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# Prosthetic heart valves in pregnancy, outcomes for women and their babies: A systematic review and meta-analysis

Claire M. Lawley BSc(Med)Hons, MBBS(Hons)[1, 2]

Samantha J. Lain BComm, BHthSci(Hons), MPH, PhD[1]

Charles S. Algert BA, BSc, MPH[1]

Jane B. Ford BA(Hons), PhD[1]

Gemma A. Figtree MBBS, DPhil (Oxon), FRACP[2]

Christine L. Roberts MBBS, DrPH, FAFPHM[1]

1. Clinical Population Perinatal Health Research, Kolling Institute, University of Sydney, Sydney, Australia
2. Department of Cardiology, Royal North Shore Hospital, St Leonards, Australia

Corresponding author:

Dr Claire Lawley
Clinical Population Perinatal Health Research
The Kolling Institute
University of Sydney at Royal North Shore Hospital
Telephone: +61 2 9462 9790
Fax: +61 2 9462 9058
Email: claw2317@uni.sydney.edu.au

Running title: Prosthetic heart valves in pregnancy: A systematic review

**Abstract**

*Background*

Historically, pregnancies among women with prosthetic heart valves have been associated with an increased incidence of adverse outcomes. While there have been advances in prosthetic heart valve design, obstetric and medical care, subsequent impact on incidence of adverse outcomes during pregnancy has not been quantified.

*Objectives*

To assess the risk of adverse pregnancy outcomes among women with a prosthetic heart valve(s) in the contemporary setting.

*Search Strategy*

Electronic literature search of Medline, The Cochrane Library, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and Embase to find recent studies.

*Selection Criteria*

Studies of pregnant women with heart valve prostheses including trials, cohort studies and unselected case series.

*Data Collection and Analysis*

Absolute risks and 95% confidence intervals for pregnancy outcomes were calculated using either a random effects model or the logit transformation of total events and participants (the latter method when multiple studies had event counts of zero).

*Main Results*

Eleven studies capturing 499 pregnancies among women with heart valve prostheses were eligible for inclusion. Pooled maternal mortality rate was 0.8/100 pregnancies (95% CI 0.3-2.1), pregnancy loss rate 32.1/100 pregnancies (95% CI 28.1-36.3) and perinatal mortality rate 4.7/100 births (95% CI 2.7-7.9).

*Conclusions*

Women with heart valve prostheses experienced higher rates of adverse outcomes then would be expected in a general obstetric population, however lower than previously reported. Multidisciplinary pre-pregnancy counselling and vigilant cardiac and obstetric surveillance throughout the perinatal period remains warranted for these women and their infants.

**Keywords: Pregnancy, heart valve prosthesis, cardiovascular diseases, perinatal mortality**

**"Tweetable" abstract**

New metaanalysis suggests reduction in maternal mortality among women with #heartvalveprosthesis #pregnancy

**Introduction**

Women with underlying cardiac disease are at higher risk of adverse outcomes during pregnancy than the general obstetric population. Pregnancy is a pro-coagulant state and contributes to an increase in haemodynamic load[1-5]. As a subgroup of women with cardiac disease, an increased incidence of adverse outcomes has been observed among pregnancies in women with prosthetic heart valves. This includes maternal mortality, miscarriage, thromboembolism and obstetric haemorrhage. Infants of these women are at an increased risk of perinatal mortality, preterm birth, small-for-gestational-age (SGA) and congenital malformations[6-12].

The design of prosthetic heart valves continues to improve. The highly thrombogenic ball-and-cage style valves have been virtually eradicated by the newer design bi-leaflet valves, lowering anticoagulant requirements[13]. Bioprosthetic heart valve prostheses are being increasingly used, as a result of developments in materials and the ability to implant using percutaneous techniques. These valves avoid the need for anticoagulation during pregnancy[13-15]. Combined with improvements in perioperative mortality and medical care, the outcome of these valve prosthesis advancements has been an overall improvement in the prognosis for heart valve prosthesis recipients, including women of reproductive age and children born with congenital heart disease[16-19].

There is a paucity of work exploring the outcomes of contemporary pregnancies in the setting of maternal heart valve prosthesis. Recent individual studies report lower rates of adverse outcomes than presented in two systematic reviews, published in 2000 and 2008, which focused only on mechanical valves and influence of anticoagulant type [6, 12, 20, 21]. Given the advances in prosthetic heart valve design, obstetric and medical care and

improvement in prognosis of contemporary heart valve prosthesis recipients, further investigation of the outcomes of pregnancies in the setting of maternal heart valve prosthesis is warranted.

A systematic review with the primary objective of assessing the risk of an adverse outcome in pregnancy among women with a prosthetic heart valve(s) in the contemporary setting was undertaken. The secondary outcome was to assess the absolute risk of adverse outcomes by prosthesis type and/or location.

**Methods**

This systematic review was performed in accordance with the previously published protocol[22], registered with the international prospective register of systematic reviews (PROSPERO), number: CRD42013006187. It was based on the guideline by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group (Appendix S1)[23].

*Search strategy and eligibility criteria*

A systematic search of Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and The Cochrane Library was undertaken to identify relevant studies published between January 1995 and August 2014. Search terms included "pregnancy" AND ("heart valves" "heart valve prosthesis" OR "heart valve replacement" OR "heart valve prosthesis implantation"). The "explode" function was used in each case. Searches were limited to studies of humans and peer-reviewed articles. Language restrictions were not applied, translations were obtained as required. Duplicates were removed. To avoid overlapping populations, in cases where participants were included in more than one

publication, the study with the largest sample size was included. Reference lists were searched for other relevant articles.

Eligible study types were randomised controlled trials, clinical trials, cohort studies, cross-sectional studies and unselected case series (participants not selected due to occurrence of an adverse event, for example valve thrombosis). The latter were eligible because a control or a comparison group was not necessary to estimate the rate of adverse outcomes among women with valve prosthesis

For a study to be eligible for inclusion it needed to contain at least six pregnancies in the setting of a maternal heart valve prosthesis, the number used in the previous systematic review of this topic[6]. To allow assessment of contemporary outcomes, only those with pregnancies exclusively beyond January 1995 with less than 5% of women with ball-and-cage style valves were eligible for inclusion. Studies with pregnancies in women with either single or multiple prostheses were eligible for inclusion, as long as other criteria were met. Conference abstracts, posters and unpublished material were not included.

