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Pregnancy with prosthetic heart valves — 30 years' nationwide experience in Denmark☆,☆☆

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Abstract

Objective: Pregnancy in women with prosthetic heart valves remains a risk factor for both mother and fetus, but unselected and unbiased outcome and complication data remain scarce. We analyzed nationwide outcome data from 1977 to 2007 for all pregnancies in women with prosthetic valves. **Methods:** Cardiac, obstetric, and neonatal data were obtained from obligatory databases and compared with general female population data. Questionnaires were used to corroborate important information. Outcome data were analyzed according to type of anticoagulation used. The data were compared between the two first and the last decades of the study period. In the last decade, patients were compared to an age-adjusted selected population of healthy, pregnant women. **Results:** Of 356 women between 15 and 40 years of age, 79 women had 155 pregnancies after valve replacement. Two women died during pregnancy, one from heart failure and one from post-partum bleeding. There were four thrombo-embolic episodes in the early study period in women with mitral prosthesis on unfractionated heparin. Important cardiac complications were otherwise almost absent. There were significantly more early miscarriages and terminations in patients compared with controls (last decade 34%, vs 20% ($p = 0.0036$) and 26% vs 13% ($p = 0.000019$)). Post-partum bleeding was more common in the patient group ($p = 0.0021$). Two late fetal losses (one from intracerebral bleeding) were seen. The remaining pregnancies resulted in 60 live births. Cesarean section was the predominant method of delivery in patients as opposed to controls (55% vs 16%, $p = 0.000000000097$). Premature births were more frequent in patients (49% vs 5.5%, $p = 0.00000000039$) as were congenital malformations (14% vs 5.7%, $p = 0.044$). Two of the six malformations were warfarin embryopathy (8% of all first-trimester warfarin exposures), both seen in high-risk patients on high warfarin dosing. Small for gestational age did not differ significantly from the general population (9.3% vs 6.0%, $p = 0.39$). **Conclusion:** Data acquired over 30 years confirm that women with prosthetic heart valves, especially aortic prostheses for congenital lesions, generally tolerate pregnancy well, although cardiac mortality, mortality related to anticoagulation and thrombo-embolic risks are raised. Our data provide further documentation on the significance and importance of the risks associated with predominantly warfarin-based treatment regimens, which still remains optional for a number of patients. Finally, the data also serve as a comparison for recently published series based on low-molecular-weight heparin (LMWH) regimens.

Keywords: Heart valves; Pregnancy; Anticoagulation; Embryopathy

1. Introduction

The vast improvement in the treatment of children and young adults with heart disease seen over the last decades has made issues related to pregnancy increasingly relevant, perhaps most importantly for the growing number of women with mechanical valve prostheses, who previously were often encouraged to avoid pregnancy. In these patients, counseling not only involves assessment of the cardiovascular risks associated with pregnancy but also the risks of anticoagulation, which impact importantly on both woman and fetus. The choice of anticoagulation strategy needs to be taken after thoroughly balancing the pros and cons of the various strategies individually in each patient. Although decision making should preferably be evidence based, no hard data are available as the current literature predominantly comprises relatively small retrospective studies from which guidelines have been extracted. Furthermore, the experience acquired in tertiary centers dealing with highly selected patients may bias treatment policies.

Although studies indicate that asymptomatic women with prosthetic heart valves usually tolerate the physiological burden of pregnancy [1], the risks associated with

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anticoagulation often remain of such concern that many surgeons favor the use of biological valves in young women listed for aortic valve replacement [2,3].

The objective of this study was to review the nationwide cardiac, obstetric, and neonatal experience with pregnancies in women with prosthetic heart valves in Denmark during a 30-year period.

2. Material and methods

From the National Patient Registry, which provides information on hospital contacts and survival after 1977, all female patients, who underwent aortic and/or mitral valve implantation between 1977 and 2007, were identified. From these, the subgroup most likely to have been pregnant after valve replacement, that is, those who survived to childbearing age arbitrarily defined as age between 15 and 40 years, were extracted. Information on pregnancies lasting more than 22 weeks was retrieved from the National Birth Registry.

