

REVIEW

Anticoagulants in pregnancy

Celia M Oakley

Increased concentration of circulating clotting factors, faster platelet turnover, and reduced fibrinolytic activity all contribute to the hypercoagulable state in pregnancy.^{1,2} The thrombotic tendency is offset by an increased cardiac output and more rapid circulation time but the risk of leg vein thrombosis,³ left atrial thromboembolism in mitral stenosis, and thrombosis on prosthetic cardiac valves is increased.⁴

Anticoagulant drugs are essential for the prevention of potentially fatal maternal thromboembolic events and the indication for these drugs must therefore be the same in pregnancy as outside it, despite possible risks to the fetus. Controversy continues concerning the magnitude of these risks and the choice and usage of anticoagulants in pregnancy.

Heparin⁵

Heparin is a natural water soluble mucopolysaccharide first introduced for clinical use nearly 80 years ago to prevent postoperative thrombosis. Commercial heparins are obtained from porcine gut or bovine lung tissue and have molecular weights of up to 40 000 daltons. Low molecular weight heparins of only 3200–6500 daltons were introduced in the hope of reducing adverse side effects. Heparin does not cross the placenta but needs to be given parenterally and its antithrombotic effect is difficult to maintain without bleeding complications.

The dose of heparin required to prevent arterial thrombosis or prosthetic valve thrombosis is higher than that needed to prevent venous thromboembolism. With long-term treatment there is a risk of haemorrhage. Side effects include thrombocytopenia, particularly if bovine heparin is used. Two types of thrombocytopenia occur. The first, occurring 3–5 days after treatment starts, is usually transient, the patient is symptom free, and the platelet count often returns to normal despite continuing heparin treatment. Although this thrombocytopenia is thought to be caused by heparin induced platelet aggregation, it is rarely associated with thromboembolism. The second type of thrombocytopenia, which develops after about 6 days of treatment, is more serious. It often results in a profound fall in the platelet

count as well as thromboembolic complications in 50% of patients and heparin should be stopped. The overall incidence of thrombocytopenia seems to be reduced with the low molecular weight heparins that cause less platelet aggregation. Heparin can also induce osteoporosis when it used long term. The mechanism of this is unknown. It has been reported most often in pregnant women perhaps because they are more likely to have had long-term treatment. Other side effects include hypersensitivity such as urticaria, bronchospasm, and anaphylaxis.

The dose is judged by the activated partial thromboplastin time (APTT), the kaolin cephalin clotting time, or the plasma heparin concentration. The frequency of testing depends on the route of administration and type of heparin, and regular blood counts are required to detect thrombocytopenia.

Oral anticoagulants⁵

Dicoumarol causes bleeding in cattle that eat improperly cured sweet clover hay. Several new coumarins have been synthesised—warfarin is the most frequently used. Warfarin acts by inducing a functional deficiency of reduced vitamin K. The coumarin oral anticoagulants have a bad reputation in pregnancy because skeletal abnormality and central nervous system defects were reported in some of the infants of mothers given such drugs during early pregnancy. Warfarin may cause “coumarin embryopathy”⁶ (chondrodysplasia punctata) if prescribed in the first trimester. In addition there is a risk of intracerebral bleeding caused by fetal overdose. It has a stronger anticoagulant effect in the fetus than in the mother because the immature fetal liver produces low concentrations of vitamin K dependent clotting factors and because the maternal procoagulant factors are too large to cross the placenta. The risk to the fetus is dose dependent and therefore will vary with the highly variable maternal dose requirement.

Venous thrombosis

The increased blood volume in pregnancy is mainly accommodated in dilated veins.⁷ Venous return from the legs is slowed especially in later pregnancy and cardiac output is

reduced in the supine position because the inferior vena cava is compressed by the uterus. This contributes to the development of varicose veins, pedal oedema, and venous thrombosis. The increased risk of venous thrombosis persists for up to a month postpartum and the thromboembolic risk is higher after caesarean delivery.³

Every calf vein thrombosis carries a risk of pulmonary embolism by extension into the larger proximal veins and in one early report when anticoagulants were not used maternal mortality was 15%.⁸ The need for anticoagulants is underlined by another study which showed that women with previous deep vein thrombosis or pulmonary embolism had a 12% risk of recurrence.⁹

Calf vein thrombosis may be treated with short-term heparin but recurrence, ileo-femoral thrombosis, or pulmonary embolism in pregnancy need longer term treatment. Full anticoagulant doses of heparin in hospital are usually followed by prophylactic dosage throughout the remainder of the pregnancy.¹⁰ The risk of extension of venous thrombosis is high after heparin is stopped because fibrin-bound thrombin is not inactivated and continues to exert its procoagulant effect.

