

CHAPTER 4

DISCUSSION

4.1 PATIENT AWARENESS

The group of women studied were, in general, literate, had been taking warfarin for many years, and mostly recalled having been given some information about the adverse effects of warfarin in pregnancy. They also appear to be a compliant group of patients, judging from the lack of variation in their INR results over time. One would therefore assume that these women would be knowledgeable about their medication, and the risks it poses in pregnancy.

This assumption is not verified by the results of this study. Only 40% of the interviewees thought that warfarin posed a personal risk in pregnancy, and very few (4/107 or 3.7%) reported bleeding as a specific harmful effect in their babies; this despite warfarin being an anticoagulant that crosses the placenta. Further, their knowledge about the exact effects of warfarin on the fetus was often inaccurate. Despite most of the interviewees recalling that they were told that warfarin could have an effect in pregnancy, the information did not appear to be specific or detailed. It must be highlighted that many of the women had gained knowledge of the effects of warfarin through direct experience rather than through health education.

Misperceptions about the contraceptive effects of warfarin and cardiac disease in general were not uncommon in the group, and are of concern. Another concern regarding contraception is that about a third of the women interviewed were using no method of contraception.

Unplanned pregnancies in these high-risk women can have serious negative implications for themselves and their fetuses. Not only can pregnancy cause deterioration in their cardiac function, but an unplanned pregnancy does not allow for careful timing of the use of warfarin and heparin to minimize the adverse effects to the fetus.

The group of interviewees lacked understanding about the basic effects of warfarin (for instance, that it causes bleeding), and about the implications of their underlying cardiac disease in pregnancy, which necessitates the need for such events to be planned. Further, they lacked specific and detailed information about warfarin therapy in pregnancy, particularly as regards the effects of warfarin on themselves and their fetuses, and what management options are available to them during pregnancy. The lack of such detailed information disempowers this high risk group of women from making critical decisions about their reproduction. The fact that the study cohort appears to be an educated, receptive and motivated group of patients suggests that their lack of understanding about the researched topic is due to inadequate or inappropriate education on the part of health care professionals rather than an unwillingness or inability on the patients' part to obtain more information.

The overall lack of awareness in this study cohort about the effects of warfarin and the implications of their cardiac disease in pregnancy, seems to be in concordance with the poor patient awareness found in the studies done by Lip et al. (2002) and Nadar et al. (2003). It would therefore appear that the education of cardiac patients on warfarin therapy is not being particularly well-addressed in multiple settings.

The knowledge obtained in this study about the demographics of this group of high risk women and the particular areas of deficiency in their knowledge should be taken into account when planning education programmes and pamphlets in the future.

4.2 PREGNANCY OUTCOMES

Warfarin has been shown to significantly influence the outcomes of pregnancy in this study. The reason that warfarin was not significantly related to pregnancy outcome for pregnancies four onward, is probably because the number of patients in each of these pregnancy groups became too small to lend statistical power to the calculations. Nevertheless, the trend toward poor pregnancy outcome continued in these pregnancies. More than half the pregnancies exposed to warfarin in this study resulted in an abnormal liveborn baby, a spontaneous miscarriage, or an intrauterine death (55.2%). These figures confirm our initial impressions about the seriousness of the local situation, and echo the results of another study with high figures for poor outcome (Sadler et al., 2000). The large sample size of the current study cohort (124 women) lends credibility to these results.

All the babies reportedly born with a physical abnormality were exposed to warfarin. Despite the fact that none of the surviving abnormal children was examined, the information gleaned from the interviewees strongly suggests that many had features in keeping with a diagnosis of warfarin embryopathy. The estimated rate of WE in this study of 4.5% - 5.4% is in keeping with rates published from local and international populations (Sareli et al., 1989; Chan et al., 2000; Ginsberg et al., 2001; Hall et al., 2001; Van Driel et al., 2002).

These results should particularly be noted by clinicians who argue that the effects of warfarin in pregnancy are overemphasized, and who regard a WE rate of about 5% as insignificant.

This study shows that if clinicians focus only on the WE rate as a measure of complications in warfarin-exposed pregnancies, they are enormously underestimating the effects of warfarin on pregnancy outcome because they are disregarding the fact that 50% of these pregnancies result in either spontaneous miscarriage or intrauterine death of the fetus. These latter complications are not insignificant to the women concerned.

