SVT) following manual delivery of the placenta and administration of repeated intravenous bolus doses (5U x 2) of oxytocic drugs (Syntocinon®).

All women were delivered by Caesarean section (seven elective and two emergency deliveries), all under general anaesthetic except for one elective and one emergency Caesarean performed under regional block. Estimated blood loss at delivery ranged from 300 to 1000 ml (mean 711). In the five most recent cases the third stage was managed with a low-dose oxytocin infusion (Syntocinon® 8-12 mU/minute over 4

hours) rather than a bolus (Syntocinon<sup>®</sup> 5-10IU), and in four women compression sutures were also used.<sup>107</sup> In one case the third stage was managed with compression sutures alone, and no oxytocics were given.

Symptomatic and functional assessment and echocardiographic measurements at baseline, during pregnancy and at follow-up, are summarized in Table 4. Patients were monitored throughout their pregnancies by echocardiography and clinical examination. Estimations of PAP were assessed from tricuspid and pulmonary artery Doppler studies.

Medical treatment is summarized in Table 5. Patient A received intravenous unfractionated heparin (UFH) following delivery. Subsequently seven women were anticoagulated with subcutaneous low-molecular-weight heparin (LMWH). The target level of anticoagulation to be achieved was determined by their thrombotic risk: patients E, F and H (who had been taking warfarin before pregnancy) received therapeutic doses of LMWH and were monitored by measurement of anti-Factor Xa levels. The other women were given prophylactic doses of LMWH. Patient A received intravenous iloprost post-partum. Six of the nine women (all from 2007 onwards) were treated with sildenafil throughout pregnancy; one of them (E) was given add-on therapy with nebulized iloprost during the pregnancy because of a significant deterioration in her symptoms. Table 3 also reports the anaesthetic management at delivery. Six cases had invasive monitoring with peripheral arterial lines and central venous pressure lines. In five cases, cardiac output was monitored intra-operatively using transoesophageal echocardiography.

#### 4.5.2 Perinatal mortality and morbidity

Three pregnancies resulted in miscarriage (two in patient D, one attributed to the development of thyrotoxicosis) and nine pregnancies resulted in a surviving child.

Five women were delivered iatrogenically preterm because of maternal decompensation, their babies requiring admission to the neonatal intensive care unit (NICU). One of the babies was small for gestational age (SGA) (< 5<sup>th</sup> centile). None of the babies in this series had any congenital abnormalities.

Table 3: Baseline characteristics, maternal and neonatal outcomes in women with PH

| Year | Patient (pregnancy no.) | Age | Parity | GA at diagnosis | Aetiology                                                   | WHO class | PASP (mmHg)            | RV function         | GA at delivery (weeks) | Mode of delivery | EBL (ml) | BW (g) | BW centile | Maternal complications                                            | Maternal outcome      | Neonatal complications | Neonatal outcome |
|------|-------------------------|-----|--------|-----------------|-------------------------------------------------------------|-----------|------------------------|---------------------|------------------------|------------------|----------|--------|------------|-------------------------------------------------------------------|-----------------------|------------------------|------------------|
| 1995 | A                       | 28  | 0      | Pre-pregnancy   | CHD (VSD, Eisenmenger)                                      | I         | 104                    | Moderately impaired | 26                     | Em LSCS          | 1000     | 620    | 5          | Fulminating PET                                                   | Death D15 PH crisis   | PTD SGA NICU           | Alive and well   |
| 1998 | B                       | 33  | 0      | Pre-pregnancy   | CHD (secundum ASD closed with Dacron patch aged 19)         | I-II      | 55-60                  | Good                | 36+4                   | Em LSCS          | 300      | 2570   | 35         | Non-sustained VT, 3 <sup>rd</sup> trimester Sustained SVT at LSCS | Intra-operative death | PTD                    | Alive and well   |
| 2003 | C                       | 24  | 0      | 24 weeks        | CHD (ToF variant with complex pulmonary atresia and MAPCAs) | III       | Assumed to be systemic | Good                | 34                     | El LSCS          | 600      | 2080   | 27         | PPH                                                               | Still living          | PTD NICU               | Alive and well   |
| 2007 | D (1)                   | 19  | 0      | Pre-pregnancy   | L heart disease (restrictive LA)                            | II        | 38                     | Good                | Misc. 6/40 ERPC        |                  |          |        |            | Nil                                                               | Still living          |                        |                  |
| 2007 | E                       | 25  | 0+1    | Pre-pregnancy   | iPH                                                         | II        | 106                    | Severely impaired   | 32                     | El LSCS          | 400      | 1650   | 37         | Worsening LV function                                             | Still living          | PTD NICU               | Alive and well   |
| 2007 | F                       | 38  | 2      | 23+5 weeks      | Thromboembolic/primary lung disease (emphysema)             | III       | 102                    | Mildly impaired     | 33+2                   | El LSCS          | 500      | 2090   | 50         | Return to theatre to evacuate wound haematoma                     | Still living          | PTD NICU               | Alive and well   |
| 2008 | G (1)                   | 24  | 1      | 36              | CHD (repaired PDA, VSD; absent LPA and hypoplastic L lung)  | II        | 65                     | Good                | 37                     | El LSCS          | 800      | 2356   | 9          | PPH                                                               | Still living          | SGA                    | Alive and well   |
| 2008 | G (2)                   | 25  | 2      | Pre-pregnancy   | CHD                                                         |           |                        |                     | Misc 12/40             |                  |          |        |            | Nil                                                               | Still living          |                        |                  |
| 2008 | H                       | 28  | 0      | 23              | CHD (AVSD with Eisenmenger)                                 | I-II      | 90                     | Good                | 34                     | El LSCS          | 1000     | 2184   | 50         | PPH                                                               | Still living          | PTD NICU               | Alive and well   |
| 2009 | D (2)                   | 21  | 0+1    | Pre-pregnancy   | L heart disease                                             | III       | 60                     | Good                | Misc. 7/40 ERPC        |                  |          |        |            | Atrial tachycardia Thyrotoxicosis                                 | Still living          |                        |                  |
| 2009 | I                       | 32  | 1      | Pre-pregnancy   | HIV                                                         | I-II      | 45                     | Good                | 39                     | El LSCS          | 800      | 3440   | 60         | PPH                                                               | Still living          | Nil                    | Alive and well   |
| 2009 | G (3)                   | 26  | 2+1    | Pre-pregnancy   | CHD                                                         | II-III    | 70                     | Mild dysfunction    | 37                     | El LSCS          | 1000     | 2786   | 50         | PPH Post-op ileus                                                 | Still living          | Nil                    | Alive and well   |

ASD: atrial septal defect; AVSD: atrioventricular septal defect; BW: birth weight; CHD: congenital heart disease; EBL: estimated blood loss; ERPC: evacuation of retained products of conception; FGR: fetal growth restriction; iPH: idiopathic pulmonary hypertension; LA: left atrium; LPA: left pulmonary artery; LSCS: lower segment caesarean section; MAPCAs: major aortopulmonary collaterals; misc.: miscarriage; NICU: neonatal intensive care unit; PASP: pulmonary artery systolic pressure; PDA: patent ductus arteriosus; PPH: post-partum haemorrhage; PTD: pre-term delivery; RV: right ventricle; SaO<sub>2</sub>: oxygen saturations in air as measured by pulse oximetry; SVT: supraventricular tachycardia; ToF: tetralogy of Fallot; VSD: ventricular septal defect; VT: ventricular tachycardia; WHO: World Health Organisation; still living: status at one year post delivery

*Table 4: Functional and echocardiographic assessment of women with PH during pregnancy and the puerperium*

| Year | Patient<br>(pregnancy<br>no.) | WHO Class                                                             |                           |                         | RSVP                         |                           |                         | RV Function            |                           |                         |
|------|-------------------------------|-----------------------------------------------------------------------|---------------------------|-------------------------|------------------------------|---------------------------|-------------------------|------------------------|---------------------------|-------------------------|
|      |                               | Baseline                                                              | Worst during<br>pregnancy | 6-12 month<br>follow-up | Baseline                     | Worst during<br>pregnancy | 6-12 month<br>follow-up | Baseline               | Worst during<br>pregnancy | 6-12 month<br>follow-up |
| 1995 | A                             | I                                                                     | I-II                      | N/A                     | 104                          | 104                       | N/A                     | Moderately<br>impaired | Moderately<br>impaired    | N/A                     |
| 1998 | B                             | I-II                                                                  | II                        | N/A                     | 55-60                        | 65                        | N/A                     | Good                   | Good                      | N/A                     |
| 2003 | C                             | III                                                                   | III                       | II                      | Assumed<br>systemic<br>(120) | Systemic                  | *                       | Good                   | Good                      | *                       |
| 2007 | D (1)                         | II                                                                    | II                        | II                      | 38                           | 38                        | *                       | Good                   | Good                      | *                       |
| 2007 | E                             | II                                                                    | II-III                    | III                     | 106                          | 120                       | 110                     | Severely<br>impaired   | Severely<br>impaired      | Severely<br>impaired    |
| 2007 | F                             | III                                                                   | III-IV                    | III                     | 102                          | 102                       | 101                     | Mildly<br>impaired     | Mildly<br>impaired        | Mildly<br>impaired      |
| 2007 | G (1)                         | II                                                                    | III                       | III                     | 65                           | 65                        | 70                      | Good                   | Good                      | Good                    |
| 2008 | G (2)                         | Spontaneous 1 <sup>st</sup> trimester miscarriage – no data available |                           |                         |                              |                           |                         |                        |                           |                         |
| 2008 | H                             | I-II                                                                  | II-III                    | II                      | 90                           | 90                        | 87                      | Good                   | Good                      | Good                    |
| 2009 | D (2)                         | III                                                                   | III                       | III                     | 60                           | 70                        | 90                      | Good                   | Good                      | Good                    |
| 2009 | I                             | I-II                                                                  | I-II                      | I-II                    | 45                           | 45                        | 25                      | Good                   | Good                      | Good                    |
| 2009 | G (3)                         | II-III                                                                | III-IV                    | III                     | 70                           | 80                        | 51                      | Mild<br>dysfunction    | Mild<br>dysfunction       | Good                    |

RVSP: right ventricular systolic pressure; WHO: World Health Organisation; \* Patient did not attend for follow-up echocardiogram

Table 5: Medical, obstetric and anaesthetic management of women with PH

| Year | Patient (pregnancy no) | Medical therapy                                           | Third stage                             | GA/RA                          | CO monitoring                    | Lines                                                                 | Induction                                          | Maintenance                                                                                           | Vasoconstrictors      | IV fluids                                            | Intraoperative complications                                                                                                                                       |
|------|------------------------|-----------------------------------------------------------|-----------------------------------------|--------------------------------|----------------------------------|-----------------------------------------------------------------------|----------------------------------------------------|-------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1995 | A                      | IV UFH (PN)<br>IV iloprost (PN)                           | Oxytocin bolus x2                       | GA                             | None                             | CVC<br>Arterial line                                                  | Fentanyl<br>Etomidate<br>Vecuronium                | IPPV with O <sub>2</sub> /N <sub>2</sub> O/halothane                                                  | Phenylephrine boluses | Crystalloid 1000ml<br>Colloid 1750ml<br>RBCs 4 units | Sinus tachycardia treated with esmolol                                                                                                                             |
| 1998 | B                      | Diltiazem                                                 | Oxytocin bolus x2                       | RA (labour epidural topped up) | None                             | CVC<br>Arterial line                                                  | N/A                                                | 14ml 0.5% bupivacaine (3ml aliquots over 30 minutes)<br>100mcg fentanyl                               | Phenylephrine boluses | Crystalloid 1000ml                                   | SVT 5 minutes post 2 <sup>nd</sup> dose syntocinon during removal of placenta, hypotension and aystole<br>Intubated and CPR initiated<br>Resuscitation for >1 hour |
| 2003 | C                      | SC LMWH                                                   |                                         | GA                             | Anaesthetic notes not available  |                                                                       |                                                    |                                                                                                       |                       |                                                      |                                                                                                                                                                    |
| 2007 | D(1)                   | SC LMWH<br>Sildenafil                                     | Miscarriage                             |                                |                                  |                                                                       |                                                    |                                                                                                       |                       |                                                      |                                                                                                                                                                    |
| 2007 | E                      | SC LMWH<br>Sildenafil<br>Nebulised iloprost<br>Furosemide | Compression suture                      | GA                             | TOE<br>Trans-oesophageal Doppler | Wide-bore peripheral access<br>Arterial line<br>PAC introducer        | Fentanyl<br>Etomidate<br>Suzamethonium             | Propofol infusion<br>Atracurium<br>Fentanyl<br>Morphine<br>Paracetamol<br>Ilio-inguinal blocks        |                       |                                                      | Bradycardia after induction                                                                                                                                        |
| 2007 | F                      | SC LMWH<br>Sildenafil                                     | Oxytocin infusion<br>Compression suture | GA                             | TOE                              | Wide-bore peripheral access<br>Arterial line<br>PAC introducer        | Fentanyl<br>Etomidate<br>Suxamethonium             | IPPV with O <sub>2</sub> /isoflurane<br>Vecuronium<br>Morphine<br>Paracetamol<br>Ilio-inguinal blocks |                       | Crystalloid 1000ml                                   | Bradycardia after induction                                                                                                                                        |
| 2007 | G(1)                   | SC LMWH<br>Sildenafil                                     | Oxytocin infusion<br>Compression suture | GA                             | TOE                              | Wide-bore peripheral access<br>Arterial line<br>CVC<br>PAC introducer | Etomidate<br>Fentanyl<br>Suxamethonium<br>Atropine | IPPV with O <sub>2</sub> /isoflurane<br>Morphine<br>Paracetamol<br>Ilio-inguinal blocks               |                       | Minimal crystalloid<br>Colloid 500ml<br>RBCs 2 units | Persistent tachycardia                                                                                                                                             |
| 2008 | G(2)                   | SC LMWH<br>Sildenafil                                     | Miscarriage                             |                                |                                  |                                                                       |                                                    |                                                                                                       |                       |                                                      |                                                                                                                                                                    |

|      |      |                                               |                                               |             |      |                                                                                |                                                                        |                                                                                                                                  |                         |                                        |      |
|------|------|-----------------------------------------------|-----------------------------------------------|-------------|------|--------------------------------------------------------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|-------------------------|----------------------------------------|------|
| 2008 | H    | SC LMWH<br>Sildenafil                         | Oxytocin<br>infusion<br>Compression<br>suture | GA          | TOE  | Wide-bore<br>peripheral<br>access<br>Arterial line<br>CVC<br>PAC<br>introducer | Etomidate<br>Fentanyl<br>Suxamethonium<br>Atropine                     | IPPV with<br>O <sub>2</sub> /isoflurane<br>Morphine<br>Paracetamol<br>Vecuronium<br>Ilio-inguinal and<br>rectus sheath<br>blocks |                         | Crystalloid<br>500ml<br>Colloid 500ml  | None |
| 2009 | D(2) | SC LMWH<br>Sildenafil                         | Miscarriage                                   |             |      |                                                                                |                                                                        |                                                                                                                                  |                         |                                        |      |
| 2009 | I    | SC LMWH<br>Sildenafil<br>Anti-<br>retrovirals | Oxytocin<br>infusion<br>Compression<br>suture | RA (spinal) | None | Wide-bore<br>peripheral<br>access                                              | Spinal of 2.5ml<br>0.5% heavy<br>bupivacaine,<br>300mcg<br>diamorphine | N/A                                                                                                                              | Phenylephrine<br>300mcg | Crystalloid<br>1000ml<br>Colloid 500ml | None |
| 2009 | G(3) | SC LMWH<br>Sildenafil<br>Furosemide           | Oxytocin<br>infusion                          | GA          | TOE  | Anaesthetic notes not available                                                |                                                                        |                                                                                                                                  |                         |                                        |      |

CO: cardiac output; CVC: central venous catheter; GA: general anaesthetic; RA: regional anaesthetic; ICU: intensive care unit; IPPV: intermittent positive pressure ventilation; IV: intravenous; LMWH: low molecular weight heparin; PAC: pulmonary artery catheter; PCA: patient-controlled analgesia; RBCs: red blood cells; SVT: supraventricular tachycardia; TOE: trans-oesophageal echocardiography; UFH: unfractionated heparin

## 4.6 Discussion

### 4.6.1 Maternal mortality and morbidity

There were two maternal deaths in 12 pregnancies, illustrating the high maternal mortality associated with PH. However both these deaths occurred before 2000.

Patient A developed fulminating PET with concomitant coagulopathy, necessitating emergency delivery at 26 weeks. She died on the 15<sup>th</sup> postnatal day as a result of a PH crisis, emphasizing the commonly fatal effect of PET when it occurs in women with PH.<sup>108-110</sup> Patient B developed a sustained SVT shortly after a manual removal of the placenta at Caesarean section. She also received two bolus doses of oxytocin intravenously. The resulting hypotension precipitated an asystolic cardiac arrest, which was unrecoverable. Oxytocin is now known to cause an increase in pulmonary vascular resistance, a reduction in systemic vascular resistance and tachycardia.<sup>85</sup> These effects, in combination with a sudden autotransfusion consequent on the rapid manual delivery of the placenta, may have contributed to the haemodynamic instability that led to cardiac arrest and the death of patient B. Subsequent to this event, the third stage in women with PH has been managed with a low-dose oxytocin infusion (8-12mU/minute of Syntocinon<sup>®</sup>) and delivery of the placenta by controlled-cord traction (CCT).<sup>4,5</sup> Both deaths occurred during the early postnatal period, supporting earlier observations that this is the time of highest risk.<sup>51</sup> Previous series have reported refractory right heart failure as the commonest cause of death,<sup>103</sup> but this was not observed in this series.

Both deaths in this series occurred in women with PH secondary to congenital heart disease, one of whom (patient A) also had Eisenmenger physiology. Patients with

Eisenmenger syndrome have significantly increased risks of bleeding, thrombotic complications and arrhythmia, with multi-organ involvement being the norm.<sup>111</sup>

However, a recent systematic review found no significant difference in mortality between different subgroups of PH.<sup>103</sup>

### *Advanced therapies*

Five out of nine women (all cases since 2007) were treated with sildenafil during pregnancy, covering a wide range of diagnostic groups: one associated with HIV infection, one IPAH, one PH associated with lung disease and two PH associated with congenital heart disease. Two women were treated with prostacyclin analogues.

Prostacyclin is produced by vascular endothelial cells. It binds to endothelial prostacyclin receptors thereby increasing production of cyclic adenosine monophosphate (cAMP), resulting in vasodilatation and inhibition of platelet aggregation. It also has anti-inflammatory and anti-proliferative effects. PH patients have reduced levels of endogenous prostacyclin and reduced expression of prostacyclin synthase in the lungs. The synthesis of stable analogues of prostacyclin, with differing pharmacokinetic properties but similar pharmacodynamics effects, has enabled its clinical use in patients with PH. Both women who died did so before the introduction of sildenafil. Sildenafil reduces degradation of cyclic guanosine monophosphate (cGMP) by inhibiting cGMP-specific phosphodiesterase type 5, resulting in local release of nitric oxide and subsequent vasodilatation. However, the Food and Drug Administration (FDA) only approved the use of sildenafil for treatment of PH in 2005 and there are limited data on its safety during pregnancy and breastfeeding. Animal studies have not shown evidence of teratogenicity, but there are no adequate and well-controlled studies in pregnant women. Sildenafil is excreted in

breast milk but there are no data at all regarding its use in breastfeeding mothers.

