RENAL FUNCTION IN PREGNANCY

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Although our understanding of many renal mechanisms has been advancing rapidly over the past few years, there is still a dearth of information about changes that occur in renal function during pregnancy—surely one of the greatest physiological disturbances possible. It is difficult in many instances to find a description of the changes that occur quite apart from the underlying alterations in mechanisms that are responsible for them.

Part of the difficulty has arisen because of the ethical and methodological problems that arise when women are used as 'experimental animals'; until recently there has not been a suitably documented animal model, though whether this was because of technical difficulties or lack of interest on the part of investigators is not known. Recently, however, it has become apparent that many changes in renal function in the rat are similar to those occurring in women and some aspects of renal function in the rat have been investigated in detail. Since not all aspects of renal function can be covered in this review we shall concentrate on three of the more important areas, namely haemodynamics, sodium and water handling and glucose excretion, and discuss how these are changed during pregnancy; comments on the possible mechanisms involved in these changes are presented where appropriate.

Haemodynamics

In pregnant women cardiac output increases during the first trimester and thereafter is maintained. The fall in cardiac output that has been noted towards the end of pregnancy [1] is now considered to be due primarily to the posture of the women while the measurements were made [2-4]. The increased cardiac output is distributed primarily to the skin, uterus, kidneys, breasts and gut [5].

The portion of the increased blood flow received by the kidney is out of proportion to its normal flow; cardiac output increases by about 30% but renal plasma flow (RPF) and glomerular filtration rate (GFR) can increase by 50% or more. There is now good evidence that changes in GFR occur very early during pregnancy, a rise of 45% occurring within the first 9 weeks [6], and that they reach a maximum at the end of the first trimester and then remain high until the end of pregnancy [7, 8]. However, if GFR is measured in late pregnancy with the subject in the supine position [9, 10] it is found to have decreased. The position is further confused in that when inulin or creatinine was infused to measure GFR, and the body fluid compartments were expanded with glucose solution, there was no change in GFR late in pregnancy; use of endogenous creatinine clearance, however, showed a fall in GFR [8]. One conflicting study shows evidence that posture has no effect on GFR [11], so the role of posture and its effect in late pregnancy still requires some clarification.

Changes in RPF are not as well documented as changes in GFR, presumably because they are more difficult to measure, but the general pattern seems to be similar to that for GFR and cardiac output, namely a sustained rise early in the first trimester [7]. The early increase in RPF has been shown to be greater than the change in GFR; thus filtration fraction is decreased. During the third trimester the RPF falls slightly and with the increased GFR this results in an increased filtration fraction [12]. The pattern of changes in RPF throughout pregnancy is very similar to that of changes in diastolic blood pressure [13]. As pregnant women have an increased vascular responsiveness to angiotensin II in late pregnancy [14] it is interesting to speculate that this reduction in RPF, without a concomitant fall in GFR, could be brought about by selective effects of angiotensin II on the efferent arteriole of the glomerulus.
Many of the changes that occur in pregnant women also occur in pregnant rats, although the time course is obviously shortened since rats have a gestation period of 21–23 days. There is general agreement that both RPF and GFR increase during pregnancy in the rat [15–22]. However, there is no general agreement on the time course of changes. Some workers would maintain that changes in GFR in rats are similar to those in humans, in that an increase occurs very early, perhaps as early as 2–3 days after mating [20], the GFR remains high during the second week of gestation [15, 17, 20–22] and either remains at these levels for the third week of gestation or falls towards virgin values [15, 17, 20–22]. A few workers, however, have been able to find a rise only late in the third week of pregnancy [16, 18, 19]. A suggestion that these differences might arise because of anaesthesia or extensive surgery in rats [19] has been shown not to be true [22], nor are the differences likely to be due to the rate of extracellular fluid volume expansion used in different studies [20, 22, 23]. The reason for the different time course is still obscure. Measurements of RPF have been less common but where they have been performed changes in RPF are similar to changes in GFR [23, 24], although occasional changes have been noted in filtration fraction [25].