The figures from this study are almost certainly an under representation of the true problem. Most of the women who declined to be interviewed gave poor pregnancy outcomes as a reason for declining the interview. Had they been included in the final analyses, the figures for poor outcome in warfarin-exposed pregnancies may well have been elevated. Further, the women who attended the Valvular Heart Clinic, and from whom the study cohort was sampled, represent a group of relatively compliant patients. Given the poor outcomes in this group, one would surmise that the non-compliant patients who do not attend the Valvular Heart Clinic (and who were not available for interviewing), are even less knowledgeable about the risks of warfarin in pregnancy, and less likely to have adequate antenatal care. These non-compliant women probably have even worse pregnancy outcomes than those recorded here; because they are non-compliant, they are less likely to have adequate anticoagulation, and they probably have INR values that fluctuate. They are less likely to present early in pregnancy and therefore less likely to have their warfarin switched to heparin timeously, and they are probably less likely to have any form of antenatal care in pregnancy given their poor compliance regarding their cardiac condition.

In this study, the outcome in the first pregnancy was shown to be significantly correlated with the outcome in the second pregnancy. Clinicians and counsellors need to be aware of this trend when regarding the group of women with prosthetic heart valves as a whole, but they

should probably not quote this trend during counselling on an individual basis. In other words, a woman who has had a normal first pregnancy, whether warfarin-exposed or not, is likely to have another normal baby, but she is not assured of this outcome. Similarly, the assumption should not be made that women who have had a poor first pregnancy outcome can never have a normal baby, though the chances are statistically higher that she will have a poor outcome in future pregnancies. Given this knowledge, women with a poor outcome in the first pregnancy should be monitored extremely closely in future pregnancies.

This correlation between first and second pregnancy outcomes suggests that some women may be genetically predisposed to having either normal or abnormal pregnancies. The results of this study do not allow one to conclude whether the adverse effects of warfarin are manifesting independently of the genotype, or whether the drug's effect is directly related to the background genotype. A woman's genotype may influence her pregnancy outcome because of a direct interaction with warfarin, such as her genetically determined ability to metabolise the drug (see section 1.2.6). However, the genetic-warfarin interaction may be more indirect. For instance, the drug may be acting at multiple sites (such as enzymes and receptors) within metabolic pathways. Such an interaction has already been shown between warfarin and the product of the *ARSE* gene (Franco et al., 1995)(see section 1.1.1).

4.3 MANAGEMENT PRACTICES

4.3.1 Concomitant medication

Of all the concomitant drugs currently being used by the women in the study, only the antiepileptics (phenytoin and carbamazepine) and second-generation ACE-inhibitors are considered teratogenic in man (Briggs, Freeman and Yaffe, 2002b,c and d). Although amiodarone, a class III antiarrhythmic drug, causes fetal abnormalities in animal studies, it is

not clear if it causes abnormalities in humans (Briggs et al., 2002a). Unfortunately, because of the inaccuracy of the data regarding the starting dates of these medications, no conclusions can be drawn about their effect on the pregnancy outcomes in the study cohort.

Since all the women interviewed are still in the reproductive age-group, they should receive genetic counselling regarding the potential teratogenic effects not only of warfarin, but of the other known and potentially teratogenic medications mentioned above (see section 4.3.4 for related discussion).

The use of concomitant medications with warfarin not only increases the risk of teratogenicity, but may also interfere with warfarin metabolism, and therefore, with anticoagulation. Amiodarone inhibits the metabolism of warfarin, and thereby potentiates anticoagulation, whereas carbamazepine enhances warfarin metabolism and may reduce anticoagulation (Hirsh et al., 2003).

It is known that dietary intake of vitamin K (in the form of green vegetables or vitamin K supplements) can also reduce the anticoagulant effect of warfarin (Hirsh et al., 2003) (see section 1.1.1). The interaction between drugs, diet, and warfarin therefore becomes complex, and adds to the difficulty in predicting exactly how much warfarin a fetus may be exposed to. Even as our understanding improves of how genotypes influence warfarin metabolism, these confounding variables will continue to complicate genetic counselling in warfarin-exposed pregnancies.

4.3.2 Warfarin and heparin use

In order to reduce the teratogenic effects of warfarin (warfarin embryopathy), it is currently recommended that women with prosthetic heart valves should not take this drug for anticoagulation between weeks six and nine of pregnancy (and preferably to the end of week twelve). To avoid haemorrhagic complications in the newborn, it is recommended that warfarin is not administered to pregnant women around the time of delivery (after 37 weeks) (Hall et al., 1980; Hirsh et al., 2003).