Development of advanced therapies such as sildenafil have revolutionized the management of PH, with improvements in symptoms, functional capacity and survival being demonstrated.<sup>112</sup> However there is no clear consensus on the use of advanced therapies for PH in pregnancy and the evidence is limited to case series and a few small reviews; however it is tempting to attribute the recent reduction in maternal mortality to the increased availability of these therapies.<sup>103</sup>

### *Anticoagulation*

Seven of the nine women in this series were anticoagulated with subcutaneous LMWH; (the degree of anticoagulation was based on their estimated thrombotic risk). There were no thrombotic complications during pregnancy or the puerperium. PH is characterized by hypertrophy, vasoconstriction and thrombus formation in the pulmonary microvasculature. Additionally pregnancy is associated with a six-fold increase in thrombosis risk compared with age-matched pregnancy controls (a risk which is doubled again in the puerperium). This is further increased in patients with Eisenmenger physiology in whom there is also a risk of paradoxical embolism due to the right-to-left shunt and significant arrhythmias in these patients. There remains however, uncertainty regarding the most effective and safest regimen for thromboprophylaxis, particularly for women with Eisenmenger physiology in whom a balance must be struck between their increased tendency to bleeding (in particular pulmonary haemorrhage) and their thrombotic risk.

Patients who had been taking warfarin before pregnancy were fully anticoagulated with subcutaneous LMWH, monitored by measuring anti factor-Xa levels (target 0.6-1.0). They were restarted on warfarin as soon as it was established that there were no

ongoing bleeding problems following surgery. Those women on prophylactic LMWH during pregnancy continued this after delivery for 6-12 weeks.

### *Delivery*

All nine deliveries were by Caesarean section; seven were elective, and only two were emergency (patients A and B, both of whom subsequently died). The ideal mode of delivery continues to be contentious.<sup>4,51,74,103,109</sup> While vaginal delivery is thought to be associated with smaller haemodynamic changes and carries benefits of lower risks of haemorrhage, infection and venous thromboembolism, a planned Caesarean delivery has the advantages of allowing the delivery to take place under optimal conditions (for example with attendance of senior staff) and avoids the possibility of emergency caesarean section in labour which may be associated with increased risks compared with both elective Caesarean section and vaginal delivery.<sup>83</sup> Also, as many women will be delivered preterm when the cervix is still unfavourable, induction of labour is likely to be difficult.

Mean blood loss at delivery was 711ml (range 300-1000ml), with a blood loss of 1000ml in three women. One of these women was patient A who had a coagulopathy associated with severe PET. This, in combination with her delivery at 26 weeks gestation, is likely to have contributed to the relatively high blood loss. Uterotonics have adverse haemodynamic effects which make them unsuitable for women with PH, and they may have contributed to the death of patient B. Avoidance of bolus doses of oxytocic drugs in preference for a low-dose oxytocin infusion and a low threshold for insertion of uterine brace sutures was introduced following the death of patient B, and is now also recommended by the ESC<sup>4</sup> and RCOG<sup>5</sup>. General anaesthesia, specifically the use of volatile agents such as halothane, isoflurane and

nitrous oxide, is known to increase uterine atony. Of the six cases with an estimated blood loss of greater than 500ml at delivery in association with a general anaesthetic, five (83%) women had anaesthesia maintained with either halothane or isoflurane.

#### *Anaesthetic considerations*

All forms of regional anaesthetic have been used successfully for the delivery of women with PH.<sup>113-116</sup> However consideration must be given to anticoagulation, the women's ability to tolerate lying flat and the potentially profound sympathetic block which may occur with regional anaesthetic which may result in reduced venous return and significant hypotension, both of which are poorly tolerated in women with PH. The avoidance of vasodilatation and reduced venous return is best achieved by using a slow incremental infusion of local anaesthetic. Use of a general anaesthetic, as was the case for seven of the nine women in this series, is well described in the literature and facilitates use of trans-oesophageal echocardiography to monitor cardiac output and diminishes the work of breathing, while allowing the anaesthetist to manipulate metabolic parameters.<sup>117-119</sup> Furthermore, direct pulmonary vasodilators such as nebulized prostacyclins and nitric oxide can be given more easily, and in the event of major complications the woman can be put onto cardiopulmonary bypass with the minimum of delay.

#### 4.6.2 Fetal and neonatal outcomes

Maternal PH is associated with an increased risk of fetal and neonatal complications,<sup>51,103,106</sup> which is highest in women with poor functional class pre-pregnancy (NYHA functional class III or IV), cyanosis or left heart obstruction.<sup>30</sup> The direct effects of the underlying cardiac disease (reduced cardiac output and

consequently placental perfusion and maternal hypoxia) may be compounded by iatrogenic preterm delivery. Only one of the babies in this series was SGA (less than the 5<sup>th</sup> customized centile). This was the baby of patient A, who also developed severe, early-onset PET (which is also associated with poor fetal growth). There were three first trimester miscarriages (2 in patient D and 1 in patient G), and no stillbirths or neonatal deaths. Five out of nine women were delivered preterm, all for maternal reasons. Of these five, only one (patient A) was severely preterm (26 weeks). This relatively high rate of preterm delivery reflects reported trends.<sup>103</sup> It seems likely that improvements in neonatal care and thus in the survival of preterm infants over the past decade have led to an increased willingness among obstetricians to undertake iatrogenic preterm delivery in the maternal interest.

#### 4.6.3 Predictors of outcome

This retrospective series does not identify any particular predictors of maternal outcome. This is likely to be a result of the small number of women and their ability to adapt to their PH (particularly when associated with congenital heart disease) which may give a misleading NYHA class status. Right ventricular function remained relatively stable with only one woman (E) having objective evidence of right ventricular decompensation prior to delivery. However, concerns regarding incomplete right ventricular recovery following pregnancy have been raised in women with congenital heart disease,<sup>120</sup> and this issue should be addressed in pre-pregnancy counselling.

Two of the women (B and D) experienced sustained arrhythmia and of these one died. Data from non-pregnant women with PH suggest that sustained atrial arrhythmias

occur in 11.7% of women.<sup>121</sup> The additional volume load and haemodynamic stress imposed by pregnancy on the already pressure-overloaded right heart may increase the tendency for both atrial and ventricular arrhythmia. This has previously been reported in other congenital lesions, where right ventricular dilatation has been shown to be associated with a higher incidence of arrhythmia.<sup>122,123</sup> Although this patient group is too small to make any statement about the relationship of arrhythmia to prognosis, maternal arrhythmia has been associated with increased adverse cardiac events during pregnancy<sup>8</sup> and adverse fetal outcomes.<sup>35</sup>

## 4.7 Conclusions

PH in pregnancy is rare making this is one of the largest consecutive series reported. Nonetheless, the small numbers limit the conclusions which can be drawn. Use of advanced therapies has revolutionized the treatment of PH outside of pregnancy and although data on their use in pregnancy are limited, the safety of prostacyclin analogues and sildenafil during pregnancy is now supported by numerous case reports and several small series in the literature.<sup>2,112</sup> Maternal and fetal outcomes for women with PH seem to be improving, but maternal risk remains extremely high such that timely and effective counselling on contraception and the hazards of pregnancy remain vital. It goes without saying that pregnancies in women with PH should be managed in a tertiary setting with ready access to the full multidisciplinary team.

## **Chapter 5: Marfan Syndrome**

## 5.1 Abstract

### 5.1.1 Aims:

To investigate maternal and neonatal outcomes in a series of pregnancies in women with Marfan syndrome

### 5.1.2 Methods:

Retrospective review of case records

### 5.1.3 Results:

There were twenty-nine pregnancies in 21 women with no maternal deaths. Significant cardiac complications occurred in five pregnancies (17%): one woman experienced a type-A aortic dissection; two women required cardiac surgery within 6 months of delivery and a further two women developed impaired left ventricular function during the pregnancy. Women with Marfan syndrome were also more likely to have obstetric complications (OR 3.29, 95% CI 1.30-8.34), the most frequent of which was postpartum haemorrhage (OR 8.46, 95% CI 2.52-28.38). There were no perinatal deaths, although babies born to mothers with Marfan syndrome were delivered significantly earlier than those born to the control group (median 39 versus 40 weeks of gestation, Mann-Whitney U-test,  $p = 0.04$ ). The babies were also significantly more likely to be small for gestational age (SGA) (24% in the Marfan group versus 6% in the controls; OR 4.95, 95% CI 1.58-15.55).

### 5.1.4 Conclusions:

Pregnancy in women with Marfan syndrome continues to be associated with significant rates of maternal, fetal and neonatal complications. Effective pre-pregnancy counselling and meticulous surveillance during pregnancy, delivery

and the puerperium by an experienced multidisciplinary team are warranted for these women.

## 5.2 Introduction

Marfan syndrome (MFS) is a hereditary multisystem connective tissue disorder with autosomal dominant inheritance. It affects approximately 1 in 5000 of the population<sup>124</sup> and is caused by a mutation in the fibrillin-1 gene (FBN1) on chromosome 15q21, (although heterozygous mutations in the tissue growth factor-B receptor 2 (TGFB2) gene on chromosome 3p24.2-25 have also been identified in other Marfan-like syndromes).<sup>125</sup> However, the defects are usually unique in each family or sporadic case and over 200 mutations have been identified. Diagnosis is based on the 2010 revised Ghent nosology<sup>124</sup>, rather than genetic markers; (mutations are not always found in those diagnosed with MFS, and conversely may be found in individuals who do not meet the diagnostic criteria). Eighty percent of patients have some cardiovascular involvement (such as aortic dilatation, aortic incompetence and mitral or tricuspid valve prolapse, with or without regurgitation), with abnormalities of the skeletal and ocular systems being the other prominent manifestations.<sup>126</sup> The major causes of death associated with MFS are aortic aneurysm rupture and aortic dissection.<sup>127</sup>

Normal pregnancy is associated with aortic dilatation and increased aortic compliance.<sup>57,58</sup> A reduction in mucopolysaccharides in the aortic wall has also been documented.<sup>59</sup> These factors, in combination with the haemodynamic changes of pregnancy, may contribute to the increased risk of aortic dissection.<sup>128,129</sup> Recent guidelines suggest a 1% risk of aortic dissection or significant cardiac event in women with an aortic root diameter of <40mm.<sup>4</sup> This risk is increased when the aortic root diameter is >40mm, if there is a rapid increase in aortic dimensions, or in the context

of a family history of dissection.<sup>130</sup> Body surface area is also important, particularly in women of short stature: an aortic diameter index of  $>27\text{mm/m}^2$  is associated with an increased risk of dissection, and prophylactic surgery should be considered.<sup>4</sup> The risk factors for distal dissection are less well characterized. Additionally, aortic dissection may occur even in the absence of dilatation.<sup>131</sup>

Fibrillin-1 is present in the myocardium, where abnormalities of its structure may predispose patients with MFS to left ventricular dilatation and impairment of left ventricular function, even in the absence of valvular pathology.<sup>132-134</sup> Such an effect has not yet been described in pregnancy.

MFS may also be associated with an increase in obstetric complications, including preterm delivery, preterm pre-labour rupture of the membranes (PPROM), cervical incompetence, poor fetal outcome and postpartum haemorrhage (PPH).<sup>135-138</sup>

### **5.3 Aims**

To investigate maternal and neonatal outcomes in a series of pregnancies in women with MFS.

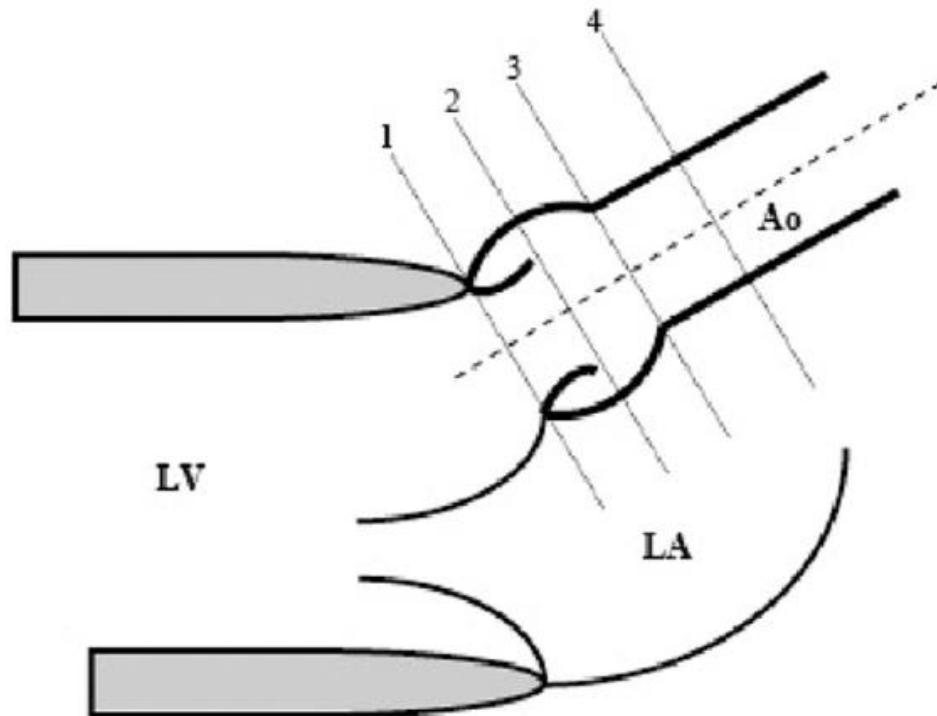
## 5.4 Methods

Women with a diagnosis of MFS, cared for by the Joint Cardiac and Obstetric Service of the Chelsea and Westminster and Royal Brompton Hospitals, were identified from a database commenced in 1994. Only singleton pregnancies progressing beyond 24 weeks were included. For each woman with MFS there were four controls: the two women who delivered immediately before and immediately after each index case, allowing comparison with the overall obstetric population at the Chelsea and Westminster Hospital while controlling for changes in demographics and practice over time. Four women with MFS delivered before 1998; data for control women were not available before this date and so women who delivered on the same date in 1999 were used as controls.

Data were collected from a detailed review of case notes supplemented by the Ciconia Maternity Information System (CMIS<sup>®</sup>, HD Clinical Ltd, Bishops Stortford, Herts, UK). In all women, demographic data and information on obstetric and anaesthetic management during pregnancy and labour, and maternal and neonatal outcomes was obtained, noting cardiac, obstetric and fetal/neonatal complications as previously described in chapter 3. In the Marfan group data on the aortic root diameter pre-pregnancy (as measured at echocardiography), as well as left ventricular dimensions and function, and aortic root diameter during pregnancy (at serial echocardiographic assessments) were also gathered. The aortic root diameters were measured at the four standard levels (the annulus, the sinuses of valsalva, the sinotubular junction and the ascending aorta) in all cases (see figure 1). Any worsening of mitral or aortic regurgitation (as seen at echocardiography), or aortic dissection was also noted.

*Figure 1: Diagram of the aortic root as seen at echocardiography.<sup>139</sup>*

*Aortic annulus (1), sinus of valsalva (2), sinotubular junction (3), ascending aorta (4)*



Data were analysed using SPSS 22 for windows. Differences in outcomes between the Marfan and control groups, and between first and subsequent pregnancies in the Marfan group, were evaluated. Continuous variables were compared with Students t-test if they were normally distributed and with the Mann-Whitney U-test if they were not. The chi-squared test or Fisher's exact test with cell numbers  $<5$  were used to test differences between relative frequencies of occurrence. All tests were two-tailed and  $p < 0.05$  was considered statistically significant.

The echocardiographic data could not be analysed by combining all the measurements, as this would create an ascertainment bias (those with any observed

deterioration would be more likely to have more echocardiograms and would therefore contribute disproportionately to the results). Each case with at least two echocardiograms more than 6 weeks apart was analysed by calculating a regression line of each echocardiographic parameter measured against gestational age, and deriving from it the predicted measurement at 12, 28 and 36 weeks of gestation. Thus, every subject contributed three values to the pooled results. This also had the advantage of smoothing some of the inter-observer variability.

## 5.5 Results

Twenty-nine pregnancies in 21 women with MFS were compared with 116 controls. Their baseline characteristics are shown in table 1. There was no statistically significant difference in age or parity between the two groups ( $p=0.10$  and  $p=0.19$  respectively). Mean age at booking in the MFS group was 31.1 years (range 17 to 42) compared with 32.8 years (range 17 to 43) in the controls. Outcomes in nulliparous ( $n=21$ ) and parous ( $n=8$ ) women with MFS were similar (table 2).

Thirteen pregnancies occurred in 9 women with mutations in the FBN1 gene. There were 2 pregnancies in 1 woman who tested negative for mutations in both the FBN1 and TGFBR2 genes. Outcomes in both groups were similar. Information on genotype was not available in the remaining cases (14 pregnancies, 11 women).

### 5.5.1 Cardiac outcomes

There were three pregnancies in women with MFS who had undergone cardiac surgery prior to pregnancy; two of these had valve-sparing aortic root replacement and one had both aortic root and valve replaced.

Sequential echocardiography data from 11 pregnancies (figures 1-4) were available for analysis as described previously and showed no significant change in either aortic root diameter, or left ventricular dimensions and function during pregnancy. The mean aortic root diameter pre-pregnancy was 39.5mm (median 40, range 26 to 81); in 12 pregnancies it was greater than 40mm. The mean increase in aortic root diameter during pregnancy was 0.47mm (median 0.40mm, range 0.00 to 0.90), although on

regression analysis this change was not statistically significant. Beta-blockers (thought to confer some protection against long-term dilatation of the aortic root<sup>125,140-142</sup>) were taken throughout 26 pregnancies (2 of the 3 pregnancies where a beta-blocker was not taken were in women with an aortic root >40mm). The women concerned had declined to take them due to side effects and because they were concerned about published reports of an increase in fetal growth restriction associated with their use.

There were no maternal deaths. However, significant cardiac complications occurred in 5 pregnancies (17%). One woman experienced a type A aortic dissection 10 days post-delivery which required emergency root and valve replacement. Two women required cardiac surgery within 6 months of delivery due to increasing dilatation of the aortic root in one and worsening aortic regurgitation in the other. A further two women developed impaired left ventricular function during the pregnancy.

### 5.5.2 Obstetric outcomes

Fifty-nine percent (17) of the index pregnancies resulted in vaginal delivery compared with 74% (86) of the controls (although this is not statistically significantly different,  $p = 0.1127$ ). However, births in women in the MFS group who delivered vaginally were more likely to be assisted (using forceps or ventouse) than those in unaffected women (71% (12/17) and 17% (15/86) respectively, OR 11.36, 95% CI 3.48 to 37.08). There was a trend towards a longer second stage in the MFS group ((median 67 minutes (range 7-136) in the MFS group and 30.5 minutes (4-187) in the controls ( $p=0.0673$ )), although the difference did not quite reach statistical significance. There was no statistically significant difference in the overall Caesarean section rate

between the groups (12/29 (41%) in the MFS group compared with 30/116 (26%) in the controls,  $p=0.11$ ); proportions of elective versus emergency Caesarean section were also similar ( $p=0.32$  and  $p=0.65$  respectively). Nine of the Caesarean sections in the MFS group were performed for obstetric reasons (1 emergency, 8 elective) and 3 for cardiac reasons (all elective): progressive aortic root dilatation or deteriorating left ventricular function. Of the pregnancies in the MFS group which resulted in vaginal delivery, 13 (76%) had regional anaesthesia compared with 40 (47%) of the controls (OR 3.7, 95% CI 1.13 to 12.39). Of those which ended in Caesarean section, two cases (16%) in the MFS group required general anaesthesia compared with two (7%) in the controls ( $p=0.56$ ).

The rate of obstetric complications was significantly higher in the MFS group (OR 3.6, 95% CI 1.48 to 8.76) with obstetric complications occurring in 12 (41%) pregnancies. One woman developed pregnancy-induced hypertension (PIH); one had a significant antepartum haemorrhage (APH) and 10 had PPH. In the control group, 19 (16%) women had obstetric complications: One woman developed PIH, 5 pre-eclampsia (PET), 1 had a significant APH, 8 PPH and 4 women experienced spontaneous preterm labour. In particular, the women with MFS had a higher incidence of PPH (OR 7.1; 95% CI 2.49 to 20.30).

