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Platelet Aggregation during Oral Contraception*

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Summary: Platelet aggregation has been found to be significantly accelerated with the coagulation-induced Chandler's tube technique in women taking combined oestrogen-progestin oral contraceptives, though this was less than in the third trimester of pregnancy. Women taking the pure progestogen, chlormadinone acetate, have not shown this change up to the sixth month of study. In contrast the accelerated platelet aggregation resulting from conventional oral contraception became normal one month after changing to the progestogen. There was no change in the platelet aggregation response to adenosine diphosphate (A.D.P.) during oral contraception.

Introduction

Oral contraception with conventional oestrogen-progestin preparations results in rises of clotting factors, including factor X, which is involved in the "intrinsic" clotting system (Poller and Thomson, 1966). When this mechanism is accelerated by physical exertion the platelet aggregation time may also be shortened (Poller *et al.*, 1969c).

We therefore carried out studies in women taking a variety of combined oral contraceptive preparations to see if "long-term" administration produces increased platelet aggregation. During the course of the investigation it became apparent that changes in platelet aggregation were present in these women. It therefore seemed important to study women taking a pure progestogen preparation as soon as this became available for clinical trials, to see if similar changes occurred.

Method of Study

Platelet aggregation was studied by both the coagulation-induced (Chandler's tube method) and the A.D.P.-induced optical density method.

Chandler's Tube Aggregation

This was performed in women taking oral contraceptives and in two control groups—that is, 63 normal women and a group of 26 women in the third trimester of pregnancy. Women taking oral contraceptives were divided into four groups:

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(1) "High-dose" Group.—Fourteen women taking the listed conventional high-dose oral contraceptive preparations (Gynovlar, 4; Norlestrin, 2; Ovulen, 2; Conovid B, 2; Anovlar, 1; Lyndiol, 1; Minovlar, 1; Dista Sequential, 1).

(2) "Low-dose" Group.—Thirty-two women taking the relatively low-dose conventional preparations Norinyl-1 and Ortho-Novin, the latter having twice the hormone content of Norinyl-1.

(3) Progestogen Group A.—Thirty-two women taking a pure progestogen preparation (chlormadinone acetate 0.5 mg. daily) and had not taken any oral contraceptive preparation previously.

(4) Progestogen Group B.—Fifteen women who had changed to chlormadinone acetate from combined conventional preparations.

All the women attended at the same time of day (9.30–10.30 a.m.) and their blood was collected at mid-cycle. Chandler's tube platelet aggregation studies were performed in the progestogen groups before starting and after one, three, and six months of chlormadinone administration. Women on the relatively low-dose combined preparations, Ortho-Novin and Norinyl-1, were tested at the 18-month stage only. The high-dose group had been taking oral contraceptives for an average of 26 months when they were tested.

A.D.P.-Induced Aggregation

The A.D.P.-induced optical density method was also used for platelet aggregation studies in a group starting oral contraception for the first time in the progestogen study, in the women taking low-dose conventional preparations, and in the normal controls.

Technique

The Chandler's tube technique was modified for smaller volumes of blood from the method described previously (Poller *et al.*, 1969a) as follows: the tube of internal diameter 0.6 cm. was rotated at 16 r.p.m.; 4 ml. of 0.9% sodium chloride and 0.2 ml. of M/4 calcium chloride were used; 2 ml. of platelet-rich plasma was added.

The technique for the optical density method was identical to that used previously (Poller *et al.*, 1969a) but slightly modified from O'Brien *et al.* (1966). The difference between the initial and final optical density readings was measured. The figure was corrected for a platelet count of 400,000/cu. mm. The concentration of A.D.P. was 5×10^{-6} M.

Results

Results are given in the Table and the Chart; they were analysed for significance at the 5% level.

Chandler's Tube Platelet Aggregation.—The high-dose oestrogen-progestogen group showed significantly shortened platelet aggregation times. The women tested after 18 months on Norinyl-1 or Ortho-Novin also showed significantly accelerated platelet aggregation. Eighteen of them were receiving Norinyl-1 and 14 were receiving Ortho-Novin, containing twice the amount of hormone, but there was no inter-group difference in their platelet aggregation results at this stage, so the two are presented together. There was no significant difference between the low-dose and the high-dose women. The progestogen series who had not taken an oral contraceptive previously did not differ from normal initially and showed no significant change in their platelet aggregation throughout the six-month period of study. The group starting progestogen who were already taking conventional combined preparations showed significantly accelerated platelet aggregation. This became normal one month after the start of chlormadinone acetate and remained normal subsequently. The pregnant patients, in their third trimester, gave Chandler's tube platelet aggregation times significantly shorter than the normal group and significantly shorter than the oral contraceptive group.

