CHAPTER 5

CONCLUSION

The results of the study reported here follow analysis of information obtained after interviews with 124 women of child-bearing age who take warfarin, and have had at least one pregnancy while taking the drug. This is the largest cohort of SA women to be studied regarding the outcomes of their pregnancies while taking warfarin. To our knowledge, it is also the first study to assess patient awareness of the effects of warfarin in pregnancy in a group of women of childbearing age taking this medication, and to assess how they recall being managed in their pregnancies. The majority of the women interviewed took warfarin to prevent clotting of a prosthetic heart valve.

5.1 PATIENT AWARENESS

Previous studies on patients taking warfarin have shown that their awareness is suboptimal regarding their cardiac disease and the effects of warfarin (Lip et al., 2002; Nadar et al., 2003). This study has confirmed these findings in a group of women of child-bearing age. The importance of the current study is that this lack of awareness impacts not only on the health and reproductive choices for the women studied, but on their fetuses and babies.

The study showed that women taking warfarin lack knowledge about the effects of warfarin in general, the effects of warfarin in pregnancy, the need for planned pregnancies, and what management options are available to them. Anecdotes from the interviews also showed that misperceptions exist about the effects of warfarin, and the effects of cardiac disease and

warfarin on fertility. Specific areas of deficiency in patient awareness have thus been identified that should be addressed in future patient education programmes. Further, knowledge gained in this study about the demographics of the group of SA urban women taking warfarin should be utilized in the construction of such education programmes and literature.

Patient education programmes that are designed to provide information focusing on the effects of warfarin in pregnancy should be instituted not only at specialized clinics like the Valvular Heart Clinic at CHB, but at all facilities where warfarin is prescribed for women of childbearing age. The demographics of the local populations concerned should be determined in all cases so that such programmes can be tailored to best serve the patients. In addition, education programmes about the general effects of warfarin should be implemented at all facilities where warfarin is prescribed, irrespective of whether women of childbearing age are being treated.

5.2 PREGNANCY OUTCOMES

It is well documented that warfarin is teratogenic, resulting in WE and CNS abnormalities in the fetus, and also causing spontaneous miscarriage and intrauterine death when taken by pregnant women. Early studies quoted WE rates of about 16% (1/6) (Hall et al., 1980). More recent studies have found WE rates of 4% (Sareli et al., 1989), 6% (Hall et al., 2001), 6.4% (Chan et al., 2000), and 11% (Ginsberg et al., 2001). The estimated WE rate in the current study was 4.5% - 5.4%; in keeping with other local and international rates.

The study confirmed our impression that local pregnant women taking warfarin have poor pregnancy outcomes. Overall, 55.2% of warfarin-exposed pregnancies resulted in a poor

outcome (abnormal liveborn baby, a spontaneous miscarriage, or an intrauterine death). These figures are among the highest reported in the literature, and as discussed previously (see section 4.2), may be an under representation of the true extent of the problem. Even if the figure represents a minimum prevalence of the poor outcome rate in this group of high-risk women, it provides a baseline from which to work. It is imperative that this prevalence rate is communicated not only to the clinicians dealing with the group of women studied, but to clinicians across the country, since women with prosthetic heart valves taking warfarin during their pregnancies are treated nationwide. Making clinicians aware of the extent of the problem will hopefully result in improved care and more careful monitoring for this group of women, and result in a reduction in the poor pregnancy outcome rate in the future.

The effect of warfarin on pregnancy outcome was statistically significant (p-value <0.0001). Similarly, the outcome of the first pregnancy (normal liveborn or poor outcome) was found to be significantly correlated to the outcome in the second pregnancy (p-value <0.001). Although these figures suggest that a genetic component plays some role in the pregnancy outcome in the group of women studied, it is not clear whether this is acting in concert with or independently from the effects of warfarin. Some genes have been identified which interact with warfarin. In particular, the *CYP2C9* gene influences the metabolism of warfarin, and may therefore affect how much warfarin fetuses are exposed to if pregnant women take the drug, or how fetuses metabolise warfarin. Studies to identify the frequencies of variants of this gene and their effects on warfarin metabolism in the black SA population are planned. The results of these studies may allow correlation between maternal and/or fetal genotype with pregnancy outcomes in the future. The results of this study may also aid clinicians in choosing optimal doses of warfarin for patients depending on their genotype.

5.3 MANAGEMENT PRACTICES

At present it is not clear how the CNS abnormalities produced by warfarin in fetuses can be prevented. However, WE can largely be avoided if women do not take the drug between weeks six and nine of pregnancy, and preferably not at all in the first trimester of pregnancy. Further, the haemorrhagic complications related to warfarin exposure in the newborn can be avoided if women do not take the drug after 37 weeks gestation.