Rheumatic heart disease

Most patients with rheumatic heart disease are young and therefore still in sinus rhythm when they become pregnant. Only a few are in atrial fibrillation with large left atria that require chronic oral anticoagulant treatment. Patients who are in stable sinus rhythm with no history of previous atrial fibrillation are not given anticoagulants but patients with mitral stenosis run an increased risk of left atrial thrombus formation in pregnancy despite maintenance of sinus rhythm.

Prosthetic valves

In patients with cardiac valve prostheses pregnancy increases the risk of thromboembolic complications.¹¹⁻²⁹ Such women need scrupulous treatment with anticoagulants. The risk is greater for mechanical valves and for mitral valves compared with aortic valves. Women with bioprostheses are also at risk,³⁰ particularly if they are in atrial fibrillation or have large left atria or a history of thromboembolism. The appearance of spontaneous echo contrast ("smoke") within the left atrium is evidence of an increased thromboembolic risk.³¹

Patients with all currently available mechanical valves require lifelong anticoagulation but there are considerable differences in thrombogenicity among the various prostheses. Even bioprostheses are affected by thrombus deposition, showing a gradation of thrombogenicity from homografts and pulmonary autografts through pericardial valves to porcine valves. The risk of thrombosis also varies with the site of attachment of the prosthesis (tricuspid, mitral, or aortic—in that

order) and with the level of anticoagulation.³²

Major bleeding complications in non-pregnant patients with prosthetic valves are more common in the United States, where the dose is higher, than in the United Kingdom and Europe.^{32,33} Most of the conventional North American thromboplastins have an International Sensitivity Index (ISI) of between 1.7 and 2.8. This means that the International Normalised Ratio (INR), which is equivalent to a prothrombin time (PT) ratio of 1.8, lies between 2.7 and 5.2 and PT ratios between these limits might be equivalent to INRs between 5.0 and 10.0. These differences make the early reports of oral anticoagulants during pregnancy impossible to interpret. Most later personal series have come from countries with a continuing high incidence of rheumatic heart disease where good anticoagulant control is often difficult.

The risk of fetal damage caused by coumarin drugs given in pregnancy has probably been exaggerated³⁴⁻³⁶ and it is likely that disaster rather than success determined the reporting of anecdotal cases. Salazar's group, from the National Institute of Cardiology in Mexico, looked at the maternal and fetal complications of giving a subcutaneous fixed dose of heparin (5000 units every 12 hours) in the first trimester and last two weeks of pregnancy.^{22,23} Three of their patients had massive thrombosis of the prosthetic valve, two in the first trimester and one in the immediate postpartum period. The incidence of spontaneous abortion was just as high in 23 patients transferred to heparin from the sixth to the twelfth week (12 from only the seventh week) as in 37 pregnancies in which coumarin continued throughout. No coumarin embryopathies were seen in the infants of women who were treated with heparin from the sixth to the twelfth week but two out of eight live born infants whose mothers had received heparin from seventh to twelfth week were affected, as were eight out of 27 live born infants of mothers treated with coumarin until the last two weeks of pregnancy. These children, however, were assessed by a clinical geneticist who found facial defects such as slight nasal hypoplasia: no children had epiphyseal stippling, central nervous system abnormalities, or optic atrophy.

Ben Ismail *et al* reported the difficulties of achieving accurate anticoagulation in Tunisia.¹⁸ Two out of five women given heparin had thromboembolic episodes and three had spontaneous abortions. Oral anticoagulants were given during 53 pregnancies: there were eight spontaneous abortions but no embryopathies. Ben Ismail *et al* did not think that use of heparin in the first trimester was justified.

Forty seven pregnancies in 37 patients with prosthetic valves were reported from India.²⁷ Oral anticoagulants were continued throughout pregnancy and replaced by heparin before labour. Forty infants were born at full term and three were premature. There were two spontaneous abortions, one stillbirth, and one

ectopic pregnancy—a total fetal mortality of 8.5%. Valve thrombosis developed in two patients but surgical intervention was successful in both and one of the pregnancies continued to term. There were no embryopathies.