The fact that 95% of the women in this study reported taking warfarin during weeks six to ten (considering only pregnancies one and two), is concerning. There are a number of explanations as to why they were exposed to warfarin during the first trimester:

- As stated previously, there is no consensus among clinicians about which anticoagulant regimen should be followed for pregnant women with prosthetic heart valves, a situation which also exists at CHB Hospital, where the interviewees were managed during their pregnancies. The attending clinicians may have intentionally decided to use warfarin throughout pregnancy because of the high risk of TEC with anticoagulant regimens not containing warfarin. This would explain why at least some of the women were exposed to warfarin during the six to twelve week period of the first trimester.
- Women who were taking warfarin in the first trimester may not have presented to the Antenatal Clinic before 12 weeks, and clinicians would therefore not have had an opportunity to use an alternative anticoagulant regimen. The women's decision not to present to CHB before 12 weeks may have been intentional (fear of using injectable heparin as an anticoagulant, reluctance to disclose a pregnancy, disbelief that warfarin poses a risk in pregnancy), or unintentional (lack of knowledge that warfarin

embryopathy can result if the fetus is exposed to warfarin in the first trimester, lack of knowledge that ‘early’ presentation in pregnancy when on warfarin amounts to presenting at four to six weeks).

- Women taking warfarin may have presented timeously to have their anticoagulation changed. However, the attending clinician may have omitted to do so. This omission may have been intentional, or unintentional due to a lack of knowledge of the effects of warfarin in pregnancy, and that alternatives to using warfarin anticoagulation throughout pregnancy (namely, heparin), exist.

More than 50% of the pregnancies (pregnancies one and two) were exposed to warfarin after 36 weeks; a time when delivery is imminent. Even when a decision is made to use warfarin throughout pregnancy, it is accepted that warfarin should be discontinued at about 37 weeks to allow coagulation to return to normal in the fetus before delivery, and therefore minimize the risk of haemorrhagic complications as a result of labour and birth. Certainly a percentage of women taking warfarin may have presented to CHB in premature labour, precluding clinicians from switching to heparin timeously. However, many women delivered at term and were allowed to continue taking warfarin after 37 weeks. This latter scenario is an indication of less than optimal health care in this group of high risk patients, and is contrary to accepted medical practice (Hirsh et al., 2003).

Further, only 30% of pregnancies were reportedly exposed to heparin, suggesting that most women are not being treated according to internationally recommended guidelines (see section 1.2.3 for guidelines). There is clearly scope for the management of pregnant women taking warfarin to be improved. As a minimum, attention should be paid to the timing of the use of warfarin and heparin in the first and third trimesters of pregnancy.

There was no statistical significance between the reported timing of warfarin use in pregnancy and pregnancy outcome in this study. This result is at variance with the current understanding that warfarin use in the critical time periods mentioned above, has significant bearing on the pregnancy outcome; a view that has been held since the publication of the study by Hall et al in 1980. The reason for the result in the current study is probably a statistical phenomenon. Because 95% of the pregnancies were reportedly warfarin-exposed in the critical time period of six to ten weeks, the number of pregnancies not exposed to warfarin is too small to allow a statistical correlation to be shown between warfarin exposure and outcome. A prospective study on a group of pregnant women taking warfarin, including detailed information about the timing of their warfarin, should clarify this issue.

The other area of interest related to pregnancy outcome is that of warfarin dose. The data collected in this study related to non-pregnant doses only. Given that it seems that warfarin doses in pregnancy are higher than those in the non-pregnant state (Brooks et al., 2002), no comment can or should be made about the current dose of the study cohort and pregnancy outcomes in the past. The numbers of patients in other studies which have related pregnancy outcome to warfarin dose have been small (Sadler et al., 2000; Cotrufo et al., 2002). This question of how maternal warfarin dose in pregnancy relates to pregnancy outcome should also be addressed in a prospective study using a group of patients large enough to confer sufficient statistical power.

Although not the focus of the current study, other high-risk women in the child-bearing age who take warfarin, are those for whom the drug is prescribed for non-cardiac reasons (like venous thromboembolic disease, pulmonary hypertension, antiphospholipid syndrome etc). Unfortunately, as we have noted at our Genetic Clinics, many of these women are continued

on warfarin for the above-mentioned conditions when they fall pregnant, which is contrary to international guidelines (see section 1.2.3). These patients potentially never have to be exposed to warfarin, and they represent another source of individuals whose management, particularly during pregnancy, can be improved to reduce the risk of warfarin-related complications.

