OESTRIOL DEFICIENCY, A POSSIBLE FACTOR IN THE AETEOLOGY OF THROMBO-EMBOLISM IN PILL USERS

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INTRODUCTION

Recent reports regarding the common incidence of thrombo-embolic phenomena in women taking the pills are controversial. Kocen et al (1965), Cahal (1965), and others stated that it was not possible to establish a statistical relationship between thrombo-embolic deaths and the use of oral contraceptives. However, Vessey and Doll (1968, stated that oral contraceptives may still have an aggravating effect in leading to coronary occlusion in highly prone woman. Inman and Vessey (1968), studied the relationship between oral contraceptives and myocardial infraction. In an analysis of 205 deaths from coronary thrombosis, there was a slight excess of oral contraceptive users who had a coronary thrombosis when compared with the expected incidence. Oliver (1970), found that 50 per cent of women with myocardial infarctions aged 41 years or less, met with between 1965—1969, were taking an oral contraceptive. A positive correlation was found between the dose of oestrogen in the pill and the risk of pulmonary embolism, deep vein thrombosis, cerebral thrombosis or coronary thrombosis in the United Kingdom, Sweden and Denmark (Inman et al, 1970). The combined results showed an excess of cases of thrombo-embolism at the highest dose of oestrogen. In clinical trials involvng 797 women, Grant (1969), found that leg vein complaints including thrombophlebitis occurred most frequently with combined preparations containing a relatively low dose of progestogen and a high dose of oestrogen. Sartwell et al (1969), found that sequential oral contraceptives appear to be more likely to cause thrombo-embolism than combined ones.

Report of a case : Mrs. N. A. H. thirty years old, married July 1955. Para 2, first delivery April 1956 associated with eclampsia.

Second pregnancy which ended in May 1960 with full-term normal delivery was associated with medically controlled toxæmia of pregnancy.

Contraceptive history : She had 2 induced abortions in the following 3 years. Used condom for 2 years and contraceptive pills (Conovid & Anovlar) for the following 7 years regularly. Seen in Jan. 1970, she was found to have blood pressure 170/90, with marked oedema and hence advised to stop the pill. She returned to the pill on her own between March and May 1970. On the 22nd. of May 1970, she had an accute cerebral accident which ended in a right hemiplegia from which she recovered progressively.

The aim of the present investigation is to correlate the observed high incidence of thrombo-embolic phenomena in association with pill intake with a suggested hypothesis for the possible endocrinological bases of such phenomena.

MATERIAL & RESULTS

Urinary oestriol excretion in women taking the pills :

Multiparous healthy women having contraceptive pills (lyndiol 2.5 or gynanovlar) for different periods were selected for urinary oestriol assays. Twenty parous women with regular periods, not having the pills, were taken as controls. Oestriol was estimated in 24 hour urine collections between the 13th and 16th days of the cycle (expected oestriol peak), using a method slightly modified from that of Eberlein et al (1958).

Data obtained show that the mean oestriol excretion in the control group was 28.5 $\pm$ 4.79 ug/24 hrs.

Women having the pills were subgrouped as follows :

Table 1. Women who were taking the pills for variable periods between 3 & 12 months.

Table 2. Women having the pills, who were followed up by repeated oestriol assays after 3, 6, and 9 months.

DISCUSSION

It is worth mentioning that all data available up to date put all the blame of thrombo-embolic phenomena encountered with pill intake on its oestrogenic component as well as the converted progestogen to oestrogen. It must be noted that different pills contain different

types of progestogens. Some of these have inherent oestrogenic activity or are metabolized to oestrogens and hence adding to the oestrogen component. Other progestogens have anti-oestrogenic effects. This may explain the variation in the incidence of thrombo-embolic phenomena with different pills.