Chandler's Tube Platelet Aggregation

Group	No. in Group	Mean Aggregation Time (min.)	S.D.
Normal controls	63	6.01	1.08
High dose combined	14	5.16	1.34
Low dose combined	32	5.09	0.73
Progestogen (A):			
Before starting	32	6.14	1.38
After 1 month	21	5.62	1.23
After 3 months	20	5.83	1.51
After 6 months	17	6.21	1.30
Progestogen (B):			
Baseline	15	5.33	0.72
After 1 cycle	13	5.94	1.62
After 3 cycles	12	5.67	1.05
After 6 cycles	8	5.76	0.68
Normal pregnancy	26	4.38	1.26

Response to A.D.P.—The response to the A.D.P.-induced optical density system showed no suggestion of change either with the conventional oral contraceptives or in the progestogen series.

Discussion

The results show that women taking conventional combined "pill" preparations for 18 months or longer have significantly accelerated platelet aggregation times with the coagulation-induced method. This does not seem to be an effect which can be related to the dose of hormone, as there is no difference between the Ortho-Novin and Norinyl-1 groups. The results of the high-dose group are also almost identical with those of the low-dose group. We have previously shown that coagulation factor increases results from this form of contraception and also that platelet aggregation in the Chandler's tube reflects rises and falls in clotting factors of the "intrinsic" system,

producing acceleration and slowing respectively (Poller *et al.*, 1969a, 1969c). Like the changes in clotting factors the increase in platelet aggregation does not seem to be dose-dependent (Poller *et al.*, 1968).

The acceleration of the Chandler's tube test was, however, far less than during the third trimester of pregnancy, when the thrombosis risk is increased but still not very great. The changes in platelet aggregation, therefore, are possibly less than the clotting factor increases which in the case of factor VII reached the level of the third trimester of normal pregnancy after two years of combined oral contraception. It would perhaps be interesting to see in a further study whether the increases in platelet aggregation mirror the clotting factor changes on a time basis.

The progestogen preparation became available to us for study on only a limited number of women recently, and therefore it has not been possible to study a strictly comparable group from a long-term viewpoint. The results are nevertheless very striking. In contrast with the combined group there is no evidence of acceleration of platelet aggregation. Perhaps more significant and important, however, is the fact that the shortened aggregation times in women who were taking combined preparations lengthen to normal during the first month of chlormadinone acetate. It may be recalled that the raised clotting factors in this same group reported elsewhere also fell towards normal on progestogen, but this took longer (Poller *et al.*, 1969b). It should be emphasized that these results, though encouraging, reflect changes to only the sixth-month stage. A longer study is necessary to exclude gradual cumulative effects, but results given in the Table and the Chart do not suggest any trend to increased aggregation.

The study again shows the divergence of results with the two systems of platelet aggregation. We have shown previously that platelet aggregation in the A.D.P.-induced optical density system is insensitive to the clotting factor changes which affect platelet aggregation (Poller *et al.*, 1969a, and 1969b).

Bolton *et al.* (1968) studied platelet sensitivity to A.D.P., using an electrophoretic technique, and in contrast to our present findings found increased sensitivity in women taking combined preparations. The electrophoretic technique depends on a completely different principle from the optical density method. In a further report Elkeles *et al.* (1968) described an increased response to A.D.P. after oestrogen administration. They used the Born technique on which our method is based. This effect, however, was obtained in nine normal men. There may be a difference in response to A.D.P. in men and women (Poller *et al.*, 1969c), or it could be explained by a sex difference in response to oestrogen.

The absence of changes in platelet aggregation with chlormadinone, taken in conjunction with the disappearance of established increases following conventional oral contraceptives when chlormadinone was substituted, is encouraging. This trial was not designed to survey the value of chlormadinone as a contraceptive, but there has been no "method failure" in our series in 1,056 women-cycles. The full clinical evaluation of this agent will have to await the results of field trials at present in progress in the United Kingdom and France.

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