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### Eating fish associated with significant health benefits: pooled analysis

There is a significant protective benefit of fish consumption in people with cardiovascular disease, as well as with significant improvements in multiple other health outcomes.

An umbrella review of meta-analyses found that increased fish consumption also improved rates of cardiovascular and all-cause mortality. However, fish consumption had no significant effects on rates of hypertension, atrial fibrillation, or type 2 diabetes.

Although not directly reflected in the findings, modest fish consumption also appears to be associated with significant improvements in multiple health outcomes, including the risks for myocardial infarction, stroke and heart failure to have cardiac benefits, according to a *Journal of the American Medical Association* commentary.

*Medscape Medical News* reports that researchers Jayedi and Shab-Bidar examined 34 meta-analyses of prospective observational studies, which featured a total of 40 different outcomes. Greater fish consumption of 100 g/day was associated with significant improvements in multiple health outcomes, including the risks for myocardial infarction, stroke and heart failure.

*Medscape Medical News* comments that there is a lack of large studies that have differentiated the effects of fish consumption among adults with and without a history of cardiovascular disease (CVD). The current study addresses this gap.

People with CVD who regularly ate fish had significantly fewer major CVD events and there were fewer total deaths compared with similar individuals who did not eat fish, but there was no beneficial link from eating fish among the general population in prospective data collected from more than 191 000 people from 58 countries.

Despite the neutral finding among people without CVD, the finding that eating fish was associated with significant benefit for those with CVD or who were at high risk for CVD confirms the public health importance of regular fish or fish oil consumption, says one expert.

A little more than a quarter of those included in the new study had a history of CVD or were at high risk for CVD. In this subgroup of more than 51 000 people, those who consumed on average at least two servings of fish weekly (at

least 175 g, or about 6.2 ounces per week) had a significant 16% lower rate of major CVD events during a median follow up of about 7.5 years.

The rate of all-cause death was a significant 18% lower among people who ate two or more fish portions weekly compared with those who did not, say Dr Deepa Mohan and associates. The researchers saw no additional benefit when people regularly ate greater amounts of fish.

‘There is a significant protective benefit of fish consumption in people with cardiovascular disease,’ summed up Dr Andrew Mente, a senior investigator on the study and an epidemiologist at McMaster University in Hamilton, Canada. ‘This study has important implications for guidelines on fish intake globally. It indicates that increasing fish consumption, and particularly oily fish, in vascular patients may produce a modest cardiovascular benefit,’ he said in a statement released by McMaster.

The neutral finding of no significant benefit (as well as no harm) regarding either CVD events or total mortality among people without CVD ‘does not alter the large body of prior observational evidence supporting the cardiac benefits of fish intake in general populations,’ notes Dr Dariush Mozaffarian, in a commentary that accompanies the report.

Although the new analysis failed to show a significant association between regular fish consumption and fewer CVD events for people without established CVD or CVD risk, ‘based on the cumulative evidence from prospective observational studies, randomised clinical trials, and mechanistic and experimental studies, modest fish consumption appears to have some cardiac benefits,’ he adds.

‘Adults should aim to consume about two servings of fish per week, and larger benefits may accrue from non-fried oily (dark meat) fish,’ writes Mozaffarian, a professor of medicine and nutrition at Tufts University School of Medicine, Boston, Massachusetts. Oily, dark fishes include salmon, tuna steak, mackerel, herring and sardines. Species such as these contain the highest levels of long-chain omega-3 fatty acids, eicosapentanoic and docosapentanoic acid; these nutrients likely underlie the CVD benefits from fish, Mozaffarian says.

# Prosthetic heart valve thrombosis in pregnancy: a case series on acute management

S Foolchand, H Ramnarain

## Abstract

Rheumatic heart disease is one of the leading causes of valve dysfunction, resulting in prosthetic valve implantation. Changes in physiology and the haemodynamics of pregnancy increase the susceptibility of thrombosis to the prosthetic valve in the pregnant woman. Valve redo surgery carries a considerable risk of maternal and perinatal morbidity and mortality. Women of reproductive age should be well counselled regarding compliance with anticoagulation, contraception and pre-pregnancy planning.