### 5.5.3 Fetal and Neonatal Outcomes

There were no fetal or neonatal deaths, but complications occurred more often in the MFS group (OR 3.12; 95% CI 1.272 to 7.652). Median gestational age at delivery in the MFS group was 39 weeks (range 35 to 42), significantly earlier than in the control group (median 40, range 27 to 42;  $p=0.04$ , MWU test). Pre-term delivery rates were

similar in both groups. Of the babies born to mothers with MFS, two (7%) were delivered pre-term compared with 5 (4%) of those with unaffected mothers. Both of the pre-term babies in the MFS group were delivered iatrogenically early for maternal reasons compared with only one of the 5 pre-term babies in the control group. Mean and median birth weight and birth weight centile were lower in the MFS group: 3068g (median 3030g, range 2300 to 3900g), 29<sup>th</sup> centile (median 20, range 0 to 92) versus 3324g (median 3380g, range 920 to 4450g), 49<sup>th</sup> centile (median 48, range 0 to 100) in the controls ( $p=0.0067$  ( $t$  test) and  $p=0.0012$  (MWU test) respectively). The MFS group babies were also more likely to be small for gestational age (SGA) with 7 (24%) of babies in the MFS group being SGA compared with 7 (6%) of those born to control women (OR 4.95; 95% CI 1.58 to 15.55). Additionally in the MFS group, there was no relationship between birth weight and maternal height ( $r=0.03$ ,  $p=0.346$ ) (Fig 5). Six of the babies born to index cases were subsequently found to have the same genotype as their mothers, with 8 found to be unaffected. In 15 babies the genotype is unknown. There were insufficient data to determine whether any of the offspring met the Ghent criteria for diagnosis of MFS.

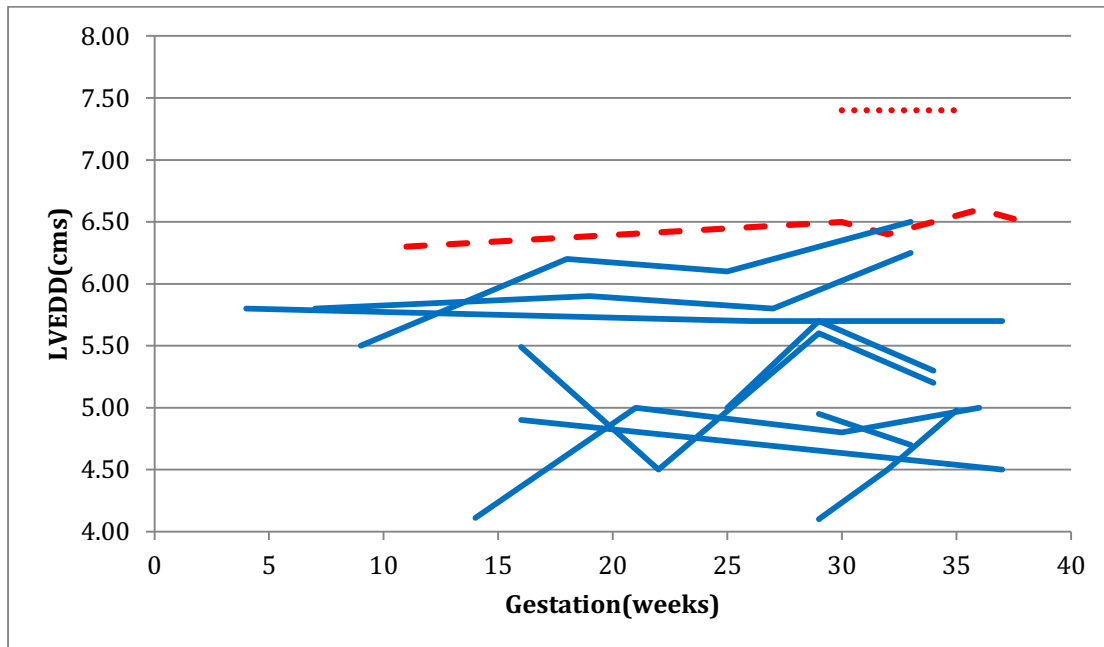
Table 1: Baseline characteristics, mode of delivery, use of anaesthesia, birth weight and birth weight centiles, and complications in women with MFS and controls

|                                           | MFS            | Controls       |                           |
|-------------------------------------------|----------------|----------------|---------------------------|
| Number of women                           | 21             | 116            |                           |
| Number of pregnancies                     | 29             | 116            |                           |
|                                           | mean (SD)      | mean (SD)      |                           |
| Age at booking(yrs)                       | 31.1 (5.0)     | 32.8 (5.5)     | p=0.1                     |
| Maternal Height (cm)                      | 179 SD 8.7     | 164 SD 7.7     | p<0.0001                  |
|                                           | median (range) | median (range) |                           |
| Maternal Weight (kg)                      | 69 (49 – 120)  | 60 (45 – 102)  | p=0.007                   |
|                                           | n (%)          | n (%)          |                           |
| Parity                                    |                |                |                           |
| Nulliparous                               | 21 (72)        | 69 (59)        |                           |
| Para 1                                    | 8 (28)         | 47 (41)        |                           |
| Mode of delivery                          |                |                |                           |
| SVD                                       | 5(17)          | 71 (61)        | OR 0.13<br>(0.04 - 0.37)  |
| Assisted vaginal delivery                 | 12(41)         | 15(13)         | OR 4.75<br>(1.9 – 11.9)   |
| Elective CS                               | 9 (31)         | 24 (21)        |                           |
| Emergency CS                              | 3 (11)         | 6 (5)          |                           |
| Regional anaesthesia for vaginal delivery | 13 (76)        | 40 (47)        | OR 3.7<br>(1.13 – 12.39)  |
|                                           | median (range) | median (range) |                           |
| Length of 2 <sup>nd</sup> stage (mins)    | 67 (7-136)     | 30.5 (4-187)   | p=0.07                    |
| Gestational age at delivery(wks)          | 39 (35-42)     | 40 (27-42)     | p=0.04                    |
|                                           | mean (SD)      | mean (SD)      |                           |
| Birth weight(g)                           | 3068 (471)     | 3324 (505)     | p=0.007                   |
|                                           | median (range) | median (range) |                           |
| Customised birth weight centile           | 29 (0-92)      | 49 (0-100)     | p=0.001                   |
|                                           | n (%)          | n (%)          |                           |
| Distribution of birth weight centiles     |                |                |                           |
| 90-100                                    | 2 (7)          | 11 (10)        |                           |
| 75-89                                     | 0 (0)          | 20 (17)        |                           |
| 50-74                                     | 6 (21)         | 25 (22)        |                           |
| 25-50                                     | 4 (13)         | 34 (29)        |                           |
| 10-24                                     | 6 (21)         | 12 (10)        |                           |
| 0-9                                       | 11 (38)        | 14 (12)        |                           |
| Obstetric complications                   | 10 (34)        | 16 (14)        | OR 3.29<br>(1.3 – 8.34)   |
| PPH                                       | 8 (28)         | 5 (4)          | OR 8.46<br>(2.52 – 28.38) |
| Neonatal complications                    | 9 (31)         | 12 (10)        | OR 3.9<br>(1.45 – 10.47)  |
| SGA                                       | 7 (24)         | 7 (6)          | OR 4.95<br>(1.58 – 15.55) |

Table 2: Comparison of 1<sup>st</sup> and 2<sup>nd</sup> pregnancies in women with MFS

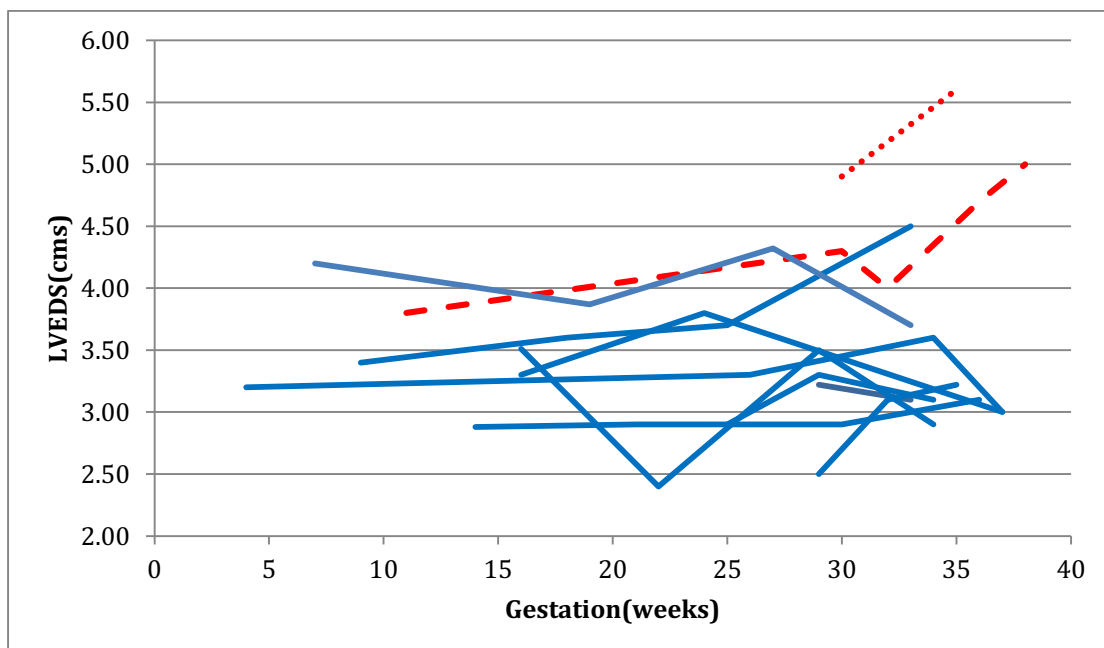
|                                            | 1 <sup>st</sup> Pregnancy | 2 <sup>nd</sup> Pregnancy |        |
|--------------------------------------------|---------------------------|---------------------------|--------|
| <b>Number of pregnancies</b>               | 21                        | 8                         |        |
|                                            | <b>mean (SD)</b>          | <b>mean (SD)</b>          |        |
| <b>Maternal age at booking</b>             | 30.19 (5.4)               | 33.5 (2.3)                | p=0.03 |
|                                            | <b>median (range)</b>     | <b>median (range)</b>     |        |
| <b>Maternal Weight (kg)</b>                | 63 (49 – 120)             | 71 (59 – 120)             | p=0.21 |
|                                            | <b>n (%)</b>              | <b>n (%)</b>              |        |
| <b>Mode of Delivery</b>                    |                           |                           |        |
| <i>SVD</i>                                 | 3 (14)                    | 2 (25)                    |        |
| <i>Assisted vaginal delivery</i>           | 9 (43)                    | 3 (38)                    |        |
| <i>Elective CS</i>                         | 7 (33)                    | 2 (25)                    |        |
| <i>Emergency CS</i>                        | 2 (10)                    | 1(12)                     |        |
|                                            | <b>median (range)</b>     | <b>median (range)</b>     |        |
| <b>Gestational age at delivery (weeks)</b> | 39.1 (35 – 42)            | 38.4 (37 – 40)            | p=0.19 |
|                                            | <b>mean (SD)</b>          | <b>mean (SD)</b>          |        |
| <b>Birth weight (g)</b>                    | 2995 (476.8)              | 3258 (430.1)              | p=0.18 |
| <b>Birth weight centile</b>                | 25.2 (25.8)               | 40.5 (36.9)               | p=0.31 |
| <b>Aortic root pre-pregnancy (mm)</b>      | 39 (1.3)                  | 40 (0.5)                  | p=0.86 |
|                                            | <b>n (%)</b>              | <b>n (%)</b>              |        |
| <b>Cardiac complications</b>               | 4 (19)                    | 1(12)                     |        |
| <b>Obstetric complications</b>             | 7 (33)                    | 3 (38)                    |        |
| <b>Neonatal complications</b>              | 7 (33)                    | 2 (25)                    |        |
|                                            |                           |                           |        |

*Figure 2: Echocardiographic measurement of left ventricular diastolic dimensions during pregnancy in women with MFS  
(Women who developed LV dysfunction in red)*



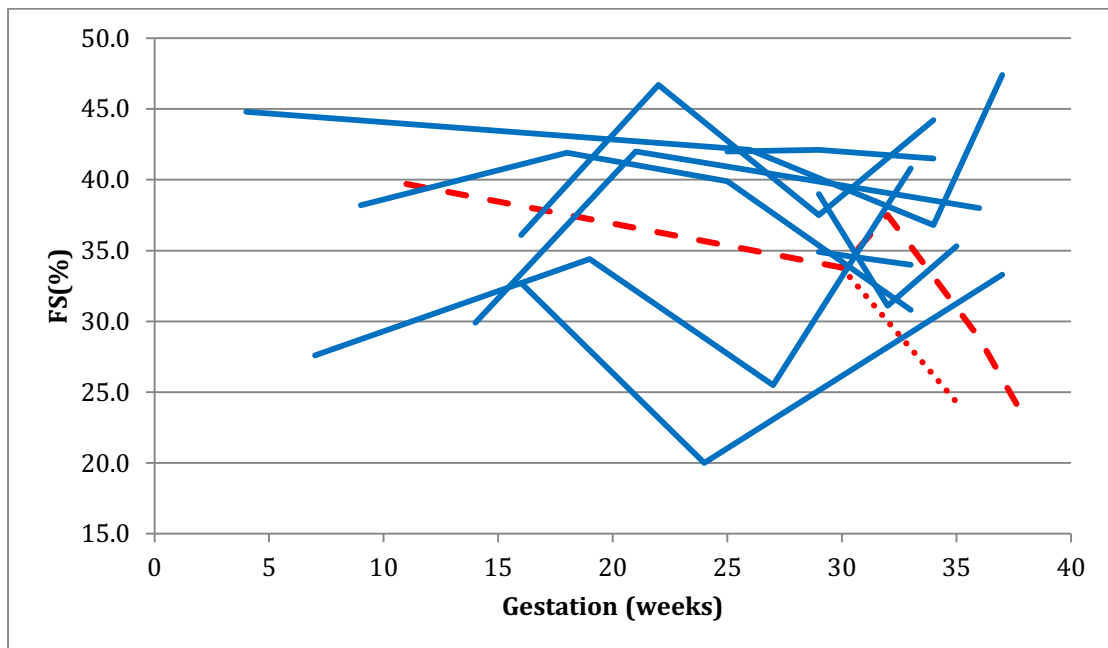
*LVEDD: left ventricular end-diastolic diameter*

*Figure 3: Echocardiographic measurement of left ventricular systolic dimensions during pregnancy in women with MFS  
(Women who developed LV dysfunction in red)*



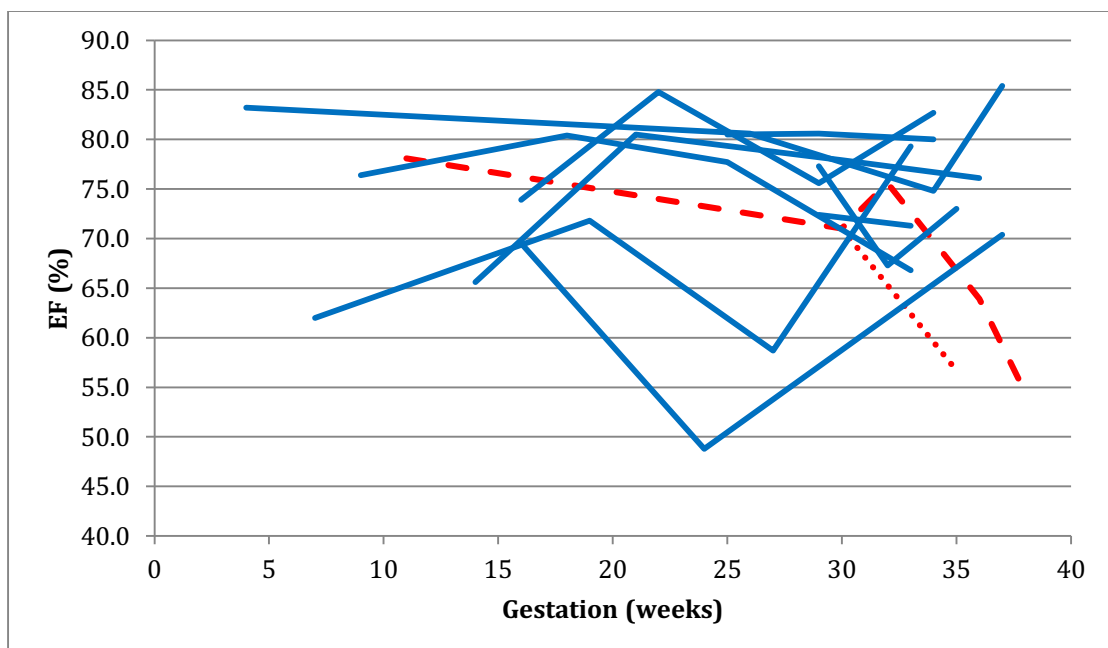
*LVESD: left ventricular end-systolic diameter*

Figure 4: Echocardiographic measurement of fractional shortening during pregnancy in women with MFS  
(Women who developed LV dysfunction in red)



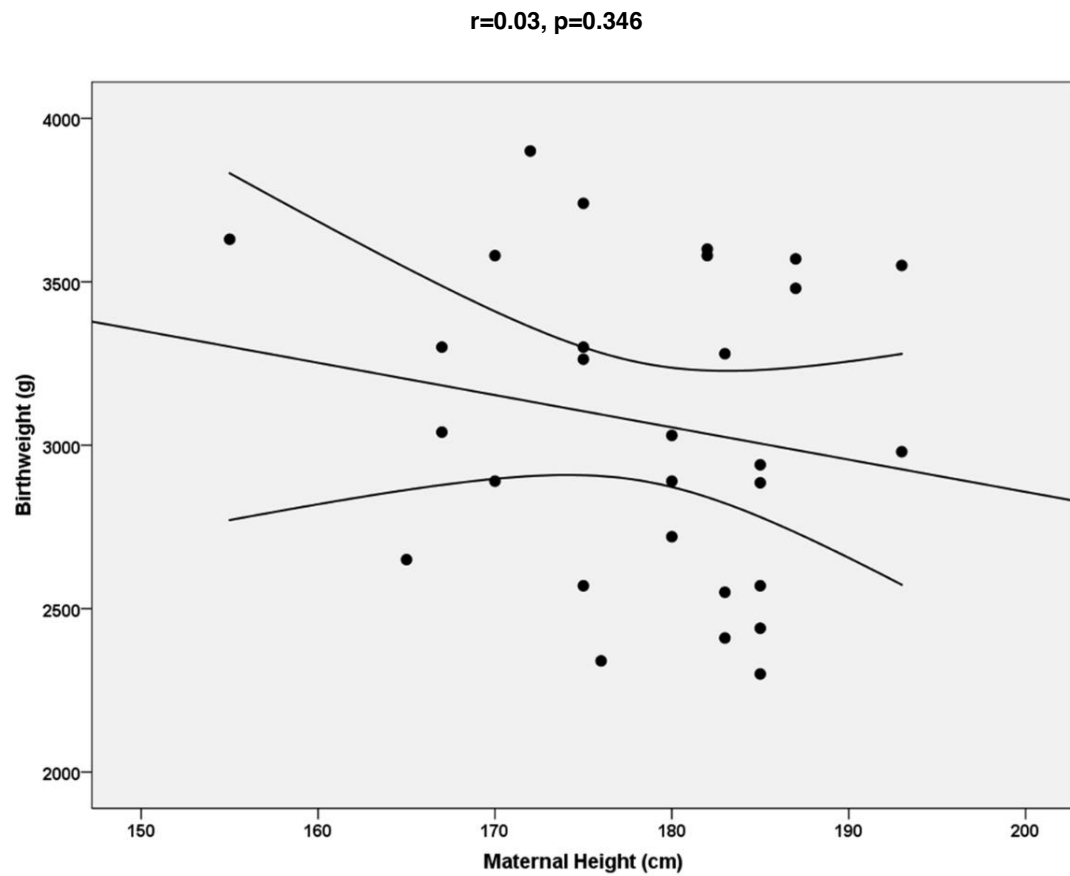
FS: fractional shortening

Figure 5: Echocardiographic measurement of ejection fraction during pregnancy in women with MFS  
(Women who developed LV dysfunction in red)



EF: ejection fraction

Figure 6: Relationship between maternal height and birth weight in Marfan women



## 5.6 Discussion

Pregnancy in women with MFS is associated with a high risk of maternal and fetal complications. In this series of 29 pregnancies in 21 women with MFS, there were no maternal or fetal deaths, but there was a significantly higher rate of obstetric and fetal adverse outcomes in the MFS group compared with healthy controls. Other than age at booking, baseline characteristics and outcomes between first and second pregnancies in the MFS group were similar (table 2). This may reflect a selection bias in that women with signs of deterioration in their first pregnancy may have been counselled against a further pregnancy, but there is no direct evidence that this was the case.

