SERIAL STUDIES OF THE RENAL CLEARANCE OF URATE AND INULIN DURING PREGNANCY AND AFTER THE PUERPERIUM IN NORMAL WOMEN

P. F. SEMPLE, W. CARSWELL AND J. A. BOYLE

Glasgow Royal Infirmary, Glasgow, Scotland

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SUMMARY

1. A serial study of renal clearance of urate and inulin was made in thirteen normal women in early, mid and late pregnancy and 6–15 weeks after delivery.

2. The mean serum urate concentration was low in early and mid pregnancy but rose in late pregnancy towards the control value.

3. Clearances of urate and inulin were consistently elevated throughout pregnancy to about 150% of the post-partum values. The ratio of clearance of urate to clearance of inulin was the same in pregnancy as it was after the puerperium.

4. The urinary excretion of urate was increased only in late pregnancy.

Key words: gout, pregnancy, renal clearance, urate.

Gout is an uncommon disease in premenopausal women. Mean serum urate concentration is lower than in men of the same age (Mikkelsen, Dodge & Valkenberg, 1965) and this may be due to a higher renal clearance of urate in women (Wolfson, Krevshy, Levine, Kadota & Cohn, 1949; Wolfson, Hunt, Levine, Guterman, Cohn, Rosenberg, Huddlestun & Kadota, 1949). It has been observed that the symptoms of gout may be ameliorated by pregnancy (Lee & Loeffler, 1962), although acute episodes of gouty arthritis may occur in the puerperium (Greenhut, Silver & Campbell, 1953; Weingold, 1960).

A low serum urate concentration has been observed in early and middle pregnancy (Steenstrup, 1963) with a rise towards normal values in late pregnancy (Boyle, Campbell, Duncan, Greig & Buchanan, 1966). The latter authors, in a cross-sectional study and with a colorimetric assay used for urate, reported increased rates of urate excretion in middle and late pregnancy with normal urate excretion in early pregnancy.

The present study was designed to examine, in a serial manner, serum urate, urate clearance and inulin clearance in normal women in early, mid and late pregnancy and after the puerperium, with a specific enzymatic assay for urate.

Correspondence: Dr P. F. Semple, M.R.C. Blood Pressure Unit, Western Infirmary, Glasgow G11 6NT.

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METHODS

Thirteen normal women were studied in early, mid and late pregnancy and after the puerperium. They all gave informed consent and the study was approved by the Ethical Committee of Glasgow Royal Infirmary. The women had a mean age of 27 years (range 20–34) and varied in parity. None had a history of hypertension, gout, renal disease or pre-eclampsia. At each attendance for study, the blood pressure was measured and the urine cultured and tested for protein. None showed a resting blood pressure above 140/85 mmHg, oedema, proteinuria or significant bacteruria. None was on diuretic therapy and all delivered normal babies.

Clearance measurements

Renal clearance measurements were made between 10 and 20 weeks (mean 14-3), between 20 and 30 weeks (mean 25-8), between 30 and 40 weeks (mean 35-0) of pregnancy and between 6 and 15 weeks (mean 9-8) post partum. Gestational age was estimated by Naegele’s rule. No patient was receiving regular drug therapy, apart from iron and folic acid, and all were advised to eschew aspirin and foods with a high purine content for 3 days before each clearance measurement.

The patients fasted overnight before attending for study. At 09.00 hours, 150 ml of water was given by mouth and repeated at 30 min intervals until the end of the clearance periods. Blood

![Graph showing serum urate values and clearance measurements](image-url)

**Fig. 1.** Mean serum urate values ± SEM and mean urate clearance ± SEM in early, mid and late pregnancy and after the puerperium. Serum urate values expressed in μmol/l may be converted into values in mg/100 ml by multiplying by 1.68 × 10⁻². SEM values are denoted by the vertical bars.
was then drawn by venepuncture and a urine specimen obtained for inulin blanks. At 09.30 hours, a cannula was inserted into a forearm vein and a priming dose of 26 mg of inulin/kg (Kerfoot and Co. Ltd, Vale of Bardsley, Lancashire) was given intravenously. An infusion of 1500 mg of inulin in 50 ml of saline (154 mmol/l NaCl) was then started by syringe pump (Palmer) and continued at a rate of 50 ml/h until the end of the study. The patients were comfortably seated throughout the study but rose to void. At 10.30 hours, the patients voided and thereafter voided at 60 min intervals for two clearance periods. Venous blood was drawn by venepuncture at the mid-point of each clearance period and allowed to clot in a glass container. Serum was separated within 6 h and stored at \(-20^\circ\text{C}\) until assay. Urine volumes for each period were recorded and aliquots stored with a small amount of toluene preservative at \(-20^\circ\text{C}\) until assay.

