CHAPTER 3

RESULTS

3.1 DEMOGRAPHIC DATA

Of the women approached, 126 agreed to be interviewed. Two of these interviews were not included in the final analysis because the women did not fulfill the inclusion criteria (one older than 45 years, and one not on warfarin during any of her pregnancies). The average age of the patients was 35 years (range 23 – 45 years), and they appeared to represent a literate population, since the average patient had 8.8 years of formal education (range 0 – 12 years). Most of the women (111/124 or 89.5%) took warfarin for anticoagulation of a prosthetic heart valve, and of the remaining 13 women, only one took warfarin for a non-cardiac indication (pulmonary hypertension). The median number of pregnancies was 2, with a range of one to eight pregnancies per woman.

3.2 MEDICATION

The group of study subjects had taken warfarin, on average, for 14 years (range 2 – 28 years), and their average current dose of warfarin was 41.8 mg per week (6 mg/day). We chose to express warfarin dose as a weekly figure because some patients take different doses on alternate days, making daily dosage analysis difficult. The smallest dose of warfarin being taken at the time of the interview by any of the patients was 12.5 mg/week (1.8 mg/day), and the highest dose was 87.5 mg/week (12.5 mg/day). Of the women interviewed, 106 (85%) took other medication. This concomitant medication consisted of one or more of the following: digoxin, the diuretic furosemide, beta-blockers, other antihypertensives (including

second generation ACE-inhibitors), antiarrhythmics, antiepileptics, and low-dose aspirin. Antiepileptics were used by 4/124 women (3/4 on carbamazepine, and 1/4 on phenytoin), and ACE-inhibitors by 18/124 (15/18 used second generation ACE-inhibitors). Amiodarone was used by 7/124 women. One woman was taking both amiodarone and phenytoin (see section 4.3.1 for further discussion).

3.3 PATIENT AWARENESS

3.3.1 Family planning

Of the study cohort, 35.5% (44/124) of women could recall having been told that they should use some method of contraception for family planning because they were taking warfarin. Of the 124 women, 86 (69%) were actually using some method of contraception at the time of the interview, and the most popular method being used was injectable hormones.

3.3.2 Information about the effects of warfarin in pregnancy

Most women (80/124 or 64.5%) could recall having been given some information about warfarin in pregnancy. The majority thought that they had received this information from a doctor (49/80 or 61%), and the remainder reported that they had been given information by a nurse (28/80 or 35%) or another patient (2/80 or 2.5%). The source of information was not recorded in one patient. The interview did not contain a specific question regarding exactly what information was given about the effects of warfarin in pregnancy. However, judging by what was said by the interviewees, it can be noted anecdotally that information amounted to a warning to come to hospital ‘early’ when pregnant and on warfarin, but not about the specific potential adverse effects of warfarin in pregnancy. There was also no specific information that women should come to the hospital before six weeks of pregnancy, and many perceived the word ‘early’ to mean three months (12 weeks) of pregnancy.

In response to question 2.4 (see appendix A, page 52), "How do you think warfarin can affect your pregnancy?" the majority of women in the study thought that warfarin could harm their fetus in some way (107/124 or 86%). The commonest harmful side effects mentioned that could be experienced by the fetus or baby included physical and mental abnormalities (47/107 (44%) and 18/107 (16.8%) respectively), miscarriage (26/107 or 24%), and death (18/107 or 16.8%). Only 4/107 (3.7%) women considered bleeding to be a harmful effect that could be experienced by the fetus or baby. Some of the women stated more than one of the above-mentioned complications in their response. Anecdotally, it should be mentioned that the physical and mental abnormalities related to the fetus or baby were often reported as external ear anomalies, short stature and mental retardation.

The perception that warfarin also poses a health risk to the mother in pregnancy was however lower (50/124 or 40%). The most commonly mentioned harmful effects that could be experienced by the mother included bleeding (8/50 or 16%), stroke (8/50 or 16%), and death (7/50 or 14%).