### 5.6.1 Maternal Outcomes

#### *Cardiovascular complications*

Significant cardiovascular complications occurred in 5 pregnancies (17%) with 3 women requiring surgery within 6 months of delivery. There was one case of aortic dissection (3% of pregnancies). Pregnancy in the general population has been shown to increase the risk of aortic dissection;<sup>128,143</sup> this risk is even higher in women with MFS. Several studies have sought to evaluate the rate of aortic dissection in women with MFS during pregnancy<sup>135,144,145-148</sup>. European Guidelines<sup>4</sup> suggest that women with minimal cardiovascular involvement and an aortic root diameter of <40mm have an estimated risk of 1% of dissection or other serious cardiac complications, whereas in high risk women (aortic root diameter > 40mm, rapid aortic dilatation or previous dissection) the risk may be as high as 10%.<sup>4</sup> The 5 patients in this study who

experienced serious cardiovascular complications all had pre-pregnancy aortic root diameters in excess of 40mm. However, there is still disagreement over the aortic root diameter above which pregnancy should be discouraged: in their prospective study of 127 women with MFS, Meijboom and colleagues suggest that in low-risk women, without prior history of cardiovascular complications, a root diameter of up to 45mm appears to be relatively safe.<sup>130</sup> In this study aortic dissection occurred in one woman with a pre-pregnancy root diameter of 42mm and no previous history of cardiovascular events, and left ventricular dysfunction developed in a woman with a pre-pregnancy root-diameter of 41mm who had in fact undergone a previous elective valve-sparing aortic root replacement. Elective aortic root replacement in high risk Marfan women has been shown to reduce the risk of complications during pregnancy, and prophylactic surgery has been suggested if the diameter is >44mm in women who desire pregnancy; this could potentially have been offered to 3 women<sup>4</sup>. Four of the five women who developed cardiac complications during pregnancy did not have pre-pregnancy counselling, highlighting the need to raise awareness of the issues of heart disease and pregnancy among professionals and patients alike. Three women had their care transferred to the Chelsea and Westminster and Royal Brompton Hospitals during the pregnancy and it is not clear what, if any, pre-pregnancy counselling they had received. Aortic dissection has been reported in MFS women with a normal aortic root diameter.<sup>149</sup> Therefore it may be prudent to recommend that all pregnant women with MFS (regardless of aortic root diameter) remain in hospital for seven days following delivery, with echocardiography prior to discharge to exclude rapid postnatal aortic dilatation.

Two women developed impaired left ventricular function during their pregnancies. Although this may occur in MFS as a consequence of significant aortic or mitral valve disease, it has also been described (in non-pregnant subjects) in the absence of valvular pathology.<sup>132,134,150</sup> In this series one woman had no valvular pathology prior to pregnancy and another had mild to moderate mitral regurgitation, which remained stable throughout the pregnancy. The pathogenesis of MFS-related left ventricular dysfunction is poorly understood. It has been suggested that mutations in the FBN1 gene may cause structural or functional abnormalities in the microfibrils which subsequently lead to impairment of myocardial contraction.<sup>134</sup> It is important to distinguish the deterioration in left ventricular function seen in these two women from that seen in peripartum cardiomyopathy (PPCM). PPCM is defined as '*an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion. The left ventricle may not be dilated but the ejection fraction is nearly always reduced below 45%*'.<sup>151</sup> The incidence of PPCM is estimated to be around 0.025 to 0.04%.<sup>151</sup> This compares with an incidence of left ventricular dysfunction in our index group of 6.8%. Neither of our patients displayed signs or symptoms of heart failure; the diagnosis was based entirely on echocardiographic findings. In the first case a dilated left ventricle was found in the second trimester and in the second it was discovered in the third trimester. Both women showed a rapid improvement in left ventricular function at one week postnatal, and by the sixth postnatal week left ventricular function had returned to baseline in both, although the dilatation persisted. Left ventricular dysfunction in MFS patients may be mediated through the transforming growth factor- $\beta$  (TGF- $\beta$ ) signalling pathway and elevated TGF- $\beta$ 1 gene expression

has been noted in ventricular biopsies from patients with dilated cardiomyopathy (DCM).<sup>134</sup> In contrast, it is now accepted that PPCM is not simply an aggravation of underlying DCM, but is a separate entity.<sup>151</sup> It is likely that the changes in left ventricular function seen in MFS are accelerated by the physiological volume overload of pregnancy.

Beta-blockers were taken in 26 of the 29 pregnancies studied. Three women declined them due to their inability to tolerate the side effects of dizziness, tiredness and hypotension, and concern about fetal growth. In non-pregnant patients, beta-blockers have been shown to have a small impact on the rate of growth of the aortic root.<sup>125,140-142</sup> In addition to their negative inotropic effect, they also increase aortic distensibility and reduce aortic stiffness.<sup>125,140-142</sup> Beta-blockers have been used extensively in pregnancy, especially for treatment of hypertension. However they are excreted in breast milk and their use is associated with side effects including fetal growth restriction, and neonatal hypoglycaemia, hyperbilirubinaemia and bradycardia. Use of beta-blockers may account for the significant difference in birth weight seen between the study group and the control population.

### *Obstetric Complications*

Obstetric complications occurred in 12 (41%) of pregnancies in the index group, a significantly higher rate than in the controls. The most frequent complication seen was PPH, which occurred in 10 of the 29 (34%) MFS pregnancies studied compared with 8 of 116 (6.7%) pregnancies in the control group. Rates of other complications such as PET, PIH and gestational diabetes were similar in both groups. Higher rates of PPH have previously been reported in women with MFS and other connective

tissue disorders.<sup>138,152</sup> FBN1 is present in the myometrium<sup>153</sup> and might explain the higher rate of PPH as a result of uterine atony. There may also be an association with the low dose syntocinon infusion (to prevent the systemic hypotension associated with its use) used to manage the third stage of labour in women with significant cardiac disease.<sup>4,5</sup> However, a recent double-blind, randomised controlled trial reported that higher doses of oxytocin did not reduce rates of PPH when compared to a low dose,<sup>154</sup> (the low dose was similar to that used for the patients in this study, and recommended by the RCOG<sup>5</sup> and the ESC<sup>4</sup>).

Vaginal delivery rates in the two groups were similar (59% for the MFS group versus 74% for the controls), however the rate of assisted delivery was significantly higher for women with MFS. This reflects the policy at the Chelsea and Westminster and Royal Brompton Hospitals to recommend either an elective assisted delivery or a shortened active second stage in women with serious cardiac disease in order to minimise the cardiovascular stress associated with active bearing down (despite a lack of evidence proving any benefit<sup>78</sup>). It is therefore surprising that the length of the second stage was longer in the Marfan group (median 67 minutes (range 7-136) in the MFS group and 30.5 minutes (4-187) in the controls ( $p=0.0673$ )), although the difference did not quite reach statistical significance. This may be due to the women with MFS having a relatively longer passive second stage to allow for adequate descent of the fetus prior to commencement of active pushing or assisted delivery. Epidural analgesia is recommended as it thought that the avoidance of pain will limit the haemodynamic changes and progressive rise in cardiac output seen with contractions.<sup>28</sup> Caesarean section rates were similar between the two groups. The data presented in this study suggests that vaginal delivery under controlled conditions

would appear to be safe for MFS women, and avoids the increased risks of haemorrhage, infection and thromboembolism associated with caesarean section.<sup>83</sup>

#### 5.6.2 Fetal and Neonatal Outcomes

There were no fetal or neonatal deaths. However, complications were more likely for babies born to mothers with MFS. The MFS group had a significantly earlier gestational age at delivery (median 39 weeks) than the control group (median 40 weeks), although there was no significant difference in preterm delivery rates. MFS and other connective tissue disorders have been associated with PPROM and spontaneous preterm labour and it has also been suggested that there is a relationship between PPROM and connective tissue disease in the neonate.<sup>136,137</sup> However, none of the women with MFS in this series experienced either of these complications. This may be a chance finding due to small numbers.

Significantly more babies in the MFS group were SGA (24% versus 7%). Mean/median birth weight and birth weight centile were also significantly lower. This may be explained by the use of beta-blockers in the majority of these women, whereby the negative inotropic effect reduces cardiac output and thus utero-placental perfusion; (beta-blockers were taken throughout 26 of 29 pregnancies). A computer generated chart was used to calculate customized birth-weight centiles, taking into account maternal ethnicity, parity, height and weight.<sup>88,89</sup> The women with MFS were significantly taller than the controls ( $p < 0.0001$ ) as might be expected, and this might explain some of the difference between the two groups. However, even when standard centile charts (ie. not customized for maternal ethnicity, height and weight) were used, the MFS group neonates still had significantly lower birth weight centiles

compared with the controls (mean 42 +/- 29 versus mean 54 +/- 27;  $p=0.0485$ ).

Additionally there was no relationship between maternal height and birth weight in the MFS group (figure 5), which is contrary to that usually found (taller mothers usually have bigger babies). It is possible that this is a reflection of the severity of MFS in these women.

## **5.7 Conclusions**

This study demonstrates that pregnancy in women with MFS continues to be associated with significant rates of maternal, fetal and neonatal complications. Unfortunately the small numbers limit the conclusions that can be drawn; further prospective multi-centre studies, in particular investigating changes in cardiac function, dimension and haemodynamics in these women, are indicated. The cohort studied reflects women under the care of the Royal Brompton and Chelsea and Westminster Hospitals and therefore a referral bias is possible, if not likely. However, the findings reinforce the need for effective pre-pregnancy counselling, as well as meticulous surveillance during pregnancy, delivery and the puerperium by an experienced multidisciplinary team.

## **Chapter 6:      Valvular Heart Disease**

## 6.1 Abstract

### 6.1.1 Aims:

To investigate maternal and neonatal outcomes in a series of pregnancies in women with valvular heart disease

### 6.1.2 Methods:

Retrospective review of case records

### 6.1.3 Results:

There were one hundred and thirty-one pregnancies in 73 women with valvular heart disease. Significant cardiac complications occurred in nine pregnancies (6.5%), and were most frequent in women with left heart obstruction or mechanical valves (19.4% and 25% respectively). There was one maternal death in a woman who suffered thrombosis of a mechanical aortic valve. Cardiac events during the pregnancy correlated with adverse perinatal outcomes ( $r=0.24$ ,  $p=0.0006$ ). Rates of obstetric complications in women with valvular heart disease and controls were similar, although postpartum haemorrhage occurred more frequently in women with mechanical prostheses than in the control women (OR 8.98, 95% CI 2.07-39.07,  $p=0.004$ ). Perinatal complications occurred more frequently in women with valvular heart disease, (and were most frequent in those with left heart obstruction and mechanical valves) than in the control women. Presence of a mechanical prosthetic valve was independently associated with adverse perinatal outcome (OR 7.26, 95% CI 1.33-44.73,  $p=0.01$ ). There were three neonatal deaths and one pregnancy was terminated at 25 weeks following diagnosis of severe intracranial haemorrhage in the fetus. Babies born to women with valvular

heart disease were significantly more likely to be delivered preterm (before 37 completed weeks' gestation) for medical reasons (OR 11.92, 95% CI 54.62,  $p<0.001$ ) and to be small for gestational age (birth weight less than the 5<sup>th</sup> customized centile) (20.6% in the valve group versus 2.7% in the controls; OR 9.46, 95% CI 3.99-22.40,  $p<0.001$ ).

#### 6.1.4 Conclusions:

Pregnancy in women with valvular heart disease, in particular those with left heart obstruction, mechanical prosthetic valves and those who have undergone previous surgery, is associated with significant rates of maternal, fetal and neonatal complications. Previous cardiac surgery is an independent predictor for adverse fetal/neonatal outcomes.

## 6.2 Introduction

Valvular heart disease (VHD) is common in pregnancy (25% of patients enrolled in an international registry between 2007 and 2011 had VHD<sup>38</sup>) and significantly increases maternal and fetal risk. Furthermore, patients with VHD are often not known to have heart disease prior to pregnancy, the diagnosis only being made when the haemodynamic challenges of pregnancy lead to decompensation and development of symptoms. The aetiologies are varied and may result from congenital abnormalities or acquired lesions (table 1)<sup>155</sup> and one or more valves may be involved. In pregnant women in the developed world, aortic stenosis (AS) is usually congenital, and mitral stenosis (MS) usually rheumatic, in origin.

Despite a decline in the incidence of rheumatic heart disease (RHD) in Europe and North America it accounts for over 90% of cardiac disease in pregnancy worldwide, with rheumatic MS the most common lesion.<sup>156,157</sup> One in four women giving birth in the UK are born abroad, many having emigrated from countries where rheumatic fever is endemic.<sup>79</sup> Approximately 3% of patients with untreated group A streptococcal pharyngitis go on to develop rheumatic fever. It is thought that cross-reactivity of either the streptococcus toxin or a bacterial antigen, with proteins in the valvular endocardium results in inflammatory changes and formation of scar-tissue, and subsequent valve dysfunction.<sup>157,158</sup> RHD in developing countries is characterized by the occurrence of severe VHD at a younger age than that generally seen in developed countries.

*Table 1: Aetiology of valvular heart disease in women of childbearing age (adapted from Nanna & Stergiopoulos, 2014)<sup>155</sup>*

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Aortic valve</b> <ul style="list-style-type: none"> <li>• Congenital bicuspid valve</li> <li>• Rheumatic valvular disease</li> <li>• Connective tissue disorder</li> <li>• Marfan syndrome, Ehlers Danlos syndrome, Turner's syndrome or other aortic disease resulting in or associated with aortic valve disease</li> <li>• Prosthetic valve (mechanical or bioprosthesis)</li> <li>• Prior history of infective endocarditis</li> <li>• Ross procedure</li> </ul> |
| <b>Mitral valve</b> <ul style="list-style-type: none"> <li>• Congenital valvular stenosis</li> <li>• Myxomatous valve disease (mitral valve prolapse)</li> <li>• Rheumatic valvular disease</li> <li>• Prior infective endocarditis</li> <li>• Prosthetic valve (mechanical or bioprosthesis)</li> <li>• Hypertrophic cardiomyopathy with systolic anterior motion of the mitral valve</li> <li>• Tethered mitral valve related to dilated cardiomyopathy</li> </ul>    |
| <b>Pulmonary valve</b> <ul style="list-style-type: none"> <li>• Congenital pulmonary stenosis, Noonan syndrome, post-operative Tetralogy of Fallot</li> <li>• Pulmonic regurgitation (native or residual after interventional or surgical correction of more complex congenital heart disease)</li> <li>• Prosthetic valve (bioprosthesis)</li> </ul>                                                                                                                   |

Increases in aortic root dimensions and the size of the mitral and tricuspid annuli have been observed in normal pregnancy using echocardiography.<sup>57,58,159</sup> As a result, mild valvular regurgitation is a common occurrence in healthy pregnant women with the mitral, tricuspid and pulmonary valves exhibiting a degree of insufficiency in up to 28%, 94% and 94% of pregnancies respectively.<sup>159</sup>

Maternal and fetal risks vary with the type and severity of the valve lesion; the presence of resulting abnormalities of functional capacity, left ventricular function

and pulmonary artery pressure are important prognostic factors. Left-sided stenotic lesions are particularly poorly tolerated.<sup>4,52,54-56,155-158</sup>

The first successful heart valve replacement in a human was reported in the US in 1960.<sup>160</sup> Prosthetic heart valves (PHVs) may be bioprosthetic (heterografts (commonly of porcine origin), homografts and autografts (as used in the Ross procedure)) or mechanical. While bioprosthetic valves (BPVs) are associated with a low risk of thromboembolism during pregnancy, (thus obviating the need for anticoagulation and the haemorrhagic risks to both mother and fetus associated with this), if they are used in young women there is a high risk of structural valve deterioration and the need for re-operation over time. Early mortality for re-operation in such populations has been reported to be as high as 8.7%.<sup>160</sup> It has been suggested that pregnancy accelerates this process, although the data are conflicting.<sup>78,160</sup> Mechanical prostheses (MPVs) have been shown to have excellent long-term durability and have a superior haemodynamic profile compared with bioprostheses. However, they are highly thrombogenic and life-long anticoagulation is required. This presents particular problems during pregnancy, with a need to balance the risk of valvular thromboembolism with haemorrhagic risk. There remains contention as to the ideal anticoagulant regimen in pregnancy for women with MPVs.<sup>4,78</sup>

### **6.3 Aims**

To investigate maternal and neonatal outcomes in a series of pregnancies in women with VHD.

## 6.4 Methods

Women with VHD cared for by the Joint Cardiac and Obstetric Service of the Chelsea and Westminster and Royal Brompton Hospitals, were identified from a database commenced in 1994. For each birth to a woman with VHD there were two controls (matched for parity): the first woman who delivered immediately before and after each index case. Seventeen women with VHD delivered before 1998; data for control women were not available prior to this date and so the first women who delivered on the same date in 1999 were used as controls.

Data were collected from a detailed review of case notes supplemented by the Ciconia Maternity Information System (CMIS<sup>®</sup>, HD Clinical Ltd, Bishops Stortford, Herts, UK). In all women, demographic data and information on obstetric and anaesthetic management during pregnancy and labour, and maternal and neonatal outcomes was obtained, noting cardiac, obstetric and fetal/neonatal complications and intra-partum events as previously described in chapter 3. The VHD population was divided into six subgroups: those associated with left heart obstruction (LHO), left heart regurgitation (LHR), right heart obstruction (RHO), right heart regurgitation (RHR), and those associated with bioprosthetic (BPV) and mechanical prosthetic valves (MPV).

Women with isolated mitral valve prolapse and isolated bicuspid aortic valve (ie. with no haemodynamic consequences) were excluded.

Data were analysed using SPSS 22 and GraphPad Prism version 6.0d. Descriptive statistics for nominal data are expressed in absolute numbers and percentages. Mean value and standard deviations are presented for normally distributed continuous

variables and for non-normally distributed continuous variables, median and range. Differences in outcomes between the VHD and control groups, and between first and subsequent pregnancies in the VHD group, were evaluated. Continuous variables were compared with the Student t-test if they were normally distributed and the Mann-Whitney U-test if they were not. When comparing frequencies the chi-squared test or Fisher exact test where applicable, was used. All tests were two-tailed and  $p < 0.05$  was considered statistically significant. Binary logistic regression was performed to identify patient characteristics associated with adverse pregnancy outcome divided into 3 composite endpoints (as defined previously): cardiac, obstetric and fetal/neonatal complications. The following baseline variables were assessed: LHO, LHR, RHO, RHR, presence of a BPV, presence of an MPV, use of any anticoagulant, use of warfarin, use of therapeutic doses of LMWH, use of prophylactic doses of LMWH, use of beta-blockers, parity, maternal cigarette smoking during the pregnancy, previous cardiac surgery and cardiac events prior to pregnancy. Variables that were associated with an increased incidence of the studied endpoints ( $p < 0.1$ ) were brought forward to multivariable analysis.

