prophylaxis of postoperative leg vein thrombosis (Kakkar *et al.*, 1972; Gordon-Smith *et al.*, 1972; Lahnborg *et al.*, 1974). The obstacle to the universal acceptance of heparin prophylaxis has been the fear of haemorrhage resulting from interference with the clotting mechanisms. Numerous alternative methods have been designed to promote venous return from the legs during operation. The best of these (which include leg bandaging, leg elevation, intermittent ankle movements, rhythmic calf muscle stimulation, and pneumatic compression) seem to be the last two, both of which in controlled clinical trials have reduced the incidence of leg vein thrombosis (Browse and Negus, 1970; Roberts and Cotton, 1974).

Our results show that a regimen of low-dose subcutaneous heparin is an effective prophylaxis for patients undergoing laparotomy. Electrical calf muscle stimulation was nearly as effective in these patients but only when the operation was for a benign condition. That this may have been due to the different duration of prophylaxis is suggested by the work of Gordon-Smith *et al.* (1972), who reported that heparin administration confined to the 24 hours during and after operation was ineffective in patients suffering from malignant disease.

It is generally thought that leg vein thrombi originate during operation but we detected only two-thirds of the episodes of thrombosis in the control group on the first day after operation. The remainder apparently formed on the second day or later and prophylaxis confined to the period of the operation could not be expected to prevent them.

Though the electrical method is safe and without side effects (so long as the apparatus is adequately designed) and may be the method of choice in patients undergoing laparotomy for benign disease it seems to be a poor alternative to heparin for routine use.

Some of the patients studied were under the care of Mr. T. F. R. Griffin, Mr. D. M. Fletcher, and Mr. G. M. R. Smith, and we are indebted to them for their cooperation.

We thank Laboratoire Choay Ltd., Paris, who supplied the heparin calcium, and the Leeds Regional Hospital Board for financial support.

References

British Medical Journal, (1973), **2**, 1.
Browse, N. L., and Negus, D. (1970). *British Medical Journal*, **3**, 615.
Browse, N. L., Clemenson, G., and Croft, D. N. (1974). *British Medical Journal*, **1**, 603.
Department of Health and Social Security (1974). Circular R/M1069/1089.
Doran, F. S. A. (1971). *British Journal of Hospital Medicine*, **6**, 773.
Gordon-Smith, I. C., *et al.* (1972). *Lancet*, **1**, 1133.
Kakkar, V. V., *et al.* (1970). *Lancet*, **1**, 540.
Kakkar, V. V., *et al.* (1972). *Lancet*, **2**, 101.
Lahnborg, G., *et al.* (1974). *Lancet*, **1**, 329.
Roberts, V. C., and Cotton, L. T. (1974). *British Medical Journal*, **1**, 358.

Maternal Serum α-Fetoprotein Levels in Multiple Pregnancy

NICHOLAS WALD, SHEILA BARKER, RICHARD PETO, D. J. H. BROCK, J. BONNAR

British Medical Journal, 1975, **1**, 651-652

Summary

Maternal serum α-fetoprotein (AFP) levels were higher in 10 twin pregnancies and one triplet pregnancy than in 22 control singleton pregnancies matched for maternal age, parity, and the time of gestation at which the serum sample was taken. In twin pregnancies the average AFP levels were double those found in singleton pregnancies and the level in the triplet pregnancy was even higher. Raised maternal serum AFP values due to multiple pregnancy should not cause unnecessary amniocentesis in the diagnosis of anencephaly or spina bifida if an ultrasound investigation is routinely performed first.