Article titles and abstracts were evaluated by two reviewers (CR, CL) for suitability of study type and in regards to eligibility criteria. Where there was disagreement or ambiguity at this stage, the article remained included until the full text was reviewed.

At least two independent reviewers (CF, GF, JF, CA, SL, CL) assessed the full text of the remaining studies. Where information pertinent to the other inclusion criteria was not contained within the article text, efforts were made to contact the listed corresponding author. Where no reply was received after reasonable effort, the article was excluded. Consensus between the two reviewers examining the article was reached before it was

included. Where consensus was not reached, a third reviewer was involved as an arbitrator. A log of rejected studies maintained.

*Outcomes*

The primary outcomes of interest were maternal mortality, any pregnancy loss (including miscarriage, termination of pregnancy and perinatal mortality or as defined by study) and perinatal mortality (stillbirth or neonatal mortality)[24]. Stillbirth was defined as fetal death *in utero* ≥ 22 weeks gestation or as defined by the study and neonatal mortality as death in the first 28 days of extra-uterine life[24].

The secondary outcomes were divided into adverse maternal outcomes, mode of delivery and adverse birth outcomes. Adverse maternal outcomes included any thromboembolic events during the pregnancy (stroke or transient ischaemic event (TIA), valve thrombosis or other), any obstetric haemorrhage (whether antenatal or postpartum), any cardiovascular compromise (as defined by study), valve deterioration (bioprosthetic valves only, as defined by study), any new maternal arrhythmia, infective endocarditis, myocardial infarction and pregnancy hypertension including gestational hypertension, pre-eclampsia and eclampsia. Mode of delivery was either cesarean section or vaginal birth. Adverse birth outcomes included preterm birth (delivery <37 weeks of gestation), small for gestational age (SGA) (less than tenth birth weight percentile for sex and gestational age), low birth weight (LBW) (birth weight <2 500 grams), infant admission to Neonatal Intensive Care Unit (NICU) and congenital malformation.

*Data extraction*

Data extraction from each identified article was undertaken by two independent reviewers (CR, GF, JF, CA, SL, CL) using a uniform template. Discrepancies were resolved by discussion, and where applicable, arbitration by a third reviewer. Information extracted from each study included study characteristics (authors, year of publication, study design, location, time period of included pregnancies), population characteristics (number of participants, number of pregnancies, maternal age, parity), heart valve characteristics (number of mechanical valves, number of bioprosthetic valves, implanted valve type, implanted valve location, anticoagulation regimen) and outcomes (frequency of primary and secondary outcomes as outlined above).

*Analysis*

The absolute risk, or event rate, of maternal mortality and any pregnancy loss was expressed as the proportion of the total number of pregnancies in women with heart valve prostheses. The absolute risk, or event rate, of perinatal death and secondary adverse birth outcomes was expressed as a proportion of pregnancies beyond 22 weeks gestation or 500 grams or resulting in a live birth[24] in women with heart valve prostheses. If insufficient details to differentiate between early pregnancy loss and fetal death >22 weeks were provided, the study was excluded from analysis for those outcomes relying on this information for the denominator. For consistency across outcomes and with published studies rates were reported per 100 pregnancies or births, as appropriate.

Pre-specified subgroup analyses of primary and secondary outcome risk, or event rate, by valve location and valve type were undertaken if the outcome was reported by at least two studies, each with at least six pregnancies in the subgroup[22]. For these analyses, women with more than one valve prosthesis type were excluded. Pooled event rates were

preferentially calculated using a random effects model, with variances calculated using a logit conversion in Comprehensive Meta Analysis (Version 2.0) software (Biostat, Englewood, NJ, USA). Graphical summaries of individual study estimates and overall estimates were also produced. The possible effect of sampling error was assessed using 95% confidence intervals (CI) around risk estimates. When the event count in any given study was zero, the zero was replaced with a value of 0.001. When more than 10% of the total population contributing to a particular meta analysis came from studies with an event rate of zero, the logit transformation of the total events and total participants was used to calculate the pooled event rate and 95% CI. This avoided the overweighting of studies with non-zero event rates if the random effects method was used. To compare rates (proportions) between subgroups (i.e. mechanical versus bioprosthetic valves) a standard chi-square test of two proportions was performed to identify significant differences.

Where applicable, heterogeneity of rates within a meta-analysis was assessed with the $I^2$ statistic. Study heterogeneity was explored by the study design, the year of publication, the time period within which pregnancies occur and population characteristics (ethnicity, age range, aetiology of underlying disease, type and location of heart valve prosthesis, anticoagulant regimen).

To assess the risk of bias in non-randomised studies, the Newcastle–Ottawa scale (NOS) for assessing the quality of non-randomised studies in meta-analyses was used [25]. The NOS for case-control and cohort studies was adapted to meet the specific needs of this systematic review; with a modified scale for use in case series[22]. Using this scale, studies were awarded a star based on points for items related to the selection of study groups, the comparability of groups and the ascertainment of outcome of interest. If a control group was present, a

maximum of nine stars could be achieved. Case series (no control group) were eligible for a maximum of six stars. Scoring was undertaken by two independent reviewers (SL, CL), with a third reviewer (CR) as an arbitrator if disagreement occurred.

The strength of evidence was assessed with respect to the study designs, the methodological quality of individual studies, consistency of results across studies and for studies with a comparison group, the strength of associations. Given that most studies were uncontrolled case series, the strength of evidence was assessed primarily by the width of the confidence interval around pooled outcome rates. Consistency of effect was demonstrated visually in the plots and via the $I^2$ estimate[26]. For analyses where multiple studies with zero event rates dictated use of the logit transformation for the pooled result rather than a random effects analysis, no $I^2$ estimate was calculated.

**Results**

The literature search identified 1402 original articles (Figure 1). After initial screening, 1 364 records were excluded. The full-text of the remaining 38 articles was reviewed to assess eligibility. A further 27 articles were excluded (Appendix S2), leaving 11 studies deemed suitable for inclusion. Search of reference lists of relevant systematic reviews and included studies did not yield any further relevant articles.

