# Anticoagulant Management of Pregnancy following Heart Valve Replacement in the United Kingdom, 1986-2002

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***Background and aim of the study:*** **Patients with mechanical heart valves require anticoagulation which is associated with significant maternal mortality (1-4%) and fetal complications (31%) in pregnancy. The study aim was to identify anticoagulant protocols and outcomes for pregnant women undergoing heart valve replacement (HVR) in the United Kingdom.**

***Methods:*** **Women aged between 18 and 45 years and registered with the United Kingdom Heart Valve Registry (UKHVR) each completed a questionnaire, and their obstetric notes were reviewed. The data analyzed included valve type (mechanical, bioprosthetic, homograft), valve site (mitral, aortic, tricuspid, pulmonary), anticoagulation at confirmation of pregnancy, between 6-12 weeks and from 12 weeks to term, delivery, maternal and fetal outcomes, and cause of death. The summary statistics and a descriptive review of the findings are reported.**

***Results:*** **Of 2,532 women eligible for the study, 922 responded. Among these women, 72 became pregnant, with 60 pregnancies in the mechanical valve (MV) group and 45 in the tissue valve (TV) group. Three anticoagulation regimes were used during early pregnancy: unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) or warfarin. All women received warfarin in the second trimester and heparin for delivery. Live births were recorded in 30% of MV pregnancies and in 60% of TV pregnancies. Miscarriage rates differed markedly (37% MV versus 2% TV). Fetal outcome was poorest in the warfarin-only group, with embryopathy occurring at a dose level of 6 mg. The maternal outcomes did not differ significantly among groups. High-dose heparin during the first trimester and for delivery was effective for the majority of mechanical valves.**

***Conclusion:*** **The study results illustrate the diverse and uncertain manner in which UKHVR patients are managed during pregnancy. A national notification system would record much-needed prospective information on anticoagulation and pregnancy outcomes, thus aiding evidence-based management.**

The Journal of Heart Valve Disease 2008;17:526-532

Cardiac surgeons in the United Kingdom show a preference for mechanical heart valves in women of childbearing age, despite their inherent thrombogenicity (1). Advances in biomaterials, valve design and anticoagulation have resulted in prolonged survival and a reduction in thromboembolic risk to between 0.1% and 5.7% per patient-year (2). Thus, women who have undergone heart valve replacement (HVR) surgery are less likely to be advised to avoid pregnancy than previously (3-5). Although anticoagulation for mechanical valves is known to adversely affect maternal and fetal outcomes (6), the reports are anecdotal and contradictory. Moreover, a lack of consensus among clinicians and differing European and US anticoagulant guidelines (6,7) has led to anxiety and confusion (8).

In this survey of women in the UK who have undergone HVR surgery and subsequently became pregnant, the aim was to identify anticoagulant treatment for mechanical valves during pregnancy, maternal and fetal complications due to anticoagulation, and to determine which treatment resulted in optimal maternal and fetal outcomes.

## Clinical material and methods

### Patients

Women of childbearing age (18 to 45 years) who underwent HVR in the UK between 1986 and 2002 were identified from The United Kingdom Heart Valve

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*Table I: Numbers of women and pregnancies by valve type and site.*

| Valve type and site | No. of women | No. of pregnancies |
|---|---|---|
| Mechanical | | |
| Total | 39 (54) | 60 (57) |
| Aortic | 21 | 30 |
| Mitral | 15 | 27 |
| Tricuspid | 1 | 1 |
| Mitral/aortic | 2 | 2 |
| Tissue | | |
| Total | 33 (46) | 45 (43) |
| Aortic | 20 | 26 |
| Mitral | 8 | 12 |
| Tricuspid | 3 | 4 |
| Pulmonary | 2 | 3 |

Values in parentheses are percentages.

Registry (UKHVR) database. This system prospectively collects preoperative and postoperative implant data from all UK cardiac surgical centers, including the occurrence of reoperation and death. As pediatric cases have only been recorded in the UKHVR since 2000, those patients aged <18 years at the time of surgery were excluded from the study.

Multi-ethics approval to conduct the study was granted by the London Multi-Centre Research Ethics Committees, Central Middlesex Hospital London (reference MREC/01/2/75).