Many of the women stated that they knew about the harmful effects of warfarin in pregnancy because of previous personal experience of such adverse events (e.g. miscarriage), rather than from information received from a health professional. Some important misperceptions expressed by some of the interviewees included that warfarin itself prevented them from falling pregnant, and that women with any cardiac problem could not fall pregnant.
Only 4/124 (3.2%) women categorically stated that warfarin posed no health risk to mother or baby in pregnancy.

3.4 PREGNANCY OUTCOMES

3.4.1 Overall outcome

There were a total of 318 pregnancies in 124 women. The pregnancies resulted in normal liveborn babies in 56% (178/318) of cases, and 44% (140/318) of women therefore had a poor pregnancy outcome (miscarriage, intrauterine death, abnormal liveborn, ectopic pregnancy, or termination of pregnancy). Ectopic pregnancies and elective terminations of pregnancy (TOP) constituted 1.6% (5/318) and 1.3% (4/318) of all pregnancies respectively. Since ectopic pregnancies are not caused by warfarin exposure, 3 of the 4 TOP were for social reasons (only one TOP was for a clinical indication of maternal ill health), and because these numbers are too small for statistical significance, these pregnancies will not be considered in the further analysis.

3.4.2 Warfarin exposed group

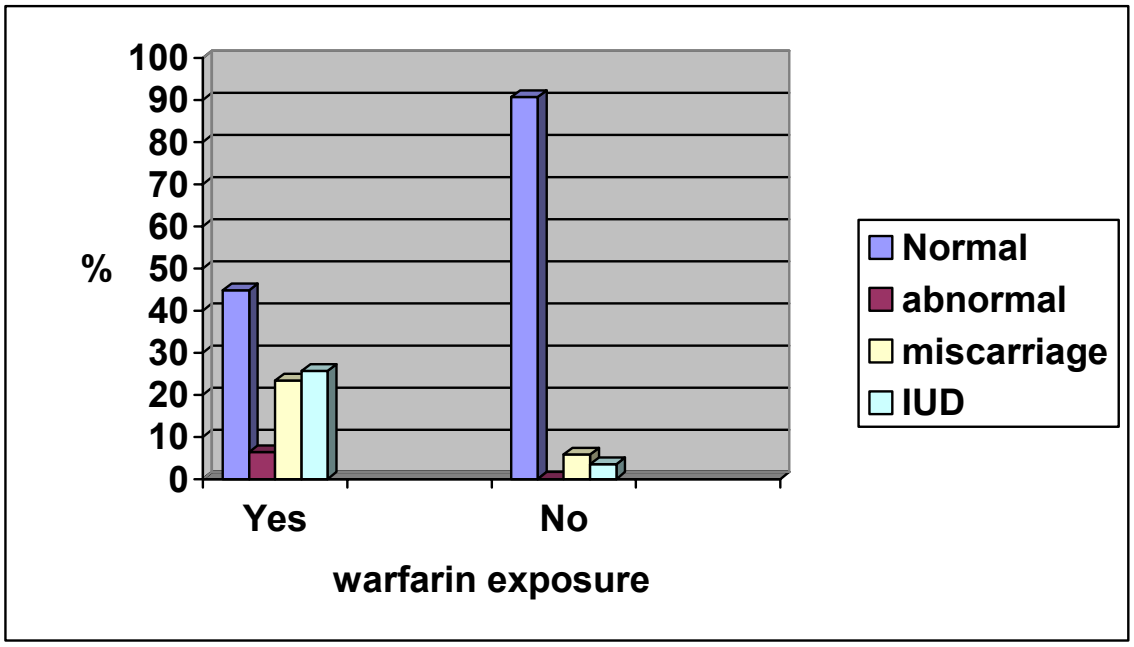
Warfarin-exposed pregnancies totaled 223, excluding ectopic pregnancies or TOP (see 3.4.1). The majority of pregnancies in this group had a poor outcome, with 55.2% (123/223) ending in the birth of an abnormal baby, spontaneous abortion or intrauterine death.