TABLE 1

Oestriol Excretion—Mid-Cycle Levels

Group		Number of Cases	Oestriol Excretion (ug./24 hours) mean ± S. D.)	
Control		20	28.5	4.75
Lyndiol 2.5				
	3 Months	14	9.46	2.01
for	6 Months	16	7.53	1.89
	9 Months	18	6.26	0.88
	12 Months	14	6.00	1.02
Gynanovlar				
	3 Months	17	11.37	1.81
for	6 Months	14	10.72	2.49
	12 Months	13	5.83	1.42

TABLE 2

Oestriol Excretion—Mid Cycle Levels in Cases Taking Lyndiol 2.5 or Gynanovlar and Followed up for 9 Months

Group	Number of Cases	Oestriol Excretion (ug./24 hours) (mean ± S. D.			
		Before	3 M.	6 M.	9 M.
Lyndiol 2.5	11	30.27 ± 5.66	9.93 ± 2.28	8.0 ± 2.21	6.3 ± 1.05
Gynanovlar	7	28.4 ± 3.3	12.1 ± 2.36	10.1 ± 2.57	5.6 ± 1.23

Progesterone augments the quantity of oestrogens excreted by the body, and its administration or its secretion by an active corpus luteum facilitates the conversion of oestradiol to oestriol. Hence,

progesterone is considered a protector against the effects of oestradiol (Smith & Smith, 1938). Varangot and Cedar (1957), confirmed that progesterone favoured the transformation of oestradiol to oestriol in menopausal or castrated women as well as in males injected with oestradiol.

Oestriol which is the metabolic product of oestradiol has been found to have a protective action on the different organs of the body especially the vascular and perivascular connective tissue of capillaries, arteries, and venulæ, reducing their permeability and fragility (Poliwoda et al, 1963 & 1965, Pierer, 1964, Bergmann & Humber, 1965). It acts by converting the acid mucopolysaccharides of the vascular and perivascular basic substance to a higher degree of polymerization whereby the sol-gel ratio is altered in favour of the gel constituent. This beneficial effect of oestriol has a great value in inhibiting the possibility of thrombosis as well as in the protection of essential organs as the liver, lung, heart, and brain.

Experimental work on rats given different types of steroid combined contraceptive pills (under publication), has shown variable picture of congestion of the vital organs (liver, spleen, lungs etc.) as well as thrombosis and generalised fibrosis in these organs associated with narrowing of the blood vessels.

Oestriol assays, in women having the pill, has shown marked reduction in the peak value at the mid cycle (tables 1 & 2). This reduction becomes more marked with time. This finding has been found by other authors (Shearman, 1963 a & b, 1964, Loraine et al, 1963 & 1965, Baldratti & Castegrano, 1967). Pregnandiol assays by the latter authors has similarly shown a marked reduction throughout the cycle in pill users and is taken as a criterion for the effeciency of the pill concerned.

From the above data, one may conclude that the anovulatory cycles associated with pill intake deprive the body from the endogenous oestrogens, progesterone, and oestrogen metabolites mainly oestriol. Such oestriol deficiency may be responsible for the vascular bed changes which may lead to the thromboembolic manifestations reported to occur with pill intake.

The higher the dose of either ethinyl oestradiol or mestranol in the pill, the more the inhibition of pituitary gonadotrophins and the lower the oestriol level. This may lead one to suggest lowering the

dose of ethinyl oestradiol or mestranol as it is the tendency nowadays not to exceed 50 ug. However, as this dose will still inhibit ovulation to be of contraceptive value, it is still not promising to decrease the associated danger of thrombo-embolic phenomena due to oestriol deficiency. The natural hormone oestriol as well as the oestriol succinate has been used for a long time for the prophylaxis and therapy in cases of bleeding in all branches of medicine. It acts, in this respect, by improving the vascular and perivascular bed. Such improvement, in turn, can be considered of beneficial effect not only in prophylaxis against bleeding but also as a major prophylactic measure against thrombo-embolic phenomena. A side issue in this respect is the common incidence of moniliasis which is noticed with the pill. Oestriol has been used for years to improve the epithelial changes in the lower vaginal tract in atrophic conditions of this part. It is therefore apparent that the addition of oestriol to the pill may also be of beneficial effect in guarding against such side effects.

Trials should be carried out on these lines to find out what could be gained by the addition of oestriol to the pill.

SUMMARY

Data about the incidence of thrombo-embolic phenomena in association with the pill has been reviewed. A case of hemiplegia following the use of the pill has been reported.

Oestriol assays in women having the pill has shown marked reduction in the peak value especially on prolonged use. A suggestion was put forward to add oestriol to the pill as a protective agent against the thrombo-embolic phenomena.

As the maximum drop in oestriol level was found to be after 9 months, the authors suggest that every patient should stop using the pill for at least two cycles every nine months. This will give a chance for ovulation to occur and hence the hormonal pattern returns to normal. This point is now under investigation.

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