**Laboratory methods**

Inulin assays were performed by a resorcinol colorimetric method (Schreiner, 1950) and urate assays by the enzymatic spectrophotometric method (Liddle, Seegmiller & Laster, 1959). All assays were performed in duplicate within 2 months of collection. Uricase was obtained from the Sigma Chemical Co. Ltd, London, and other chemicals from British Drug Houses Ltd, Poole, Dorset.
RESULTS

The mean serum urate concentration in early pregnancy was 180 μmol/l (SEM 10), in mid pregnancy 190 μmol/l (SEM 10), in late pregnancy 230 μmol/l (SEM 10) and post partum 280 μmol/l (SEM 20) (Fig. 1). The values in early, mid and late pregnancy were lower than those after delivery (paired t = 5.6, 5.3 and 4.3 respectively; all P values <0.001). Serum urate in late pregnancy was elevated compared with values in early and mid pregnancy (paired t = 5.6 and 2.5; P<0.001 and <0.05 respectively).

![Graph showing mean urate/inulin clearance ratio ± SEM and the mean urine flow rates ± SEM in early, mid and late pregnancy and after the puerperium. SEM values are denoted by the vertical bars.](image)

**Fig. 3.** Mean urate/inulin clearance ratio ± SEM and the mean urine flow rates ± SEM in early, mid and late pregnancy and after the puerperium. SEM values are denoted by the vertical bars.

The mean clearance of urate (Curate) in early pregnancy was 14.2 ml/min (SEM 1.4), in mid pregnancy 15.3 ml/min (SEM 1.1), in late pregnancy 15.8 ml/min (SEM 1.6) and post partum 9.8 ml/min (SEM 0.9) (Fig. 1). The values throughout pregnancy were raised compared with those after delivery (paired t = 3.5, 4.9 and 3.3; P<0.01, <0.001 and <0.01 respectively) and there was no significant difference between the values in early, mid and late pregnancy (paired t values between 0.3 and 0.5). The mean Curate in pregnancy was 15.1 ml/min (SEM 1.4) compared with a mean value of 9.8 ml/min (SEM 0.9) after the puerperium.

The mean rate of uric acid excretion was 2.6 μmol/min (SEM 0.2) in early pregnancy, 2.8 μmol/min (SEM 0.2) in mid pregnancy, 3.4 μmol/min (SEM 0.3) in late pregnancy and 2.7 μmol/min (SEM 0.3) after delivery (Fig. 2). There was a rise in mean uric acid excretion rate in late
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pregnancy compared with early pregnancy (paired \( t = 2.3, P<0.05 \)); the mean value after delivery was lower than the mean value in late pregnancy but this result is not significant (paired \( t = 1.9, P<0.1 \)).

The mean clearance of inulin (\( C_{\text{inulin}} \)) was raised in early, mid and late pregnancy compared with the mean value after the puerperium (paired \( t = 7.3, 9.5 \) and \( 8.1; P \) values all \( <0.001 \)) (Fig. 2). The mean \( C_{\text{inulin}} \) was 141 ml/min (SEM 7) in pregnancy compared with 96 ml/min (SEM 6) after delivery. These values have not been corrected for surface area. The mean algebraic difference between the \( C_{\text{inulin}} \) values obtained in the first hour of each study and the \( C_{\text{inulin}} \) values obtained in the second hour was \(-0.4\%\) (range \(-23\%\) to \(+25\%\)). This suggests that the patients were in a reasonably steady state.

The mean ratio of \( C_{\text{urate}} \) to \( C_{\text{inulin}} \) was unchanged by pregnancy (Fig. 3). Urine flow rate was consistently high in all the stages of pregnancy and after delivery (Fig. 3), although the mean value was slightly lower in late pregnancy than in the other periods.