**Keywords:** thrombosis, prosthetic valves, pregnancy, cardiac surgery, cardiopulmonary bypass pregnancy

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Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality worldwide,<sup>1</sup> and remains one of the top five causes of maternal death in South Africa.<sup>2</sup> Cardiac disease accounted for 34.3% of maternal deaths in the sub-category of medical and surgical conditions as a cause of maternal mortality in the Sixth Triennial report.<sup>2</sup> The burden of rheumatic heart disease and its sequelae contribute to a large proportion of women presenting with CVD in low- and middle-income countries (LMIC) such as South Africa.<sup>1</sup> The increased risk of heart failure secondary to valve degeneration may be abrogated by valve-replacement surgery,<sup>1</sup> resulting in a marked improvement of an individual's quality of life as well as life expectancy.<sup>3</sup>

Mechanical and biological prosthetic (bio) heart valves are used in replacement surgery depending on clinical presentation, preference of the patient and availability of the various types of prosthetic valves.<sup>3</sup> However, bio prosthetic valves often result in re-operation due to dysfunction, especially when implanted in younger patients.<sup>3</sup> Mechanical valve prostheses are more commonly used in South Africa. These operations are generally

performed on younger women in the reproductive age group and the implications of surgery and especially the use of warfarin (an oral anticoagulant) and its potential problems associated with pregnancy are often poorly understood.

The use of warfarin is lifelong, which poses the risk of teratogenicity in pregnancy, particularly in the first trimester, and foetal wastage later in the pregnancy.<sup>3,4</sup> The use of unfractionated heparin is associated with adverse effects on the mother.<sup>4</sup> Reports also include the risk of postpartum haemorrhage at delivery in patients who have been anticoagulated.<sup>5</sup>

Cardiac surgical intervention in pregnancy historically carries a greater risk to both mother and foetus. A recent meta-analysis, assessing maternal and foetal outcomes after cardiac surgeries during pregnancy involving cardiopulmonary bypass (CPB), found the following in women: per 100 pregnancies, the pooled unadjusted estimate of maternal mortality was 11.2 (95% CI: 6.8–17.8), pregnancy loss was 33.1 (95% CI: 25.2–41.2), maternal complications were 8.8 (95% CI: 2.8–24.2) and neonatal complications were 10.8 (95% CI: 4.2–25.2).<sup>6</sup>

Thrombosis of prosthetic valves is a medical/surgical emergency and all healthcare workers attending to pregnant women with prosthetic valves should have a high index of suspicion for valve thrombosis and resultant valve dysfunction. It can be life-threatening and appropriate management reduces maternal and foetal adverse outcomes.<sup>7</sup> Pregnant women are at greater risk for valve thrombosis due to poor compliance secondary to risk of possible foetal affectation, poor knowledge of healthcare workers in counselling patients on the different anticoagulation regimes in pregnancy, resource limitations in terms of assessments and monitoring, poor access to healthcare, nausea and vomiting during pregnancy, and a reduction in fibrinolysis and anti-thrombin III, contributing to the prothrombotic nature of pregnancy.<sup>5</sup>

Open-heart surgery carries considerable risk, especially in early pregnancy.<sup>8</sup> Therefore, CVD is considered a significant non-obstetric cause of maternal mortality.<sup>9</sup> In resource-limited countries such as South Africa, the management of such patients is challenging due to the obstetric risks and complications of anticoagulant therapy.<sup>9</sup>

The following are six cases of pregnant patients on anticoagulant therapy with malfunctioning prosthetic mitral valves, seen during the period of a year at two tertiary institutions in KwaZulu-Natal, requiring emergent valve replacement.