Because some women had pregnancies before starting warfarin therapy, a natural control group of 86 pregnancies that were not exposed to warfarin exists within the cohort for comparison with the warfarin-exposed pregnancies. The comparison between these two groups is shown in table 3.1, and graphically depicted in figure 3.1. The difference in outcome between the two groups was highly statistically significant (p-value < 0.001). Of note is the fact that 100% of the abnormal liveborn babies were warfarin-exposed.

Table 3.1 Outcomes for warfarin-exposed and warfarin non-exposed pregnancies.

	On warfarin n (%)	No warfarin n (%)	Total (n)
Normal alive	100 (44.8)	78 (90.7)	178
Abnormal alive	14 (6.3)	0 (0)	14
Miscarriage	52 (23.3)	5 (5.8)	57
Stillbirth	57 (25.6)	3 (3.5)	60
Total	223 (100)	86 (100)	309

Figure 3.1 Pregnancy outcomes comparing women on and off warfarin



Of the 14 babies noted to have abnormalities at birth, five died. Considering the whole group:

- Five had nasal abnormalities causing breathing problems (two requiring nasal stenting) with neurodevelopmental delay and/or hydrocephalus. One of these babies died.
- Three had nasal abnormalities only, causing breathing problems, and one of these babies died.
- Two had limb abnormalities only (one with clubfoot, one unspecified).
- Two had CNS abnormalities, and one of these also had a cardiac defect and died (see paragraph below).
- Two were physically abnormal (unspecified) and died soon after birth.

Two babies were reported as having cardiac abnormalities (one with an unspecified heart abnormality, and the other with a ventriculoseptal defect). The baby with an unspecified heart abnormality also had hydrocephalus and was one of the babies who died (five days after birth). The baby with the ventriculoseptal defect also apparently has a markedly flat nasal bridge, but is otherwise normal.

If one accepts that the eight babies with nasal abnormalities and the two with CNS abnormalities have features in keeping with a diagnosis of warfarin embryopathy, the rate of WE in this study is 4.5% (10/223). If one includes the two babies with unspecified physical abnormalities who died as neonates, the WE rate rises to 5.4% (12/223).

3.4.3 Initial pregnancy outcome as a predictor of future pregnancy outcome

Pregnancy outcome for pregnancies one to three (n = 267) was significantly related to warfarin exposure (p-value = 0.001). The outcome for pregnancies four or more (n = 51) was

not statistically significantly related to warfarin exposure, but this is probably a function of the small numbers.

First pregnancy outcome (normal liveborn versus poor outcome) was compared to second pregnancy outcome. The pregnancy outcomes were only compared for these two pregnancies because the numbers of subsequent pregnancies became too small to be statistically significant. It would appear that first pregnancy outcome (normal liveborn versus poor outcome) is significantly correlated with outcome in a second pregnancy, if warfarin-exposed and non-exposed pregnancies are considered as a whole (p-value <0.001). This means that women in the cohort who had a normal liveborn in their first pregnancy were more likely to have another normal liveborn in their second pregnancy, and, conversely, that women who had a poor outcome in their first pregnancy were more likely to have a poor outcome in their second pregnancy.

The number of warfarin-exposed first and second pregnancies, together with respective pregnancy outcomes is shown in table 3.2. The correlation between the outcome in the two pregnancies approached, but did not reach, statistical significance (p-value = 0.067). The reason that statistical significance was not proven is probably a function of the small numbers in this sub-analysis.

Table 3.2 Outcomes for first and second warfarin–exposed pregnancies

	Normal liveborn (2^{nd} pregnancy)	**Poor outcome (2^{nd} pregnancy)**
Normal Liveborn (1^{st} pregnancy)	12	8
Poor outcome (1^{st} pregnancy)	7	15

Pregnancy outcomes for first and second pregnancies not exposed to warfarin are shown in table 3.3. The numbers available for this group of women were too small for a chi-square statistical analysis to be considered accurate, and a p-value was therefore not calculated.