To corroborate the database information, questionnaires were sent to all survivors, specifically addressing pregnancy history, including number and year of abortions (including terminations), number and year of pregnancies, modes of delivery, birth weights, perinatal complications, anticoagulation scheme used during each pregnancy, and congenital malformations in live-born children. If applicable, women were asked to define the reasons for not attempting pregnancy.

Using a cross-reference of the data provided by the questionnaires and the National Birth Registry, the group of women, who became pregnant after valve implantation, was identified. Chart data regarding primary operation, subsequent cardiology follow-up, and individual pregnancies were reviewed. Information on the anticoagulation strategy used during each pregnancy was sought from hospital notes and questionnaires. This information could mostly be determined for pregnancies lasting more than 22 weeks.

For the pregnancies, subgroup analysis of events based on the following four anticoagulation strategies was performed: (1) warfarin or phenprocoumon (used in the early study period) throughout pregnancy, (2) warfarin or phenprocoumon substituted by unfractionated heparin or low-molecular-weight heparin (LMWH) between weeks 6 and 12 of pregnancy, (3) unfractionated heparin (predominantly used in the early study period) or LMWH throughout the pregnancy, or (4) no anticoagulation (biological valves).

Information on adverse cardiac, obstetric, and neonatal events observed up to 3 months post-partum was included. Cardiac events were defined as cardiac death, as cardiac conditions requiring hospital admission and as thromboembolic complications including transient cerebral ischemia, stroke, and myocardial infarction. Obstetric events were defined as spontaneous abortion, terminations, peripartum bleeding with or without the need for blood transfusion, and as emergency cesarean section (defined as non-elective cesarean section for whatever indication). Neonatal events included premature birth (before 36 weeks of gestation), small for gestational age (SGA), that is, birth weight below 2 standard deviations of normal [4], intraventricular hemorrhage, fetal death (after 22 weeks), neonatal death (within the first 28 days), and congenital malformations of all causes, including warfarin embryopathy.

For each pregnancy occurring in the past decade and extending beyond 22 gestational weeks, a control group of 10 randomly chosen pregnancies during the same decade with the same maternal age was drawn from the National Birth Registry. Information on neonatal and obstetric events, excluding spontaneous abortions, was also available in the controls.

2.1. Statistics

Incidences were characterized by percentages. Continuous variables were characterized by medians and interquartile ranges (IRs).

For continuous outcomes, the difference within the study group and between the study and control group was assessed by a three-way analysis of variance taking matching and clustering within patients (in patients with multiple pregnancies) into account. For binary outcomes, a logistic regression with the same structure was performed and adjusted for matching and clustering. The assumption of normality was assessed by visual inspection of residuals.

Table 1. Valvular (accessed December 2010) lesions, prosthesis position and valve types in the 79 patients with a total of 41 aortic, 38 mitral and 3 unknown valves.

Lesion type Number (% of patients)	Position	Number (% of patients)	Valve type[a]	Number (% of patients)
Congenital 56 (71)	Aortic	33 (42)	Mechanical	28 (35)
			Biological	5 (6.3)
	Mitral	20 (25)	Mechanical	20 (25)
	Combined	3 (3.7)	Mechanical	3 (3.8)
Acquired (rheumatic, endocarditis, etc.) 20 (25)	Aortic	5 (6.3)	Mechanical	4 (5.1)
			Biological	1 (1.3)
	Mitral	10 (13)	Mechanical	10 (13)
	Combined	5 (6.3)	Mechanical	5 (6.3)
Unknown 3 (3.7)		3 (3.7)		

[a] Mechanical valves (n = 70, 89% of patients) were St. Jude (n = 22, 31%), Carbomedics (n = 9, 13%), Sorin (n = 1, 1.4%), Björk-Shiley (n = 1, 1.4%) and unknown (n = 35, 50%).Biological valves (n = 6, 7.6%) were Carpentier–Edwards (n = 4, 66%), and unknown (n = 2, 33%).