## Case reports

### Patient 1

A 30-year-old patient, P3G4, presented at 15 weeks' gestation. She had a routine echocardiography, which revealed dysfunction of a single mitral leaflet. This was confirmed by fluoroscopy. The patient had defaulted on multiple follow-up appointments and obtained warfarin from her local clinic. She had utilised an

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intra-uterine contraceptive device for contraception, which was removed due to abnormal bleeding, and no further contraception was offered to the patient. She was discussed in a multi-disciplinary team (MDT) involving cardiothoracic surgery/ cardiology/maternal-foetal medicine/high-risk obstetrics.

The patient elected to have a valve redo and a 25-mm ON-X valve was inserted. The patient recommenced oral anticoagulation after a period of intravenous heparin post operatively and the foetal heart was confirmed. She had an uneventful vaginal delivery of a 3-kg female neonate with good apgars.

### **Patient 2**

A 20-year-old P0G1 presented at 21 weeks' gestation to her local hospital with a history of mitral valve prosthesis at age six years. She had defaulted on follow up at cardiology since 2017 and had stopped taking warfarin at least eight months previously. Screening of her valves confirmed that one leaflet was stuck. She was counselled in a MDT about valve redo surgery and the complications to her herself and the foetus.

At surgery, a thrombus and pannus were noted, which were impeding the valve leaflet movement. Her valve was replaced with a 25-mm ON-X prosthesis. She had an uneventful postoperative course and the foetal heart was confirmed on ultrasound pre- and post surgery. She went into spontaneous labour and delivered a 2.75-kg female with good apgars.

### **Patient 3**

A 26-year-old primigravida was referred in active labour with hypertension and cardiac failure. Her warfarin was stopped by her local clinic mid-second trimester and the patient was not referred for tertiary care. The patient rapidly progressed and delivered vaginally. Valve screening showed suspicion of a stuck valve. She was assessed by the MDT and counselled for an emergent redo valve surgery.

The intra-operative findings included the mitral valve leaflet stuck in an open position with thrombus formation around the valve hinge. The valve was replaced with a 25-mm ON-X prosthetic valve. She recovered well post operation and was discharged to her referral centre for follow up, with counselling on contraception, compliance with anticoagulation therapy and pre-pregnancy assessment should she contemplate future pregnancies.

### **Patient 4**

A 24-year-old patient, P1G2, presented with an anembryonic pregnancy. She had had a previous stillbirth at 28 weeks' gestation, most likely due to warfarin exposure. Screening of her valves revealed a stuck mitral valve leaflet.

The patient agreed to a suction curettage and valve-redo surgery. On day seven post evacuation, she had her mitral valve explanted and replaced with a 27/29-mm ON-X mechanical prosthesis as the mitral valve prosthesis was thrombosed with a large clot on both the left atrial and ventricle sides. The aortic valve was inspected and found to be incompetent and a 21-mm ON-X mechanical aortic prosthesis was implanted. The patient had an uneventful recovery and was counselled on compliance, contraception and booking at the pre-pregnancy clinic when planning her next pregnancy.

### **Patient 5**

A 19-year-old primigravida in her first pregnancy presented to cardiology with a stuck mitral valve and poor compliance with warfarin. She was counselled and admitted for intravenous heparin and review by cardiothoracic surgery for possible mitral valve-redo surgery.

At surgery, the mitral valve leaflet was seen to be thrombosed at the hinge. She had her mitral valve prosthesis replaced with a 27/29-mm ON-X prosthesis and her native aortic valve replaced with a 21-mm ON-X mechanical valve due to severe aortic valve disease. She made an uneventful postoperative recovery.

The high-risk obstetrics unit was consulted immediately post operation as there was now a suspicion that she was pregnant. Subsequent ultrasound assessment revealed an 18-week intra-uterine gestation with an absent foetal heart pulsation. She was counselled and had a termination of pregnancy with misoprostol. The patient was counselled on contraception and the importance of a pre-pregnancy planning for the future. She was returned to the care of the cardiothoracic team.

