Renal physiology in pregnancy

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Summary

The changes which occur in renal excretory function during pregnancy are discussed. The relationship between glomerular filtration rate and effective renal plasma flow is examined in the light of new serial data obtained under conditions of saline diuresis. Changes in the renal handling of nutrients and in the excretion of waste products during pregnancy are reviewed.

Introduction

The kidney plays a central role in maintaining the equilibrium of many physiological systems in the body. Virtually all of these systems show changes during normal pregnancy; those occurring in renal excretory function are now dealt with.

Glomerular filtration rate and effective renal plasma flow

In the process of urine formation, plasma from the glomerular capillaries is filtered through Bowman's membrane, molecules larger than albumin (mol. wt, 68 000) remaining in the circulation. The glomerular filtrate thus contains concentrations of crystalloids and ions virtually equi-molar with glomerular plasma. The character of the filtrate is modified during passage through the remainder of the nephron by the processes of reabsorption and secretion so that the urine finally excreted by the kidney contains higher concentrations of waste materials and lower concentrations of essential nutrients than plasma. Inulin, an exogenous inert substance which is neither reabsorbed nor secreted by the nephron, is used to measure the rate of filtration. Renal excretory function is traditionally described in terms of clearance, calculated as the ratio of the excretion of a given solute in unit time to its plasma concentration. Thus, substances which are reabsorbed from the glomerular filtrate will show a lower clearance than inulin and substances which are secreted, a higher clearance.

It has been known for more than 25 years that glomerular filtration rate (GFR), as measured by inulin clearance, is substantially increased during pregnancy (Bucht, 1951). The reason for this increase, which is central to the understanding of all

renal excretory function, remains incompletely investigated. One important factor, which has been studied, is the rate at which plasma flows through the glomerular capillaries. This can be indirectly estimated by using another exogenous solute, para-amino hippurate (PAH), which is not only freely filtered at the glomerulus, but which is also so actively secreted in the proximal tubule that 90-95% of the substance is cleared from the plasma flowing through the kidney when plasma concentrations are low (Smith, 1951a). Because of the slight discrepancy from 100% extraction of PAH from plasma, this clearance is conventionally known as effective renal plasma flow (ERPF). The classical study using this technique during pregnancy was published by Sims and Krantz in 1958. They showed an increase of ERPF during pregnancy roughly proportional to that of GFR. However, they studied a relatively small population at inconstant intervals throughout pregnancy and it was therefore difficult accurately to quantify this relationship.

This work has been repeated in Newcastle upon Tyne. Inulin and PAH were infused in normal saline into 25 healthy women at intervals during and after a normal pregnancy. The results must be interpreted with some caution because of published evidence of augmentation of GFR and ERPF after saline loading (Lindheimer and Weston, 1969). Each subject was studied at 16, 26 and 36 weeks' gestation and subsequently 8 weeks after delivery. The results confirm the dramatic elevation of ERPF and GFR during normal pregnancy. By 16 weeks' gestation, GFR had increased 50% and RPF 75%. GFR remained at this level throughout pregnancy, but RPF fell significantly between 26 and 36 weeks' gestation.

This terminal fall in ERPF has previously been ascribed to the effect of posture (Chesley and Sloan, 1964), it being argued that the supine position (commonly used in early studies) compromised renal perfusion during late pregnancy. The Newcastle studies were performed with subjects in a comfortable sitting position, which was considered more physiological and which facilitated urine collection

by spontaneous voiding. It was therefore important to examine the effect of posture upon ERPF and GFR during late pregnancy. Eighteen healthy women were studied at 36 weeks' gestation and again 8 weeks after delivery. Each subject was investigated consecutively in 2 out of 3 possible positions (supine, sitting and left lateral), the choice and sequence of positions being randomly determined. No significant differences in ERPF or GFR were observed on changing position (Dunlop, 1976).

What, then, is responsible for the third trimester fall in ERPF? A possible clue may be obtained by studying the relative degree of change of the 2 variables. In the Newcastle study, the percentage increment in ERPF was consistently greater than that in GFR, but during late pregnancy the discrepancy between the 2 diminished. The relationship may be expressed as the filtration fraction, the ratio of GFR : ERPF. Thus, mean filtration fraction fell during early pregnancy, rising again at 36 weeks to a value no longer statistically distinguishable from the non-pregnant. This pattern of change in filtration fraction was remarkably similar to that of mean diastolic blood pressure, which followed the pattern described by MacGillivray, Rose and Rowe (1969).

Glomerular filtration is essentially a passive process, dependent upon the balance of hydrostatic and osmotic forces and is therefore directly related to intraglomerular hydrostatic pressure. Thus, a relationship between arterial blood pressure and the proportion of plasma filtrate forced through Bowman's membrane is to be expected (Brenner, Baylis and Deen, 1976). Blood flow, on the other hand, is dependent not upon absolute hydrostatic pressure, but upon the rate of pressure decrease along the length of the vessel concerned. A much more important factor in regulating flow rate is the resistance offered by the vessel wall. (In Poiseuille's equation, flow varies directly as the first power of the pressure difference but as the fourth power of the vessel radius.) A rise in blood pressure during late pregnancy in the absence of a rise in cardiac output is circumstantial evidence of increasing vascular resistance. Constriction of the post-glomerular (efferent) arteriole as part of this process could thus account for the observed decrease in ERPF without decrease in GFR during late pregnancy.