D.H.S.S. Cancer Epidemiology and Clinical Trials Unit, Department of the Regius Professor of Medicine, Radcliffe Infirmary, Oxford. OX2 6HE
NICHOLAS WALD, M.R.C.P., Lecturer in Medicine
SHEILA BARKER, B.SC., Research Officer
RICHARD PETO, M.SC., Lecturer in Statistics

University Department of Human Genetics, Western General Hospital, Edinburgh
D. J. H. BROCK, PH.D., Lecturer in Human Genetics

Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Oxford
J. BONNAR, F.R.C.O.G., Clinical Reader in Obstetrics and Gynaecology

Introduction

Maternal serum α-fetoprotein (AFP) levels are abnormally high with anencephaly and spina bifida (Wald *et al.*, 1974; Brock *et al.*, 1974), and their measurement may be useful in screening pregnant women for these abnormalities. There is, however, a lack of information on other factors which can cause high AFP levels. It has been suggested that the fetus is the source of the increased maternal serum AFP in pregnant women (Seppälä and Ruoslahti, 1972), and we therefore examined the relation between multiple pregnancy and maternal serum AFP levels early in pregnancy.

Methods

In Oxford, where a large prospective survey of the outcome of pregnancy has been in progress for nearly two years, about 40 000 antenatal serum samples have been stored routinely at −40°C. From this survey 10 twin pregnancies and one triplet pregnancy were each matched with two control singleton pregnancies for age of mother (within three years), parity, and time of gestation at which a serum sample was obtained (within 17 days). Sera were taken at or before 20 weeks gestation in all the multiple pregnancies except one, which was taken at 25 weeks. No patient had had a previous child with a neural tube defect, and all the pregnancies had resulted in normal infants. None of the women with a twin pregnancy or their controls had a past history of abortion. The patient with the triplet pregnancy (case 11) had had three previous abortions and was matched with two control patients, each with two previous abortions. Sera from these 33 pregnant women were assayed for AFP using a double-antibody radioimmunoassay (Brock *et al.*, 1974). All the reagents used in the assay were from the same batch, and the estimations were performed without knowledge of details of the women or their pregnancies. Each sample was assayed three times.

Details of Patients and α-Fetoprotein Levels in each of 11 Multiple Pregnancies and their Two Matched Singleton Pregnancies A and B. Results of Three Assays of α-Fetoprotein Levels are given, and Median Values are given in Italics

Multiple Pregnancy					Control Singleton Pregnancies				
					A		B		
Case No.	Parity	Maternal Age (Years)	Time of Blood Sample (Week + Day of Gestation)	AFP (μg/l)	Maternal Age (Years)	Time of Blood Sample (Week + Day of Gestation)	AFP (μg/l)	Maternal Age (Years)	Time of Blood Sample (Week + Day of Gestation)	AFP (μg/l)
1	1+0	25	18+0	133 *140* 235	25	17+4	36 *42* 65	24	19+0	35 *42* 70
2	0+0	29	11+5	29 *42* 60	29	11+5	<8 *22* 25	29	10+6	32 *34* 41
3	0+0	24	18+6	75 *110* 113	24	18+2	37 *44* 63	24	20+0	28 *49* 49
4	1+0	23	15+3	73 *85* 153	23	15+1	53 *68* 75	23	16+2	55 *75* 80
5	1+0	35	17+2	73 *88* 100	35	16+2	13 *29* 44	35	17+2	41 *48* 58
6	0+0	28	9+6	<8 *15* 15	28	10+4	<8 *9* 15	28	10+0	<8 *<8* 21
7	0+0	25	11+5	13 *26* 50	25	12+6	<8 *10* 11	25	12+4	<8 *<8* <8
8	0+0	36	25+1	260 *300* 350	34	24+0	100 *115* 118	33	24+3	53 *68* 75
9	0+0	27	12+2	19 *29* 44	27	11+2	<8 *18* 29	27	10+6	<8 *<8* <8
10	1+0	22	18+3	65 *75* 108	22	17+2	55 *70* 70	22	17+1	46 *53* 68
11*	1+3†	35	18+3	90 *173* 183	33	17+4	60 *85* 115	33	17+4	12 *16* 17

*Triplet pregnancy; cases 1 – 10 are twin pregnancies. †See text.