**Data acquisition**

Following an initial pilot study among a small number of clinicians to assess the effectiveness of the questionnaire, some amendments were made. The variables analyzed included valve type (mechanical, bioprosthetic, homograft), valve site (mitral, aortic, tricuspid, pulmonary), patient status (alive/deceased) and date and cause of death. Precise data were provided by the national agencies registering deaths in the UK. The UKHVR receives a copy of each patient's death certificate, which includes the date, place and certified cause of death, and also identifies whether the patient has undergone an autopsy examination. Thus, the Registry is able to report accurately on valve performance and mortality. Details of valve-related deaths, including thrombosis, embolism, hemorrhage and cerebrovascular accident (CVA), were compared with a UKHVR-derived, age-matched male population.

**The questionnaire**

Pregnancy-related information was obtained using questionnaires sent to patients via their general practitioner (GP). Information was requested regarding the number and dates of all pregnancies following HVR, any maternal complications such as bleeding, thromboembolism, heparin-induced thrombocytopenia and cardiac complications or any others arising in pregnancy, and fetal complications such as bleeding and congenital malformation/embryopathy. The name of the managing hospital or obstetrician was obtained and all obstetric notes of those women who had provided their informed consent to participate were reviewed independently by two researchers. The data collected included anticoagulation at the confirmation of pregnancy, between six and 12 weeks of pregnancy, from 12 weeks to term, and for delivery. Details of maternal and fetal outcome were also recorded.

**Data analysis**

The findings were compared and the information validated. As a result of the paucity of available medical notes, the data analysis was limited to summary statistics and a descriptive review of the findings from this small cohort.

## Results

**Population characteristics**

Between 1st January 1986 and 31st December 2002, out of 2,532 women who fulfilled the inclusion criteria 922 women responded (36%). Of these women, 72 (8%) had become pregnant, with a total of 105 pregnancies. Medical notes were available for only 30 women (14 of the MV group, with 29 pregnancies; 16 of the TV group, with 27 pregnancies). Information on the remaining pregnancies was extracted only from patient questionnaires. Among the entire patient cohort, 22% (n = 563) were deceased and 41% (n = 1,047) were either lost to follow up or did not respond.

Among the valves implanted, 39 (54%) were mechanical (group MV), while 33 (46%) were tissue valves (group TV). The tissue valves included 21 xenografts (29%) and 12 homografts (17%); hereafter, xenograft and homograft valves are collectively referred to as 'tissue valves'. The mean age was similar in both groups (mean 29.8 years; range: 18 to 42 years in MV; mean 29.1 years; range: 19 to 45 years in TV). Details of the valve site and numbers of pregnancies are listed in Table I. In total, 49 women had a single pregnancy post HVR, and 21 women had two or more pregnancies. The mean time period between HVR and pregnancy was 3.3 years (range: 3 months to 16 years) for MV patients, and 5.1 years (range: 1 to 17 years) for TV patients.

