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EFFECTS OF PRE-ECLAMPSIA ON THE CHANGES IN IODINE METABOLISM DURING PREGNANCY

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STUDIES of iodine metabolism in man are frequently based on observing the manner in which the thyroid gland and the kidney remove iodine from the plasma. The measures obtained in the investigation of these functions are the thyroid clearance and the renal clearance of radioactive iodine respectively. While these values provide indices of the metabolism of stable iodine (as opposed to radioiodine) it is necessary to ascertain the plasma level of stable iodine at the same time to obtain the absolute amounts of iodine removed from the blood by the thyroid and the kidney. The former is an extremely important measure, described as the absolute iodine uptake, since it is a more direct indicator of thyroid hormone production than the thyroid clearance of radioiodine alone.

The changes in iodine metabolism during normal pregnancy have been measured by Aboul-Khair *et al.* (1964) using the short-lived isotope ^{132}I. Renal clearance of iodine increased early in pregnancy and remained high throughout. The plasma inorganic iodine fell but a compensatory increase in thyroid clearance of iodine maintained the absolute iodine uptake by the thyroid within normal limits. All these changes gradually regressed to normal after delivery, but non-pregnant levels were not reached until between the sixth and twelfth week after delivery.

At first, the primary cause of these changes appeared to be the increased renal clearance of iodine, but Tulloch (1966) has produced evidence to suggest that the primary cause is expansion of the iodide space during pregnancy, leading to lowering of the plasma inorganic iodine level. This paper describes an investigation of iodine metabolism in pre-eclampsia, a condition known to modify renal function.

MATERIALS AND METHODS

Selection of Patients

Thirty-five patients were studied. They were divided into two groups according to the severity of their symptoms.

The diagnosis and classification of pre-eclampsia were based on the criteria described by Nelson (1955) who defines pre-eclampsia as a condition in which the diastolic blood pressure rises after the 26th week of pregnancy to 90 mm. Hg on two or more occasions, separated by at least a day; or shows a definite or progressive pattern if the rise occurs in labour. The classification of the severity of the condition depends on the presence or absence of albuminuria in a mid-stream specimen of urine. The term "moderate" indicates that albuminuria is less than 2 g. per litre while "severe" cases have values exceeding this. Patients fulfilling the criteria of hypertension but without albuminuria, are included in a grouping described as "other hypertension" which in the nature of things must include some cases of essential hypertension. The presence of oedema is not considered in the diagnosis or grading.

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In the present investigation 21 cases were included in the group classified as "other hypertension" while the remaining 14 were cases of moderate or severe pre-eclampsia.

In 28 patients iodine metabolism was studied shortly before delivery, but in 7 the pre-eclampsia was so severe that the procedure had to be carried out within the first few days after delivery. This is unlikely to invalidate the results since no detectable changes normally occur during the first week of the puerperium (Aboul-Khair *et al.*, 1964).

Methods

The following measurements of iodine metabolism were made:

Measurement	*Units*
2½ hour uptake of radioiodine	Percentage of dose
Thyroid clearance of radioiodine	ml. of plasma per minute
Plasma inorganic iodine	μg. per 100 ml. plasma
Absolute iodine uptake	μg. per hour
Serum protein bound iodine	μg. per 100 ml. serum
Renal clearance of iodine	ml. of plasma per minute

The short-lived isotope ^{132}I (physical half-life 2·3 hours) was supplied as sodium iodide by the Radiochemical Centre, Amersham, free from carrier iodine, and was given intravenously, after sterilization, in doses ranging from 3 to 7 μc. Counts over the thyroid gland were obtained using an Ekco scintillation counter fitted with a large sodium iodide crystal (type 609/A). Inaccuracy in the thyroid uptake measurements due to backscatter radiation was eliminated by efficient shielding of the crystal, using a lead filter of 1·5 mm. thickness and by checking the results with a "phantom" thyroid. Direct observations have been made on the irradiation dose to the fetal thyroid gland in women given ^{131}I who had their pregnancies terminated for obstetrical reasons between the 8th and 20th weeks (Aboul-Khair *et al.*, 1966). This data was used to calculate the irradiation dose to the fetal thyroid gland by ^{132}I in the present investigation. Administration of 7 μc. of ^{132}I gave a maximum irradiation dose of 0·1 to 0·4 rads.