## 6.5 Results

One hundred and thirty-one pregnancies in 73 women with VHD were compared with 262 controls.

### 6.5.1 Baseline characteristics

Baseline characteristics for women with VHD and controls are shown in table 2.

Women with VHD were significantly younger than the control women. Mean age at booking in the VHD group was 30 years (SD 5.7) compared with 34 years (SD 5.0) in the controls ( $p<0.0001$ , student t-test). Women with VHD were also significantly more likely to be taking cardiac medication, in particular anticoagulants (OR 18.09, 95% CI 4.09-79.98,  $p<0.001$ ) or aspirin (OR 8.71, 95% CI 2.41-31.44,  $p<0.001$ ). In women with VHD outcomes in nulliparous ( $n=73$ ) and parous ( $n=58$ ) women were similar (table 3), although as was expected nulliparous women were more likely to require an assisted vaginal delivery (ventouse or forceps) than parous women (OR 3.99, 95% CI 1.50-10.61,  $p<0.01$ ).

### 6.5.2 Diagnoses

The types of valvular lesions are shown in figure 1 below. Most pregnancies were in women with aortic valve disease (34%), followed by mitral valve disease (32%). Eighteen pregnancies (14%) occurred in women with PHVs: ten of these were in women with BPVs and eight in women with MPVs.

### 6.5.3 Maternal and fetal/neonatal outcomes

Table 4 outlines the mode of delivery, gestational age, birth weight, birth weight centile and cardiac, obstetric and neonatal complications in women with VHD and the controls. Table 5 displays the subgroup analysis, with outcomes in each subgroup of valvular heart disease (LHO, LHR, RHO, RHR, BPV and MPV) being compared with those in the control group. Outcomes in women taking anticoagulants are detailed in Table 6.

#### *Cardiac outcomes*

Significant cardiac complications occurred in 9 pregnancies (6.5%) in the VHD group. There was one maternal death. Cardiac complications were most likely to arise in women with LHO or MPVs. There were 7 adverse events in pregnancies in women with LHO, including myocardial infarction (1), pulmonary oedema (1) (in women with moderate and severe MS respectively), clinically significant arrhythmia (2) and acute angina (1) (all in women with severe AS) and endocarditis (2 – in one woman with a previous mitral valve repair, and in another with moderate AS). 3 complications arose in 2 pregnancies in women with MPVs: a woman with a Starr-Edwards mitral valve developed endocarditis and subsequent valve thrombosis at 25 weeks' gestation, requiring emergency valve replacement and delivery by caesarean section. The baby did not survive. A further woman with a St Jude's aortic valve suffered valve thrombosis at 36 weeks' gestation and died.

#### *Obstetric outcomes*

Frequencies of the different modes of delivery (spontaneous vaginal delivery (SVD), assisted vaginal delivery and Caesarean section – both elective and emergency) were

similar in both the women with VHD and the controls. Overall there was no statistically significant difference in rates of obstetric complications between the two groups ( $p=0.08$ ). However, women with MPVs were more likely than control women to have obstetric complications (87.5% versus 27.9%, OR 18.12, 95% CI 2.19-150.0,  $p=0.0010$ ), specifically an increased rate of postpartum haemorrhage (PPH) (71.4% versus 15.6%, OR 8.98, 95% CI 2.07-39.07,  $p=0.004$ ), although there was a correlation between the presence of an MPV and the use of anticoagulants ( $r=0.66$ ,  $p=0.01$ ).

#### *Fetal and neonatal outcomes*

Neonatal complications occurred in 40 (30.5%) of the index pregnancies compared with 18 (6.9%) in the controls (OR 5.54, 95% CI 3.01-10.19,  $p<0.0001$ ) and arose most frequently in pregnancies in women with LHO or MPVs (41.7% and 75.0% respectively).

There were 3 neonatal deaths in the VHD group. The baby born to the woman who suffered mitral valve thrombosis and was delivered at 25 weeks, died of complications of prematurity. In her next pregnancy she was delivered at 32 weeks after developing pre-eclampsia. The baby developed necrotizing enterocolitis and died on the 7<sup>th</sup> postnatal day. The last neonatal death occurred in an SGA baby born at 35 weeks' gestation to a woman with moderate to severe AS, following an abruption and preterm labour. One woman with a metallic mitral valve who was taking warfarin opted for termination of pregnancy at 24 weeks following diagnosis of severe intracerebral haemorrhage in the fetus.

Women with VHD were more likely than control women to be delivered preterm for medical reasons (OR 11.92, 95% CI 2.60 to 54.62,  $p<0.001$ ), especially if they had LHO or PHVs. Iatrogenic preterm delivery occurred more frequently in women being treated with dose-adjusted LMWH than in those taking prophylactic doses (71.4% vs 12.5%, OR 20.0, 95% CI 1.42-282.6,  $p=0.035$ ). Median birth weight and mean birth weight centile were lower in women with heart disease: 3230g (range 420-4630) and 38<sup>th</sup> centile (SD 28) versus 3420g (range 1500-4650) and 49<sup>th</sup> centile (SD 54) in the controls ( $p=0.0006$  (MWU test) and  $p=0.003$  (student t-test) respectively). The VHD babies were also more likely to be small for gestational age with 27 (20.6%) of the babies in this group having a birth weight less than the 5<sup>th</sup> customized centile compared with 7 (2.7%) of the control women (OR 9.46, 95% CI 3.99-22.40,  $p<0.001$ ).

Perinatal complications were associated with both maternal cardiac complications and obstetric complications ( $r=0.24$ ,  $p=0.0006$  and  $r=0.27$ ,  $p=0.02$  respectively).

#### 6.5.4 Logistic Regression

Tables 7-8 illustrate the results of the univariable and multivariable logistic regression analysis. There were no independent predictors of cardiac or obstetric complications in women with VHD. Presence of an MPV was independently associated with neonatal complications (OR 7.26, 95% CI 1.33-44.73,  $p=0.01$ ).

Table 2: Baseline characteristics in women with VHD and controls

|                        | VHD       | Controls   |                             |
|------------------------|-----------|------------|-----------------------------|
| Number of women        | 73        | 262        |                             |
| Number of pregnancies  | 131       | 262        |                             |
|                        | mean (SD) | mean (SD)  |                             |
| Age at booking (years) | 30 (5.7)  | 34 (5.0)   | p<0.0001                    |
|                        | n(%)      | n(%)       |                             |
| Parity                 |           |            |                             |
| Nulliparous            | 73 (55.7) | 141 (55.7) |                             |
| Para 1                 | 45 (34.4) | 90 (34.4)  |                             |
| Para >1                | 13 (9.9)  | 321(9.9)   |                             |
| Cardiac medications    |           |            |                             |
| Any                    | 22 (16.7) | 5 (1.9)    | OR 10.37<br>(3.83-28.11)*** |
| $\beta$ -blocker       | 1 (0.8)   | 0 (0.0)    |                             |
| Other antiarrhythmic   | 1 (0.8)   | 0 (0.0)    |                             |
| Diuretic               | 1 (0.8)   | 0 (0.0)    |                             |
| Anticoagulant          | 16 (12.2) | 2          | OR 18.09<br>(4.09-79.98)*** |
| Warfarin               | 1 (0.8)   | 0          |                             |
| Therapeutic LMWH       | 7 (5.3)   | 0          | OR 36.63<br>(1.79-558.6)*** |
| Prophylactic LMWH      | 8 (6.1)   | 2 (0.8)    | OR 8.46<br>(1.77-40.4)**    |
| Aspirin                | 12 (9.2)  | 3 (1.1)    | OR 8.71<br>(2.41-31.44)***  |
| Other antihypertensive | 0 (0.0)   | 2 (0.8)    |                             |
| Smoking                | 9 (6.9)   | 12 (4.6)   |                             |

VHD: valvular heart disease; LMWH: low molecular weight heparin; OR: odds ratio

P values: Fisher's exact test

\*p<0.05

\*\* p<0.01

\*\*\* p<0.001

Table 3: Comparison of pregnancy outcomes in nulliparous and parous women with VHD

|                                     | 1 <sup>st</sup> pregnancy | Subsequent pregnancies |                        |
|-------------------------------------|---------------------------|------------------------|------------------------|
| Number of pregnancies               | 73                        | 58                     |                        |
|                                     | mean (SD)                 | mean (SD)              |                        |
| Age at booking (years)              | 29 (6.0)                  | 32 (5.0)               | p=0.0048               |
|                                     | n (%)                     | n (%)                  |                        |
| Previous cardiac surgery            | 32 (43.8)                 | 36 (62.1)              |                        |
| Previous cardiac events             | 5 (6.8)                   | 6 (10.3)               |                        |
| Cardiac medications                 |                           |                        |                        |
| None                                | 62 (84.9)                 | 48 (82.8)              |                        |
| B-blocker                           | 0 (0.0)                   | 1 (1.7)                |                        |
| Other antiarrhythmic                | 1 (1.4)                   | 0 (0.0)                |                        |
| Diuretic                            | 0 (0.0)                   | 1 (1.7)                |                        |
| Anticoagulant                       | 9 (12.3)                  | 7 (12.1)               |                        |
| Warfarin                            | 1 (1.4)                   | 0 (0.0)                |                        |
| Therapeutic LMWH                    | 4 (5.5)                   | 3 (5.2)                |                        |
| Prophylactic LMWH                   | 4 (5.5)                   | 4 (6.9)                |                        |
| Aspirin                             | 6 (8.2)                   | 5 (8.6)                |                        |
| Other antihypertensive              | 0 (0.0)                   | 0 (0.0)                |                        |
| Smoking                             | 5 (6.8)                   | 4 (6.9)                |                        |
| Mode of delivery                    |                           |                        |                        |
| SVD                                 | 26 (35.6)                 | 33 (57.0)              | OR 0.42 (0.21-0.85)*   |
| Assisted vaginal delivery           | 23 (31.5)                 | 6 (10.3)               | OR 3.99 (1.50-10.61)** |
| Elective CS                         | 8 (11.0)                  | 9 (15.5)               |                        |
| Emergency CS                        | 16 (21.9)                 | 10 (17.2)              |                        |
|                                     | median (range)            | median (range)         |                        |
| Gestational age at delivery (weeks) | 40 (25-42)                | 39 (29-42)             |                        |
| Birth weight (g)                    | 3230 (420-4630)           | 3235 (1225-4370)       |                        |
|                                     | mean (SD)                 | mean (SD)              |                        |
| Customised birth weight centile     | 40 (27)                   | 36 (29)                |                        |
|                                     | n (%)                     | n (%)                  |                        |
| Cardiac complications               | 5(6.8)                    | 3 (5.2)                |                        |
| Obstetric complications             | 25 (34.2)                 | 20 (34.5)              |                        |
| Neonatal complications              | 23 (31.5)                 | 17(29.3)               |                        |

VHD: valvular heart disease; LMWH: low molecular weight heparin; SVD: spontaneous vaginal delivery; CS: Caesarean section; OR: odds ratio

*P values: Fisher's exact test*

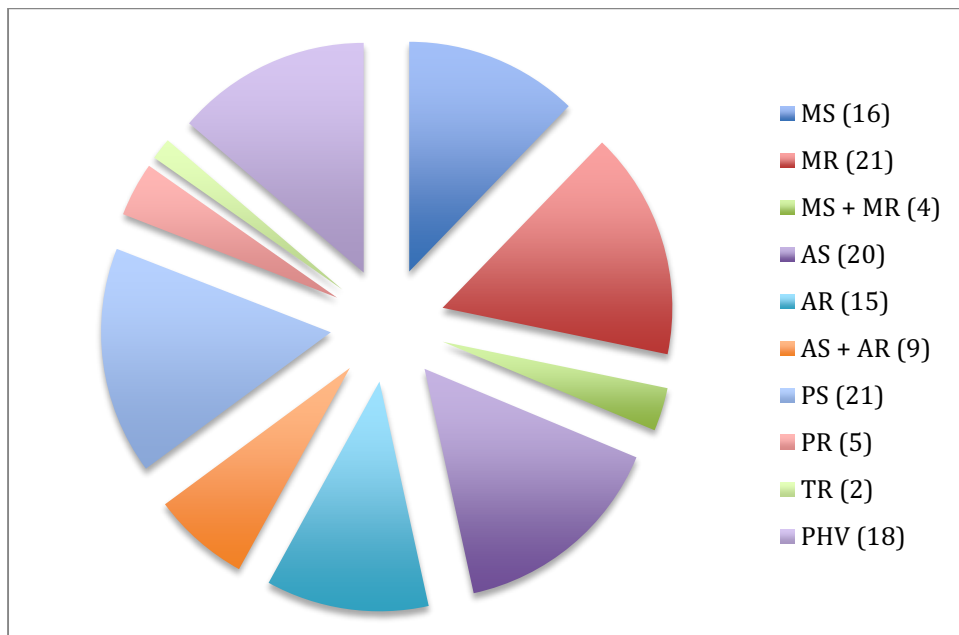
\*p<0.05

\*\* p<0.01

\*\*\* p<0.001

Figure 1: Distribution of VHD in the pregnancies studied

a. All diagnoses



*MS: mitral stenosis; MR: mitral regurgitation; AS: aortic stenosis; AR: aortic regurgitation; PS: pulmonary stenosis; PR: pulmonary regurgitation; TR: tricuspid regurgitation; PHV: prosthetic heart valve*

b. Prosthetic Heart Valves

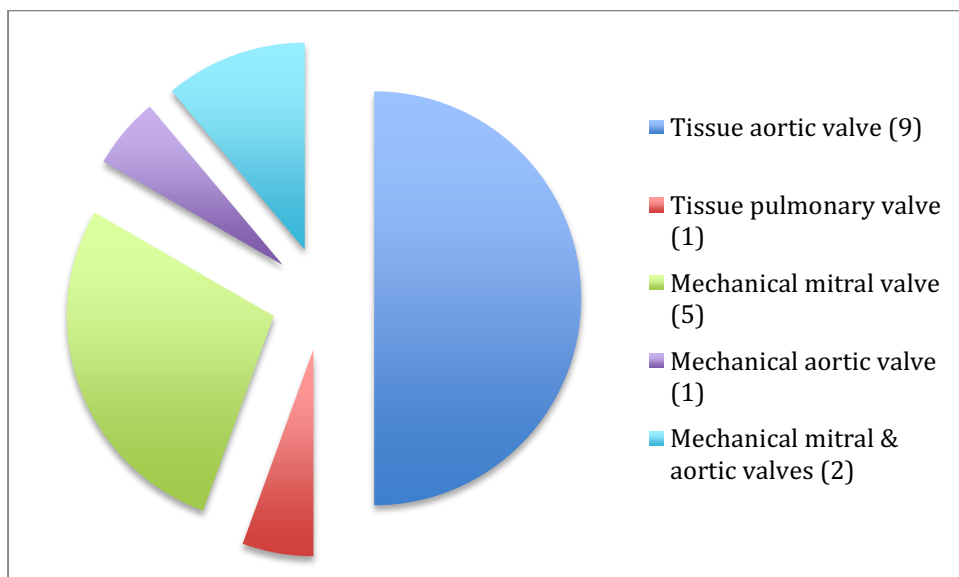


Table 4: Outcomes in all women with VHD vs controls

|                                            | VHD                    | Controls                |                                 |
|--------------------------------------------|------------------------|-------------------------|---------------------------------|
| <b>Number of pregnancies</b>               | 131                    | 262                     |                                 |
|                                            | <b>n (%)</b>           | <b>n (%)</b>            |                                 |
| <b>Mode of delivery</b>                    |                        |                         |                                 |
| SVD                                        | 59 (45.0)              | 138 (52.7)              |                                 |
| Assisted vaginal delivery                  | 29 (22.1)              | 44 (16.8)               |                                 |
| Elective CS                                | 17 (13.0)              | 45 (17.2)               |                                 |
| Emergency CS                               | 26 (19.9)              | 35 (13.3)               |                                 |
|                                            | <b>median (range)</b>  | <b>median (range)</b>   |                                 |
| <b>Gestational age at delivery (weeks)</b> | <b>39 (25-42)</b>      | <b>40 (33-42)</b>       | <b>p=0.0019</b>                 |
| <b>Birth weight (g)</b>                    | <b>3230 (420-4630)</b> | <b>3420 (1500-4650)</b> | <b>p=0.0006</b>                 |
|                                            | <b>mean (SD)</b>       | <b>mean (SD)</b>        |                                 |
| <b>Customised birth weight centile</b>     | <b>38 (28)</b>         | <b>49 (54)</b>          | <b>p=0.003</b>                  |
|                                            | <b>n (%)</b>           | <b>n (%)</b>            |                                 |
| <b>Cardiac complications</b>               | <b>9 (6.5)</b>         | <b>0 (0.0)</b>          | <b>OR 40.71 (2.35-705.7)***</b> |
| <b>Obstetric complications</b>             | 45 (34.3)              | 73 (27.9)               |                                 |
| <b>Neonatal complications</b>              | <b>40.0 (30.5)</b>     | <b>18 (6.9)</b>         | <b>OR 5.96 (3.25-10.93)***</b>  |
| <i>Preterm delivery</i>                    | <b>16 (12.2)</b>       | <b>11 (4.2)</b>         | <b>OR 3.16 (1.43-7.06)**</b>    |
| <i>Iatrogenic preterm delivery</i>         | <b>11 (8.4)</b>        | <b>2 (0.8)</b>          | <b>OR 11.92 (2.60-54.62)***</b> |
| <i>SGA</i>                                 | <b>27 (20.6)</b>       | <b>7 (2.7)</b>          | <b>OR 9.46 (3.99-22.40)***</b>  |

VHD: valvular heart disease; SVD: spontaneous vaginal delivery; CS: Caesarean section; SGA: small for gestational age

P values: Fisher's exact test

\* $p < 0.05$

\*\*  $p < 0.01$

\*\*\*  $p < 0.001$

Table 5: Outcomes in women with VHD: subgroups

|                                   | LHO                 | LHR                 | RHO                 | RHR                 | Mixed valvular disease | BPV                 | MPV                |
|-----------------------------------|---------------------|---------------------|---------------------|---------------------|------------------------|---------------------|--------------------|
| Number of pregnancies             | 36                  | 36                  | 21                  | 7                   | 13                     | 10                  | 8                  |
| Mode of delivery                  |                     |                     |                     |                     |                        |                     |                    |
| SVD                               | 15 (41.7)           | 20 (55.6)           | 8 (38.1)            | 3 (42.8)            | 7(53.9)                | 4 (40.0)            | 2 (25.0)           |
| Assisted vaginal delivery         | 10(27.8)            | 8 (22.2)            | 6 (28.6)            | 2 (28.6)            | 1 (7.7)                | 2 (20.00)           | 0 (0.0)            |
| Elective CS                       | 7 (19.4)            | 2 (5.5)             | 2 (9.5)             | 1 (14.3)            | 2 (15.3)               | 0 (0.0)             | 3 (37.5)           |
| Emergency CS                      | 4 (11.1)            | 6 (16.7)            | 5 (23.8)            | 1 (14.3)            | 3 (23.1)               | 4 (40.0)            | 3 (37.5)           |
| Gestational age at delivery (wks) | 39<br>(29-42)       | 40<br>(33-42)       | 39<br>(35-42)       | 39<br>(38-41)       | 40<br>(34-41)          | 39<br>(36-42)       | 36<br>(25-40)      |
| Birth weight (kgs)                | 3155<br>(1225-4320) | 3375<br>(1816-4630) | 3354<br>(2380-4090) | 3110<br>(2880-3970) | 3200<br>(1525-3840)    | 3205<br>(2450-3940) | 2025<br>(420-3206) |
| Customised birth weight centile   | 42 (30.3)           | 43 (27.2)           | 52 (32)             | 38 (44)             | 26 (20.9)              | 55 (25)             | 15 (23)            |
| Cardiac complications             | 7 (19.4)            | 0 (0.0)             | 0 (0.0)             | 0 (0.0)             | 0 (0.0)                | 0 (0.0)             | 2 (25.0)           |
| Obstetrics complications          | 12 (33.3)           | 8 (22.2)            | 11 (52.4)           | 1 (14.3)            | 0 (0.0)                | 6 (54.5)            | 7 (87.5)           |
| PPH                               | 5 (13.9)            | 5 (13.9)            | 7 (33.3)            | 1 (14.3)            | 0 (0.0)                | 4 (36.3)            | 5 (71.4)           |
| Neonatal complications            | 15 (41.7)           | 8 (22.2)            | 4 (19.0)            | 2 (28.6)            | 2 (15.3)               | 3 (27.3)            | 6 (75.0)           |
| Preterm delivery                  | 5 (13.9)            | 2 (5.5)             | 1 (4.8)             | 0 (0.0)             | 1 (7.7)                | 2 (18.2)            | 5 (71.4)           |
| Iatrogenic preterm delivery       | 3 (8.3)             | 1 (2.8)             | 0 (0)               | 0 (0.0)             | 0 (0.0)                | 2 (18.2)            | 5 (71.4)           |
| SGA                               | 9 (25.0)            | 6 (16.7)            | 3 (14.3)            | 2 (28.6)            | 2 (15.3)               | 1 (9.1)             | 4 (57.1)           |