Table 2. Cardiac, obstetric and neonatal events in the study group (155 pregnancies and 62 births). Numbers (%).

Period	Total study group 1977–2007	Study group 1977–1997	Study group 1997–2007	p value*
Pregnancies/births	155/62	48/20	107/42	
Cardiac events				
Cardiac death[b]	2 (1.3)	0 (0)	2 (1.9)	0.69
Thrombo-embolism	4 (2.6)	3 (6.3)	1 (0.9)	0.22
Other[a]	3 (1.9)	0 (0)	3 (2.8)	0.33
Obstetric events				
Miscarriages	51 (33)	15 (31)	36 (34)	0.50
Induced abortion	42 (27)	14 (29)	28 (26)	0.47
Post-partum bleeding	9 (15)	4 (21)	5 (12)	0.27
Emergency cesarean section	12 (19)	2 (11)	10 (23)	0.21
Neonatal events				
Premature birth	25 (40)	4 (21)	21 (49)	0.11
Neonatal death	1 (1.6)	0 (0)	1 (2.3)	0.69
SGA[c]	6 (9.7)	2 (11)	4 (9.3)	0.60
Malformations	6 (9.7)	0 (0)	6 (14)	0.099

[a] Heart failure, pulmonary edema or atrial fibrillation.
[b] One patient with fatal bleeding due to warfarin treatment.
[c] Small for gestational age.
* Difference between 1977–1997 and 1997–2007 study groups.

3. Results

Of the 6594 women, who had valve replacements during the study period, 356 (5.4%) matched the age criteria. Seventy-nine (22%) underwent a total of 155 pregnancies, whereas 181 (51%) had never been pregnant of whom 20 had been advised against pregnancy. There were 48 pregnancies during the first 20 study years (1977–1997), but 107 during the last decade.

Questionnaires were sent to the 269 survivors, of whom 181 (67%) responded.

Underlying valve disease and type of implanted valve in the 79 patients is summarized in Table 1. The majority had congenital lesions. Only six patients had bioprosthetic valves. Median age at surgery and at pregnancy was 28 (IR 22–38) and 30 (IR 27–34) years, respectively. Three of 70 women with mechanical valves (4.3%) required valve replacement 3, 8, and 13 years later, whereas two of the six with a bioprosthesis (33%) underwent valve replacement early post-partum (1 month, 1 year).

3.1. Cardiac, obstetric and neonatal events

Cardiac, obstetric, and neonatal events in the study group and control group are seen in Tables 2 and 3.

There were two maternal fatalities of which one was anticoagulation related. Both occurred in women with mechanical aortic prostheses. A 26-year-old woman died from bleeding in 2004, 3 days after an uneventful cesarean section at 35 weeks for ruptured membranes performed in her local hospital. Enoxaparin (1 mg kg^{-1} bid) was given for the last 3 weeks of pregnancy and continued post-partum when warfarin was added within 24 h after delivery. The other patient died in 2008 from rapidly progressive and irreversible left-heart failure at 27 weeks, 2 years after valve replacement. She was asymptomatic at pre-pregnancy counseling with a reasonable exercise tolerance (nine metabolic equivalent of tasks (METs), moderately reduced left-ventricular function (ejection fraction 40%), mild pulmonary hypertension, and a peak aortic gradient of 52 mm Hg. The baby succumbed 20 h post-partum and represents the only infant mortality in the study.

Table 3. Comparison of the 1997–2007 study group and control group. Numbers (%).

Pregnancy/birth	Study group 107/42	Control group 625/420	p value
Miscarriage	36 (34)	123 (20)	0.0036
Induced abortion	28 (26)	82 (13)	0.000019
Post-partum bleeding	5 (12)	18 (4.3)	0.0021
Emergency cesarean section	10 (23)	12 (2.9)	0.000014
Premature birth	21 (49)	23 (5.5)	0.00000000039
Neonatal death	1 (2.3)	5 (1.2)	0.54
Fetal death	2 (4.7)	4 (1.0)	0.065
SGA[a]	4 (9.3)	25 (6.0)	0.39
Malformations	6 (14)	25 (5.7)	0.044

[a] Small for gestational age.