There are several theoretical possibilities which might be invoked to explain the increase in GFR; only some of these have been investigated directly. It has long been thought that changes in maternal hormone levels could be important in the genesis of the vascular changes, since it is known that progesterone relaxes smooth muscle [26]. To test this directly, pseudopregnant animals have been used (pseudopregnancy in the rat is a state characterized by all the maternal hormonal changes of the first 11–12 days of pregnancy without the complication of fetuses, and can be induced by sterile mating, mechanical stimulation of the cervix uteri or hormone injections). In animals stimulated by sterile mating, changes in GFR were comparable with those observed in the first half of pregnancy [27]. It was suggested many years ago [28] that prolactin, which increases in early pregnancy in humans, was the hormone responsible for the changes in GFR although recently other factors such as dopamine have been suggested [29]. Prolactin may also play a significant role in rats. Acute administration of prolactin had no effect on GFR but chronic administration over 7 days, with divided doses over the first 3 days to mimic the twice-daily prolactin surge [30], produced a significant increase in GFR. It is not known whether prolactin produces this increase by a direct effect on the glomerulus or indirectly through changes in plasma volume [31], which may be induced by increased drinking behaviour [32]. It is of interest that in Munich–Wistar rats, which do not have an increased GFR at 6 days of pregnancy (24), there is no early rise in prolactin (Garland, Atherton, Bayliss & Morgan, unpublished observations). Progesterone, the other hormone which rises early in pregnancy in the rat, had no effect when administered acutely or chronically [33].

Although the early changes in GFR could be produced by changes in prolactin it is not known whether this hormone is responsible for the maintenance of GFR throughout the later stages of pregnancy. There is some evidence that placentae are necessary to maintain GFR at the raised level even though the fetus is not [15].

Much is now known of the physiological determinants of GFR [34], but only two studies, at different stages of pregnancy, have been performed to determine single nephron glomerular filtration rate, glomerular pressures and the permeability of the membrane [23, 24]. These showed that in Munich–Wistar rats the rise in GFR, which was apparent at 12 but not 6 days, could be accounted for solely by the change in plasma flow; there were no changes in other determinants of GFR. Pseudopregnant rats showed similar changes [35].

In only one study has the intrarenal distribution of blood flow been estimated and even then the methods used were indirect. It was suggested, however, that much of the change in GFR occurs in the juxtamedullary nephrons [21]. It was also suggested that the glomerular tubular feedback mechanism which helps to control GFR through the renin–angiotensin system was more effective in pregnant animals, though the underlying reason for this was not clear. Although of great interest these latter results require confirmation by more direct methods.

As a consequence of the increased GFR during pregnancy the nephron receives a much greater load of solute and water. It is pertinent to consider how the kidney deals with this extra load.

Salt and water transport

Although in women there is much more sodium and water filtered at the glomeruli during pregnancy than in the non-pregnant state (amounting to approximately 5–10 mol of sodium/day and 35–70 litres of fluid/day) proportionately more is reabsorbed by the kidney, so that by the end of pregnancy there is an increase in body fluid content of 6–8 litres [36] and an increase in sodium content of about 950 mmol [37]. Although some of this increase is accounted for by the fetus and the uterine contents most of the increase is ex-
pressed by an increase in the maternal extracellular fluid volume.

Reabsorption of sodium increases reabsorption of fluid by the proximal nephron but, in addition, the osmolality of the plasma is under control of antidiuretic hormone (ADH), which can alter water reabsorption independently of sodium in distal segments of the nephron. In the human, however, it is not known which part of the nephron is responsible for the increased sodium and water reabsorption, nor what factor (or factors) is responsible for causing the increased reabsorption.

Several hormones, whose concentration in plasma increases during pregnancy, are known to be natriuretic (that is, they increase the loss of sodium) at least in non-pregnant individuals. Of these the most relevant are progesterone [38], which acts as a partial competitive inhibitor of aldosterone, dopamine [24] and the prostaglandins [39]. The role of melanocyte-stimulating hormone, circulating neurophysins and even arginine vasopressin [40], all of which increase in human pregnancy, as potential natriuretic substances is not yet clear. On the other hand several antinatriuretic hormones also increase during pregnancy. Of these the most important is aldosterone [41-43], which possibly increases in response to the natriuretic effect of progesterone; deoxycortisone, cortisol, oestrogen, prolactin [44] and human placental lactogen may also play a significant role.

Many other factors might be important in the sodium retention, at least from a theoretical point of view: e.g. the decrease in albumin concentration, the decrease in mean arterial pressure, the increase in renal plasma flow, the increase in intrarenal pressure in the upright and supine positions and the effect of the so-called 'arteriovenous shunt' through the newly formed uterine vessels [45] might all be expected to influence the final sodium reabsorption. Added to these are the effects of posture. Although the upright posture causes an antinatriuresis in non-pregnant women, the response is exaggerated during pregnancy [46-48].