**Mortality data**

Cardiac failure (CF) proved to be the most common

*Table II: Anticoagulant treatment data for mechanical valve group.*

| Patient i.d. | Operation year | Valve site | Pregnancy year | Anticoagulant 1st trimester | Anticoagulant 2nd trimester | Anticoagulant 3rd trimester | Warfarin (mg) | INR (actual) | Adverse maternal outcome | Fetal outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| Regime 1: warfarin throughout pregnancy; UFH unfractionated heparin for delivery | | | | | | | | | | |
| A | 1986 | Aortic | 1989 | Warfarin | NA | NA | 15 | NK | - | TOP |
| E | 1994 | Aortic | 1995 | Warfarin | NA | NA | 4-5 | 3.2-3.9 | - | Spontaneous abortion |
| E | 1994 | Aortic | 1996 | Warfarin | NA | NA | 5 | 2.3-2.6 | - | Spontaneous abortion |
| E | 1994 | Aortic | 1997 | Warfarin | NA | NA | 5 | 2.8 | - | Spontaneous abortion |
| E | 1994 | Aortic | 2000 | Warfarin | Warfarin | UFH iv infusion; 30,000-35,000 u o.d. | 5-6 | 1.6-2.5 | - | Live birth, Warfarin embryopathy |
| C | 1989 | Mitral | 1990 | Warfarin | Warfarin | UFH iv infusion; 22,000-30,000 u o.d. | 3 | 3.0-4.0 | PPH 3000 ml | Live birth |
| C | 1989 | Mitral | 1991 | Warfarin | NA | NA | 6 | 3.0-4.0 | | Spontaneous abortion |
| C | 1989 | Mitral | 1992 | Warfarin | NA | NA | 6 | 3.0-4.0 | | Spontaneous abortion |
| D | 1994 | Mitral | 1994 | Warfarin | NA | NA | 4 | NK | | Spontaneous abortion |
| D | 1994 | Mitral | 1995 | Warfarin | NA | NA | 4 | NK | | Spontaneous abortion |
| D | 1994 | Mitral | 2003 | Warfarin | NA | NA | 4 | NK | | Spontaneous abortion |
| Regime 2: UFH to 12 weeks; warfarin after 12 weeks; UFH for delivery | | | | | | | | | | |
| B | 1987 | Aortic | 1990 | UFH sc 5,000 u, b.d. | Warfarin | UFH sc 5,000 u, b.d. | 6 | 1.5-4.0 | Bleed 300 ml | Live birth |
| A | 1986 | Aortic | 1993 | UFH sc 12,500 u, b.d. | Warfarin | UFH ivi dose unknown | 10 | NK | - | Live birth |
| F | 1991 | Aortic | 1995 | UFH sc 17,500 u, b.d. | Warfarin | UFH sc 17,500 u, b.d. | 12 | NK | - | Live birth |
| C | 1989 | Mitral | 1992 | UFH sc 5,000 u, t.d.s. | Warfarin | UFH sc 5,000 u, t.d.s. | 6 | 3.0-4.0 | - | Live birth |
| Regime 3: LMWH to 12 weeks; warfarin after 12 weeks; LMWH /warfarin for delivery | | | | | | | | | | |
| E | 1994 | Aortic | 1998 | 12,250 u, o.d. | NA | NA | NK | NK | - | Spontaneous abortion |
| G | 1996 | Aortic | 1999 | Dalteparin 12,000 u, o.d. | Warfarin | Dalteparin 6,000 u, b.d. | 6 | NK | PPH 2000 ml | Live birth |
| H | 1992 | Aortic | 2001 | Dalteparin 14,000 u, o.d. | Warfarin | Dalteparin 14,000 u, o.d. | 7 | NK | - | Live birth |
| I | 2001 | Aortic | 2002 | Dalteparin 10,000 u, o.d. | Warfarin | Enoxaparin 40 mg, o.d. | NK | NK | - | Live birth |
| J | 1998 | Mitral | 2002 | Enoxaparin 60 mg, b.d. | Warfarin | Warfarin | 4-5 | 2.91-4.0 | - | Live birth |

LMWH: Low-molecular-weight heparin; NA: Not applicable; NK: Not known; PPH: Post-partum hemorrhage; TOP: Termination of pregnancy; UFH unfractionated heparin.

cause of death in these patients (n = 169; 30%). Valve-related causes accounted for 44 deaths overall (CVA 8%, thrombosis 2%, hemorrhage 0.4%, embolism 0.2%). There were no maternal deaths during pregnancy, at delivery, nor during the post-partum period. In an aged-matched male control group there were 681 deaths (15%) overall, with CF-related deaths accounting for a similar percentage as females (31%). Numbers of fatal valve-related deaths from hemorrhage (0.9%) or embolism (0.2%) were comparable in males, but significantly fewer deaths occurred due to CVA (4%) and thrombosis (0.3%).

**Outcomes**

***Anticoagulant therapy***

Evaluable anticoagulant data were available in the medical notes for only 20 pregnancies (Table II). Among four women administered warfarin throughout pregnancy, 73% (8/11) of the pregnancies ended in spontaneous abortion at 12 weeks or less (dose levels and International Normalized Ratio (INR) values are shown in Table II); one woman taking 15 mg warfarin daily had a termination, while two pregnancies continued to term and were switched to therapeutic unfractionated heparin (UFH) infusion for delivery. In the remaining nine pregnancies (45%), UFH was used before 1995, and subsequently low-molecular-weight heparin (LMWH) was given with variable drug doses in each group (see Table II). Four pregnancies were managed with UFH (subcutaneous) from early in the first trimester (less than five weeks); monitoring was recorded in only one patient who had a trough anti-Xa assay of 0.05-0.15 while receiving 5,000 units three times daily. All four patients were changed to warfarin at 12 weeks, with INR values of 1.5 to 4.0. For delivery, three patients were managed on UFH (subcutaneous) as in the first trimester, and one patient was given UFH (intravenous) for delivery (dose not stated). From 1998 onwards, subcutaneous LMWH was given during the first trimester in five pregnancies. Four pregnancies were switched to warfarin after 12 weeks, but the INR values were not recorded. Three pregnancies treated initially with dalteparin were switched back to LMWH for delivery, and one remained on warfarin for delivery (Table II).