Results

Details of the 11 multiple pregnancies and the 22 control singleton pregnancies are given in the table. In each multiple pregnancy the maternal serum AFP level was higher than in either of the two corresponding control pregnancies ($P < 0.001$). In the twin pregnancies the geometric mean level was 2·1 times (90% confidence interval 1·5-3·2) that in singleton pregnancies. In the triplet pregnancy the level was 4·7 times higher than in the corresponding controls though it was not possible to place any confidence limits on this result.

Discussion

Our results indicate that maternal serum AFP levels in the first half of pregnancy are higher in multiple pregnancies than in singleton pregnancies. Garoff and Seppälä (1973) and Ishiguro (1973) have shown that this is also the case during the second half of pregnancy, but from their data it is impossible to assess whether this effect may have been due to other factors which might influence AFP levels such as maternal age, parity, or previous history of abortion.

The association between multiple pregnancy and maternal serum AFP is consistent with the fetus being the source of the AFP. To avoid an unnecessary amniocentesis for the diagnosis of anencephaly or spina bifida in patients with raised serum AFP levels an ultrasonic examination should first be performed to exclude multiple pregnancy and identify anencephaly (Campbell, 1974). If the pregnancy is single and has not been shown to be associated with anencephaly amniocentesis may then be performed under the guidance of the ultrasound scan. Measurement of AFP in the amniotic fluid enables the diagnosis of neural tube defects to be made with some confidence (Brock *et al.*, 1975). The main difficulty, however, in using maternal serum AFP levels in all pregnant women to indicate whether an amniocentesis should be performed is that the definition of a raised level is still uncertain. When the distributions of "normal" and "abnormal" values are better established, and as AFP assay techniques are improved, the critical level of maternal serum AFP may become clear.

In a twin pregnancy one or both infants might be affected by a neural tube defect. To cover this possibility for spina bifida it would be necessary to judge whether the maternal serum AFP level were high in relation to a normal distribution of AFP levels in twin pregnancies. If it were and if amniocentesis were performed the AFP level in the amniotic fluid would similarly have to be compared with normal levels in twin pregnancies before any decision could be reached. This is largely an academic point, however, since spina bifida in a twin pregnancy occurs very rarely (about one in 40 000 of all births; Leck, 1974). Moreover, establishing normal and abnormal distributions for such pregnancies will not be possible for a considerable time.

Since multiple pregnancy produces high maternal serum AFP values investigators quoting normal values should state whether they relate entirely to singleton pregnancies. This will tend to separate the distribution of normal and abnormal values by reducing the "overlap" of the two distributions, and thus increase the specificity of the test in the diagnosis of anencephaly and spina bifida.

We thank Dr. S. Nishi of Hokkaido University, Japan, for a gift of purified AFP; Dr. A. E. Bolton for performing the radiolabelling of the AFP; Sister Hazlewood and Staff Nurse Davies for administering the Oxford study of pregnancy; Lilias Barron, Rosemary Brett, Marjorie Hall, Cathy Harwood, Edith Ritchie, and Nancy Wald for their technical help; Peter Smith, Martin Vessey, and Leo Kinlen for their advice; and the staff of the John Radcliffe Hospital, Oxford, for their co-operation. The research was supported by the Department of Health and Social Security and by the Association for Spina Bifida and Hydrocephalus.

References

Brock, D. J. H., Bolton, A. E., and Scrimgeour, J. B. (1974). *Lancet*, **1**, 767.
Brock, D. J. H., Nelson, M. M., and Scrimgeour, J. B. (1975). *Clinical Genetics*. In press.
Campbell, S. (1974). *Excerpta Medica*, International Congress Series, No. 297.
Garoff, L., and Seppälä, M. (1973). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **80**, 695.
Ishiguro, T. (1973). *Lancet*, **2**, 1214.
Leck, I. (1974). *British Medical Bulletin*, **30**, 158.
Seppälä, M., and Ruoslahti, E. (1972). *American Journal of Obstetrics and Gynecology*, **112**, 208.
Wald, N. J., Brock, D. J. H., and Bonnar, J. (1974). *Lancet*, **1**, 765.