### **Patient 6**

A 27-year-old patient, P2G3, was referred at 29 weeks' gestation. She had a history of poor compliance. Although asymptomatic, screening revealed a stuck mitral valve leaflet. She was extensively counselled by a MDT and consented to valve-redo surgery.

The patient had her mitral valve prosthesis redone with the foetus *in utero*. At surgery the leaflet was noted to be thrombosed and the valve was replaced with a 27/29-mm ON-X mechanical prosthetic valve. The patient did not consent to foetal monitoring during surgery and an intra-uterine foetal death was noted post procedure. She underwent induction while still on intravenous heparin and delivered a 1.2-kg stillbirth vaginally. She was bridged onto oral anticoagulation and discharged via the cardiothoracic ward on optimal oral anticoagulation and contraception.

## **Discussion**

The cases outlined above reinforce the areas of concern in the management of pregnant women with cardiac prosthetic valves. Maternal mortality as a result of valve thrombosis ranges between two and 15%, even on heparin therapy.<sup>8</sup> Pregnant women are at increased risk for valve thrombosis, which may be exacerbated by the physiological changes of pregnancy.<sup>8</sup>

Pregnancy is a hypercoagulable state due to the increase in factors VII, VIII and X.<sup>7</sup> The formation of a thrombus or pannus at the valve impacts on its functionality, leading to stenosis or regurgitation.<sup>10</sup> Management of patients with thromboses is complex due to the risk of perinatal morbidity and mortality. Poor compliance and follow up contributed significantly to the presentation of the above patients. Compliance failure is a well-known problem to all healthcare workers in our country and reasons include lack of insight into the need for anticoagulation, poor follow up, the reluctance or failure of medical professionals outside of obstetrics and gynaecology to actively advocate contraceptive use in women of reproductive age, lack of resources and knowledge regarding the management of anticoagulation in pregnancy, as well as financial constraints on the part of the patient.

The use of subcutaneous low-molecular weight heparin in pregnant women with mechanical prosthetic valves without meticulous anti-Xa monitoring is not an option and cannot be emphasised enough. The administration of anticoagulants and thrombolytic agents during pregnancy increases the risk of sub-placental bleeding and embolism.<sup>8</sup>

The index of suspicion for valve thrombosis must be high for all pregnant women with mechanical heart valves. Patients may present with worsening dyspnoea, palpitations or cardiac failure, new murmurs, and new symptoms of cardiac or respiratory compromise.

A detailed clinical examination and transthoracic echocardiography (TTE) should be the basic assessment for all pregnant women with mechanical prosthetic valves,<sup>11</sup> irrespective of symptoms, as some may be asymptomatic, similar to our second patient. TTE should be the imaging used as first line, as a normal prosthetic heart valve function seen on TTE is reassuring.

The echocardiographic signs of obstructive valve thrombosis include reduced valve mobility, presence of thrombus, abnormal trans-prosthetic flow, central prosthetic regurgitation, elevated trans-prosthetic gradients, and reduced effective prosthetic area (as seen in patient 2).<sup>12</sup> The 2017 guidelines from the American Heart Association recommends urgent multimodality imaging in patients with suspected mechanical heart valve thrombosis to assess valvar function, leaflet motility and the presence and extent of thrombus.

Surgery is considered in the presence of a thrombus.<sup>7</sup> CPB surgery has implications for both the patient and her foetus. Surgery carries a risk of up to 30% for foetal mortality. Over the years, techniques have been introduced to decrease the risk to the foetus, such as avoiding hypothermia during bypass,<sup>13</sup> maintenance of a high flow rate ( $> 2.5$  l/min/m<sup>2</sup>), mean arterial pressure  $> 70$ – $75$  mmHg,<sup>14</sup> maintenance of the haematocrit above 28%, avoiding maternal hypoglycaemia and hypoxia, as well as by placing the patient in the left lateral recumbent position during CPB to avoid inferior vena cava compression by the uterus.<sup>15,16</sup>