Sareli *et al* reported no maternal thromboembolic complications or deaths among 49 South African patients with 60 mechanical valves who were treated with warfarin.³⁷ Because of late presentation no patient had received heparin in the first trimester: in 23 heparin replaced warfarin at 36 weeks and there was one stillbirth. The remaining 18 patients went into labour prematurely while they were still taking warfarin: there were six stillbirths. Two warfarin embryopathies were seen (4%) with nasal hypoplasia in both infants and stippled epiphyses in one. Two neonatal deaths were caused by intracranial haemorrhage in premature babies whose mothers were still taking warfarin (INR 4.2 and 3.2). The high incidence of premature labour and low birth weight was similar to that already reported in valve disease. There was no relation between haemodynamic status and fetal outcome. Sareli *et al* concluded that with the new generation mechanical valves (Medtronic Hall and St. Jude Medical) the maternal risk is low and, although fetal wastage is high, the risk of malformation in live born infants is low.

No major cardiac centre in the western world sees enough young women with prosthetic valves to be able to gain a large experience of the use of oral anticoagulants in pregnancy under optimal circumstances. The reports from the developing world have been encouraging and results are likely to be even better with improved anticoagulant management. Experience with mechanical valves in pregnancy has been reduced in North America and in Europe by selection of bioprostheses in young women as well as by cautioning women with mechanical heart valves against pregnancy.

Two recent European surveys have compared the outcome with different regimens of warfarin or heparin.^{38,39} The limitations of the surveys were that they were retrospective (by questionnaire) and so may have been biased and that the levels of anticoagulation actually achieved could not be fully assessed; however, the quality of anticoagulant control was likely to have been high. Sbarouni and I found 14 valve thromboses among 133 patients with mechanical valves: 11 occurred during heparin treatment, two during warfarin, and one while no anticoagulant was being taken.³⁸ There were major complications from either bleeding or thrombosis in 16 of the 34 pregnancies treated with heparin throughout.³⁸ In Hanania *et al*'s study 10 mechanical valve thromboses were reported among 108 mechanical valves.³⁹ Six of the patients were on heparin, two were unsatisfactorily controlled on an oral anticoagulant, and two were not on any anticoagulant at the time. The thromboembolic risk was 4.5 times higher for women on heparin than for women

taking an oral anticoagulant. Wang *et al* reported five thromboembolic events in ten patients treated with subcutaneous heparin (5000 intravenously twice a day) during the first trimester. Iturbe-Alessio *et al*, Larrea *et al*, and Vitali *et al* also reported valve thromboses, all occurring while their patients were on heparin (in three, three, and two cases, respectively, with five deaths).^{20,23,25}

Transfer from oral anticoagulants to heparin in pregnancy has been widely advocated⁴⁰⁻⁴⁴ but no published series justifies this practice. Low dose heparin carries a grave risk of valve thrombosis whereas high doses over a long period when the patient cannot be retained in hospital for observation carry a risk of serious maternal haemorrhage and a considerable risk of fetal death or prematurity caused by retroplacental haemorrhage. It is virtually impossible to achieve continuous anticoagulant control within the very narrow therapeutic index of heparin, which is less safe and less effective than warfarin in preventing valve complications during pregnancy.

Revised US recommendations published in 1992⁴⁵ still advise discontinuing oral anticoagulants during the first trimester and particularly during the sixth to twelfth weeks of gestation when the fetal skeleton is believed to be most vulnerable to the teratogenic effects of oral anticoagulants. Prolongation of the APTT to one and a half times control (sub-therapeutic) was advised (but since then the recommendation has increased to at least twice the control⁴⁶) using an adjusted dose of subcutaneous heparin until the thirteenth week of gestation, re-starting warfarin until the middle of the third trimester with subcutaneous heparin recommended until delivery. It seems clear, however, that any period without warfarin puts a pregnant woman with a mechanical prosthesis at risk from valve thrombosis, a complication that can result in the death of both mother and fetus.

No embryopathies were recognised in studies of 36,³⁸ 22¹⁹, 53,¹⁸ and 47²⁷ women who took warfarin throughout pregnancy or during the first trimester and the risk of coumarin induced malformation has been estimated to be under 5% based on incidences of between 4% and 7.9%.^{20,23,37} If Cotrufo *et al* are correct, women with a low dose requirement (less than 5 mg warfarin) may be at little risk.⁴⁷ Cotrufo *et al* go further by suggesting that elective caesarean section at 38 weeks (with only brief interruption of warfarin therapy) would avoid the need for administration of intravenous heparin in hospital while waiting for spontaneous labour to start. This approach offers a better chance of a healthy child than a normal delivery and avoids 2 to 3 weeks of heparin treatment.