There were four thrombo-embolic episodes (in 1988, 1989, 1996, and 1998), all in women with mitral prostheses on unfractionated heparin. Information on exact heparin dosage and activated partial thromboplastin time at the time of the insults was not available. One poorly compliant woman had a stroke at 21 weeks, while two patients suffered transient cerebral ischemia at weeks 27 and 39, respectively. Finally, a 20-year-old woman with an iatrogenic lesion to the circumflex artery during valve replacement 12 years earlier had an inferior myocardial infarction at 20 weeks of pregnancy.

The rate of miscarriages was fairly static throughout the study period (Table 2), but much higher compared with healthy controls (34% vs 20%) as seen in the last decade (Table 3). The relative number of terminations was similarly raised in the patients, and, during the last decade, was virtually twice the rate in controls (Tables 2 and 3).

There were two late intrauterine fetal deaths during the 30 years. Both occurred during the last decade in patients on warfarin at the time of fetal demise. One fetus had an intracerebral hemorrhage at 34 weeks (in 1999) in a woman with an aortic prosthesis. The other occurred at 31 weeks (in 2007) in a woman with a mitral prosthesis. Although autopsy revealed growth retardation and signs of warfarin embryo-

pathy, a definite cause for this outcome could not be established. It was, however, decided to include the case as potentially warfarin associated.

Twenty-eight infants (45%) were delivered vaginally and 34 (55%) by cesarean section, making this the most frequent method of delivery in patients as opposed to controls (55% vs 16%, $p = 0.000000000097$).

Post-partum bleeding was seen in more than 10% of the patients (Table 2), and, in the most recent decade, was threefold higher than in controls (12% vs 4.3%, $p = 0.0021$). In the last decade, bleeding was more prevalent after vaginal delivery (18% vs 4.5%, $p = 0.060$), but not significantly increased after cesarean section (12 vs 3.1%, $p = 0.21$).

The dominant neonatal event was prematurity (Table 2), and, in the most recent period, nearly half were delivered prematurely compared with only 5.5% in the controls. For this reason, gestational age was significantly lower in the patient offspring (259 days (IR 244–272) vs 282 days (IR 273–288), $p = 0.000032$). One-third of the premature infants were delivered vaginally compared with half of those born at term (33% vs 50%, $p = 0.83$).

In the last decade, growth retardation (SGA) as well as neonatal mortality was similar in the study (9.3% vs 6.0%, $p = 0.39$) and control groups (2.3% vs 1.2%, $p = 0.54$). SGA was, however, exclusively seen in women with mechanical valves. At the time of delivery, 34 (56%) patients were either on unfractionated or LMWH, while 17 (28%) were on warfarin. Six patients with biological valves were not anticoagulated, and, in five patients, the anticoagulation status at the time of delivery could not be established.

The only infant mortality occurred in the woman, who died from heart failure.

The incidence of all-cause congenital malformations was higher in the patient offspring, for example, in the last decade: 6 (14%) versus 25 (5.7%) ($p = 0.044$). Only one child and the fetus described above were reported to have signs of warfarin embryopathy, which translates to an overall incidence of 8% (2 of the 25) exposed to vitamin K antagonists during weeks six through 12. Both were seen in women with mitral prostheses and high, daily, warfarin requirement (10–12.5 mg). Following detailed preconception counseling, both elected to continue warfarin treatment as they were considered at high risk of valve thrombosis. Other malformations included two cases (out of 25) in the warfarin-only group (one with a ventricular septal defect (VSD) and one with a VSD, an atrial septal defect (ASD), and a pulmonary stenosis) and one (vaginal and anal atresia) out of the 23 in whom warfarin was transiently changed to heparin during the first trimester. An ASD was also seen in one of the six patients, who were not anticoagulated.