VHD: valvular heart disease; LHO: left heart obstruction; LHR: left heart regurgitation; RHO: right heart obstruction; RHR: right heart regurgitation;

BPV: bioprosthetic valve; MPV: mechanical prosthetic valve; SVD: spontaneous vaginal delivery; CS: caesarean section; PPH: postpartum haemorrhage; SGA: small for gestational age

Table 6: Outcomes in women with VHD taking anticoagulants

|                                           | Warfarin<br>(n=1) | Therapeutic<br>LMWH<br>(n=7) | Prophylactic<br>LMWH<br>(n=8) |
|-------------------------------------------|-------------------|------------------------------|-------------------------------|
|                                           | n (%)             |                              |                               |
| <b>Maternal cardiac complications</b>     |                   |                              |                               |
| • Cardiomyopathy                          | 0 (0.0)           | 0 (0.0)                      | 0 (0.0)                       |
| • Myocardial infarction                   | 0 (0.0)           | 0 (0.0)                      | 1 (12.5)                      |
| • Heart failure                           | 0 (0.0)           | 0 (0.0)                      | 1 (12.5)                      |
| • Aortic dissection                       | 0 (0.0)           | 0 (0.0)                      | 0 (0.0)                       |
| • Arrhythmia                              | 0 (0.0)           | 0 (0.0)                      | 0 (0.0)                       |
| • Endocarditis                            | 0 (0.0)           | 2 (28.6)                     | 0 (0.0)                       |
| • Valve thrombosis                        | 0 (0.0)           | 2 (28.6)                     | 0 (0.0)                       |
| • Cardiac death                           | 0 (0.0)           | 1 (14.3)                     | 0 (0.0)                       |
| <b>Maternal obstetric complications</b>   |                   |                              |                               |
| • Pregnancy-induced hypertension          | 0 (0.0)           | 0 (0.0)                      | 0 (0.0)                       |
| • Pre-eclampsia                           | 0 (0.0)           | 1 (14.3)                     | 0 (0.0)                       |
| • Eclampsia                               | 0 (0.0)           | 0 (0.0)                      | 0 (0.0)                       |
| • Antepartum haemorrhage                  | 0 (0.0)           | 0 (0.0)                      | 0 (0.0)                       |
| • Gestational diabetes mellitus           | 0 (0.0)           | 0 (0.0)                      | 0 (0.0)                       |
| • Preterm pre-labour rupture of membranes | 0 (0.0)           | 0 (0.0)                      | 0 (0.0)                       |
| • Spontaneous preterm labour              | 0 (0.0)           | 0 (0.0)                      | 0 (0.0)                       |
| • Postpartum haemorrhage                  | 1 (100.0)         | 5 (71.4)                     | 5 (62.5)                      |
| • Venous thromboembolism                  | 0 (0.0)           | 0 (0.0)                      | 0 (0.0)                       |
| <b>Fetal/neonatal complications</b>       |                   |                              |                               |
| • Preterm delivery                        | 0 (0.0)           | 5 (71.4)                     | 1 (12.5)                      |
| • Iatrogenic preterm delivery             | 0 (0.0)           | 5 (71.4)                     | 1 (12.5)                      |
| • Fetal intracranial haemorrhage          | 1 (100.0)         | 0 (0.0)                      | 0 (0.0)                       |
| • Small for gestational age               | 0 (0.0)           | 4 (57.1)                     | 0 (0.0)                       |
| • Stillbirth                              | 0 (0.0)           | 0 (0.0)                      | 0 (0.0)                       |
| • Neonatal death                          | 0 (0.0)           | 3 (42.9)                     | 0 (0.0)                       |

*n=number of pregnancies*

*Table 7: Univariable analysis for predictors of complications during pregnancy in women with VHD*

| <b>Complications</b>  | <b>Predictor</b>            | <b>Odds Ratio</b> | <b>95% CI</b> | <b>p</b> |
|-----------------------|-----------------------------|-------------------|---------------|----------|
| <b>Cardiac</b>        | Left heart obstruction      | 6.13              | 1.45-26.04    | 0.014    |
|                       | Mechanical valve prosthesis | 14.75             | 2.68-81.30    | 0.002    |
|                       | Use of therapeutic LMWH     | 19.83             | 3.28-119.77   | 0.001    |
|                       | Previous cardiac event      | 7.13              | 1.50-33.92    | 0.014    |
|                       |                             |                   |               |          |
| <b>Obstetric</b>      | Mechanical valve prosthesis | 5.88              | 1.09-31.68    | 0.039    |
|                       | Use of any anticoagulant    | 5.25              | 1.67-16.56    | 0.005    |
|                       | Previous cardiac surgery    | 2.45              | 1.14-5.27     | 0.022    |
|                       |                             |                   |               |          |
| <b>Fetal/neonatal</b> | Mechanical valve prosthesis | 6.12              | 1.15-36.12    | 0.002    |
|                       | Use of any anticoagulant    | 3.59              | 1.20-10.79    | 0.023    |
|                       | Previous cardiac surgery    | 3.95              | 1.68-9.31     | 0.021    |
|                       | Previous cardiac event      | 3.60              | 1.03-12.65    | 0.046    |

*VHD: valvular heart disease; 95% CI: 95% confidence interval; LMWH: low molecular weight heparin*

*Table 8: Multivariable analysis for predictors of complications during pregnancy in women with VHD*

| <b>Complications</b>  | <b>Predictor</b>            | <b>Odds Ratio</b> | <b>95% CI</b> | <b>p</b> |
|-----------------------|-----------------------------|-------------------|---------------|----------|
| <b>Fetal/neonatal</b> | Mechanical valve prosthesis | 7.26              | 1.33-44.73    | 0.010    |

*VHD: valvular heart disease; 95% CI: 95% confidence interval*

## 6.6 Discussion

Pregnancy in women with VHD is frequently associated with adverse maternal and fetal/neonatal outcomes. In this series of 131 pregnancies in 73 women there was 1 maternal death and 3 neonatal deaths, as well as a significantly higher rate of cardiac, obstetric and fetal/neonatal complications in the VHD group compared with healthy controls.

### 6.6.1 Baseline characteristics

Women with VHD were significantly younger than the control women (mean 30 years, SD 5.7, and 34 years, SD 5.0 respectively,  $p < 0.0001$ ). VHD is often progressive; for example degenerative dystrophic calcification of a bicuspid aortic valve gradually worsens over time with increasing valve dysfunction. This may result in women being advised to, or feeling the need to, complete their families at an earlier age, although there is no evidence to support this. Parity did not appear to have a deleterious effect on outcomes. This may reflect a selection bias in that women who with adverse outcomes in their first pregnancy may choose (or be advised) to avoid further pregnancies. Interestingly the usual increase in birth weight seen in second or subsequent pregnancies in healthy women did not appear to occur in this cohort of women with VHD, although ideally this should be studied by paired comparison.

### 6.6.2 Diagnoses

Aortic valve disease was the most common diagnosis (34%) followed by mitral valve disease (32%). The ROPAC registry reported mitral valve disease as the commonest type of VHD (63% of all VHD reported).<sup>38</sup> However, this is an international registry

with contributions from 28 countries, including several developing countries where the incidence of rheumatic fever and RHD is higher than in the UK.

### 6.6.3 Maternal outcomes

#### *Cardiac complications*

Cardiovascular complications occurred in 6.5% of pregnancies in women with VHD, including 1 maternal death. These findings are consistent with those reported by the CARPREG and ZAHARA investigators, among others.<sup>8,30,33,35-37,161</sup> Cardiac complications occurred most frequently in women with LHO (19.4%) or an MPV (25.0%) and were associated with adverse perinatal outcomes ( $r=0.24$ ,  $p=0.0006$ ).

Cardiac complications occurred in 25% (2) of pregnancies in women with MPVs: valve thrombosis leading to cardiac death in a woman with a St Jude aortic valve, and endocarditis with subsequent thrombosis of a Starr Edwards mitral valve in the other. This is a similar rate to that reported in the literature.<sup>36,93</sup> Women with well-functioning MPVs are generally able to tolerate the haemodynamic challenges of pregnancy. The need for anticoagulation due to the risk of valve thrombosis, (which is increased during pregnancy), raises specific concerns. The optimal anticoagulant regimen for pregnant women with MPVs remains a topic for debate and to date there are no adequate randomized controlled trials comparing the different options.<sup>78</sup> The two options described in the ESC guidelines<sup>4</sup> are to either continue with oral anticoagulants (OACs) throughout pregnancy or to convert to either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) between weeks 6 and 12. In both regimens, OACs should be converted to either UFH or LMWH for delivery. Use of oral anticoagulation, under strict INR control, is safest for the mother and is

associated with the least risk of valve thrombosis when used throughout pregnancy.<sup>4,162</sup> However, OACs such as warfarin cross the placenta and their use in the first trimester results in embryopathy in up to 10% of cases<sup>4,162</sup> (although this relationship appears to be dose dependent with a lower incidence of embryopathy (2.6%) reported when the warfarin dose is less than 5mg daily).<sup>163</sup> Fetal haemorrhage may also occur throughout pregnancy. A particular problem is intracranial haemorrhage in the second trimester because of the vulnerability to rupture of the developing choroid plexus. Although UFH and LMWH do not cross the placenta, UFH is associated with a significantly increased risk of valve thrombosis, both when used only in the first trimester and when used throughout pregnancy.<sup>4,162</sup> In comparison the risk of valve thrombosis when LMWH is used instead of UFH appears to be lower, but strict dose control according to anti-Xa levels is required. The optimal timing for checking anti-Xa levels (peak versus trough) is unclear.<sup>4,164,165</sup> In this series, 7 out of 8 pregnancies in women with MPVs were managed with dose-adjusted LMWH throughout, with anti-Xa generally being measured about four hours after the last dose. The woman with a Starr Edwards mitral valve had taken OACs in a previous pregnancy. Unfortunately intracranial fetal haemorrhage was diagnosed at 23 weeks and she opted for a termination of pregnancy. Consequently she refused to take warfarin in subsequent pregnancies and in her next pregnancy was treated with dose-adjusted UFH. However, she developed endocarditis and suffered a valve thrombosis at 25 weeks' gestation. She underwent an emergency valve replacement and was delivered by caesarean section, but the baby did not survive. Another woman with two metal valves had terminations of pregnancy in her first 2 pregnancies at 20 and 25 weeks due to fetal intracranial haemorrhage whilst taking warfarin; (the first pregnancy is not included in the study as termination occurred prior to 24 weeks of

gestation). In her third (and successful) pregnancy (included in the analysis) she chose to take dose-adjusted LMWH instead.

The remaining cardiac complications all occurred in women with LHO. There was 1 case of pulmonary oedema (0.8% of all pregnancies in women with VHD) in a woman with severe MS. The same woman had required open valvotomy within a few months of her first delivery, but did not attend for follow-up for several years and was again found to have severe MS when she booked in her second pregnancy. Heart failure is the most frequently observed maternal complication in women with VHD with rates of up to 31% reported in association with MS, (commonly in association with atrial tachyarrhythmia),<sup>38,55,56,166</sup> significantly higher than described in this series. The risk of decompensation is related to the severity of the stenosis.<sup>56,157,161,166-167</sup> In this cohort, 2 pregnancies were complicated by severe MS (valve area  $\leq 1.0\text{cm}^2$  at echocardiography in the year prior to pregnancy), and 6 by severe AS (peak gradient  $\geq 80\text{mmHg}$ ). However, echocardiographic estimation of the degree of valvular stenosis is subject to both intra- and inter-observer variability and it may be that this cohort actually represents a group of women with less severe disease.

There was one myocardial infarction in a woman with moderate MS. Myocardial infarction in women with MS is commonly embolic in origin particularly in the presence of atrial arrhythmia. A woman with severe AS developed acute angina at the beginning of the third trimester. The increase in left ventricular pressure and in the pressure gradient across a stenotic aortic valve leads to a fall in systemic venous return with subsequent reduction in coronary perfusion pressures, resulting in ischaemia.

Clinically significant arrhythmias occurred in 2 pregnancies (1.5%), which is similar to the rate of arrhythmia in women with VHD reported to the ROPAC registry<sup>38</sup> (2/131 (1.5%) versus 12/334 (3.6%),  $p=0.53$ ). Both occurred in women with severe AS. Mortality in pregnant women with AS is now rare. However, severe AS continues to be associated with high levels of maternal morbidity, with heart failure in approximately 10% and arrhythmias in 3-25%.<sup>55,161</sup>

Three pregnancies were complicated by endocarditis: in the woman described above with a metallic mitral valve, in another woman who had previously undergone mitral valve repair and had residual mild MS, and in a third woman with moderate sub-aortic stenosis. The incidence of endocarditis in pregnant women with VHD is 0.5% and is associated with high levels of maternal and fetal mortality and morbidity.<sup>4,168,169</sup>

Antibiotic prophylaxis is now only recommended for those women deemed to be at greatest risk of endocarditis (those with PHVs, previous endocarditis, untreated cyanotic congenital heart disease and those with cyanotic congenital heart disease who have postoperative palliative shunts, conduits or other prostheses) during high risk procedures such as extensive dental work. It is not recommended for vaginal (spontaneous or assisted) or caesarean delivery as there is a lack of evidence showing benefit.<sup>4,170,171</sup> Despite this some clinicians continue to advise prophylaxis at delivery for these women.<sup>74</sup> However, the 3 women in this series who developed endocarditis did so during the pregnancy, unrelated to any procedure, highlighting the need for a high index of suspicion, and prompt treatment when the diagnosis is made.

### *Obstetric complications*

There were no significant differences in mode of delivery between women with VHD and healthy controls. The rate of obstetric complications in the VHD group and the controls was also similar (34.3% in the women with VHD and 27.9% in the controls,  $p=0.15$ ). However, in the subgroup analysis, women with MPVs were shown to have significantly more obstetric complications than the control women because of an increased rate of PPH (OR 8.98, 95% CI 2.07-39.07,  $p=0.004$ ). This may be associated with administration of anticoagulants, (in this cohort there was a significant correlation between the presence of an MPV and the use of anticoagulants ( $r=0.66$ ,  $p=0.01$ ) and also between the use of anticoagulants and PPH ( $r=0.57$ ,  $p=0.03$ )). However the evidence for this from other studies is conflicting.<sup>33,38,43</sup>

#### 6.6.4 Fetal/neonatal outcomes

Perinatal outcomes are impaired in women with VHD, particularly in women with LHO or MPVs. Fetal/neonatal complications occurred in 30.5% of women with VHD (similar to rates reported in the literature<sup>55,56,167</sup>) compared with 6.9% of the control population and were significantly correlated with maternal cardiac complications ( $r=0.24$ ,  $p=0.0006$ ). Multivariable analysis identified the presence of MPVs as being independently associated with adverse perinatal outcomes ( $p=0.010$ ), which is consistent with the findings of the ZAHARA investigators.<sup>36</sup>

There were 3 neonatal deaths in the VHD group (2.3%) and none in the controls. One baby died as a result of complications of prematurity, having been delivered at 25 weeks' of gestation following thrombosis of an infected mechanical mitral valve in

the mother. Perinatal death risk in women with MPVs has been reported to be as high as 28%.<sup>93</sup>

Preterm delivery, and in particular the rate of iatrogenic preterm delivery, in women with VHD was significantly higher than in the control group (8.4% compared with 0.8%, OR 11.92, 95% CI 2.60-54.62,  $p<0.001$ ), particularly in women with LHO (8.3%) or PHVs (38.9%), similar to findings in other reported studies.<sup>55,56,93,161</sup>

Significantly more babies in the VHD group were SGA (20.6% versus 2.7%, OR 9.46, 95% CI 3.99-22.40,  $p<0.001$ ). Overall birth weight and customized birth weight centiles were lower in the valve group, especially in women with MPVs. In normal pregnancies a significant correlation between maternal cardiac output in the early third trimester and birth weight has been demonstrated.<sup>172</sup> Pregnancies complicated by idiopathic fetal growth restriction (FGR) appear to be characterized by lower cardiac output than healthy pregnancies,<sup>173</sup> and in women with heart disease, an association between conditions associated with reduced cardiac output or central cyanosis and lower birth weight has been observed.<sup>30,77</sup> It is presumed that these effects are mediated via reduced placental perfusion and/or hypoxia. The cardiovascular physiological response to pregnancy in women with cardiac disease has not yet been reported and it is likely that any effects on fetal growth are multifactorial and cannot simply be explained by changes in cardiac output.

## **6.7 Conclusions**

This study demonstrates that pregnancy in women with VHD is associated with significant rates of maternal, fetal and neonatal complications. In particular LHO and the presence of an MPV are associated with an increased frequency of adverse cardiac and perinatal events, and mechanical valve replacement is an independent predictor of poor perinatal outcomes. There is an urgent need for the optimal method of anticoagulation in these women to be tested in a randomised controlled trial.

## **Chapter 7:      Left ventricular outflow tract obstruction**

## 7.1 Abstract

### 7.1.1 Aims:

To investigate maternal and neonatal outcomes in a series of pregnancies in women with left ventricular outflow tract obstruction

### 7.1.2 Methods:

Retrospective review of case records

### 7.1.3 Results:

There were eighty-six pregnancies in 47 women with left ventricular outflow tract obstruction. Significant cardiac complications occurred in seven pregnancies (8.1%). Rates of obstetric complications in the index and control groups were similar, although pregnancy-induced hypertension occurred more frequently in women with left ventricular outflow tract obstruction (OR 3.90, 95% CI 1.27-12.04,  $p=0.018$ ) and was most common in women with coarctation of the aorta (15.8%). Fetal/neonatal complications were more common women with left ventricular outflow tract obstruction, and there were 2 neonatal deaths and 1 stillbirth. Babies born to women with left ventricular outflow tract obstruction were significantly more likely to be small for gestational age (birth weight less than 5<sup>th</sup> customized centile) (12.8% in the heart disease group versus 2.9% of the controls; OR 4.90, 95% CI 1.64-14.60,  $p=0.0038$ )

### 7.1.4: Conclusions:

Pregnancy in women with left ventricular outflow tract obstruction is associated with significant rates of maternal and perinatal complications. Aortic stenosis and maternal cigarette smoking during pregnancy are

independent predictors for cardiac events, use of beta-blockers is associated with fetal/neonatal complications.