Most women with prosthetic heart valves require warfarin for anticoagulation of the valve, even in pregnancy. Currently recommended management regimens attempt to balance the risk of fetal warfarin effects and maternal risk of TEC and death if warfarin is not used.

Clinic attendance at the Obstetric Cardiac Clinic in the women interviewed was suboptimal. Even though the attendance rose from 55.3% to 69.5% during warfarin-exposed pregnancies, the number of women taking warfarin while pregnant and not attending a specialized antenatal clinic designed for their needs is a matter of concern, and one that needs to be addressed.

The fact that <50% of INR values in the cohort were not in the recommended therapeutic range, and that this trend was consistent over time, suggests that suboptimal anticoagulation in this high-risk group is a long-standing problem. The issue of suboptimal anticoagulation must be considered together with that of overcoagulation, reflected in the 10% of INR values that were >4.0, also consistent over time. An improvement in coagulation, as reflected by monitoring INR values could perhaps be improved not only be increasing patient awareness and hence compliance, but also be the implementation of home INR testing with patient self-management.

Of the women interviewed in this study, 95% reported having taken warfarin during weeks six and ten of pregnancy, and more than 50% reported using warfarin after 36 weeks gestation. They were therefore exposed to warfarin during time periods in pregnancy known to be critical in the determination of at least some of the adverse effects of warfarin in pregnancy, and completely at odds with internationally accepted guidelines. The reasons for this situation are complex, but relate to issues regarding both the patients and clinicians attending them.

Only 5/124 (4%) of the women interviewed had ever received genetic counselling regarding the implications of warfarin in pregnancy. Of these, only 3/5 reported that they had attended such counselling. Further, 25/124 (20%) of the interviewees were taking additional medications known to be teratogenic; a further indication for genetic counselling. Although a genetic counselling service exists and is readily available to women at all the teaching hospitals in Johannesburg, these figures highlight the fact that the women are not being referred for counselling. Referral for genetic counselling is therefore another area in the management of women of child-bearing age who take warfarin that should be improved so that they are making informed choices regarding their pregnancies.

In order to improve the management of pregnant women taking warfarin, and bring management practices in line with international guidelines, both patient and clinician issues will need to be addressed. Appropriate patient education should help to raise their awareness about the need for planned pregnancies, that they need to present to the Antenatal Clinic before six weeks of pregnancy, and the need to attend this clinic regularly during pregnancy. If patients understand the effects of warfarin and that the management regimens in pregnancy are designed to help them and their babies, they will probably be more inclined to present at

appropriate times in pregnancy, and be compliant about attending the Obstetric Cardiac Clinic.

Improving the reported trends quoted above depends not only on patients improving their compliance with treatment, but depends largely on the clinicians attending to these women taking a more active role in their care. The first step in improving the situation is that clinicians need to acknowledge that poor pregnancy outcomes are unacceptably high in women taking warfarin in pregnancy, and accept that this is a health issue that needs urgent attention. Secondly, they have to accept some responsibility for the gravity of the current situation, since the education and management of patients falls directly under their control. Thirdly, if clinicians truly wish to provide a comprehensive service to these women, they need to adopt a broader multidisciplinary approach, including recognizing the need for adequate genetic counselling in these women.

5.4 FUTURE CONSIDERATIONS

Women of childbearing age who require warfarin therapy, will always be a high-risk group of patients. Both their underlying medical conditions requiring warfarin therapy, and the warfarin itself, impair their ability to have a high percentage of normal pregnancy outcomes. Although these women tend to have less than favourable pregnancy outcomes worldwide, the current local situation, as reported here, appears to be more serious than that seen in most other countries.

This study has also highlighted the lack of adequate patient awareness about the effects of warfarin, and the shortcomings in the current management of pregnant women taking warfarin. These areas are both amenable to improvement. Future campaigns to provide

appropriate patient education about the effects of warfarin, specifically among women of childbearing age, should help to reduce at least some of the spontaneous miscarriages, intrauterine deaths, and abnormal liveborn babies that occur in these women. In addition, a concerted effort on the part of clinicians attending to women of childbearing age to improve the current deficiencies in the management of these patients should further help to reduce the poor pregnancy outcomes quoted above.

A novel approach to the care of patients on chronic warfarin therapy, like POC INR testing at home with patient self-management, may need to be considered. Contrary to initial assumptions, this approach may provide accessible and cost-effective care to many patients currently receiving sub-optimal or no care.

Finally, it is hoped that with further genetic studies a correlation between genotype and pregnancy outcome may emerge. This kind of information may allow for individualization of warfarin therapy, and may also allow more accurate prediction of which women (or fetuses) in this already high-risk group of women, are at particularly high risk for having adverse pregnancy outcomes. Such an advance may further help to reduce the high incidence of poor pregnancy outcomes reported in this urban black SA group of women.