Three patients received different anticoagulant regimes during their consecutive pregnancies. Patient A had a termination in her first pregnancy due to a high warfarin dose, but went on to have a live birth following a second pregnancy that was managed on UFH in the first and third trimesters. Patient C had four pregnancies of which two resulted in live births; the first pregnancy was managed on warfarin throughout with intravenous infusion of UFH for delivery, while the fourth pregnancy was managed with subcutaneous UFH during the first and third trimesters, with warfarin in the second trimester. Patient C's two other pregnancies miscarried at six and 12 weeks' gestation on high-dose warfarin. Patient E had five pregnancies; pregnancies 1 to 3 were managed on warfarin and ended in early spontaneous abortion, while pregnancy 4 miscarried at 11 weeks despite being managed on therapeutic tinazaparin from week 5. Pregnancy 5 was managed on warfarin (5-6 mg; INR 1.6-2.5) and UFH for delivery (see Table II). However, the infant had nasal hypoplasia, which is characteristic of coumarin embryopathy. Two women received other medications (one had methyldopa, and the other co-amilofruse). No further medications were recorded.

In the TV group, three patients (two xenografts, one homograft) received antibiotics throughout pregnancy; the homograft patient also received digoxin 0.125 mg daily during the second trimester of her first pregnancy, but not in her two subsequent pregnancies. Another homograft patient received enoxaparin 40 mg per day from 16 to 40 weeks in each of her two pregnancies.

***Fetal outcome***

Aortic valve replacement (AVR) was almost threefold more likely to result in a successful pregnancy in MV patients (43%) compared to mitral valve replacement (MVR) (15%). In comparison, and despite there being more live births among TV patients, those in this group who had undergone AVR had fewer successful pregnancies (54% versus 83% for MVR). Five patients were pregnant during the period of the study with unknown outcomes. Twenty-three pregnancies ended in spontaneous abortion (22 MV, one TV), and nine were terminated. The reasons for termination included: congestive heart failure (CHF) in early pregnancy, requiring the insertion of a mechanical valve and subsequent termination at 15 weeks; fetal abnormality leading to termination at 20 weeks (hypoplastic heart; anticoagulation regime unknown); and concern regarding a warfarin dose of 15 mg in the first trimester (MV). The reasons for the remaining five terminations were not specified. None of the four pregnancies which occurred less than one year after mechanical valve surgery went to term; two ended in spontaneous abortion, and there was one still-birth and one termination for fetal abnormality unrelated to anticoagulation. In 22 (21%) of the pregnancies the outcomes were unknown (Table III).

Obstetric records noted that 10 pregnancies (50%) in the MV group resulted in live births, although one neonate died at four weeks from *Haemophilus influenzae* infection. Nine of these babies were normal (four each in the LMWH and UFH groups, and one in the warfarin group; dose ≤3 mg, INR 3.0 and 4.0). In the TV