## 7.2 Introduction

Lesions that result in obstruction to the left ventricular outflow tract (LVOT) may occur at any point between the anatomical LVOT and the descending portion of the aortic arch. The association of obstructive left heart disease with adverse pregnancy outcomes is well documented.<sup>8,30,32,36,161</sup> Left ventricular outflow tract obstruction (LVOTO) lesions in women of childbearing age are frequently related to bicuspid aortic valve (BAV) disease, although this lesion is less common in women than in men.<sup>173</sup>

Congenital aortic stenosis (AS) has an incidence of 5% in patients with congenital heart disease.<sup>161</sup> Obstruction can occur at the subvalvular, valvular or supra-ventricular level.<sup>161,173</sup> Generally pregnancy is well-tolerated in women with mild to moderate disease and normal left ventricular systolic function. However, despite a recent series in pregnant AS patients reporting more favourable outcomes than in the past,<sup>8,54,55,166</sup> women with severe aortic stenosis continue to remain at considerable risk of developing complications.<sup>4,37</sup>

Coarctation of the aorta (COA) is a narrowing in the aorta that usually occurs at the site of the ductus arteriosus. It accounts for 5-8% of congenital heart disease<sup>63,173</sup> and as with BAV disease, predominates in males. It is often associated with other cardiovascular abnormalities including BAV (22-42% of cases), ventricular septal defect (VSD), aortic arch hypoplasia, multi-level left heart obstruction, abnormal head and neck vessels (5%) and intra-cerebral berry aneurysms (5-10%).<sup>173,174</sup> Even in the absence of BAV, COA is associated with diffuse aortopathy, with cystic changes in the aortic media being described in the segment adjacent to the coarctation and the

ascending aorta.<sup>173-175</sup> Most women of childbearing age will have undergone repair and generally do well during pregnancy<sup>94,176</sup> although an excess of hypertensive disorders and miscarriage has been reported.<sup>4</sup> Both women with unrepaired native COA, and those who have undergone surgical repair but have residual hypertension, coarctation and/or aortic aneurysm are at particular risk of significant hypertension, (which may be refractory to drug therapy) and of aortic rupture during pregnancy.

Hypertrophic cardiomyopathy (HCM) is diagnosed in approximately 1 in 500 of the adult population and is often identified for the first time during pregnancy. It is the most common genetic cardiac disease.<sup>53,177,178</sup> At least 40% of cases are familial, with an autosomal dominant inheritance, usually involving mutations of the cardiac sarcomere proteins.<sup>98,178</sup> HCM is characterized by asymmetric hypertrophy of the left ventricle, dynamic LVOTO (which may be severe), a non-dilated left ventricular cavity and preserved systolic function with reduced diastolic function due to impaired relaxation of the left ventricle. The degree of LVOTO is directly related to the severity of hypertrophy of the basal septum, as this determines the contour of the LVOT. The phenotype is extremely heterogeneous. Clinical presentation ranges from asymptomatic to severe events such as heart failure, clinically significant arrhythmias and sudden cardiac death. Treatment with beta-blockers may help mediate the haemodynamic burden associated with pregnancy. They are also used for rate control in patients with atrial fibrillation (AF) and to suppress ventricular arrhythmias.<sup>4</sup> The rate of maternal morbidity is mainly related to the NYHA functional class pre-pregnancy, with clinical deterioration and development of overt cardiac failure being more likely in patients with outflow obstruction than those without.<sup>98,179</sup> Fetal and

neonatal outcomes also appear to be impaired in this group, particularly in women who develop heart failure during the pregnancy.<sup>180</sup>

### **7.3 Aims**

To investigate maternal and neonatal outcomes in women with LVOTO.

## 7.4 Methods

Women with LVOTO cared for by the Joint Cardiac and Obstetric Service of the Chelsea and Westminster and Royal Brompton Hospitals, were identified from a database commenced in 1994. Multiple pregnancies were excluded because they pose special risks and the numbers were too small for meaningful analysis. For each birth to a woman with LVOTO there were two controls (matched for parity): the first woman with a parity  $\leq 1$  who delivered immediately before and after each index case. Fourteen women with LVOTO delivered before 1998; data for control women were not available prior to this date and so the first women who delivered on the same date in 1999 (matched for parity) were used as controls.

Data were collected from a detailed review of case notes, supplemented by the Ciconia Maternity Information System (CMIS<sup>®</sup>, HD Clinical Ltd, Bishops Stortford, Herts, UK). In all women, demographic data and information on the obstetric and anaesthetic management during pregnancy and labour, and maternal and neonatal outcomes was obtained, noting cardiac, obstetric and fetal/neonatal complications and intra-partum events as previously described in chapter 3. The LVOTO population was divided into three subgroups: COA, HCM, and AS.

Data were analysed using SPSS 22 and GraphPad Prism version 6.0d. Descriptive statistics for nominal data are expressed in absolute numbers and percentages. Mean value and standard deviations are presented for normally distributed continuous variables and for non-normally distributed continuous variables, median and range. Differences in outcomes between the LVOTO and control groups, and between first

and subsequent pregnancies in the LVOTO group, were evaluated. Continuous variables were compared with the Student t-test if they were normally distributed and the Mann-Whitney U-test if they were not. When comparing frequencies the chi-squared test or Fisher exact test where applicable, was used. All tests were two-tailed and  $p < 0.05$  was considered statistically significant. Binary logistic regression was performed to identify patient characteristics associated with adverse pregnancy outcome, divided into 3 composite endpoints (as defined previously): cardiac, obstetric and fetal/neonatal complications. The following baseline variables were assessed: COA, HCM, AS, previous cardiac surgery, previous cardiac event, NYHA functional class pre-pregnancy, pre-existing hypertension, administration of cardiac medication during pregnancy, administration of beta-blockers during pregnancy and maternal cigarette smoking during pregnancy. Variables that were associated with an increased incidence of the studied endpoints ( $p < 0.1$ ) were brought forward to multivariable analysis.

## 7.5 Results

Eighty-six pregnancies in 47 women with LVOTO were compared with 172 controls.

### 7.5.1 Baseline characteristics

Baseline characteristics for women with LVOTO and controls are shown in table 1.

Women with LVOTO were significantly younger than the control women. Median age at booking in the LVOTO group was 28 years (range 14-45) compared with 33 years (range 17-45) in the controls ( $p<0.0001$ , Mann-Whitney U-test). Women with LVOTO were significantly more likely to be taking cardiac medication, in particular beta-blockers (OR 80.74, 95% CI 4.78-1365.0,  $p<0.0001$ ) or calcium channel blockers (OR 23.28, 95% CI 1.27-426.4,  $p<0.01$ ), and were also more likely to have pre-existing hypertension (OR 55.58, 95% CI 12.91-239.30,  $p<0.0001$ ). In the case women, outcomes in nulliparous ( $n=47$ ) and parous ( $n=25$ ) women were similar (table 2), although as was expected nulliparous women were more likely to have an assisted vaginal delivery (OR 7.10, 95% CI 2.36-21.31,  $p<0.001$ ).

There were fifty-seven pregnancies (66.3%) in 30 women with a diagnosis of COA. Of these 6 were in women who had not undergone previous repair. Twenty-seven pregnancies were complicated by pre-existing hypertension. Beta-blockers were the commonest anti-hypertensive taken, (14 pregnancies, 24.6%), followed by calcium channel blockers (3 pregnancies, 5.3%).

There were nine pregnancies (10.5%) in 6 women with HCM. One woman was diagnosed in the immediate postpartum period after she developed pulmonary oedema

at delivery. Two pregnancies occurred in women with Noonan's syndrome. Four women (in whom there were 5 pregnancies) had a history of arrhythmia: one had a pacemaker and a second had undergone a previous unsuccessful ablation for supraventricular tachycardia (SVT); another woman (who had pre-existing left ventricular dysfunction) took verapamil (a calcium channel blocker also used as an anti-arrhythmic) and frusemide in both her pregnancies, while a fourth was taking amiodarone.

Twenty pregnancies (23.2%) occurred in 12 women with AS. Two women (4 pregnancies) had a bicuspid aortic valve, and 5 women (6 pregnancies) had subaortic stenosis. There were 7 pregnancies in 6 women who had previously undergone surgery.

#### 7.5.2 Maternal and perinatal outcomes

Table 3 outlines the mode of delivery, gestational age, birth weight, birth weight centile and complications in women with LVOTO and the controls.

##### *Cardiac outcomes*

There were no maternal deaths. Significant cardiac complications occurred in 7 pregnancies (8.1%). There were 4 adverse events in pregnancies in women with AS including clinically significant arrhythmia (2 - both in women with severe AS), acute angina (1 – in a woman with severe AS) and endocarditis (1 - in a woman with moderate sub-aortic stenosis). Two pregnancies in women with COA were affected by cardiac complications: one woman developed pulmonary oedema and left ventricular failure, while another suffered a clinically significant arrhythmia. A

further woman developed pulmonary oedema at delivery and was admitted to the intensive care unit, where she was subsequently diagnosed with HCM.

#### *Obstetric outcomes*

Frequencies of the different modes of deliveries were similar in case women and in the controls. Overall there was no statistically significant difference in rates of obstetric complications between the two groups ( $p=0.34$ ), although women with LVOTO were significantly more likely to develop pregnancy-induced hypertension (PIH) (10.5% vs 2.9%, OR 3.90, 95% CI 1.27-12.04,  $p=0.018$ ). However, they were also more likely to have hypertension prior to pregnancy (39% of women with LVOTO vs 1.2% of control women, OR 55.58, 95% CI 12.91-239.30,  $p=0.013$ ) which is a risk factor for development of hypertensive disorders of pregnancy.

#### *Fetal and neonatal outcomes*

Neonatal complications occurred in 22 (25.6%) of the index pregnancies compared with 16 (9.3%) in the controls (OR 3.35, 95% CI 1.65-6.80,  $p=0.0007$ ). There were 2 neonatal deaths. One was an SGA baby born at 35 weeks of gestation to a woman with moderate to severe AS, following abruption and preterm labour. The other baby was also SGA and was born by emergency caesarean at 29 weeks of gestation for fetal reasons, to a mother with HCM. 1 stillbirth occurred in a woman who sustained a ruptured uterus during an attempt at vaginal birth after one previous caesarean section.

Gestational age at delivery was lower in the LVOTO group ( $p=0.0049$ ). Median birth weight and mean birth weight centile were also significantly lower: 3230g (range 595-4160) and 41<sup>st</sup> centile (SD 28.4) versus 3355g (range 1500-4480) and 60<sup>th</sup> centile

(SD 29.0) in the controls ( $p=0.0079$  (MWU test) and  $p=0.041$  (t-test) respectively).

The LVOTO babies were more likely to be SGA: eleven (12.8%) of the babies in this group had a birth weight less than the fifth customized centile compared with 5 (2.9%) of babies born to the control women (OR 4.9, 95% CI 1.64-14.60,  $p=0.0038$ ).

### 7.5.3 Logistic regression

The results of the univariable logistic regression are shown in table 5. The multivariable model is shown in table 6. Independent predictors associated with cardiac complications were AS ( $p=0.04$ ) and maternal cigarette smoking during the pregnancy ( $p=0.007$ ). None of the investigated variables were associated with obstetric complications. Use of beta-blockers ( $p=0.009$ ) was associated with adverse perinatal outcomes, specifically SGA (OR 4.53, 95% CI 1.06-19.35,  $p=0.041$ ).

Table 1: Baseline characteristics in women with LVOTO and controls

|                           | LVOTO      | Controls   |                               |
|---------------------------|------------|------------|-------------------------------|
| Number of women           | 47         | 172        |                               |
| Number of pregnancies     | 86         | 172        |                               |
|                           | mean (SD)  | mean (SD)  |                               |
| Age at booking            | 28 (14-45) | 33 (17-45) | p<0.0001                      |
|                           | n (%)      | n (%)      |                               |
| Parity                    |            |            |                               |
| Nulliparous               | 47 (54.7)  | 94 (54.7)  |                               |
| Para 1                    | 25 (29.0)  | 50 (29.0)  |                               |
| Para >1                   | 14 (16.3)  | 28 (16.3)  |                               |
| Cardiac medications       |            |            |                               |
| Any                       | 26 (30.2)  | 4 (2.3)    | OR 18.20<br>(6.10-54.32)***   |
| $\beta$ -blocker          | 16 (18.6)  | 0 (0.0)    | OR 80.74<br>(4.78-1365.0)***  |
| Calcium-channel blocker   | 5 (5.8)    | 0 (0.0)    | OR 23.28<br>(1.27-426.4)**    |
| Diuretic                  | 2 (2.3)    | 0 (0.0)    |                               |
| Other antiarrhythmic      | 1 (1.2)    | 0 (0.0)    |                               |
| Anticoagulant             | 2 (2.3)    | 0 (0.0)    |                               |
| Aspirin                   | 5 (5.8)    | 2 (1.2)    | OR 5.25<br>(1.01-27.64)**     |
| Other antihypertensive    | 1 (1.2)    | 2 (1.2)    |                               |
| NYHA >1                   | 2 (2.3)    | 0 (0.0)    |                               |
| Pre-existing hypertension | 34 (39.5)  | 2 (1.2)    | OR 55.58<br>(12.91-239.30)*** |
| Smoking                   | 6 (7.0)    | 7 (4.1)    |                               |

LVOTO: left ventricular outflow tract obstruction; OR: odds ratio

*P values: Fisher's exact test*

\* $p<0.05$

\*\*  $p<0.01$

\*\*\*  $p<0.001$

Table 2: Comparison of pregnancy outcomes in nulliparous and parous women with LVOTO

|                                     | 1 <sup>st</sup> pregnancy | Subsequent pregnancies |                         |
|-------------------------------------|---------------------------|------------------------|-------------------------|
| Number of pregnancies               | 47                        | 39                     |                         |
|                                     | mean (SD)                 | mean (SD)              |                         |
| Age at booking (years)              | 27 (5.3)                  | 30 (5.6)               | p=0.049                 |
|                                     | n (%)                     | n (%)                  |                         |
| COA                                 | 30 (63.8)                 | 27 (69.2)              |                         |
| HOCM                                | 5 (10.7)                  | 4 (10.3)               |                         |
| AS                                  | 12 (25.5)                 | 8 (20.5)               |                         |
| Previous cardiac surgery            | 33 (70.2)                 | 32 (82.1)              |                         |
| Previous cardiac events             | 2 (4.3)                   | 2 (5.1)                |                         |
| Cardiac medications                 |                           |                        |                         |
| Any                                 | 10 (21.3)                 | 16 (41.0)              |                         |
| β-blocker                           | 6 (12.8)                  | 10 (25.6)              |                         |
| Calcium-channel blocker             | 2 (4.3)                   | 3 (7.7)                |                         |
| Diuretic                            | 1 (2.1)                   | 1 (2.6)                |                         |
| Other antiarrhythmic                | 0 (0.0)                   | 0 (0.0)                |                         |
| Anticoagulant                       | 1 (2.1)                   | 0 (0.0)                |                         |
| Aspirin                             | 1 (2.1)                   | 3 (7.7)                |                         |
| Other antihypertensive              | 0 (0.0)                   | 1 (2.6)                |                         |
| Pre-existing hypertension           | 12 (25.5)                 | 22 (56.4)              | OR 0.26 (0.11-0.66)**   |
| Smoking                             | 5 (7.0)                   | 1 (2.6)                |                         |
| Mode of delivery                    |                           |                        |                         |
| SVD                                 | 9 (19.1)                  | 21 (53.8)              | OR 0.20 (0.08-0.53)***  |
| Assisted vaginal delivery           | 24 (51.1)                 | 5 (12.8)               | OR 7.10 (2.36-21.31)*** |
| Elective CS                         | 3 (6.4)                   | 8 (20.6)               |                         |
| Emergency CS                        | 11 (23.4)                 | 5 (12.8)               |                         |
|                                     | median (range)            | median (range)         |                         |
| Gestational age at delivery (weeks) | 40 (26-42)                | 39 (29-41)             |                         |
| Birth weight (g)                    | 3240 (595-4160)           | 3210 (1225-4050)       |                         |
|                                     | mean (SD)                 | mean (SD)              |                         |
| Customised birth weight centile     | 38 (26.9)                 | 47 (29.9)              |                         |
|                                     | n(%)                      | n(%)                   |                         |
| Cardiac complications               | 6 (12.8)                  | 1 (2.6)                |                         |
| Obstetric complications             | 12 (25.5)                 | 7 (17.9)               |                         |
| Neonatal complications              | 11 (23.4)                 | 9 (23.1)               |                         |

SVD: spontaneous vaginal delivery; CS: Caesarean section; OR: odds ratio

*P values: Fisher's exact test*

\*p<0.05

\*\* p<0.01

\*\*\* p<0.001

Table 3: Outcomes in all women with LVOTO vs controls

|                                                  | LVOTO                  | Controls                |                                 |
|--------------------------------------------------|------------------------|-------------------------|---------------------------------|
| <b>Number of pregnancies</b>                     | 86                     | 172                     |                                 |
|                                                  | <b>n (%)</b>           | <b>n (%)</b>            |                                 |
| <b>Mode of delivery</b>                          |                        |                         |                                 |
| SVD                                              | 30 (34.9)              | 77 (44.8)               |                                 |
| Assisted vaginal delivery                        | <b>29 (33.7)</b>       | <b>30 (17.4)</b>        | <b>OR 2.41 (1.33-4.37)**</b>    |
| Elective CS                                      | 11 (12.8)              | 25 (14.5)               |                                 |
| Emergency CS                                     | 16 (18.6)              | 40 (23.3)               |                                 |
| <b>Regional anaesthesia for vaginal delivery</b> | <b>48 (81.4)</b>       | <b>50 (46.7)</b>        | <b>OR 4.98 (2.33-10.61)***</b>  |
|                                                  | <b>median (range)</b>  | <b>median (range)</b>   |                                 |
| <b>Gestational aged at delivery (weeks)</b>      | <b>39 (26-42)</b>      | <b>40 (31-42)</b>       | <b>p=0.0039</b>                 |
| <b>Birth weight (g)</b>                          | <b>3230 (595-4160)</b> | <b>3355 (1500-4480)</b> | <b>p=0.0079</b>                 |
|                                                  | <b>mean (SD)</b>       | <b>mean (SD)</b>        |                                 |
| <b>Customised birth weight centile</b>           | <b>41 (28.4)</b>       | <b>60 (28.2)</b>        | <b>p=0.041</b>                  |
|                                                  | <b>n (%)</b>           | <b>n (%)</b>            |                                 |
| <b>Cardiac complications</b>                     | <b>7 (8.1)</b>         | <b>0 (0.0)</b>          | <b>OR 32.55 (1.84-577.3)***</b> |
| <b>Obstetric complications</b>                   | 19 (22.1)              | 55 (32.0)               |                                 |
| PIH                                              | <b>9 (10.5)</b>        | <b>5 (2.9)</b>          | <b>OR 3.90 (1.27-12.04)**</b>   |
| <b>Neonatal complications</b>                    | 22 (25.6)              | 16 (9.3)                | <b>OR 3.35 (1.65-6.80)**</b>    |
| Iatrogenic preterm delivery                      | <b>8 (9.3)</b>         | <b>5 (2.9)</b>          | <b>OR 3.43 (1.09-10.81)**</b>   |
| SGA                                              | <b>11 (12.8)</b>       | <b>5 (2.9)</b>          | <b>OR 4.90 (1.64-14.60)**</b>   |

LVOTO: left ventricular outflow tract obstruction; SVD: spontaneous vaginal delivery; CS: Caesarean section; PIH: pregnancy induced hypertension; SGA: small for gestational age; OR: odds ratio