Renal handling of nutrients

Small molecules, having been forced through the glomerular filter, are to be found in the filtrate in concentrations virtually equal to those in the capillary plasma. Many of these substances are either essential metabolites or are required for the maintenance of homeostasis and are reabsorbed during the passage of the filtrate through the re-

mainder of the nephron. Amino acids, folate and glucose are examples of the first category of substances; and sodium, chloride and water are examples of the second category. The kidney's handling of salt and water is complex, and understanding of the changes which occur during pregnancy is still poor (Lindheimer and Katz, 1975). Reclamation of essential nutrients, being predominantly localized to the proximal tubule, is a simpler phenomenon and has been more intensively studied. Most of these substances are so completely reabsorbed that in the non-pregnant state only minimal quantities are excreted in the urine. During pregnancy, however, their excretion may be quite markedly increased. Hytten and Cheyne (1972) demonstrated an increase in the excretion of 18 out of 19 amino acids studied during pregnancy, and Landon and Hytten (1971) found that a significant increase also occurred in folate excretion.

It has long been known that clinically detectable glycosuria is more common during pregnancy (Blot, 1856) and it was assumed that this was due to a 'reduced renal threshold for glucose'. Davison and Hytten (1975) have shown that the concept of a transfer maximum for glucose (Shannon and Fisher, 1938) is invalid: in fact there is a continuing increase in glucose excretion with increase in the filtered load. Thus, the idea of a threshold beyond which all filtered glucose is excreted is not tenable. The increased glycosuria of pregnancy appears to be due to disturbance of the equilibrium between the filtration of glucose and its reabsorption by the proximal tubule. Transient disequilibrium is common towards the end of the first trimester (Davison, 1974) and the magnitude of continuing imbalance varies from subject to subject and also from time to time during the day in any given subject (Lind and Hytten, 1972). Davison and Hytten (1975) have shown that women who have heavy glycosuria during pregnancy also exhibit impaired reabsorption of filtered glucose under infusion conditions in the non-pregnant state, and have suggested that this may result from intrinsic renal damage. Thus, not only is the testing of a random urine sample in pregnancy unrepresentative of the degree of glycosuria present, but it is probable that the phenomenon itself reflects altered renal function rather than altered carbohydrate metabolism. Indeed, Davison (1975) and Lind (1975) have reported patients with gestational diabetes who did not exhibit persistent glycosuria during pregnancy.

Excretion of waste materials

The kidney's handling of waste products is rather more complex than the reclamation of essential materials. The clearances of urea and uric acid are substantially lower than GFR, suggesting that

partial reabsorption of these substances occurs in the kidney. Urea is thought to be of intrinsic importance to the kidney in maintaining the osmotic gradient between medulla and cortex necessary for the reabsorption of salt and water. The reason for the kidney's net reabsorption of uric acid is less clear, but it has been postulated that this is a mechanism to prevent saturation of the urine which might lead to crystallization of urates within the renal parenchyma (Gutman, 1964).

Uric acid is freely filtered at the glomerulus and is then both secreted and reabsorbed during its passage through the nephron (Gutman, Yü and Berger, 1959). The net result of this process is the reabsorption of approximately 90% of the filtered load. Dunlop and Davison (1977) assessed the renal handling of uric acid serially in 24 healthy women at the intervals previously described during and after a normal pregnancy. They found that the increase in uric acid excretion in early pregnancy was disproportionately larger than the increase in filtered load. Thus net reabsorption of uric acid was reduced in early pregnancy and plasma uric acid concentration fell. As pregnancy advanced, however, the excretion of uric acid remained constant despite a gradual increase in filtered load, so that by 36 weeks' gestation the net reabsorption and plasma concentration of uric acid were no longer statistically distinguishable from mean values in the non-pregnant state. In patients who developed pre-eclampsia, a further increment in net reabsorption and plasma concentration occurred (Dunlop, 1977), confirming the hypothesis of Chesley and Williams (1945).

The renal clearance of creatinine, another end-product of metabolism, is much higher than those of urea and uric acid: under most circumstances creatinine clearance is approximately equal to inulin clearance and is therefore widely used in clinical practice as a convenient method of estimating GFR. Serial studies, such as that of Davison and Hytten (1974), have confirmed that endogenous creatinine clearance under infusion conditions does not differ significantly from inulin clearance during pregnancy. However, it must be remembered that creatinine is not renally inert in the same way as inulin: it is probable that in man a small proportion of the creatinine in the urine is secreted by the proximal tubule (Smith, 1951b). In severe renal impairment this tubular supplement may form a significant proportion of excreted creatinine, thus leading to overestimation of GFR (Chesley, 1978). Finally, it has been shown that at low rates of urine flow, creatinine clearance may not be a valid measurement of GFR during pregnancy (Noble, Landon and Davison, 1977). Over the course of 24 hr, variations in urine flow rates probably make such considera-

tions of little practical importance, but the results of clearances over periods substantially less than this must be interpreted with caution

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