J Heart Valve Dis
Vol. 17. No. 4
September 2008

*Table III: Pregnancy outcomes by type and site of valve.*

| Valve type and site | Pregnancies | No details | Live birth | Miscarriage | Termination | Ante-natal | Still-birth |
|---|---|---|---|---|---|---|---|
| Total | 105 (100) | 22 (21) | 45 (43) | 23 (22) | 9 (8.5) | 5 | 1 |
| Mechanical valves | | | | | | | |
| Total | 60 (57) | 11 (18) | 18 (30) | 22 (37) | 7 (12) | 1 | 1 |
| Aortic | 30 | 7 | 13 (43) | 8 (27) | 2 (7) | - | - |
| Mitral | 27 | 3 | 4 (15) | 14 (52) | 4 (15) | 1 | 1 |
| Tricuspid | 1 | 1 | - | - | - | - | - |
| Mitral/aortic | 2 | - | 1 (50) | - | 1 (50) | - | - |
| Tissue valves | | | | | | | |
| Total | 45 (43) | 11 (25) | 27 (60) | 1 (2) | 2 (4.5) | 4 | - |
| Aortic | 26 | 9 | 14 (54) | - | 1 (4) | 2 | - |
| Mitral | 12 | 1 | 10 (83) | - | - | 1 | - |
| Tricuspid | 4 | - | 2 (50) | - | 1 (25) | 1 | - |
| Pulmonary | 3 | - | 2 (67) | - | 1 (33) | 1 | - |

Values in parentheses are percentages.

group, 23 pregnancies (86%) resulted in live births. One patient underwent valve replacement with a tissue valve during pregnancy and subsequently had a live birth. No fetal abnormalities were reported, but one baby required transfer to the Special Care Baby Unit. One pregnancy was current at the time of the survey, while in two pregnancies no outcome data could be found in the notes. Insufficient data were available for analysis on gestation, birth weight and APGAR score at delivery in both valve groups.

***Maternal outcome***

Among the MV group, nine women suffered complications: four suffered intra- or post-partum hemorrhage. Patient C (iv UFH) bled 3,000 ml and required a blood transfusion (3 units), patient B (sc UFH) bled 300 ml but was not transfused, while patient G (LMWH) required 4 units of blood, having bled 2,000 ml (Table II). One other patient suffered a 'major' post-partum hemorrhage, but no other details were available. Among other complications, one patient suffered a stroke; she was on warfarin (dose and INR not stated) at five weeks of pregnancy, three months after MVR, and subsequently suffered a spontaneous miscarriage; no information was available as to whether the event was embolic or hemorrhagic. Other complications included an ovarian cyst; this was removed at 14 weeks and a subsequent live birth occurred at term (managed with LMWH). Other complications were not reported.

In the TV group, only one woman suffered maternal complications; these were pneumonia coupled with prosthetic valve endocarditis, which led to a termination of pregnancy at 15 weeks.

Although the medical records confirmed there were no cases of valve deterioration during any of the pregnancies, eight TV patients subsequently underwent prosthetic valve replacement (PVR) with a mechanical valve after pregnancy. In five patients the time to reoperation was between three and 17 years; in two the interval was not specified; and in one patient PVR was performed a few months after a second successful pregnancy. The NYHA status was not recorded for any patient.

## Discussion

During pregnancy, a hypercoagulable state develops making it essential that women with mechanical heart valves receive anticoagulation. Prophylactic anticoagulation throughout pregnancy is not without risks, however, to both mother and fetus (5,9). Controversy persists regarding anticoagulation in pregnancy following HVR, with opposing US and European views. The current US recommendations are to administer 'aggressive' doses of UFH or LMWH subcutaneous twice daily, either throughout pregnancy or with warfarin substituted from 13 to 36 weeks (6). In contrast, European guidelines recommend continuing oral anticoagulation throughout pregnancy, because this is known to reduce mechanical valve thrombosis by a factor of ten in non-pregnant patients (when the INR is >2.5) (10), and thus confers greatest protection to the mother (9,11). Unfortunately, coumarins are able to cross the placenta and have an unpredictable effect on the fetus, increasing the likelihood of adverse fetal outcomes by up to 31% (3,12), including embryopathy in 4-6% of fetuses exposed to >5 mg daily during the first

trimester (13).

A systematic review of the literature by Chan et al. (14) concluded that fetal wastage was high following mechanical HVR, irrespective of anticoagulant regime, but that embryopathy was abolished by the substitution of heparin before six weeks gestation. Heparin is known to provide greater protection to the fetus, particularly between 6-12 weeks of gestation, because it does not cross the placenta. However, this protection comes at the expense of the mother. In Chan's study, prophylactic UFH led to the highest maternal death rates due to thrombotic valve complications. These findings have been supported by others, who reported that therapeutic doses of UFH given either by carefully monitored intravenous infusion or subcutaneously, not only failed to abolish the thromboembolic risk but also increased the risk of other serious maternal complications (5,11), such as hemorrhage, dose-related osteoporosis (15) and heparin-induced thrombocytopenia and thrombosis (6). LMWHs have been tried as an alternative therapeutic thromboprophylatic option for women with mechanical heart valves, and are now the preferred treatment of venous thromboembolic disease in pregnancy (16). They are easier to use, have fewer side effects, can be reliably monitored, and have been used for thromboprophylaxis for mechanical heart valves (17,18). However, episodes of valve thrombosis are reported even with apparently therapeutic doses (19). Nevertheless, LMWHs appear to be safer than UFH in pregnancy for both the mother and the fetus (13,19), and successful pregnancy outcomes have been reported (20).