Of the 11 included studies[20, 27-35], four were prospective unselected case series, three from single centres[29, 34, 35] and one multiple centre[27]. There were seven retrospective studies, two population-based cohort studies[20, 21], two multicentre unselected case series [28, 32, 33] and three single centre unselected case series[28, 30, 31] (Table 1). Ten studies captured a total of 305 women undertaking 392 pregnancies. For the remaining study, only the number of

pregnancies could be identified[20]. In total 499 pregnancies to women with a heart valve prosthesis were eligible for inclusion in this review.

The studies were published from 2007 to 2014 and included pregnancies occurring from 1997 to 2012 with both mechanical and bioprosthetic heart valves. Anticoagulant regimens used in the setting of mechanical heart valve prostheses included low molecular weight heparin and oral anticoagulation (Table 1). The aetiology of underlying heart disease was both congenital and acquired.

*Assessment of the methodological quality of the included studies*

Using the modified Newcastle-Ottawa scale[22], the two cohort studies were awarded seven and eight stars respectively, one study[20] controlled for only one factor, maternal age, the other did not control for any factors in the comparison group [21]. Of the remaining studies without control groups, one study[32] was awarded the maximum six stars, seven awarded five stars[27-29, 31, 33-35] and one awarded three stars[30]. All included studies were assessed as including an adequate representation of cases, with appropriate follow-up. The most common reason for failure to be allocated a star was non-blinded assessment of outcomes (Table 1).

*Outcomes*

Meta-analysis of event rates was undertaken for the 11 included studies given the similar pregnancy cohorts and acceptable methodological quality of the studies. Unadjusted pooled event rates and 95% confidence intervals (CI) are reported in Table 2. All included studies reported information on maternal mortality and any pregnancy loss. Eight of the eleven studies allowed identification of perinatal mortality[20, 21, 27-29, 31, 32, 34], three studies had

insufficient details to differentiate early pregnancy loss from fetal death at greater than 22 weeks[30, 33, 35]. No studies reported the incidence of infective endocarditis or neonatal admissions to the intensive care unit.

There were four maternal deaths in 499 pregnancies, giving a maternal mortality rate of 0.8 per 100 pregnancies (95% CI 0.3-2.1) (Figure 2). Of the maternal deaths, one was due to heart failure in the antenatal period[20], one during delivery[35] and two due to haemorrhage. Of those due to haemorrhage, one was due to an intracerebral bleed in the setting of an elevated International Normalised Ratio (INR) of 6[31] and the other due to an obstetric haemorrhage on day three following caesarean section[20]. Pregnancy loss occurred in 160 of the 499 pregnancies, giving a pregnancy loss rate of 32.1 per 100 pregnancies (95% CI 28.1-36.3) (Figure 3). There were 14 perinatal deaths in 279 births, giving a perinatal mortality rate of 4.7 per 100 births (95% CI 2.7-7.9) (Figure 4). Other adverse maternal outcomes are outlined in Table 2.

For the pre-specified subgroup analysis there were 256 pregnancies where the maternal heart valve prosthesis was known to be *mechanical*. Among these pregnancies there were 2 maternal deaths, giving a maternal mortality rate of 0.8 deaths per 100 pregnancies (95% CI 0.2-3.1). There were 8 perinatal deaths in 124 births, giving a perinatal mortality rate of 9.9 per 100 births (95% CI 5.7-16.7). The rate of thromboembolism was 16.2 per 100 pregnancies (95% CI 11.6-22.2). Among women the 59 women with *bioprosthetic* valves there were no maternal deaths, giving a rate of 0 per 100 pregnancies (95% CI not calculable). There were 2 perinatal deaths in 47 births giving a perinatal mortality rate of 5.3 deaths per 100 births (95% CI 1.3-19.1). The rate of thromboembolism was 0.8 per 100 pregnancies (95% CI 0.1-12.0). The remainder of the adverse events by valve type are

summarised in Table 3 below. When undertaking the Chi-square analysis, the only statistically significant difference between the two valve types was in the rate of thromboembolism (32 events in 256 pregnancies in mechanical group versus no events in 59 pregnancies in bioprosthetic group, two tailed p-value <0.01).

Subgroup analysis by prosthetic valve location (mitral or aortic) was undertaken (Table 4). In the *aortic valve group* the maternal mortality rate was 0.8 deaths per 100 pregnancies (95% CI 0.0-11.3). The rate of thromboembolism was 15.3 per 100 pregnancies (95% CI 7 0.3-29.4). The maternal mortality rate in the *mitral valve group* was 1.3 deaths per 100 pregnancies (95% CI 0.2-8.4). The rate of thromboembolism in the mitral valve group was 11.4 per 100 pregnancies (95% CI 0.6-20.5).

**Discussion**

*Main Findings*

This systematic review quantifies the outcomes of contemporary pregnancies among women with prosthetic heart valves, including bioprosthetic valves. The risk of maternal and infant adverse outcomes during and following pregnancy remains significant.

The maternal mortality rates for any prosthesis (0.8/100 pregnancies, 95% CI 0.3-2.1), and for mechanical heart valve prostheses alone (0.8/100 pregnancies (95% CI 0.2-3.1), were lower than the previously reported 2.9/100 (95% CI 1.9-4.2) by Chan et al. including only pregnancies in the setting of mechanical valves in their earlier systematic review[6]. The causes of maternal mortality appear to have changed; in the previous systematic review 17 of the 25 maternal deaths were attributable to valve thrombosis and related complications [6] compared to no deaths due to valve thrombosis in the current review, potentially reflecting

improvement in mechanical prosthesis design and modified anticoagulation regimens and monitoring. The rate of maternal mortality in women with a prosthetic heart valve (800/100 000) was higher than overall maternal mortality rates in the included countries which ranged from 4/100 000 (Italy) to 140/100 000 (South Africa)[36].

The rate of pregnancy loss in the setting of maternal heart valve prosthesis remains high (32/100 pregnancies), and is potentially underreported in the retrospective studies. The two largest studies reported vastly different rates of pregnancy loss rates, 23/136 (17%) and 67/107 (63%)[20, 21]. Both were retrospective population-based studies that scored favourably when assessed for risk of bias (Table 1). However, methods varied; Sillesen et al.[20] attempted to contact women to identify spontaneous first trimester abortions. The Australian study relied on routinely collected data that only included miscarriages or terminations of pregnancy requiring hospital admission[21]. In the previous systematic review, Chan et al. reported a similar rate of any fetal loss, 31/100 pregnancies (356/1 145), from both prospective and retrospective studies[6].

