SERUM LEVELS OF IgG AND α -MACROGLOBULIN AND INCIDENCE OF CRYOFIBRINOGENAEMIA IN WOMEN TAKING ORAL CONTRACEPTIVES

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(Received 14th September 1971, accepted 27th October 1971)

The effectiveness and ease of administration of combined oestrogen–progestagen preparations as oral contraceptives generated considerable optimism in the field of fertility control, but the demonstration of associated metabolic changes and side effects has dampened the enthusiasm for a universal acceptance of this technique. The most serious of these complications is thromboembolism. The controversial data reviewed by Doll (1971) indicate that women taking oral contraceptives are at a four to eight times greater risk of developing thrombosis of the deep veins of the lower limbs, pulmonary vessels, cerebrovascular system, mesenteric and other abdominal arteries, hepatic vein radicles and coronary arteries. The delicate physiological balance between the complex systems of blood clotting and fibrinolysis may be disturbed by several means, one of which is the change in α -macroglobulin concentration which diminishes the fibrinolytic activity of plasmin *in vitro*. An increase in thromboplastin activity generates thrombin intravascularly which acts on fibrinogen. If this reaction is incomplete, cold-precipitable intermediates are formed. It was considered, therefore, that the estimation of α -macroglobulin and the detection of cryofibrinogenemia might throw some light on the possible aetiopathogenesis of thromboembolism associated with the use of oestrogen–progestagen contraceptives.

Twenty healthy women were studied. Venous samples of blood were taken on three occasions: (1) before initiation of contraceptive therapy; (2) towards the end of a 12 weeks' course of treatment; and (3) 12 weeks after the discontinuation of oral contraceptives. The preparations used were 'Noracyclin 22' (CIBA) containing 2.5 mg lynestrenol with 0.075 mg mestranol, or 'Norlestrin' (Parke-Davis) containing 2.5 mg norethisterone acetate with 0.05 mg ethinyl oestradiol USP, or 'Minovlar ED' (Schering) containing 1.0 mg norethisterone acetate with 0.05 mg ethinyl oestradiol IP given according to the manufacturers' directions. Serum IgG and α -macroglobulin were estimated by the single radial immunodiffusion method of Mancini, Carbonara & Heremans (1965) using specific antisera, and the results were expressed as a percentage of the World Health Organization Reference Standard. The technique for the detection and the grading of cryofibrinogen in the plasma was essentially that of Pindyck, Lichtman & Kohl (1970).

The results are shown in Table 1. There was a significant increase in the

levels of serum IgG and α -macroglobulin during the period of contraceptive administration. These changes tended to persist, though at a reduced level, after discontinuation of hormone therapy. Cryofibrinogen was detected more often in the phase of contraceptive intake.

Our data confirm and extend the observations of Horne, Howie, Weir & Goudie (1970) and Pindyck *et al.* (1970). Significantly, we found that the changes in α -macroglobulin and IgG concentration persisted for at least 3 months after the discontinuation of the hormones. Perhaps the increased risk of thrombo-

TABLE 1
SERUM PROTEIN LEVELS AND INCIDENCE OF CRYOFIBRINOGENAEMIA IN TWENTY WOMEN
TAKING ORAL CONTRACEPTIVES

Phase	IgG (% W.H.O. Standard)	α -Macroglobulin (% W.H.O. Standard)	Cryo- fibrinogen (%)
A. Before contraceptive intake Range Geometric mean $\pm$ S.E.	88 to 176 137 $\pm$ 32	95 to 200 124 $\pm$ 37	5
B. During contraceptive therapy Range Mean $\pm$ S.E.	112 to 240 188 $\pm$ 43	100 to 324 210 $\pm$ 41	30
C. After contraceptive therapy Range Mean $\pm$ S.E.	100 to 196 168 $\pm$ 29	100 to 240 172 $\pm$ 50	15
P	<0.01 for A and B <0.05 for A and C	<0.01 for A and B <0.02 for A and C	<0.01 for A and B <0.05 for A and C

embolism also does not terminate immediately on giving up the pill. The elevation in serum IgG level associated with the administration of oestrogen-progestagen preparations would indicate that a non-antigenic stimulation of the immunologically competent cells, including perhaps the forbidden clones, is taking place and this may underlie the increased frequency of autoimmune phenomena in women in general.

Similar changes have been observed during pregnancy, except that IgG levels were lower in women at term compared to the non-pregnant controls, possibly due to the haemodilution effect (Chandra, Bhasin, Vasuki & Malkani, in preparation).

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