The reported incidence of spontaneous abortion in women taking oral anticoagulants throughout pregnancy varies widely, probably because of incomplete reporting, with rates of between 4.2%¹⁸ and almost 50%²⁵ being cited. Ayan found no difference in fetal wastage between their heparin and their

coumarin treated patients.⁴⁸ Lee *et al* found a 50% incidence of abortion with subcutaneous heparin even when treatment was adjusted to an APTT of 1.5 as recommended in the United States.²⁴ The changes in coagulation factors during pregnancy demand high doses of heparin⁴⁹ and the higher doses now recommended in the United States increase the danger of bleeding.

In pregnant women who are treated scrupulously the risks of thromboembolic events are probably no greater than reported in the non-pregnant population with mechanical heart valves and the view has been expressed that in asymptomatic or mildly symptomatic patients with prosthetic heart valves who are willing and able to follow a strict regimen of medical care, pregnancy is not associated with increased morbidity in the mother or fetus.^{47 50} Though this may be true for oral anticoagulants it does not apply to heparin, which does not improve the fetal outcome and increases maternal mortality.

The choice of a bioprosthesis confers only temporary advantage because accelerated deterioration of bioprostheses in pregnancy^{22 38 51 52} may lead to early need for re-operation. Nearly 60% of bioprostheses failed in Bortolotti *et al*'s series⁵¹ and 59% required replacement in Badduke *et al*'s series.⁵² Salazar *et al* found that 13% of bioprostheses had to be replaced 7–12 months after delivery²² and primary valve dysfunction needing replacement was reported in more than a third of the patients in our survey.³⁸

The inevitable re-replacement carries an unpredictable risk of death or disaster while the children, for whom the choice of prosthesis was made, are still young and dependent. These mothers should understand why the use of bioprostheses is otherwise confined to the elderly or others whose life span is likely to be shorter than that of their valve. They should know that premature failure of bioprostheses is expected in young people and is even more rapid in pregnancy and, importantly, that because re-operation is technically more difficult than the first operation it carries more risk and should not be undertaken lightly.

Properly controlled trials of antithrombotic therapy for women with mechanical heart valve prostheses during pregnancy have not been possible because of small numbers and the many variables of valve type, site, and size. Agreement has only been reached about explaining the options to women before valve replacement and before pregnancy.^{53 54} Whenever possible women with valve disease should complete their pregnancies before valves are replaced.

- 1 Todd ME, Thompson JH Jr, Bowie ETJ, Owen LA. Changes in blood coagulation during pregnancy. *May Clin Proc* 1965;40:370–83.
- 2 Shaper AG. The hypercoagulable states. *Ann Intern Med* 1985;102:814–28.
- 3 Bolan JC. Thromboembolic complications of pregnancy. *Clin Obstet Gynaecol* 1983;26:913–22.
- 4 Renzulli A, De Luca L, Caruso A, Verde R, Galzerano D, Cotrufo M. Acute thrombosis of prosthetic valves: a multivariate analysis of the risk factors for a life threatening event. *Eur J Cardiothorac Surg* 1992;6:412–21.
- 5 Routledge PA, Shetty HGM. Pharmacology of