The perinatal mortality rate, 4.7 per 100 births (95% CI 9.3-17.8) was in keeping with the overall global perinatal mortality rate, 4.7/100[24]. Although, of the 8 studies reporting this outcome, 5 of the smaller studies reported no perinatal deaths[27-29, 32, 34]. Both the highest[31] and lowest [34] rates of perinatal mortality were reported from South African studies. Differing study populations, designs and time periods are all likely contributors to this observed difference. The number of perinatal deaths in the Australian study (2 deaths in 115 births) [21] and Danish study (3 deaths in 43 births)[20] were significantly higher than the overall perinatal mortality rate for the regions to which these countries belonged[24],

suggesting perinatal mortality remains a risk for pregnancies in women with heart valve prostheses.

*Strengths and Limitations*

Strengths of this review include the contemporary population, reflecting present day management with the exclusion of older-style valve prostheses. Bias was reduced by including articles independent of language and removing duplicate study populations. Unpublished studies were excluded. Sources of bias included lack of blinding in outcome assessment and the possible selective nature or incomplete reporting of outcomes in individual studies. There was also a lack of methodologically superior study types. There was a moderate degree of heterogeneity in the analyses which could be assessed using the $I^2$ estimate[26]. Although the analysis by valve type and position provides information for counselling, the relatively small number of pregnancies available for subgroup evaluation by valve type and valve location limited the conclusions that could be drawn from these analyses.

*Interpretation*

From this review, the ongoing need for multidisciplinary pre-pregnancy counselling and vigilant cardiac and obstetric surveillance throughout the perinatal period is clear. This is particularly evidenced by the increased risk of maternal and perinatal mortality, fetal loss and other adverse events during pregnancy in women with heart valve prostheses. In the future there may be potential to specifically tailor counselling and monitoring to valve type and location, as explored below, in light of the findings of this review and other evidence. Ongoing work in this area is needed.

Previous studies have reported varying rates of thromboembolic events by anticoagulation regimen during pregnancy among women with mechanical heart valve prostheses. This review found the thromboembolic event rate to be 13.3/100 pregnancies (95% CI 9.3-17.8), higher when including only women with mechanical valves and lower among women with bioprosthetic valves. A variety of anticoagulation regimens were included in the mechanical valve group; oral anticoagulation with conventional and low-dose protocols, low molecular weight heparin and no anticoagulation. Subgroup analysis by anticoagulation type has been addressed in detail by two earlier systematic reviews[6, 12] reporting rates of thromboembolism from 3.9/100 (oral anticoagulation) to 33.3/100 (heparin)[6].

Few studies reported outcomes for women with bioprosthetic heart valves[21, 28]. Pregnancy has been purported to be safer in the presence of bioprosthetic as opposed to mechanical valves, largely due lack of routine anticoagulation. In this review, bioprosthetic valves were associated with lower rates of thromboembolic events than mechanical valves. This is not surprising given the lack of a thrombogenic substrate in bioprosthetic valves. Rates of other outcomes were generally lower for bioprosthetic valves although no other comparisons achieved statistical significance, partly due to smaller sample size in the bioprosthetic group. Further work is needed to clarify the contemporary outcomes of women undertaking pregnancy with a bioprosthetic heart valve, particularly given the recommendation that this valve type be considered for women wishing to have children[14, 37, 38].

Mitral valve prostheses have been previously associated with a higher incidence of mortality and complications compared to aortic[39-41]. In this review the rate of thromboembolic events was similar for women with an aortic compared to a mitral valve prosthesis (15.3/100 and 11.4/100 respectively). Further research on the impact of valve location on

pregnancy outcome among a larger pregnancy cohort would allow tailored counselling and management of valve-type for location specific subgroups.

The observed rate of obstetric haemorrhagic events (7.1/100 pregnancies), remained higher than current global population estimates of post partum haemorrhage (6.0/100)[42], potentially due to the impact of anticoagulation required for women with mechanical valves. The previous systematic review reported "major bleeding events" only, occurring in 2.5% of pregnancies[6]. Caregivers of pregnant women with prosthetic heart valves need to remain vigilant in early recognition of significant bleeding throughout the perinatal period.

The relationship between maternal cardiac disease and adverse neonatal outcomes is not fully understood; there is a higher incidence of prematurity (both iatrogenic and spontaneous), SGA and congenital malformation reported in other studies and this review[43-45]. As heart valve replacements occur for both acquired and congenital cardiac disease, the finding of higher incidence of congenital heart disease in infants is not surprising given the genetic basis of some of these conditions[46]. In accordance with guidelines, fetal echocardiography is warranted in these high risk women[37].

**Conclusion**

Pregnancies in the contemporary setting undertaken by women with prosthetic heart valves remain at an increased risk of adverse outcomes, including maternal mortality, pregnancy loss and perinatal mortality. The risk of maternal mortality is lower than previously reported. While deaths due to valve thrombosis appears to have declined, women with mechanical heart valves remain at increased risk of thromboembolic events. Amongst infants, higher rates of prematurity, SGA and congenital malformations, including not only

the historically-reported warfarin embryopathy but also congenital heart disease, were seen. Multidisciplinary pre-pregnancy counselling as well as vigilant cardiac and obstetric surveillance throughout the perinatal period remains warranted for these women and their infants.

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**Disclosure of Interests**

CR, GF, JF, CA and CL are listed as authors on one of the included studies [21].

**Contribution to Authorship**

CR and GF conceived the study. All authors were involved in the design of the published protocol and in drafting and revising the manuscript. CR and CL undertook the initial screening of articles. All authors were involved in review of full text of all studies with pregnancies occurring exclusively beyond January 1995 and data extraction. CR, CL and SL undertook assessment of methodological quality. CL, SL, CA, and JF were involved in the design of the previously published protocol and in drafting and revising the manuscript. All authors read and approved the final manuscript.

**Details of Ethics Approval**

Not applicable.