Apart from thrombo-embolism, which was only seen with unfractionated heparin, none of the other predefined adverse events could be linked to any specific type of anticoagulation. Table 4 summarizes events according to the method of anticoagulation used.

Based on the predefined events, a subgroup analysis comparing biological versus mechanical valves and mitral versus aortic valves was performed. No significant difference in adverse events was identified, but subgroup numbers were small and statistical power clearly reduced. The six women with aortic bioprostheses, and, thus, no need for anticoagulation, did extremely well with four women giving birth to six healthy children (1989–2005). The remaining two women had three terminations (for non-cardiac reasons) and two miscarriages, respectively. Two did, however, require re-operation within the first 12 months post-partum.

4. Discussion

As more children and young adults with prosthetic heart valves survive to childbearing age [5], the need for optimal preconception counseling becomes increasingly relevant. Unfortunately, only few and mostly small series [1,6–9] comprise the basis from which current guidelines and recommendations are extracted [10,11]. Although our study appears small, it comprises one of the largest series published, covers 3 decades and the whole Danish population, that is, predominantly patients with congenital and other non-rheumatic valve lesions. As expected, the absolute number of pregnancies seen during the last decade was more than double the number seen during the first 2 decades under study.

Of the eligible women that included females down to 15 years of age, almost half had never been pregnant. Most patients had mechanical valves as the general policy was and to some extent still is to favor these valves, while accepting the potential problems associated with pregnancy.

Whereas significant cardiovascular problems such as pulmonary edema and heart failure in previous reports have been reported in up to 27% [12] of pregnant women with mechanical valves, the low incidence of cardiac events seen in this study confirms that relatively low-risk patients can be identified before pregnancy [1,6]. Although a restrictive preconception screening policy clearly will reduce the incidence of serious cardiac events during pregnancy, the fact that only 10% of patients were advised against pregnancy supports that counseling was not too restrictive. The final decision to pursue pregnancy lies, however, with the patient and her partner, and some women are willing to trade a slightly higher risk of pregnancy-associated problems for motherhood. If so, this will, of course, negatively influence outcome data as seen for with the two cases with warfarin embryopathy.

Maternal mortality remains the most devastating complication, and even contemporary series confirm that neither mortality nor near-misses can be not necessarily avoided [13–15]. The overall mortality in this study was 3.3%. Although the mortality rate appears small compared with previous reports [1,16], it remains more than 400 times higher than currently seen in the general population [17]. However, simply comparing mortality in this patient group with healthy controls may not be appropriate as young patients with significant cardiac problems *per se* will have higher mortality rates, irrespective of pregnancy and anticoagulation [5]. The woman who died in her local hospital from bleeding after a cesarean section represents the only fatal case seen in 149 pregnancies (0.67%) directly related to anticoagulation. The other woman died from progression of pre-existing mild heart failure. Both cases could theoretically have been avoided and mortality thereby reduced. As a direct consequence of the first case, all women now deliver in

Table 4. Cardiac, obstetric and neonatal events stratified to anticoagulation regimens. Numbers (%).

	Warfarin throughout	Heparin throughout[a]	Warfarin substituted for heparin[b] at week 6–12	None
Number	25	8	23	6
Cardiac events				
Cardiac death[c]	0 (0)	1 (13)	1 (4.3)	0 (0)
Thrombo-embolism	0 (0)	3 (38)	1 (4.3)[d]	0 (0)
Other[e]	1 (4.0)	2 (25)	0 (0)	0 (0)
Obstetric events				
Post-partum bleeding	2 (8.0)	1 (13)	5 (22)	1 (17)
Emergency cesarean section	5 (20)	1 (13)	6 (26)	0 (0)
Neonatal events				
Premature birth	10 (40)	2 (25)	5 (22)	0 (0)
Neonatal death	2 (8.0)	0 (0)	0 (0)	0 (0)
Fetal death	1 (4.0)	0 (0)	1 (4.3)	0 (0)
SGA[f]	3 (12)	1 (13)	2 (8.7)	0 (0)
Intracranial bleeding	0 (0)	1 (13)	0 (0)	0 (0)
Malformations	1 (4.0)	0 (0)	0 (0)	0 (0)