However, during normal pregnancy the homeostatic mechanisms still function and the increased extracellular fluid volume is maintained at its new level. It is as though the normal set point about which variations occur has been altered.

In rats as well as in women there is increased absolute fluid and sodium reabsorption during pregnancy, which more than compensates for the increased GFR, so that there is an increased fractional reabsorption at least during saline infusion [20-22, 25]. This agrees well with metabolic balance studies showing increased sodium and fluid retention throughout pregnancy in the rat [16, 30, 49, 50] and the concomitant increase in extracellular fluid volume [20, 50] and plasma volume [31].

As with changes in GFR, many of the changes in salt and water handling that occur during early pregnancy in the rat also occur in pseudopregnant animals, suggesting that they have a hormonal basis [27]. It has been shown that administration of prolactin for several days causes an increase in absolute salt and water reabsorption, but not in fractional reabsorption [33], and an increased tubular length [51]. Prolonged administration of progesterone produced an alteration in potassium handling but no significant change in sodium and water reabsorption [52]. Prolactin has also been shown to increase fluid and sodium retention as well as producing the characteristic weight gain of pregnancy, but progesterone, while increasing body weight and fluid retention, does not increase sodium retention [52]. The relation of other hormones to renal function during pregnancy in the rat has not yet been studied.

Experiments to determine the site of the increased reabsorption have given equivocal answers. There is no increase in the amount of sodium and water reabsorbed by each millimetre of proximal tubule [21], but nevertheless because the proximal tubules are much longer in pregnant animals [20, 53] the proximal tubule may still reabsorb more fluid. These changes may be offset by changes which occur in the loop of Henle; certainly the fractional reabsorption of fluid in early distal tubular samples was similar in saline-infused virgin and pregnant animals, implying that although some of the increased fluid reabsorption occurs proximally, the final adjustment, which results in increased fractional reabsorption by the whole kidney, occurs in the distal tubule or the collecting ducts [21].

What is striking is that the sodium concentration of fluid entering the distal tubule is reduced in the rat from 6 days of pregnancy onwards, implying that more sodium is reabsorbed relative to water [21]. Although there are results which would not support these findings [54] there is reason to believe that in these latter experiments the preparation of the kidney for micropuncture altered renal function, whereas the experiments of Garland & Green [21] gave changes in GFR and salt and water reabsorption similar to those occurring both in animals which were prepared in a similar way but did not undergo micropuncture [20] and in conscious animals infused with saline [22]. The underlying cause of this increased sodium reabsorption has yet to be determined. It might be related to (a) the increased blood flow to juxtaglomerular glomeruli, and hence to the vasa recta,
which occurs (vide supra), resulting in increased washout of sodium from the medulla, and so increased loss of sodium from the ascending limb or decreased entry of sodium in the descending limb of the loop of Henle along electrochemical concentration gradients, or to (b) a direct effect on the sodium chloride transport in the thick part of the ascending limb of Henle’s loop, or (c) changes of permeability in some segment of the loop. Study of sodium reabsorption in more distal segments of the nephron has not yet been undertaken in pregnant animals.

Glucose

Glucose was detected in the urine of pregnant women over 125 years ago [55] and, because at that time it was thought that urine normally did not contain glucose it was termed ‘glycosuria’. There have been numerous reports in the literature since that date, many of them stressing the random or intermittent nature of this phenomenon (e.g. [56]). Although for over 60 years it has been recognized that all urine contains glucose, and so the term ‘glycosuria’ should be discarded [57], it is still a term in frequent medical use and is now hallowed by tradition. Throughout this review, however, we shall refer to the increased excretion of glucose during pregnancy. It was not until 1966 that a reliable test for glucose, one which did not underestimate glucose in the urine, was used in a study of pregnant women [58], but this work was presented only in abstract form and a full study had to wait a few more years [56].

By using this method, the hexokinase glucose 6-phosphate dehydrogenase method, it is now well established that all women tested excrete more glucose during pregnancy than at 8-12 weeks after delivery. Losses vary widely between women within pregnancy, even though for the women tested there was no evidence of an abnormally high (>8 mmol/24 h) glucose excretion post partum. When the glucose reabsorptive capacity of the kidney was stressed by infusing large amounts of glucose the differences between pregnant and post-partum women were magnified [59, 60].