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**Table/Figure/Appendix List**

## Table 1: Characteristic of included studies

| Study, year of publication, reference (country) | Type | Participants | Exposure | Outcome | Risk of bias* |
|---|---|---|---|---|---|
| Abildgaard, 2009, (26) (Norway) | Prospective, case series, multicentre | 11 women (12 pregnancies) with PHV managed in Norway 1997-2008. | Mechanical PHV inserted prior to pregnancy with LMWH used during. | No maternal or perinatal mortality or any pregnancy loss reported. | 5 stars, assessment of outcome non-blinded |
| Basude, 2014, (27) (United Kingdom) | Retrospective case series, single centre | 16 women (32 pregnancies) with PHV managed 1998-2012. | Aortic PHV only (except in setting of Ross procedure) inserted prior to pregnancy. | 1 maternal death, 17 pregnancy losses, 1 perinatal death. | 5 stars, assessment of outcome non-blinded |
| De Santo, 2012, (28) (Italy) | Prospective case series, single centre | 20 women (20 pregnancies) with PHV managed 2000-2010 | Mechanical PHV inserted prior to pregnancy with low dose OAC during. | No maternal or perinatal mortality or any pregnancy loss reported. | 5 stars, assessment of outcome non-blinded |
| Lawley, 2014, (21) (Australia) | Retrospective cohort study, population based | 87 women (136 pregnancies) with PHV managed 2000-2011 | PHV inserted prior to pregnancy | No maternal mortality, 23 pregnancy losses, 2 perinatal deaths | 7 stars, comparison group with unadjusted risk |
| Lee, 2007, (29) (Korea) | Retrospective case series, single centre | 25 women (31 pregnancies) with PHV managed 1997-2005 | Mechanical PHV inserted prior to pregnancy. | No maternal death, 6 pregnancy losses, perinatal mortality unable to be ascertained. | 3 stars, exclusion criteria not stated, no description of ascertainment of exposure, assessment of outcome non-blinded |
| Mazibuko, 2012, (30) (South Africa) | Retrospective case series, single centre | 61 women (61 pregnancies) with PHV managed 2005-2009 | PHV inserted prior to pregnancy. | 1 maternal death, 18 pregnancy losses, 8 perinatal deaths (2 neonatal deaths, 6 stillbirths) | 5 stars, assessment of outcome non-blinded |
| Nelson-Piercy, 2013, (31) (United Kingdom) | Retrospective case series, multicentre | 9 women (9 pregnancies) with PHV managed 1998-2006 | Mechanical PHV inserted prior to pregnancy with Tinzaparin during. | No maternal or perinatal mortality or any pregnancy loss reported. | 6 stars |
| Popelova, 2012, (32) (Czech Republic) | Retrospective case series, multicentre | 14 women (23 pregnancies) with PHV managed 2006-2010 | Mechanical PHV inserted prior to pregnancy. | No maternal death, 6 pregnancy losses, perinatal mortality unable to be ascertained. | 5 stars, assessment of outcome non-blinded |
| Saeed, 2011, (33) (South Africa) | Prospective case series, single centre | 15 women (15 pregnancies) with PHV managed 2007-2009 | Mechanical PHV inserted prior to pregnancy with Enoxaparin during. | No maternal or perinatal mortality or any pregnancy loss reported. | 5 stars, assessment of outcome non-blinded |
| Samiei, 2012, (34) (Iran) | Prospective case series, single centre | 47 women (53 pregnancies) with PHV managed 1999-2009 | Mechanical mitral PHV inserted prior to pregnancy. | 1 maternal death, 21 pregnancy losses, perinatal mortality unable to be ascertained. | 5 stars, assessment of outcome non-blinded |
| Sillesen, 2011, (20) (Denmark) | Retrospective cohort study, population based | 79 women (155 pregnancies, 107 of which were managed 1997-2007 | PHV inserted prior to pregnancy | 2 maternal deaths, 66 pregnancy losses, 3 perinatal deaths (2 stillbirths, 1 neonatal death) | 8 stars, comparison group controlled for only one factor |

PHV prosthetic heart valve, LMWH low molecular weight heparin, OAC oral anticoagulant

*Risk of bias assessed using adapted Newcastle–Ottawa scale (NOS) for assessing the quality of non-randomised studies in meta-analyses (22, 24), case series eligible for maximum of six stars and cohort studies for a maximum of nine stars

Table 2: Pooled event rates of outcomes in pregnancy

| **Outcomes*** | **Number of studies (references)†** | **Number of events /sample size** | **Pooled event rate per 100 (95% Confidence interval)** | **$I^2$ estimate (%)** |
|---|---|---|---|---|
| Maternal mortality† | 11 (20, 21, 26-34) | 4/499 | 0.8 (0.3-2.1) | NC |
| Any pregnancy loss including neonatal death† | 11 (20, 21, 26-34) | 160/499 | 32.1 (28.1-36.3) | NC |
| Perinatal mortality† | 8 (20, 21, 26-28, 30, 31, 33) | 13/279 | 4.7 (2.7-7.9) | NC |
| Thromboembolic event | 10 (20, 21, 26-34) | 34/499 | 13.3 (9.5-18.2) | 72.2 |
| Obstetric haemorrhage† | 8 (20, 21, 26-28, 30, 31, 33) | 21/295 | 7.1 (4.7-10.7) | NC |
| Cardiovascular compromise | 5 (20, 21, 26, 27, 34) | 9/302 | 4.2 (2.2-8.0) | 37.6 |
| Pregnancy-associated hypertension | 3 (21, 26, 27) | 20/143 | 14.1 (9.3-20.9) | 0.0 |
| Caesarean delivery | 4 (21, 26, 30, 31) | 98/185 | 52.2 (44.8-59.6) | 74.8 |
| Vaginal delivery | 4 (21, 26, 30, 31) | 87/185 | 47.8 (40.4-52.2) | 74.8 |
| Preterm birth | 5 (20, 21, 26, 27, 33) | 50/201 | 26.5 (20.5-33.5) | 76.7 |
| SGA | 2 (20, 21) | 27/274 | 16.4 (11.5-22.9) | 38.3 |
| Congenital malformation† | 4 (20, 26, 28, 30) | 11/124 | 8.9 (5.0-15.3) | NC |

SGA small-for-gestational-age, NC not calculated due to multiple trials with zero events.

*As defined in objectives. Outcome only included if reported in more than 1 study.