4.3.3. Obstetric Cardiac Clinic attendance

All the women interviewed in the study have a cardiac condition, and therefore represent a high-risk group. They should all attend the Obstetric Cardiac Clinic at the CHB Hospital during their pregnancies, which is dedicated to the specialized antenatal care of such patients. It is concerning to note that reported attendance at this clinic decreased as the number of pregnancies increased. The fact that just over half of the pregnancies (55.3%) were monitored at the clinic (both pregnancies exposed and not exposed to warfarin), is another area of concern. This again suggests that the women's understanding about the implications of their underlying cardiac conditions is suboptimal, and that the seriousness of the impact of pregnancy on their cardiac condition is perhaps not being emphasized to them. However, the fact that attendance at this clinic increased when the women are taking warfarin (69.5% of pregnancies monitored at the specialized clinic), suggests that there is an awareness, if not a full understanding, that warfarin adds to the risks in pregnancy. Although this figure represents an improvement in clinic attendance, the corollary remains that 30.5% of warfarin-exposed pregnancies were not monitored at this clinic. It is unclear whether these latter pregnancies were not monitored at all, were monitored at primary health care clinics, or were monitored at routine antenatal clinics either at CHB Hospital or at other peripheral hospitals. All of these scenarios would represent suboptimal care for such a high-risk group of women.

4.3.4 INR results

The trend in INR results did not change with time, suggesting compliance and stability within the cohort. Of note, however, is the fact that the number of patients with INR levels in the suggested therapeutic range of 2.0 – 3.5 (see section 1.2.3) was never more than 50%, and almost 10% of patients had INR values >4.0 at any one time, putting them at increased risk of having a haemorrhagic complication. Both these percentages represent less than satisfactory results which could perhaps be improved by the implementation of measures like patient self-testing and self-management, a measure that will also be cost-effective (see section 1.2.6).

The 5/13 women who had INR values >4.0 both on the interview day and at the previous visit, may represent a subgroup of women who are genetically predisposed to metabolizing warfarin differently, and may be at higher risk of haemorrhagic complications (see section 1.2.6).

4.3.5 Genetic counselling

Genetic counselling has been available weekly at the Antenatal Clinic at CHB Hospital since 1999, and on three days of the week since July 2003. Only 5/124 (4%) women interviewed have ever had such counselling, of which only 3/5 reported that they had received the counselling (see section 3.5.5). The two women who had been counselled about the effects of warfarin in pregnancy but failed to report this in the study interview may have done so for the following reasons:

- They truly did not recall having received any counselling about the effects of warfarin in pregnancy. If this is the case, it raises concerns about the efficacy of the genetic counselling session if patients do not recall even having attended such a session. It also raises the question about whether counselling during pregnancy is optimal.

Pregnancy is a time of natural anxiety. Adding to this anxiety with information about

less than favourable outcomes due to warfarin exposure in pregnancy may have resulted in complete denial of the counselling session by the women. Ideally counselling regarding the teratogenic effects of warfarin should be reserved for either before or after the pregnancy, unless fetal abnormalities are detected during a pregnancy, necessitating immediate counselling to explain the abnormalities.

- They did not understand that the counselling they received constituted ‘genetic counselling’, which is how the question is phrased in the questionnaire. The concept of ‘genetic counselling’ is not widely understood, especially in the lay public. When the interviewees therefore heard the words ‘genetic counselling’ in the interview, they may not have related the question to the counselling session they attended regarding the effects of warfarin in pregnancy.
- They consciously decided not to acknowledge having received the counselling, perhaps hoping to receive more counselling during the interview. Patients often deny having received information, even when it is documented that they have been given this information. Their reasons for doing this are often related to a wish to hear different information from that already discussed, particularly if the information is of a distressing or negative nature.

At the time of the interviews, 25/124 (20%) of the women were using medications, other than warfarin, that are known to be teratogenic in humans (see sections 3.2 and 4.3.1). The fact that so few women taking known teratogens are being referred for genetic counselling suggests that the clinicians attending to this group of women are either unaware of the service, or are failing to refer these patients for counselling, and that patients themselves are unaware of the service. Clearly, this issue should be addressed in future education campaigns to both

health care professionals and patients so that patients can make informed choices about their pregnancies with an awareness of the outcomes associated with their medications.