The reasons for this increased excretion of glucose have been difficult to elucidate. Until recently it was assumed that either the load of glucose filtered at the glomeruli in the kidney was increased [61] or that the reabsorptive capacity of the proximal tubule was decreased [62]. Both of these explanations depended, however, on an incomplete understanding of the normal renal handling of glucose. Another more recent suggestion has been that minor degrees of renal damage associated with asymptomatic infection may compromise the renal reabsorption of glucose [60].

The conventional description of glucose handling by the mammalian kidney is deceptively simple. Glucose is reabsorbed by an active transport process in the first part of the proximal tubule until it reaches a constant maximal transport rate (Tm,G), which, at normal plasma glucose concentrations, sufficiently exceeds the filtered load to permit excretion of a glucose-free urine [63]. This description is incorrect in a number of ways, however, since it is well known (a) that glucose is always present in normal urine [64-66], (b) that Tm,G is not constant but varies with changes in GFR and extracellular fluid volume [67-72], (c) that glucose can be reabsorbed at sites other than the distal tubule [65, 73, 74]. Because of this more recent information on normal functioning, it does mean that there are more theoretical sites at which altered glucose handling can occur during pregnancy.

Rats also excrete more glucose during pregnancy than in the virgin state [75] and it has been possible to perform additional experiments to investigate directly the hypotheses given above to explain increased loss of glucose during pregnancy. With free flow micropuncture techniques it was, perhaps surprisingly, not possible to demonstrate a defect in proximal tubular mechanisms for glucose reabsorption; indeed when stressed by infusion of glucose the proximal convoluted tubule of pregnant rats was able to reabsorb more glucose than in virgin animals [76]. This offset the increased filtered load of glucose due to an increased GFR and the net result was that in pregnant animals less glucose was delivered out of the proximal convoluted tubule to more distal parts of the nephron than in virgins [77]. The implication is that the increased loss of glucose in pregnant animals is due to an increased loss from the 5% of filtered glucose which normally escapes reabsorption in the proximal convoluted tubule [74]. Direct experiments have shown that there are differences of handling of glucose in both the loop of Henle and the collecting ducts in pregnant animals [77]. Normally there is net reabsorption of glucose from the loop of Henle but if the loop is perfused with artificial solutions containing no glucose then glucose will leak back from the interstitial fluid into tubular fluid [74]. By measuring unidirectional and net reabsorptive fluxes of glucose in pregnant and virgin animals it has been possible to show that at least when glucose reabsorption from the loop is stressed by infusing glucose there is a considerable back-leak of glucose into the loop of Henle in pregnant animals [74]. The mechanism of the back-leak is thought to be
passive but other details are not known [74]. Unidirectional flux measurements from collecting ducts have also indicated a reduced capacity for reabsorption in pregnant animals. Whether there are similar mechanisms operative in the collecting duct and the loop of Henle is not known. It may be that there is a common factor which affects medullary tissues but this is in the realms of speculation.

Thus it appears that neither of the commonly accepted hypotheses to explain increased glucose excretion in pregnancy can be substantiated by direct experimentation. Instead there are defects in the handling of glucose by more distal parts of the nephron.

In summary, changes in renal haemodynamics and in salt, water and glucose handling occur during pregnancy in both humans and rats. The similarity of the changes so far described lead us to believe that the rat is a useful model for the study of some aspects of renal function during human pregnancy. However, although there are now several descriptions of the changes in renal function during pregnancy, the underlying mechanisms whereby these are achieved are not known. There are also uncertainties about the sites where altered reabsorption occurs. Furthermore, it is impossible to conclude whether the mechanisms which have been implicated in rat pregnancy are those which are important in pregnancy in humans.

Clearly for some of the changes a role for maternal hormones has been implicated; but whether this is through a direct effect of the hormones on the kidney or through indirect effects of changes in body fluid volume and composition is still to be resolved. Whatever the mechanisms involved, it appears that in both rat and human pregnancy the normal homoeostatic control mechanisms are re-set to new levels which reflect the new demands that pregnancy imposes. In this respect it is of interest that many of the changes occur at a time which appears to pre-date the demands imposed on the mother by the developing fetus and its placenta.

References


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