† Logit transform performed as greater than 10% of the population contributing in analysis had zero events

Table 3: Pooled estimates rates of outcomes in pregnancy by valve type

| Outcomes* | Number of studies (references) | Number of events /sample size | Pooled event rate per 100 (95% Confidence interval) | $I^2$ estimate (%) |
|---|---|---|---|---|
| **Mechanical valve prosthesis only** | | | | |
| Maternal mortality† | 10 (21, 26-34) | 2/256 | 0.8 (0.2-3.1) | NC |
| Any pregnancy loss including neonatal death† | 10 (21, 26-34) | 69/256 | 27.0 (21.9-32.7) | NC |
| Perinatal mortality† | 7 (21, 26-28, 30, 31, 33) | 12/121 | 9.9 (5.7-16.7) | NC |
| Thromboembolic event | 9 (21, 26-34) | 32/236 | 16.7 (11.9-22.8) | 49.1 |
| Obstetric haemorrhage† | 7 (21, 26-28, 30, 31, 33) | 14/131 | 10.7 (6.4-17.2) | NC |
| Cardiovascular compromise† | 5 (21, 26, 27, 33, 34) | 6/117 | 5.1 (2.3-10.9) | NC |
| Caesarean delivery | 5 (21, 26, 28, 30, 31) | 73/99 | 69.7 (58.8-78.8) | 60.2 |
| Vaginal delivery† | 5 (21, 26, 28, 30, 31) | 26/99 | 26.3 (18.5-35.8) | NC |
| Preterm birth | 4 (21, 26, 27, 33) | 12/48 | 26.1 (15.4-40.8) | 0.0 |
| New arrhythmia† | 2 (21, 30) | 8/79 | 10.1 (5.1-19.0) | NC |
| Congenital malformation† | 3 (26, 28, 30) | 5/76 | 6.6 (2.8-14.9) | NC |
| **Bioprosthetic valve prosthesis only** | | | | |
| Maternal mortality† | 2 (21, 27) | 0/59 | 0.0 (Not calculable‡) | NC |
| Any pregnancy loss including | 2 (21, 27) | 14/59 | 25.5 (15.4-39.2) | 81.3 |

| | | | | |
|---|---|---|---|---|
| neonatal death | | | | |
| Perinatal mortality | 2 (21, 27) | 2/47 | 5.3 (1.3-19.1) | 0.0 |
| Thromboembolic event† | 2 (21, 27) | 0/59 | 0.8 (0.1-12.0) | NC |
| Obstetric haemorrhage† | 2 (21, 27) | 7/47 | 14.9 (7.3-28.1) | NC |
| Cardiovascular compromise† | 2 (21, 27) | 3/59 | 5.1 (1.6-14.6) | NC |
| Preterm birth† | 2 (21, 27) | 6/47 | 12.8(5.8-25.6) | NC |
| SGA | 2 (21, 27) | 7/47 | 15.0 (7.3-28.3) | 0.0 |

SGA small-for-gestational-age, NC not calculated due to multiple trials with zero events
* As defined in objectives. Outcome only included if reported in more than 1 study.
† Logit transform performed as greater than 10% of the population contributing in analysis had zero events
‡ Not calculable due to event rate of zero

Table 4: Pooled event rates of outcomes by valve location

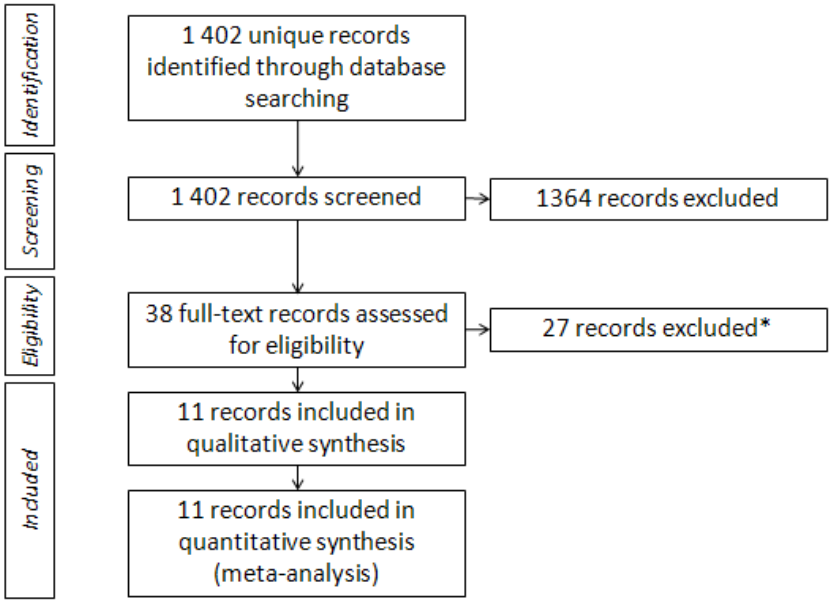
| Outcomes* | Number of studies (references) | Number of events /sample size | Pooled event rate per 100 (95% Confidence interval) | $I^2$ estimate (%) |
|---|---|---|---|---|
| **Aortic valve prosthesis** | | | | |
| Maternal mortality† | 4 (26-28, 32) | 0/63 | 0.8 (0.0-11.3) | NC |
| Any pregnancy loss including neonatal death† | 4 (26-28, 32) | 15/63 | 23.8 (14.9- 35.8) | NC |
| Thromboembolic event | 4 (26-28, 32) | 7/63 | 15.3 (7.3-29.4) | 43.9 |
| Obstetric haemorrhage† | 3 (26-28) | 2/50 | 4.0 (1.0-14.6) | NC |
| Cardiovascular compromise† | 2 (26, 27) | 1/32 | 3.1 (0.4-19.1) | NC |
| **Mitral valve prosthesis** | | | | |
| Maternal mortality† | 3 (27, 29, 30, 33) | 1/79 | 1.3 (0.2-8.4) | NC |
| Thromboembolic event† | 3 (27, 29, 30, 33) | 9/79 | 11.4 (6.0-20.5) | NC |

NC not calculated due to multiple trials with zero events

* As defined in objectives. Outcome only included if reported in more than 1 study.

† Logit transform performed as greater than 10% of the population contributing in analysis had zero events

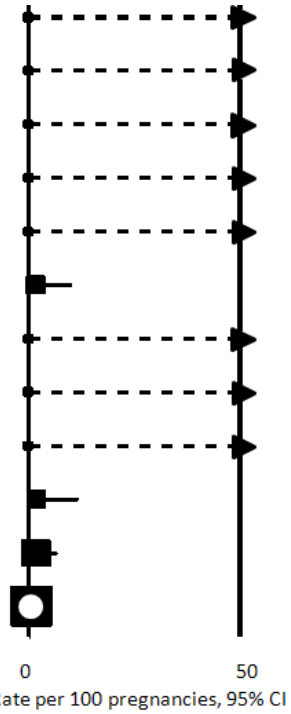
Figure 1: Process of selection of the studies for the systematic review




* Exclusion reasons: Including pregnancies prior to 1995 (n=12), ≥5% ball-and-cage valves (n=7), duplicate study population (n=3), authors unable to be contacted after reasonable attempts to clarify information relevant to inclusion criteria (n=4), no primary outcomes of interest reported (n=1), see Appendix 1.