[a] Five women treated with unfractionated heparin and three with LMWH.
[b] Unfractionated or LMWH.
[c] Including one patient death from fatal bleeding.
[d] The patient was treated with unfractionated heparin at the time of the thrombo-embolism and subsequently switched to warfarin.
[e] Heart failure, pulmonary edema or atrial fibrillation).
[f] Small for gestational age.

tertiary centers and reintroduction of warfarin is usually deferred in those who deliver by cesarean section, while on heparin, as previously suggested [14]. Thrombo-embolic complications were rare and only seen in women with mitral valve prostheses on unfractionated heparin. Most occurred during the first two 'historic' decades when heparin dosing was lower than currently recommended [11], and one was clearly related to non-compliance, which, even in contemporary series, remains a major issue [18]. The overall thrombo-embolic complication rate of 38% in the heparin-only treated pregnancies compares well with earlier reports [16,19]. Interestingly, only one assumed-but-not-proven embolic episode (acute myocardial infarction) occurred in the 107 pregnancies seen during the last decade, which suggests that dosing and monitoring have improved over time.

The risk of early miscarriage clearly exceeded the 20% seen in the control group and previously reported in Denmark [20]. Although this risk does not exceed the currently observed risk of abortion in some other women with complex congenital heart [21], it appears higher than previously reported in women with mechanical valves [16,22]. The acquisition of reliable data on spontaneous abortions is, however, fraught with difficulties, especially in retrospective studies. The fact that the number was drawn from a nationwide obstetric database corroborated by questionnaires makes our data perhaps the most reliable hitherto published. Unfortunately, our data did not allow analysis of whether the type and dose of anticoagulation used at the time of early abortion (before 22 weeks) was of importance. Whereas previous studies [16] have, however, failed to link any specific anticoagulation strategy with a particularly high miscarriage rates, recent experience with LMWH in the current era indicates that this problem largely can be avoided [14,15].

The reasons for the very high number of first-trimester terminations (twice as high as in controls) seen throughout the whole study period remain speculative. Early (within 12 weeks) interruptions are legal and generally performed on maternal and rarely on medical request. It was considered inappropriate to address this issue in the questionnaire, although this would have provided some information on this important issue. As only very few women were advised against pregnancy, even minor medical concerns or misconceptions raised by the general practitioners, general obstetricians, generally trained cardiologists, and/or patients may have influenced decision making negatively, particularly in the early study period when a large number of women were seen outside the specialized centers.

Late fetal attrition was not significantly higher in patients than in the controls, and possibly lower than reported in contemporary series predominantly based on LMWH regimens [14,15,18]. Although warfarin clearly was causative in the fetus with intracranial bleeding, the cause of death in the other fetus remained unclear although it did exhibit signs of warfarin embryopathy. The observation of only one fetus with an intracerebral hemorrhage over a period of 30 years indicates that this feared complication is rare, although minor sub-clinical bleeds may have been undiagnosed.

The high incidence of cesarean sections undoubtedly reflects the misconception that vaginal delivery poses a much higher risk than cesarean section, but perhaps also concerns that any peripartum bleeding could be more safely, if surgically, controlled. Hopefully, the increasing number of these patients and centralization to highly specialized centers with multidisciplinary teams will reduce the number of cesarean sections.

Although elective cesarean sections usually were scheduled to week 37, this only partially explains the 35% incidence of prematurity, as up to a third of all premature deliveries were spontaneous. As the significance of reducing prematurity for only a few days was not previously considered important, early induction 'for safety reasons' could account for some of the excess prematurity. Although previous studies have demonstrated a correlation between premature labor, low birth weight, and the presence of a prosthetic mitral valve [13], this does not imply that this association is mechanistic. We could not demonstrate any significant

correlation between prematurity and method of anticoagulation or valve type.