The rate of clearance of radioactive iodine by the thyroid gland was measured by the method of Myant *et al.* (1949) between 1 and 2½ hours after the intravenous administration of the isotope. Simultaneous estimation of the radioiodine and the stable iodine content of the urine excreted over the same period provided data for the estimation of the plasma inorganic iodine and the absolute iodine uptake using the method of Stanley (1949). The plasma inorganic iodine (PII) in μg. per 100 ml. was calculated from the formula:

$$\text{PII} = \frac{\text{I-urine} \times {}^{132}\text{I plasma}}{{}^{132}\text{I-urine}}$$

where I-urine represents the stable iodine of the urine in μg. per 100 ml., ^{132}I-plasma the radioiodine content of the plasma in percentage of the dose per ml. plasma, and ^{132}I-urine the radioiodine content of the urine in percentage of the dose per ml. urine. The radioactivity in plasma and urine samples was measured by using a Universal Scintillation Counter (Panax U sc/B) fitted with a well-type crystal.

The absolute iodine uptake in μg. per hour was calculated from the formula:

$$\text{AIU} = \text{PII}\ (\mu\text{g./ml.}) \times \text{thyroid clearance (ml./hr.)}$$

The renal clearance of iodine was calculated in the same way as the thyroid clearance, using the urinary excretion instead of the thyroid uptake of radioactive iodine. The validity of this method in pregnancy has been demonstrated by Aboul-Khair *et al.* (1964).

Serum protein-bound iodine measurements were obtained using a modified chloric acid digestion method (Farrel and Richmond, 1961). Stable iodine in the urine was estimated on 0·5 ml. aliquots by the same chemical reaction without protein digestion. The absence of significant amounts of organic iodide in the urine was confirmed by the use of an anion-exchange column.

Results

Table I shows the mean and range of values for the various estimations which were carried out. The findings in the cases of "other hypertension" and "moderate and severe pre-eclampsia" have been compared with the mean values obtained by Aboul-Khair *et al.* (1964)

TABLE I

Comparison of Mean Values and Ranges of Various Indices of Iodine Metabolism in Cases of Normal Pregnancy, Those With "Other Hypertension", and Those With "Moderate or Severe Pre-eclampsia"

	Thyroid Uptake 2½ hours (% dose)	Thyroid Clearance (ml. plasma/min.)	Plasma Inorganic Iodine (μg./100 ml. plasma)	Renal Clearance (ml. plasma/min.)	Absolute Iodine Uptake (μg./hour)	Serum Protein-bound Iodine (μg./100 ml. serum)
Normal pregnancy (Aboul-Khair *et al.*, 1964) ..	31·40 (24·76–49·74)	48·90 (26·70–94·60)	0·10 (0·04–0·16)	57·00 (47·86–70·76)	2·70 (1·40–4·55)	7·80 (5·72–10·55)
"Other hypertension" (21 cases)	29·79 (16·97–39·21)	52·13 (14·10–99·09)	0·11 (0·04–0·34)	44·36 (22·52–94·22)	2·86 (1·14–5·24)	8·7 (6·2–12·8)
"Moderate and Severe Pre-eclampsia" (14 cases)	33·33 (17·14–47·10)	43·92 (11·27–89·10)	0·13 (0·03–0·26)	28·45 (11·00–51·00)	3·67 (0·30–7·53)	7·9 (4·2–13·5)

Mean values and range.