Figure 2: Rate ratio for maternal mortality from all 11 included studies

| Study | Number of maternal deaths/number of pregnancies | Rate per 100 pregnancies (95% CI)* |
|---|---|---|
| Abilgaard et al. (2009) | 0/12 | |
| Basude et al. (2014) | 0/32 | |
| De Santo et al. (2012) | 0/20 | |
| Lawley et al. (2014) | 0/136 | |
| Lee et al. (2007) | 0/31 | |
| Mazibuko et al. (2012) | 1/61 | 1.6 (0.2-10.7) |
| Nelson-Piercy et al. (2013) | 0/9 | |
| Popelova et al. (2012) | 0/23 | |
| Saeed et al. (2011) | 0/15 | |
| Samiei et al. (2012) | 1/53 | 1.9 (0.3-12.2) |
| Sillesen et al. (2011) | 2/107 | 1.9 (0.5-7.2) |
| **Overall** | **4/499** | 0.8 (0.3-2.1) |

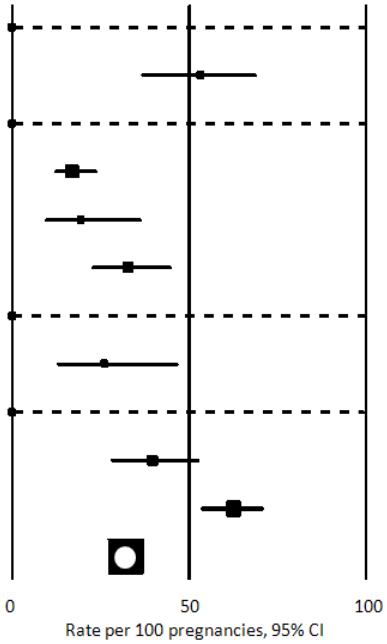



CI confidence interval

*When zero events in study 95% confidence interval not calculated, represented by dashed line in forest plot

Figure 3: Rate ratio for any pregnancy loss from all 11 included studies

| Study | Number of maternal deaths/number of pregnancies | Rate per 100 pregnancies (95% CI)* |
|---|---|---|
| Abilgaard et al. (2009) | 0/12 | |
| Basude et al. (2014) | 17/32 | 53.1 (36.1-69.4) |
| De Santo et al. (2012) | 0/20 | |
| Lawley et al. (2014) | 23/136 | 16.9 (11.5-24.2) |
| Lee et al. (2007) | 6/31 | 19.4 (9.0-36.9) |
| Mazibuko et al. (2012) | 20/61 | 32.2 (22.2-45.4) |
| Nelson-Piercy et al. (2013) | 0/9 | |
| Popelova et al. (2012) | 6/23 | 26.1 (12.2-47.2) |
| Saeed et al. (2011) | 0/15 | |
| Samiei et al. (2012) | 21/53 | 39.6 (27.5-53.2) |
| Sillesen et al. (2011) | 67/107 | 62.6 (53.1-71.2) |
| **Overall** | **160/499** | **32.1 (28.1-36.3)** |

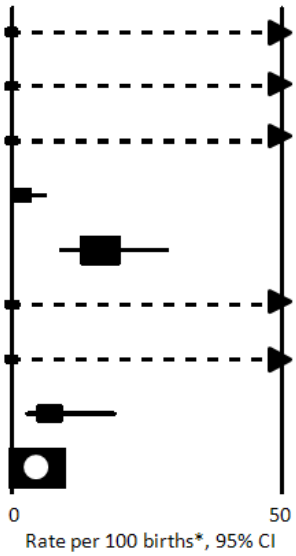



CI confidence interval

*When zero events in study 95% confidence interval not calculated, represented by dashed line in forest plot

Figure 4: Rate ratio for perinatal mortality from eight eligible studies

| Study | Number of perinatal deaths/number of included births* | Rate per 100 pregnancies (95% CI)† |
|---|---|---|
| Abilgaard et al. (2009) | 0/12 | |
| Basude et al. (2014) | 1/16 | |
| De Santo et al. (2012) | 0/20 | |
| Lawley et al. (2014) | 2/115 | 1.7 (0.4-6.7) |
| Mazibuko et al. (2012) | 8/49 | 16.3 (8.4-29.4) |
| Nelson-Piercy et al. (2013) | 0/9 | |
| Saeed et al. (2011) | 0/15 | |
| Sillesen et al. (2011) | 3/43 | 7.0 (2.3-19.5) |
| **Overall** | **14/279** | **4.7 (2.7-7.9)** |




CI confidence interval

* Births: Birth >22 weeks gestational age or 500 grams or live birth (23)

† When zero events in study 95% confidence interval not calculated, represented by dashed line in forest plot

## Appendix S1: Reporting Checklist from Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group [1]

| Requirement | Page |
|---|---|
| **Reporting of background** | |
| Problem definition | 5 |
| Hypothesis statement | 5 |
| Description of study outcome(s) | 7 |
| Type of exposure or intervention used | 6 |
| Type of study designs used | 6 |
| Study population | 6 |
| **Reporting of search strategy** | |
| Qualifications of searchers (eg, librarians and investigators) | 1 |
| Search strategy, including time period included in the synthesis and keywords | 6 |
| Effort to include all available studies, including contact with authors | 6 |
| Databases and registries searched | 5 |
| Search software used, name and version, including special features used (eg, explosion) | 5 |
| Use of hand searching (eg, reference lists of obtained articles) | 5 |
| List of citations located and those excluded, including justification | App 2* |
| Method of addressing articles published in languages other than English | 5 |
| Method of handling abstracts and unpublished studies | 6 |
| Description of any contact with authors | 6 |
| **Reporting of methods** | |
| Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | 6 |
| Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | 7-8 |
| Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability) | 7-8 |
| Assessment of confounding (eg, comparability of cases and controls in studies where appropriate) | 9 |
| Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results | 9 |
| Assessment of heterogeneity | 9 |
| Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | 8-9 |
| Provision of appropriate tables and graphics | Tables 1-4<br>Figures 1-4 |
| **Reporting of results** | |
| Graphic summarizing individual study estimates and overall estimate | Figures 2-4 |
| Table giving descriptive information for each study included | Table 1 |
| Results of sensitivity testing (eg, subgroup analysis) | NA |
| Indication of statistical uncertainty of findings | Table 2-4 |
| **Reporting of discussion** | |
| Quantitative assessment of bias (eg, publication bias) | 16-17 |
| Justification of exclusion (eg, exclusion of non-English-language citations) | 16-17 |
| Assessment of quality of included studies | Table 1 |
| **Reporting of conclusions** | |
| Consideration of alternative explanations for observed results | 13-16 |
| Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) | 16 |
| Guidelines for future research | 15-16 |
| Disclosure of funding source | 16 |