**DISCUSSION**

A low serum urate concentration in normal pregnancy has been observed in cross-sectional studies by Steenstrup (1963), who employed an enzymatic method for measuring uric acid (Praetorius & Poulsen, 1953), and by Boyle et al. (1966), who used a colorimetric method. The present serial study confirms that the serum urate concentration is low in early and mid pregnancy and rises towards control values between 30 and 40 weeks. The mean serum urate values are slightly higher than those found by Boyle et al. (1966) and this is consistent with the observation that the enzymatic method for measurement of urate in serum gives higher mean values than colorimetric methods (Praetorius, 1949). We have previously found a mean serum urate of 260 \( \mu \)mol/l (SEM 9, \( n = 26 \)) in a series of normal women at induction of labour (Carswell & Semple, 1974) and this suggests that serum urate concentration continues to rise until term.

Renal clearance of urate is consistently elevated to about 154\% of control values throughout pregnancy and this increase parallels the increase in glomerular filtration rate as measured by clearance of inulin (147\% of control values). The mean rate of urate excretion, however, is normal in early and mid pregnancy but elevated in late pregnancy. From a study of \( C_{\text{urate}} \) in normal pregnancy and pre-eclampsia, and by employing a colorimetric method for uric acid assay, Hayashi (1956) recorded values of 18.4 ml/min (SD 4.9) before 32 weeks and 13.0 ml/min (SD 4.0) after 32 weeks but control values are not given. Respective serum urate values were 190 \( \mu \)mol/l and 180 \( \mu \)mol/l.

The changes in serum urate which occur in normal pregnancy may have the following explanation. An increase in plasma volume occurs in normal pregnancy (Hyttjen & Paintin, 1963) and this probably causes a reduction of serum urate by dilution which is maintained by an increase in renal \( C_{\text{urate}} \). Urate production in early pregnancy is normal (Steenstrup, 1963) and is therefore unlikely to account for the low serum values. Boyle et al. (1966) measured 24 h urate excretion in early, mid and late pregnancy and documented a significant increase in mid and late pregnancy compared with control values. The present study has not confirmed an increase in mid pregnancy and has recorded only a slight increase in late pregnancy. These authors suggested that the rise in serum urate in late pregnancy is due to an increasing contribu-
tion of foetal urate to the maternal pool and our observations are consistent with this hypothesis.

The increase of 47% in clearance of inulin, which has been found throughout pregnancy in this study of uncatheterized patients, is similar to the 60% increase in $C_{inulin}$ observed by Sims & Krantz (1958) in catheterized patients. Values for $C_{inulin}$ have not been corrected for surface area because the patients were studied serially and because there is no evidence of an increase in kidney weight or number of glomeruli with increased surface area in pregnancy (Hytten & Leitch, 1971). The increased dead space in the urinary tract of pregnant women (Baird, 1935) is likely to reduce the accuracy of clearance measurements but this factor has been minimized in this study by ensuring high urine flow rates and employing 1 h clearance periods. In normal men, the ratio of $C_{urate}$ to $C_{inulin}$ increases with urine flow to maximal values at flow rates of 1–2 ml/min (Villa, Robecchi & Ballabio, 1958). Urine flow rates in the present study were consistently high and therefore are unlikely to have influenced the clearance values.

The mechanism whereby renal clearance of urate is increased in pregnancy remains to be established. The increase runs parallel to the increase in glomerular filtration rate but the relative roles of tubular reabsorption and tubular secretion of urate (Gutman, Yu & Berger, 1959) have not been defined. Pyrazineamide suppression of tubular secretion (Gutman, Yu & Berger, 1969) might be of discriminant value but it would seem unwise to use this drug in pregnancy. Nichols, Snith & Scott (1973) have reported a fall in serum urate, a rise in renal clearance of urate and no change in creatinine clearance in trans-sexual males given stilboestrol therapy. It is possible that the rise in blood oestrogen levels in pregnancy could influence renal clearance of uric acid although the changes in clearance observed in this study do not follow the progressive rise in blood oestrogen levels.

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REFERENCES


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