Intrauterine growth retardation or 'small for gestational age' defined as a birth weight below two standard deviations of normal for gestation was not different from controls. Interestingly, five of the six growth-retarded infants had been exposed to warfarin, of which only one had signs of warfarin embryopathy. A similar observation has previously been reported [18,23] but remains unexplained, particularly as the generally excellent cardiovascular status of the mothers seemed unlikely to impair fetal growth.

Warfarin embryopathy remains the single, most-feared fetal complication to early warfarin exposure. The incidence has been reported to range from 0% [7] to 30% [8], perhaps higher if detailed assessment of all fetuses is performed [2]. This variation may largely be related to drug exposure, as embryopathy is unlikely to occur with daily doses below 5 mg [9]. Traditionally, American experts have advised against the use of warfarin during weeks six through 12 [24], whereas European experts have found the risk of embryopathy overrated [10], especially in women on low doses. In addition, apart from the stillborn fetus with signs of embryopathy mentioned earlier, only one additional case was seen in this series. Both occurred in high-risk women with mitral prostheses, who, despite high warfarin doses, accepted the potential risks to the fetus. In all other cases, in whom warfarin was given during the first 3—4 months of pregnancy, treatment was successfully tailored in each patient, with no child being registered with embryopathy. We believe that there are some high-risk patients in whom the maternal risks of switching to heparin may outweigh the fetal risk. This may, however, change if other treatment options, preferably in randomized trials, confirm sufficient maternal safety.

The apparently slightly increased number of congenital malformations was primarily driven by minor cardiac defects. As most of the mothers had congenital heart disease themselves, inheritance, known to be important for these disorders, could well be explanatory for the observations made.

LMWH has, for a number of reasons, attracted much attention as a universally applicable regimen for all pregnant women with mechanical heart valves [14—18]. Encouraging data with strict monitoring of anti-Xa levels are now available [15], and LMWH is increasingly used and recently recommended as one of three therapeutic regimens in official US guidelines [25]. Unfortunately, this strategy does not completely prevent either fetal or maternal complications, including maternal mortality [14,18]. The fact that none of the three women in our cohort, who received LMWH, had complications does not provide sufficient safety, as all had mechanical aortic valves and as treatment was not consistently anti-Xa monitored.

Clearly, primary use of bioprostheses for aortic lesions will preclude any maternal and fetal complications associated with anticoagulation, but at the expense of an increased need for re-operations.

4.1. Limitations

Although the study represents 30 years' nationwide experience, the number of patients is limited and detailed subgroup analyses consequently impossible. Similarly, the incomplete information on treatment intensities and monitoring remains important. Although extrapolation of some of these 'historic' data may seem inappropriate, they are still within the frames of current recommendation, and, thus, representative of risk and concerns of the treatment options still widely in use. The previously often-decentralized perinatal treatment strategy used in the country undoubtedly tends to worsen outcome data, as did the insufficient heparin dosing previously used. Nevertheless, all episodes even vaguely related to treatment failure, such as poor compliance, were included to avoid underestimating any risk. This also applies to the fetal complications. A clearly detailed follow-up of all children for minor cerebral bleeds or minor features suggestive of warfarin embryopathy may have increased the number of complications, although the clinical significance of these at present is unclear.

5. Conclusions

Comprehensive data acquired over 30 years with different and individualized anticoagulation strategies confirm that women with prosthetic heart valves, especially aortic prostheses for congenital lesions, overall tolerate pregnancy well, although cardiac mortality, mortality related to anticoagulation, and thrombo-embolic risks are raised compared with healthy controls. Fetal complications primarily comprise increased numbers of miscarriages, and also growth restriction possibly linked to the use of vitamin K antagonists. Warfarin embryopathy was, however, only seen in a few high-risk patients on continued high-dose warfarin. Although aortic bioprostheses clearly would preclude complications related to anticoagulation in some patients at the expense of an increased need for re-operations, a number of women with mitral valve prostheses will still require anticoagulation. Our data provide further documentation on the significance and importance of the risks associated with predominantly warfarin-based treatment regimens, which still remain optional for a number of patients. Finally, the data also serve as a comparison for recently published series based on LMWH regimens.