*Appendix 2

1. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008-12.

Appendix S2: References of studies excluded after screening of full text

**Exclusion reasons**

**1:** Including pregnancies prior to 1995 (n=12)

**2:** ≥5% ball-and-cage valves (n=7)

**3:** Duplicate study population (n=3)

**4:** Authors unable to be contacted after reasonable attempts to clarify information relevant to inclusion criteria (n=4)

**5:** No primary outcomes of interest reported (n=1)

| Study | Reason |
|---|---|
| Al-Lawati AA, Venkitraman M, Al-Delaime T, Valliathu J. Pregnancy and mechanical heart valves replacement; dilemma of anticoagulation. European Journal of Cardio-Thoracic Surgery. 2002; 22:223-227. | 1 |
| Ashour ZA, Shawky HA, Hassan Hussein M. Outcome of pregnancy in women with mechanical valves. Texas Heart Institute Journal. 2000; 27:240-245. | 1 |
| Avila WS, Rossi EG, Grinberg M, Ramires JA. Influence of pregnancy after bioprosthetic valve replacement in young women: a prospective five-year study. Journal of Heart Valve Disease. 2002; 11:864-869. | 1, 5 |
| Ayhan A, Yucel A, Bildirici I, Dogan R. Feto-maternal morbidity and mortality after cardiac valve replacement. Acta Obstetricia et Gynecologica Scandinavica. 2001; 80:713-718. | 1 |
| Basude S, Hein C, Curtis SL, Clark A, Trinder J. Low-molecular-weight heparin or warfarin for anticoagulation in pregnant women with mechanical heart valves: what are the risks? A retrospective observational study. BJOG: An International Journal of Obstetrics & Gynaecology. 2012; 119:1008-1013; discussion 1012-1003. | 3 |
| Dong L, Shi Y, Tian Z. [The follow-up of 12 pregnant women with anticoagulation therapy after mechanical heart valve replacement]. Chung-Hua Fu Chan Ko Tsa Chih [Chinese Journal of Obstetrics & Gynecology]. 2001; 36:465-467. | 1 |
| Geelani MA, Singh S, Verma A, Nagesh A, Betigeri V, Nigam M. Anticoagulation in patients with mechanical valves during pregnancy. Asian Cardiovascular & Thoracic Annals. 2005; 13:30-33. | 1, 2 |
| Hassouna A, Allam H. Oral anticoagulation therapy during pregnancy in patients with mechanical mitral valves: a prospective study. Cardiovascular Surgery. 2001; 9:478-481. | 1 |
| Izaguirre R, De La Pena A, Ramirez A, Cortina E, Huerta M, Salazar E. Anti-Xa | 2 |

activity with low-molecular-weight heparin, enoxaparin, during pregnancy in women with mechanical heart valves. Proceedings of the Western Pharmacology Society. 2002; 45:127-128.

Kashfi F, Samiei N, Khamoushi AJ, Hosseini S, Ghavidel AA, Taheripanah R. Pregnancy after mechanical mitral valve replacement. Iranian Red Crescent Medical Journal. 2012; 14. 3

Khalil AA, Mohyuddin S, Akhtar K. Pregnancy outcome in women with prosthetic heart valves. Pakistan Journal of Medical and Health Sciences. 2012; 6:519-524. 4

Khamoushi AJ, Kashfi F, Hosseini S, Ghavidel ARA, Samiei N, Haddadzadeh M. Anti-coagulation during pregnancy in women with mechanical heart valves: A prospective study. International Journal of Fertility and Sterility. 2011; 5:47-51. 3

Lesniak-Sobelga A, Tracz W, Kostkiewicz M. Clinical and echocardiographic assessment of pregnant patients with prosthetic and homograft heart valves: Maternal and fetal outcome. Acta Cardiologica. 2007; 62:637-638. 1

Lindhoff-Last E, Schinzel H, Erbe M, Schachinger V, Bauersachs R. [Anticoagulation of pregnant women with mechanical heart valve prostheses]. Zeitschrift fur Kardiologie. 2001; 90 Suppl 6:125-130. 4

McLintock C, McCowan LM, North RA. Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin. BJOG: An International Journal of Obstetrics & Gynaecology. 2009; 116:1585-1592. 2

Plesinac SD, Darko PV, Pilic IZ, Babovic IR. Anticoagulation therapy during pregnancy of patients with artificial heart valves: fetomaternal outcome. Archives of Gynecology & Obstetrics. 2006; 274:141-145. 2

Quinn J, Von Klemperer K, Brooks R, Peebles D, Walker F, Cohen H. Use of high intensity adjusted dose low molecular weight heparin in women with mechanical heart valves during pregnancy: a single-center experience. Haematologica. 2009; 94:1608-1612. 4

Rowan JA, McCowan LM, Raudkivi PJ, North RA. Enoxaparin treatment in women with mechanical heart valves during pregnancy. American Journal of Obstetrics & Gynecology. 2001; 185:633-637. 2

Sadler L, McCowan L, White H, Stewart A, Bracken M, North R. Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. BJOG: An International Journal of Obstetrics & Gynaecology. 2000; 107:245-253. 1

Salazar E, Espinola N, Roman L, Casanova JM. Effect of pregnancy on the duration of bovine pericardial bioprostheses. American Heart Journal. 1999; 137:714-720. 5

Salehi R, Taghavi S, Imani S, Goldust M. Pregnancy in mothers with prosthetic 2

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