- Anticoagulants. In: Butchart, Bodnar, eds. *Thrombosis, embolism and bleeding*. London: ICR Publishers, 1992:263–76.
- 6 Holzgreve W, Carey JF, Gallus AS. Warfarin induced fetal abnormalities. *Lancet* 1976;ii:914–5.
- 7 Goodrich SM, Wood JE. Peripheral venous distensibility and velocity of venous blood flow during pregnancy or during oral contraceptive therapy. *Am J Obstet Gynecol* 1964;90:740–4.
- 8 Ullery JC. Thromboembolic disease complicating pregnancy and the puerperium. *Am J Obstet Gynaecol* 1954;124:3–60.
- 9 Badaracco MA, Vessey M. Recurrence of venous thromboembolic disease and use of oral contraceptives. *Br Med J* 1974;i:215–7.
- 10 Hirsh J. Heparin. *N Engl J Med* 1991;324:1565–74.
- 11 Hedstrand H, Cullhed I. Pregnancy in patients with prosthetic heart valves (Starr-Edwards). *Scand J Thorac Cardiovasc Surg* 1968;2:196–8.
- 12 Bennett GG, Oakley CM. Pregnancy in a patient with a mitral valve prosthesis. *Lancet* 1968;i:616–19.
- 13 Harker LA, Siichter SJ. Studies of platelet and fibrinogen kinetics in patients with prosthetic heart valves. *N Engl J Med* 1970;283:1302–4.
- 14 Oakley C, Doherty P. Pregnancy in patients after valve replacement. *Br Heart J* 1976;38:1140–6.
- 15 Ibarra-Perez C, Azevalo Toledo N, Alvarez de la Cadena O, Noriega Guerra L. The course of pregnancy in patients with artificial heart valves. *Am J Med* 1976;61:504–12.
- 16 Laros RK Jr, Alfer LS. Thromboembolism and pregnancy. *Clin Obstet Gynecol* 1979;22:871–8.
- 17 Lutz DJ, Noller KL, Spittal JA Jr, Danielson GK, Fish CR. Pregnancy and its complications following cardiac valve prostheses. *Ann J Obstet Gynecol* 1978;131:460–8.
- 18 Ben Ismail M, Fekih M, Taktak M, *et al*. Protheses valvulaires cardiaques et grossesse. *Arch Mal Coeur* 1979;2:192–4.
- 19 Chen WWC, Chan CS, Lee PK, Wang RYC, Wong VCW. Pregnancy in patients with prosthetic heart valves: an experience with 45 pregnancies. *Q J Med* 1982;51:358–65.
- 20 Larrea JL, Nunez L, Reque JA, Gil Aguado M, Matarros R, Mingues JA. Pregnancy and mechanical valve prostheses a high risk situation for the mother and the fetus. *Ann Thorac Surg* 1983;36:459–63.
- 21 Guidozzi F. Pregnancy in patients with prosthetic cardiac valves. *S Afr Med J* 1984;65:961–3.
- 22 Salazar E, Zajarias A, Gutierrez N, Iturbe I. The problem of cardiac valve prostheses: anticoagulants and pregnancy. *Circulation* 1984;70:169–77.
- 23 Iturbe-Alessio I, Delcarmen Fonesca M, Mutchinik D, Santos MA, Zajarias A, Salazar E. Risks of anticoagulant therapy in pregnant women with artificial heart valves. *N Engl J Med* 1986;27:1390–3.
- 24 Lee PK, Wang RYC, Chow JSF, Cheung KL, Wong UCW, Chan TK. Combined use of warfarin and adjusted subcutaneous heparin during pregnancy in patients with artificial heart valves. *J Am Coll Cardiol* 1986;8:221–4.
- 25 Vitali E, Donatelli F, Quaini E, Gropelli G, Pellegrini A. Pregnancy in patients with mechanical prosthetic heart valves: our experiences regarding 98 pregnancies in 57 patients. *J Cardiovasc Surg* 1986;27:221–7.
- 26 Gonzales-Santos JM, Vallejo JL, Rico MJ, Gonzales-Santos ML, Horno R, Garcia-Dorado D. Thrombosis of a mechanical valve prosthesis late in pregnancy. Case report and review of the literature. *Thorac Cardiovasc Surg* 1986;34:335–7.
- 27 Pavunkumar P, Venugopal P, Kaul U, *et al*. Pregnancy in patients with prosthetic cardiac valve. A 10 year experience. *Scand J Thorac Cardiovasc Surg* 1988;22:19–22.
- 28 McColgin S. Pregnant women with prosthetic heart valves. *Clin Obstet Gynaecol* 1989;32:76–89.
- 29 Tapanainen J, Ikaheimo M, Jouppila P, Kortelainen ML, Salmela P. Thrombosis in a mechanical aortic valve prosthesis during subcutaneous heparin therapy in pregnancy. A case report. *Eur J Obstet Gynaecol Reprod Biol* 1990;36:175–7.
- 30 Butchart EG. Prosthesis-specific and patient-specific anticoagulation. In: Butchart EG, Bodnar E, eds. *Current issues in heart valve disease. Thrombosis, embolism and bleeding*. London: ICR Publishers, 1992:293–317.
- 31 Daniel WG, Nellessen U, Schroder E, Nonnast-Daniel B, Nikutta P, Lichtlen PR. Left atrial spontaneous echo contrast in mitral valve disease: an indicator for increased thromboembolic risk. *JACC* 1988;11:1204–11.
- 32 Hirsh J. Is the dose of warfarin prescribed by American physicians unnecessarily high? *Arch Intern Med* 1987;147:769–71.
- 33 Butchart EG, Lewis PA, Kulatilake ENP, Breckenridge IM. Anticoagulation variability between centres: implications for comparative prosthetic valve assessment. *Eur J Cardiothorac Surg* 1988;2:72–81.
- 34 Bloomfield DK. Fetal deaths and malformations associated with the use of coumarin derivatives in pregnancy. A critical review. *Am J Obstet Gynecol* 1970;107:883–6.
- 35 Fillmore SJ, McDevitt E. Effects of coumarin compounds on the fetus. *Ann Intern Med* 1970;73:731–4.
- 36 Hirsh J, Cade JF, Gallus AS. Fetal effects of coumadin administered during pregnancy. *Blood* 1970;36:623–7.
- 37 Sareli P, England MJ, Berk MR, *et al*. Maternal and fetal sequelae of anticoagulation during pregnancy in patients with mechanical heart valve prostheses. *JACC* 1989;