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Appendix A. Conference discussion

Dr G. Laufer (*Vienna, Austria*): I think this is a very important piece of work covering about 30 years of mechanical valve and biological valve implantation in young female patients.

When I look at the methods you have used in your manuscript, it is clear that with covering such a long period of time, only a retrospective approach is possible. However, I will question this methodology, because, first of all, it goes back to the very early days of heart surgery, back to the very beginnings in 1977 when techniques and treatment were not standardised at all and heart surgery was in the pioneer era.

Secondly, how accurate is your research in terms of going back to government databases? You have to rely on databases that have not been generated by medical professionals, so how accurate are these data really?

You mentioned in your conclusion to the paper, which was not shown in your presentation, that a mechanical valve prosthesis should be used in young females of childbearing age. How did you come to this conclusion? In contrast, I would recommend in young females needing an aortic valve replacement a Ross operation instead of having a mechanical valve implanted!

Dr Sillesen: As I understand you, the first question you have is why we would recommend mechanical valves in favor of a biological valve or the Ross procedure.

First of all, I think it's important to understand that the patients we're dealing with here actually had a median age at the time of operation of about 28 years. So this is not actually primarily paediatric or, for that matter, a young adult population, this is a fully grown population.

With that, I would absolutely agree with you that the Ross procedure is obviously a very good choice for these patients or the younger patients. However, we also must be aware of the fact that the Ross procedure is very dependent on the surgeon and the setup. So if we do not have sufficient resources or the right surgeon to perform the Ross procedure, this might in itself be a dangerous venture. If we do have the right resources, obviously it's a very good choice.

We must also appreciate the fact that pregnancy in the setting of a Ross procedure is actually not very well described in the literature. I was able to find two abstracts, two case presentations, one from 2003 and one from 2009, describing successful pregnancies in Ross patients. But that is basically the material that we have. So we don't really know how the patients or, for that matter, the fetuses fare in the case of a Ross procedure.

Your second question, why we would prefer mechanical valves over biological valves. I think the conclusion in our paper is actually not that we would prefer one or the other. I think what we're trying to come across with as a conclusion is that the idea that has been prevalent before, that mechanical valve and pregnancy was basically contraindicated, may be not such a big problem. So that mechanical valve patients can contemplate pregnancy if a careful preconception screening is applied. But obviously, if you do have a biological valve, then the risk of anticoagulants and all that is non-existent. Whether pregnancy accelerates the degeneration of a biological valve is really not established yet, so from our perspective I'd say that the mechanical valve is probably the safer option because we have data supporting that it can actually be done if we do really rigorous preconception screening.

Dr Laufer: If you'll allow me a last question, and that refers to the high-risk period between week 6 and week 12. If you have a female patient with a mechanical mitral valve prosthesis being at high risk for thromboembolic events because of AF, huge left atrium, spontaneous contrast on echo in the left atrium, what type of anticoagulation would you recommend in this period?

Dr Sillesen: In the setting where the clinical features necessitate the use of a high dose of anticoagulants, we would definitely recommend switching from warfarin to probably low molecular weight heparin.

Now we're moving into an area of controversy here because low molecular weight heparin is not really that well examined in the setting of pregnancy and a prosthetic heart valve. But evidence is actually coming along that it might be a good option if sufficient dosing monitoring is applied, that is, we monitor anti-factor Xa levels. But if we don't do that, then it is definitely a very risky venture.

I think I skipped the first of your questions concerning the retrospective nature of our data: if I can just address that. It's important to realize as well that the burden of our pregnancies was actually in the last decades: 107 of our pregnancies were in the last decade, and most were on contemporary valves. So you're right that this is historical data, but most of it is actually in the last decade.

And besides looking at data from the hospital databases, we also did chart reviews and sent out questionnaires to the relevant patients. So there are certain limitations in a retrospective study, naturally, but we tried to work around that as well as possible with the relevant data basically being short.