Table 3.3 Outcomes for first and second pregnancies not exposed to warfarin

	Normal liveborn (2^{nd} pregnancy)	**Poor outcome (2^{nd} pregnancy)**
Normal liveborn (1^{st} pregnancy)	23	3
Poor outcome (1^{st} pregnancy)	2	1

An analysis of first pregnancy outcome compared to outcomes in a combined group of subsequent pregnancies was not done. This was mainly because combining the pregnancies would have ignored the fact that some pregnancies were exposed to warfarin, while others were not, therefore making the results of any analysis difficult to interpret.

3.5 MANAGEMENT PRACTICES

3.5.1 Warfarin and heparin use

Of the study cohort, 231/318 (72.6%) pregnancies were exposed to warfarin, and 102/318 (32%) had been exposed to heparin. Of the 102 women who used heparin, all except one were also exposed to warfarin. As stated previously, pregnancy outcome was significantly related to warfarin exposure (see 3.4.2). Because warfarin and heparin were both used in some patients, the effect of heparin on pregnancy outcome could not be independently determined.

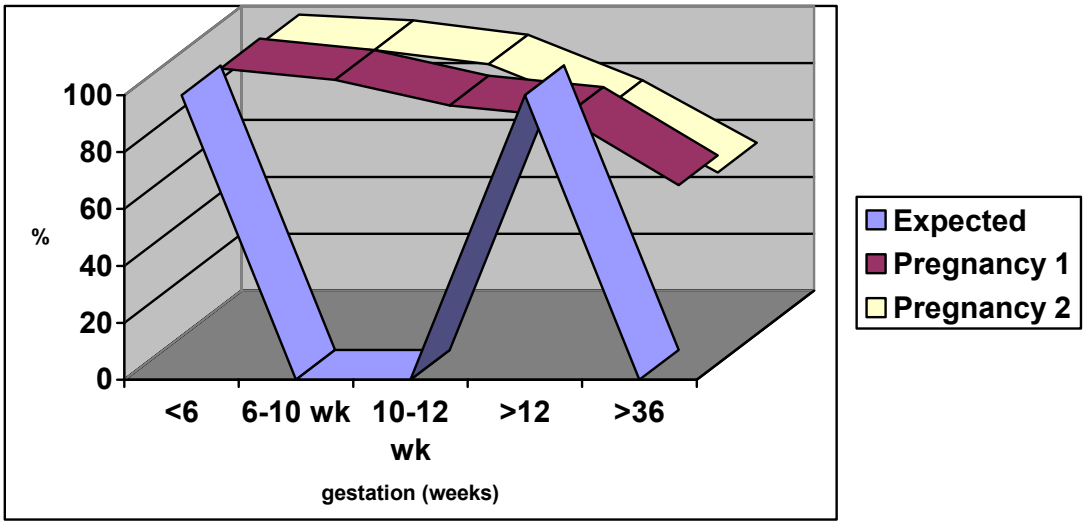
3.5.2 Timing of warfarin and heparin use in pregnancy

Data for the exact timing of warfarin and heparin use in pregnancy were not complete, because patients could often not remember this detail about a pregnancy that had occurred some years ago. Considering only the data available for pregnancies one and two, the observed numbers of pregnancies exposed to warfarin during various significant gestational periods are shown in table 3.4. The number of pregnancies exposed to warfarin during the reportedly significant period of six to ten weeks, was higher than would be acceptable under ideal management conditions. However, there was no statistical significance between the timing of warfarin use and pregnancy outcome (p-value = 0.365). Further, the number of pregnancies exposed to warfarin after 36 weeks is higher than would be expected with current management recommendations. A graph demonstrating the discrepancy between reported timing of warfarin use in pregnancies one and two and ideal management practice is shown in figure 3.2.

Table 3.4 Reported timing of warfarin exposure for pregnancies one and two.