- 63:1462-5.
- 38 Sbarouni E, Oakley CM. Outcome of pregnancy in women with valve prostheses. *Br Heart J* 1994;71:196-201.
- 39 Hanania G, Thomas D, Michel PL, Garbarz E, Age C, Acar J. Pregnancy in patients with valvular prostheses—retrospective cooperative study in France (155 cases): *J Arch Mal Coeur Vaiss* 1994;87:429-37.
- 40 Howie PW. Anticoagulants in pregnancy. *Clin Obstet Gynaecol* 1986;13:349-64.
- 41 Ginsberg JS, Hirsh J. Optimum use of anticoagulants in pregnancy. *Drugs* 1988;34:505-12.
- 42 Ginsberg JS, Hirsh J. Anticoagulants during pregnancy. *Annu Rev Med* 1989;40:79-86.
- 43 Wehrmacher WH, Messmore HL. Thromboembolic disease during pregnancy: Problems with anticoagulant therapy. *Compr Ther* 1990;16:31-5.
- 44 Hirsh J, Cade JF, O'Sullivan EF. Clinical experience with anticoagulant therapy during pregnancy. *Br Med J* 1970;i:270-3.
- 45 Ginsberg JS, Hirsch J. Use of Antithrombotic agents during pregnancy. *Chest* 1992;102 (suppl 4):385S-390S.
- 46 Brill-Edwards P, Ginsberg JS, Johnston M, Hirsh J. Establishing a therapeutic range for heparin therapy. *Ann Intern Med* 1993;19:104-9.
- 47 Cotrufo M, de Luca TSL, Calabro R, Mastrogiovanni G, Lama D. Coumarin anticoagulation during pregnancy in patients with mechanical valve prostheses. *Eur J Cardiothorac Surg* 1991;5:300-5.
- 48 Ayan A, Yapar EG, Yuce K, Kinaki HA, Nazli M, Ozmen F. Pregnancy and its complications after cardiac valve replacement. *Int J Gynaecol Obstet* 1991;35:117-22.
- 49 Whitfield LR, Lelen AS, Levy G. Effect of pregnancy on the relationship between concentration and anticoagulant action of heparin. *Clin Pharmacol Ther* 1983;34:23-8.
- 50 Elkayam U and Gleicher N. Anticoagulation in pregnant women with artificial heart valves. *N Engl J Med* 1987;316:1662-3.
- 51 Bortolotti U, Milano A, Massucco A, Valgre C, Russo R, Valente M, et al. Pregnancy in patients with a porcine valve prosthesis. *Am J Cardiol* 1982;50:1051-4.
- 52 Badduke ER, Jamieson RE, Miyashima RT, Munro AI, Gerein AN, MacNab J, Tyers GFO. Pregnancy and childbearing in a population with biologic valvular prostheses. *J Thorac Cardiovasc Surg* 1991;102:179-86.
- 53 Ginsberg JS, Barron WM. Pregnancy and prosthetic heart valves. *Lancet* 1994;344:1170-2.
- 54 Oakley M. Pregnancy and prosthetic heart valves. *Lancet* 1994;344:1643-4.