*P values: Fisher's exact test*

\* $p < 0.05$

\*\*  $p < 0.01$

\*\*\*  $p < 0.001$

Table 4: Outcomes in women with LVOTO: subgroups

|                                                  | COA                   | HCM                | AS                  |
|--------------------------------------------------|-----------------------|--------------------|---------------------|
| <b>Number of pregnancies</b>                     | 57                    | 9                  | 20                  |
|                                                  | <b>n (%)</b>          |                    |                     |
| <b>Mode of delivery</b>                          |                       |                    |                     |
| <i>SVD</i>                                       | 21 (36.8)             | 2 (22.2)           | 7 (35.0)            |
| <i>Assisted vaginal delivery</i>                 | 20 (35.1)             | 2 (22.2)           | 7 (35.0)            |
| <i>Elective CS</i>                               | 5 (8.8)               | 2 (22.2)           | 4 (20.0)            |
| <i>Emergency CS</i>                              | 11 (19.3)             | 3 (33.3)           | 2 (10.0)            |
| <b>Regional anaesthesia for vaginal delivery</b> | 35 (85.4)             | 2 (50.0)           | 12 (85.7)           |
|                                                  | <b>median (range)</b> |                    |                     |
| <b>Gestational aged at delivery (weeks)</b>      | 39<br>(26-42)         | 39<br>(28-42)      | 39<br>(29-42)       |
| <b>Birth weight (g)</b>                          | 3385<br>(595-4050)    | 3031<br>(895-4160) | 3000<br>(1225-3700) |
|                                                  | <b>mean (SD)</b>      |                    |                     |
| <b>Customised birth weight centile</b>           | 46<br>(29.9)          | 26<br>(17.7)       | 35<br>(24.3)        |
|                                                  | <b>n (%)</b>          |                    |                     |
| <b>Cardiac complications</b>                     | 4 (7.0)               | 1 (11.1)           | 2 (10.0)            |
| <b>Obstetric complications</b>                   | 11 (19.3)             | 1 (11.1)           | 7 (35.0)            |
| <i>PIH</i>                                       | 9 (15.8)              | 0 (0.0)            | 2 (10.0)            |
| <b>Neonatal complications</b>                    | 11 (19.3)             | 2 (22.2)           | 9 (45.0)            |
| <i>Iatrogenic preterm delivery</i>               | 4 (7.0)               | 2 (22.2)           | 2 (10.0)            |
| <i>SGA</i>                                       | 7 (12.3)              | 0 (0.0)            | 4 (20.0)            |

COA: coarctation of the aorta; HCM: hypertrophic cardiomyopathy; AS: aortic stenosis; SVD spontaneous vaginal delivery; CS: Caesarean section; PIH: pregnancy induced hypertension; SGA: small for gestational age

*Table 5: Univariable analysis for predictors of complications during pregnancy in women with LVOTO*

| Complications   | Predictor                | Odds Ratio | 95% CI     | p     |
|-----------------|--------------------------|------------|------------|-------|
| <b>Cardiac</b>  |                          |            |            |       |
|                 | Aortic stenosis          | 3.98       | 1.12-20.15 | 0.017 |
|                 | Smoking                  | 9.34       | 2.15-62.87 | 0.009 |
|                 |                          |            |            |       |
| <b>Neonatal</b> |                          |            |            |       |
|                 | Use of $\beta$ -blocker  | 3.25       | 1.87-40.10 | 0.006 |
|                 | Previous cardiac surgery | 8.47       | 1.68-64.27 | 0.042 |

*Table 6: Multivariable analysis for predictors of complications during pregnancy in women with LVOTO*

| Complications   | Predictor               | Odds Ratio | 95% CI      | p     |
|-----------------|-------------------------|------------|-------------|-------|
| <b>Cardiac</b>  |                         |            |             |       |
|                 | Aortic stenosis         | 8.33       | 2.13-53.46) | 0.040 |
|                 | Smoking                 | 20.25      | 2.24-183.14 | 0.007 |
|                 |                         |            |             |       |
| <b>Neonatal</b> |                         |            |             |       |
|                 | Use of $\beta$ -blocker | 4.62       | 1.46-14.56  | 0.009 |

## 7.6 Discussion

Pregnancy in women with LVOTO is associated with increased rates of adverse maternal and fetal neonatal outcomes. In this series of eighty-six pregnancies in 47 women with LVOTO, there were no maternal deaths. However, there were two neonatal deaths and one stillbirth, as well as a significantly higher rate of cardiac and fetal/neonatal complications in the LVOTO group compared with healthy control women.

### 7.6.1 Baseline characteristics

Women with LVOTO were significantly younger than the control women (median ages at booking 28 years (range 14-45), and 33 years (range 17-45) respectively,  $p < 0.0001$ ), which is concordant with the findings reported elsewhere in this thesis (chapters 4 and 5). Although there is an increasing trend among women in the UK (as well as in other developed nations) to delay pregnancy until later in life, it may be that women with heart disease are being advised to complete their families at an earlier age before their condition deteriorates. However, there is no evidence to support this. Again, as in women with valvular heart disease, there was no obvious detrimental effect of parity on outcomes, but as discussed previously this may reflect a selection bias.

### 7.6.2 Maternal outcomes

#### *Cardiac complications*

There were no maternal deaths. Adverse cardiovascular events occurred in 8.1% of pregnancies in women with LVOTO. A systematic review by the ZAHARA investigators noted that cardiovascular events occurred in 11% of 2491 pregnancies in

women with various types of congenital heart disease,<sup>39</sup> and left heart obstruction is consistently reported as a predictor for adverse cardiac outcomes.<sup>8,30,33,35-37,39</sup>

Multivariable analysis identified AS and maternal cigarette smoking during pregnancy as being independently associated with cardiovascular complications ( $p=0.04$  and  $p=0.007$  respectively). This differs from the findings of the CARPREG and ZAHARA studies which identified maternal cigarette smoking as a risk factor for adverse fetal/neonatal outcomes but not for cardiovascular events. However, other researchers have reported an association<sup>35</sup> and the detrimental effects of cigarette smoking on cardiovascular haemodynamics are well known.<sup>181,182</sup>

The commonest complication was clinically significant arrhythmia. This occurred in 3 pregnancies (4.2%), similar to the rate of arrhythmia described in 599 pregnancies in women with heart disease by the CARPREG team. Two arose in women with severe AS, which is associated with arrhythmias in 3-25% of pregnancies.<sup>55,161</sup> The third was in a woman with repaired COA who had previously suffered from atrioventricular nodal re-entrant tachycardia (AVNRT) and who developed first degree heart block. Significant arrhythmias in patients with repaired COA are uncommon in the first 20 years after repair, but thereafter the incidence increases, especially in those who develop ventricular dysfunction.<sup>183</sup> Arrhythmias are common in women with HCM, and are one of the common precipitants of cardiac failure in these women; pre-pregnancy arrhythmias are generally predictive of a recurrence during pregnancy.<sup>98</sup> It is therefore perhaps surprising that no significant arrhythmias occurred in women with HCM in this series as five of the six had arrhythmias prior to pregnancy. However, this may be because three women took anti-arrhythmic drugs throughout their pregnancies (in fact, one woman took both amiodarone and verapamil), while a

fourth had been previously fitted with a pacemaker due to a history of atrial tachycardias.

Two pregnancies (2.3%) were complicated by heart failure: one in a woman with repaired COA who was known to have left ventricular dysfunction prior to pregnancy, and the other in the woman who was only diagnosed with HCM when she developed acute pulmonary oedema immediately after delivery by caesarean section. Heart failure was the most common cardiovascular complication reported to the ROPAC registry (13.1%, 68% of whom had left sided lesions) and was documented in 7.6% of patients with COA (which is high when compared to other reports<sup>94</sup>) and 18% of patients with HCM. Delivery is a time of particular risk for women with LVOTO due to the marked haemodynamic changes that occur at this time. Heart failure has been reported to complicate up to 10% of pregnancies in women with severe AS.<sup>55,161</sup>

One woman with severe AS developed acute angina at the beginning of the third trimester. The increase in left ventricular pressure and in the gradient across a stenotic aortic valve in pregnancy results in reduced systemic venous return, and thus reduced coronary blood flow and compromised myocardial perfusion.

Finally, a woman with moderate sub-aortic stenosis developed endocarditis.

### *Obstetric complications*

There were no statistically significant differences in mode of delivery between women with LVOTO and healthy controls. The rate of obstetric complications in the LVOTO group and the controls was also similar (22% in the case women, and 32% in

the controls,  $p=0.30$ ) although women with LVOTO were more likely to develop PIH (OR 3.90, 95% CI 1.27-12.04,  $p=0.018$ ). PIH occurred most frequently in women with COA (15.8%); however, much higher rates (up to 22%) have been described.<sup>94,176</sup> In the normal population up to 8% of all gestations are affected by hypertensive disorders of pregnancy.<sup>94</sup> This cohort may represent a relatively low-risk group of women with COA as only 6 pregnancies (10.5%) occurred in women who had not undergone repair, although this is a similar proportion to that reported by other authors.<sup>176</sup> 32% of women with COA in this series were taking antihypertensive medication at the start of pregnancy, and it is possible that the lower rate of hypertensive complications reported here is a reflection of tighter long-term blood pressure control.

### 7.6.3 Fetal/neonatal outcomes

Perinatal outcomes are impaired in women with LVOTO. Fetal/neonatal complications occurred in 25.6% of women with LVOTO compared with 9.3% in the control population ( $p=0.003$ ). Obstructive left heart lesions are well known to be associated with high rates of fetal and neonatal complications.<sup>30</sup>

There were 2 neonatal deaths (2.3%) in the LVOTO group (one following abruption and preterm labour at 35 weeks of gestation in a woman with moderate AS, and the other in a woman with HCM delivered at 29 weeks of gestation due to concerns about fetal growth). One stillbirth occurred following uterine rupture during labour in a woman with COA who had previously delivered by caesarean section. Rates of perinatal mortality of up to 30% have been reported in women with severe AS. COA and HCM are not generally associated with high rates of perinatal loss.<sup>4</sup> The risk of an

adverse outcome appears to be directly related to the severity of the obstruction and consequent reduction in cardiac output and placental perfusion.<sup>161</sup>

Gestational age at delivery was lower in the LVOTO group (median 39 weeks, range 26-42) compared with the controls (median 40 weeks, range 31-42) ( $p < 0.0039$ , MWU test). Babies born to women with LVOTO were significantly more likely to be delivered prematurely for medical reasons (OR 3.43, 95% CI 1.09-10.81,  $p = 0.005$ ). Significantly more babies in the LVOTO group were SGA (13% versus 3%, OR 4.90, 95% CI 1.64-14.60,  $p = 0.0038$ ). Overall birth weight and customized birth weight centiles were also lower ( $p < 0.0079$  and  $p = 0.041$  respectively). Multivariable analysis identified use of beta-blockers as being independently associated with adverse perinatal outcomes ( $p = 0.009$ ). Beta-blockers, which were taken in sixteen pregnancies (18.6%), reduce cardiac output via a negative inotropic effect on the myocardium. An association between reduced cardiac output and lower birth weight has been observed both in healthy pregnancies and those in women with cardiac disease.<sup>30,77,97</sup> Use of beta-blockers during pregnancy has repeatedly been associated with delivery of low birth weight infants.<sup>77,78,109</sup> However, this effect has mainly been studied in women with hypertension in pregnancy, with limited data available for women with heart disease. Atenolol had previously been shown to be associated with a higher incidence of fetal growth restriction compared with other beta-blockers.<sup>98,184</sup> It has been suggested that the  $\alpha/\beta$  adrenergic receptor balance may play an important role in the regulation of the placental vascular bed, and that  $\beta_1$ -selective drugs are more prone to impair placental perfusion and cause FGR than a combined  $\alpha/\beta$ -receptor blocker such as labetalol.<sup>184</sup> However, a recent study did not show that labetalol was any less likely to be associated with FGR than selective beta-blockers.<sup>185</sup> Obstructive left heart lesions reduce the ability of the heart to increase cardiac output during pregnancy

which may restrict uteroplacental perfusion. It may be that pregnant women with more severe heart disease are more likely to require treatment with beta-blockers (which are administered specifically to reduce cardiac output, thereby reducing the strain of pregnancy on the mother's cardiovascular system), and that these women are therefore more likely to develop FGR.

## **7.7 Conclusions**

This study demonstrates that pregnancy in women with LVOTO is significantly associated with adverse cardiovascular and fetal/neonatal outcomes, but not obstetric complications. AS and maternal cigarette smoking are independent predictors of cardiovascular events, while use of beta-blockers was predictive of fetal/neonatal complications.

## **Chapter 8:      Conclusions**

## 8.1 Summary of study findings

This work describes maternal and perinatal outcomes in 489 pregnancies in 326 women with heart disease between 1994 and 2011.

### 8.1.1 Maternal mortality

Maternal mortality was 0.8%, significantly higher than in healthy women.<sup>3</sup> All maternal deaths occurred in women with conditions known to be associated with high levels of risk. There were 2 deaths in women with pulmonary hypertension (PH) (20%). Older series reported a maternal mortality of 30-56% in women with PH,<sup>51</sup> although more recent data suggest that outcomes may be improving, and describe mortality rates of 10-25%, consistent with the findings in this study.<sup>103-105</sup> One death occurred in a woman with dilated cardiomyopathy (DCM) and the last was in a woman with a mechanical prosthetic valve (MPV). The deaths in the women with PH and DCM all occurred during the early postnatal period, supporting observations that this is a time of particularly high risk for such women.<sup>51,91</sup>

### 8.1.2 Cardiovascular events

A prior history of arrhythmias and the presence of an MPV were identified as independent predictors of cardiovascular events ( $p < 0.0001$ ,  $p = 0.003$  respectively). The commonest cardiac complication overall was arrhythmia, followed by heart failure. Myocardial dysfunction prior to pregnancy was an independent predictor for developing heart failure during pregnancy ( $p = 0.007$ ). Marfan syndrome (MFS) in particular was associated with high rates of cardiac events. One woman with a grossly dilated aortic root experienced a type-A dissection shortly after delivery of her second

baby. Two others developed impaired left-ventricular dysfunction during the pregnancy. Although left ventricular dilatation and impairment of left ventricular function have been reported in MFS patients in the absence of valvular pathology,<sup>132-134</sup> this is the first time such an effect has been described in pregnancy. Another woman required replacement of the aortic root and valve, and another had replacement of the aortic valve alone, both during the first 6 postnatal months. One woman who had an MPV due to congenital mitral stenosis (MS) required valve replacement during pregnancy due to valve thrombosis after she developed infective endocarditis.

#### 8.1.3 Intrapartum events

There were high rates of assisted vaginal delivery (26% overall). This reflects practice at the Chelsea and Westminster and Royal Brompton Hospitals to recommend elective assisted delivery in women with serious cardiac disease to minimize the cardiovascular stress associated with bearing down. However, there is no evidence to support a benefit of this policy.<sup>78</sup> Caesarean section rate was also high, but not significantly different to that in the general obstetric population at the time; (during the study period the Chelsea and Westminster Hospital had a somewhat permissive view with regard to performing elective caesarean section for maternal request with no medical indication).

#### 8.1.4 Obstetric complications

Hypertensive disorders of pregnancy and postpartum haemorrhage (PPH) were the most frequently observed obstetric complications. Rates of hypertensive disorders were similar to those reported in the general population and pregnancy-induced

hypertension (PIH) (but not pre-eclampsia) was independently associated with pre-existing hypertension (OR 4.14, 95% CI 1.54-11.14,  $p=0.005$ ). Delivery by emergency Caesarean section (OR 3.25, 95% CI 1.98-5.35,  $p<0.001$ ) and use of anticoagulants (OR 7.96, 95% CI 2.31-27.40,  $p=0.001$ ) are independent predictors for PPH. However, there may also be an association with the low dose Syntocinon<sup>®</sup> infusion (to prevent the systemic hypotension associated with its use) used to manage the third stage of labour in women with significant cardiac disease.<sup>4,5</sup>

#### 8.1.5 Perinatal outcomes

There were 5 stillbirths and 5 neonatal deaths in the nulliparous women studied, rates which are comparable to other series of women with cardiac disease,<sup>39</sup> but higher than the general population of England and Wales.<sup>95,96</sup> Adverse perinatal outcomes were predicted by NYHA functional class  $\geq 2$  ( $p<0.0001$ ), use of any cardiac medication ( $p=0.022$ ), presence of an MPV ( $p=0.024$ ) and a systemic right ventricle ( $p=0.007$ ). Birth weight below the 5<sup>th</sup> customized centile was the most common complication (21%), followed by preterm delivery (12%), which was frequently performed for medical indications. Particularly high frequencies of neonatal complications were seen in pregnancies in women with PH (78%), MFS (43%), cyanotic congenital heart disease (85-100%), complete transposition of the great arteries (TGA) (65%) and Ebstein's anomaly (100%).

## **8.2 Implications of study findings**

Despite the continued rise in maternal death due to cardiac disease, current management continues to be based upon limited clinical experience (which tends to be clustered in tertiary centres) and an inadequate body of prospective research (usually observational studies). The literature is largely composed of retrospective case series. Further studies are required to assess the cardiovascular physiological response to pregnancy and delivery in women with pre-existing heart disease, as this has not yet been reported. There is also an urgent need for large collaborative randomised controlled trials to help to define optimal management. Important aspects of practice that need to be evaluated include: protective use of beta-blockers in women with aortopathy or cardiomyopathy, the ideal anticoagulant regimen in women with mechanical valves, mode of delivery (including whether there a shortened or assisted second stage is beneficial), management of the third stage and the impact of pregnancy on longer-term cardiac function.

### **8.3 Strengths and limitations**

The main strength of the data presented in this work is that the cohort of women described were all managed by the same core team of clinicians during the period of study. Most women were fully evaluated and counselled prior to embarking upon pregnancy, consistent with current guidelines. Relevant data were recorded in the Ciconia Maternity Information System (CMIS<sup>®</sup>, HD Clinical Ltd, Bishops Stortford, Herts, UK) contemporaneously and all presenting cases are reported, thus the cohort is a continuous series. The control population, where relevant, was managed in the same maternity unit.

Most of the limitations of the study relate to the retrospective design. Although most data were collected contemporaneously, in some cases the data were incomplete and needed to be supplemented by review of the case notes. Some of the maternity notes were unavailable, having been destroyed in a fire at the storage facility. However, it was usually possible to obtain the remaining data from the cardiology notes. The cohort of patients studied represents patients receiving tertiary medical care from the Royal Brompton and Chelsea and Westminster Hospitals. It includes patients with complex congenital heart disease, but only one woman with ischaemic heart disease. A referral bias is therefore likely and caution is required when extrapolating these results to populations with a different distribution of cardiac disease. The use of non-matched controls can introduce significant confounding factors. However, characteristics such as height, weight and body mass index may be influenced by the patient's cardiac disease, or may be part of a syndrome (such as MFS). Additionally, patients perceived to be at particular risk (for example, those with pulmonary

hypertension) may have been advised against pregnancy. Women whose pregnancies failed to progress beyond 24 weeks of gestation were not included in the study, and it was therefore not possible to examine associations with miscarriage or subfertility.

## **Chapter 9: Appendices**

## 9.1 Publications

1. Curry RA, Fletcher C, Gelson E, Gatzoulis MA, Woolnough M, Richards N, Swan L, Steer PJ, Johnson MR. Pulmonary hypertension and pregnancy – a review of 12 pregnancies in nine women. *BJOG* 2012 May;119(6):752-61
2. Curry RA, Gelson E, Swan L, Dob D, Babu-Narayan SV, Gatzoulis MA, Steer PJ, Johnson MR. Marfan syndrome and pregnancy: maternal and neonatal outcomes. *BJOG* 2014 Apr;121(5):610-7.

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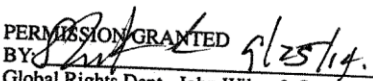
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