	Total on warfarin (n)	**< 6 wks n (%)**	**6 – 10 wks n (%)**	**10 – 12 wks n (%)**	**> 12 wks n (%)**	**> 36 wks n (%)**
Pregnancy 1	77	76 (99)	73 (95)	66 (86)	63 (82)	45 (58)
Pregnancy 2	62	60 (97)	59 (95)	56 (90)	46 (74)	32 (52)

Figure 3.2 Expected versus reported trends for timing of warfarin exposure for pregnancies one and two.



3.5.3 Attendance at Antenatal Obstetric Cardiac Clinic

The Obstetric Cardiac Clinic at CHB Hospital provides care to pregnant women with cardiac disease. This group of women needs to be carefully monitored both because the physiological effects of pregnancy can adversely affect their cardiac status, and because women whose cardiac diagnosis necessitates that they take warfarin need advice and management regarding their medication. The number of pregnancies that were monitored at the Obstetric Cardiac Clinic is shown in table 3.5. Overall, women in the cohort attended the clinic during 176/318 (55.3%) of their pregnancies. Of the women on warfarin, 155/223 (69.5%) attended the clinic during their pregnancies. The highest attendance in this latter group was in the second pregnancy, where they reportedly attended the clinic in 47/61 (77%) pregnancies. During the interview, women were only questioned about whether they attended the specialized Obstetric Cardiac Clinic. It is therefore not known where women had antenatal care if they did not attend this clinic. The possibility exists that they either had no antenatal care, that they

attended a local clinic, that they attended the routine antenatal clinic at CHB, or that they attended an antenatal clinic at another hospital.

Table 3.5. Attendance at the Antenatal Obstetric Cardiac Clinic (OCC)

Pregnancy no.	Total (n)	OCC attendance n (%)	Total on warfarin n	On warfarin attended OCC n (%)
1	124	62 (50.0)	75	53 (70.6)
2	89	53 (59.6)	61	47 (77.0)
3	54	32 (59.3)	43	30 (69.8)
4	28	18 (64.3)	24	16 (66.7)
5	15	9 (60.0)	12	7 (58.3)
6	5	2 (40.0)	5	2 (40.0)
7	2	0 (0)	2	0 (0)
8	1	0 (0)	1	0 (0)
Total	318	176 (55.3)	223	155 (69.5)

3.5.4 INR results

Data collected in this study pertained to non-pregnant INR results. There was no statistical variation between the INR results obtained on the day of the interview, at the previous visit, and six months prior to the interview date. Differentiation of INR values into the target range of 2.0 – 3.5, the sub-therapeutic range of <2.0, and a range >4.0 (considered to be the level at which risk of bleeding increases), for the groups delineated above, is shown in table 3.6. On average, across the three groups, 46.2% of patients had INR values in the target range of 2.0 –

3.5, and 9.7% of patients had levels >4.0. Of the women who had INR values >4.0 on the interview day, 5/13 (38.5%) had had a similarly high value at the previous visit.

Table 3.6. INR values for patients on the day of the interview, at the previous visit, and six months prior to the interview

INR	Interview day n (%)	Previous visit n (%)	6 months prior n (%)
Total recorded values (n)	122	119	120
<2.0	50 (41.1)	43 (36.1)	41 (34.2)
2.0 – 3.5	54 (44.3)	55 (46.2)	58 (48.3)
>4.0	13 (10.7)	12 (10.1)	10 (8.3)

3.5.5 Referral for genetic counselling

Of the 124 women interviewed, only three (2.4%) reported having been referred for genetic counselling. Of the women interviewed who reported having abnormal children, all were offered an appointment at the Genetic Counselling Clinic at CHB Hospital for an assessment of their abnormal child, but none of them have availed themselves of the offer thus far (see section 1.4). After cross checking records in the Genetic Department with patient interviews, it was found that two women had received genetic counselling during their warfarin-exposed pregnancies, but reported that they had never received such counselling in the study interview. Overall, therefore, 5/124 (4%) women in the cohort received genetic counselling.