Pulsatile flow has been suggested as being more beneficial in pregnant women than in non-pregnant women as it decreases vasoconstriction (in foetal lamb studies) by decreasing the activation of the foetal renin–angiotensin–aldosterone axis, which may reduce uterine contractions.<sup>17</sup> CPB can induce uterine contractions, especially during the cooling and rewarming phases.<sup>18</sup>

In the above case series, the patients were assessed, managed and counselled for valve-redo surgery, which was carried out successfully. The implications for both the mother and foetus were also discussed as surgical mortality rates are between five and 36%.<sup>19</sup> Therefore, the prosthetic type, and imaging and surgical risks (co-morbidities, age) are considered.<sup>19</sup> Follow up is imperative after prosthetic heart valve-replacement surgery.<sup>20</sup>

## Conclusion

Women of reproductive age with prosthetic valves should be counselled adequately for potential risks. Prosthetic valve dysfunction in pregnancy increases the risk of adverse outcomes for both mother and foetus. Therefore, careful management is warranted to ensure positive outcomes and improvement in

quality of life.

Clinicians taking care of reproductive-age women should enquire on a menstrual history and fertility desires. Patients with medical or surgical disorders should be referred for pre-pregnancy counselling and assessment. All women with mechanical prosthetic cardiac valves should be counselled on the various anticoagulant regimes available, with advantages and disadvantages discussed in detail, preferably prior to stopping contraception or planning a pregnancy. The options should include oral anticoagulants, unfractionated heparin or low-molecular weight heparin. Pregnant women with mitral valve prostheses should have a detailed history/examination and a TTE at the first antenatal consultation. The frequency of TTE depends on symptoms and available resources.

These women should also be managed in a tertiary institution. There should be a high index of suspicion for valve dysfunction. Those with a suspicion of valve malfunction should be urgently seen by a MDT consisting of cardiology/ cardiothoracic/high-risk obstetrics/neonatology (if relevant) and anaesthetics. Patients requiring urgent valve-redo surgery should be counselled extensively on the surgery and possible foetal and maternal outcomes. Measures to decrease foetal loss at CPB should be instituted in all pregnant women.

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‘Fish oil lowers heart rate, blood pressure and triglycerides (at high dosages), increases adiponectin, improves endothelial function, and in some studies improves oxygen consumption in myocardium. If there is benefit from fish, it’s from the omega-3s, and all in all the evidence supports this,’ but because the evidence is primarily observational, it can only show linkage and cannot prove causation, he explains.

Given the potential benefit and limited risk: ‘I think everyone should aim to eat two servings of fish each week, preferentially oily fish. That’s very solid,’ says Mozaffarian, who is also a cardiologist and dean of the Gerald J and Dorothy R Friedman School of Nutrition Science and Policy, Boston, Massachusetts. The investigators did not have adequate data to compare the associations between outcomes and a diet with oily fish versus less oily fish.

For people who either can’t consume two fish meals a week or want to ensure their omega-3 intake is adequate, ‘it’s very reasonable for the average person to take one [over-the-counter] fish oil capsule a day,’ Mozaffarian adds.

He acknowledges that several studies of fish-oil

supplements failed to show benefit, but several others have. ‘It’s a confusing field, but the evidence supports benefit from omega-3s,’ he concludes.

He discounts the new finding that only people with established CVD or who are at high risk benefit. ‘I’m not sure we should make too much of this, because many prior studies showed a lower CVD risk in fish-eating people without prevalent CVD,’ he said. The new study ‘provides important information, given its worldwide breadth,’ he added.

The new report used data regarding 191 558 people enrolled prospectively in any of four studies. The average age of the participants was 54 years, and 52% were women.

During follow up, death from any cause occurred in 6% of those without CVD or CVD risk and in 13% of those with these factors. Major CVD events occurred in 5 and 17% of these two subgroups, respectively. To calculate the relative risks between those who ate fish and those who did not, the investigators used standard multivariate adjustment for potential confounders and adjusted for several dietary variables, Mentz says.

Source: *MedicalBrief* 2021