In the present study, 11 patients with mechanical heart valves received warfarin throughout their first trimester, but only two continued to delivery. One case of coumarin embryopathy was confirmed suggesting that, contrary to other reports (13), warfarin doses of 5-6 mg do not abolish the risk. The type of heparin used in the remaining pregnancies varied with time, LMWH being preferred after 1998. In common with James et al. (20), the outcomes were not inferior on LMWH compared to UFH. Furthermore, fetal outcome was found to be optimal in those women treated with heparin in the first trimester, a result supported by others (4,5). Where notes were available, no thrombotic or embolic complications were observed any in any group, including those treated with low anticoagulant doses. Neither were any maternal deaths reported. Finally, contrary to the findings of Javares et al. (21), it was found that mothers with mitral bioprostheses had a better fetal outcome (83% live births) than those receiving an aortic bioprosthesis (54%).

Several problems beset the present study, notably the high non-response rate, poor access to patients' hospital notes, and the lack of information recorded in medical records. The Data Protection Act of 1998 (www.opsi.gov.uk/acts) requires explicit patient permission to be obtained before notes can be examined. Despite exhaustive efforts, responses were elicited from only 37% of patients, none of whom withheld permission. In several non-responder cases, the GP declined an approach to the patient because of an unhappy obstetric history or, previous specific advice to avoid pregnancy. Difficulty was also encountered in obtaining notes for the majority of patients who had consented, and in the notes that were made available there was poor documentation of planned or administered treatment, maternal cardiac status, fetal outcomes and post-natal follow up. Nonetheless, and, despite being able to report on only a small number of women who became pregnant following HVR (8%), it is unlikely that the numbers of pregnancies would have been increased significantly by responses from the non-responder and lost-to-follow up groups. In the first instance, valve replacement tended to be carried out in women who had completed their families; second, the consensus among GPs was that many of these women during the 1980s and 1990s were advised to avoid pregnancy. Despite the size and heterogeneity of the group, the results of this study illustrate the diverse and uncertain way in which UK heart valve replacement patients are managed during pregnancy, arising in part because no one center has many patients. A national notification system, such as that already established for rare complications of pregnancy (UKOSS; www.npeu.ox.ac.uk) would record much-needed prospective information on anticoagulation and pregnancy outcomes. The subsequent pooled experience would allow evidence-based management of pregnancy in these challenging patients.

*In conclusion*, it is argued that women with heart valve prostheses have poor pregnancy outcomes for several reasons, including a deterioration in NYHA class (22) due to degradation of the bioprosthetic valve (23), or thrombosis of mechanical valves. In the present study, anticoagulation with either UFH or LMWH in the first and third trimester resulted in live births in the majority of cases in patients with mechanical valves, but with an increased risk of intra- or post-partum hemorrhage. Warfarin in the first trimester was associated with a high rate of spontaneous abortion, and one case of embryopathy occurred just above the dose previously regarded as safe (6 mg). Although unable to comment on NYHA status, the present study - like others (24,25) - did not provide any evidence to support the findings of Sbarouni and Oakley (23), who reported high rates of bioprosthetic valve degradation during pregnancy. Women who became pregnant following HVR with a tissue valve demonstrated bet-

ter maternal and fetal outcomes than those with mechanical valves. Thus, it is concluded that tissue valves may be preferable for women who have not yet become pregnant and who have good NYHA status before pregnancy.

**Acknowledgements**

The authors wish to thank Mrs. Sharon Weafer of the United Kingdom Heart Valve Registry for her unstinting contribution and administrative support throughout all stages of this study. These studies were funded in part by the Garfield Weston Trust, which had no further involvement in the investigations.

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