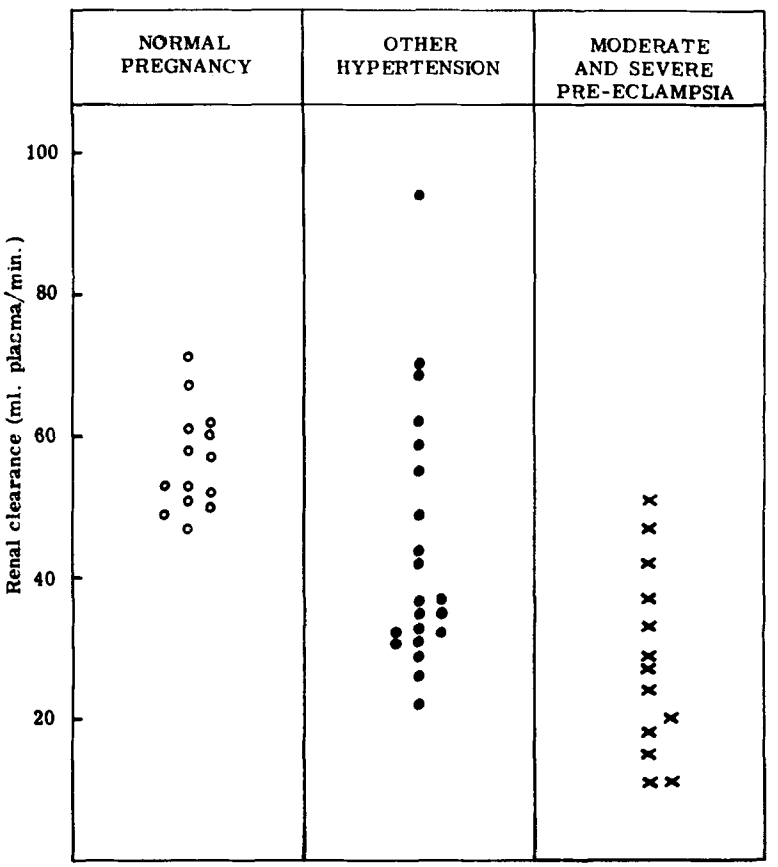

FIG. 1

The renal clearance of iodine in normal pregnancy, hypertension in pregnancy, and moderate or severe pre-eclampsia.

from serial estimations throughout pregnancy in 14 cases of normal pregnancy using the same methods. There was no significant difference in the values for thyroid uptake, thyroid clearance, plasma inorganic iodine, absolute iodine uptake, and serum protein-bound iodine between the normal and abnormal cases.

Differences were, however, found in the renal clearance measurements (Table I, Fig. 1). The mean renal clearance for the 14 normal cases was 57·0 ml. plasma per minute, while the mean value for cases of "other hypertension" was 44·69 ml. plasma per minute, and in the women with moderate and severe pre-eclampsia it was reduced to 28·45 ml. plasma per minute. Statistical analysis using Student's test showed that the difference between the normal and "other hypertensive" cases was significant at the 5 per cent level, while that between the normal cases and those with "moderate or severe" pre-eclampsia was highly significant at the 0·1 per cent level. Almost all the readings in patients with "moderate or severe" pre-eclampsia were lower than those found in the control cases.

Discussion

It is well known that renal blood flow is increased during normal pregnancy and that glomerular filtration is increased by about 50 per cent (Sims and Krantz, 1958). These changes occur very early in the pregnancy and are maintained to within 1 to 2 weeks of delivery. The increase in renal clearance of iodine found during normal pregnancy follows a similar pattern to the change in renal blood flow (Aboul-Khair *et al.*, 1964; Tulloch, 1966).

In cases of moderate and severe pre-eclampsia Browne and Veall (1953) have shown that placental blood flow is greatly reduced, while other workers (Kenney *et al.*, 1950; Bucht and Werkö, 1953; Assali *et al.*, 1953) have demonstrated that renal blood flow is also greatly reduced. These effects have been ascribed to a generalized increase in arterial tone of unknown aetiology which produces varying effects in different organs.

Histological changes rapidly appear in the glomerulus in the presence of moderate or severe pre-eclampsia in the form of swelling of the endothelial cytoplasm and to a lesser extent of epithelial cells, resulting in a narrowing of the capillary lumen (Pirani *et al.*, 1961; Pollack and Nettles, 1960).

In the present study the reduction of the renal clearance of iodine found in pregnant women with moderate or severe pre-eclampsia is in keeping with both the structural and functional changes known to occur in the kidneys of such cases. The slighter reduction in renal clearance of iodine found in the "other hypertensive" group suggests that the changes are unlikely to be due to hypertension alone, and that another factor associated with the pre-eclamptic state is responsible. This hypothesis is supported by the facts that the level of hypertension does not correlate with the degree of renal vascular spasm (Kenney *et al.*, 1950), and that the amount of proteinuria is a better guide to the severity of the pre-eclampsia. Low renal iodide clearances have been found in other cases of renal insufficiency (McConahey *et al.*, 1951; Perry and Hughes, 1952).

If the fall in plasma inorganic iodine found in normal pregnancy depends on the elevated renal clearance of iodine, the fall in renal clearance in pregnancy complicated by pre-eclampsia might be expected to cause an increase in plasma inorganic iodine and thus to avoid the compensatory increase in thyroid clearance, but this did not occur. The fact that plasma inorganic iodine remained low and the thyroid clearance remained high supports the contention of Tulloch (1966) that increased renal clearance in pregnancy has little effect on the level of plasma inorganic iodine, and that the major cause of its fall is an increased iodide space.

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