PART XVI

GUEST LECTURE

Chairmen: A Taraba
N Lameire
RENAL HAEMODYNAMICS AND SALT BALANCE IN PREGNANCY

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Renal haemodynamics in human pregnancy

Significant changes in renal haemodynamics during normal pregnancy have been recognized for many years [1]. Some confusion, however, existed in the past about the time after conception when these modifications first occur, the maximum extent to which they progress, and the way by which they evolve during gestation. Recently, Davison and Dunlop [2] have critically reviewed 40 years' literature and have detailed the methodological reasons that may account for many discrepant results. Taking into account only serial studies with sufficient data to permit comparison, avoiding correction of data by different surface area factors, and grouping results of different studies for the purpose of analysis, Davison and Dunlop have eventually drawn the conclusions illustrated in Figure 1. Effective renal plasma flow (ERPF) starts to rise early, in the first trimester, attains a maximum increment by 60–70 per cent at mid-pregnancy, then remains steady until the 30th week, when ERPF declines moderately to a final value higher by 40 per cent than the pre-gestational control. Glomerular filtration rate (GFR) increases at approximately the same time as ERPF, reached a maximal increase of 40–50 per cent at the 20th week and this is maintained until term. Due to the greater increase in ERPF than in GFR, filtration fraction (FF) is reduced, except in the few final weeks of gestation when the relative increases in ERPF and GFR are similar. These conclusions have been recently confirmed by Dunlop in a large serial study [3]. It is of interest that the range equal to one standard deviation of the mean of both ERPF and GFR in Dunlop's study encompasses the very different patterns of change found in the past [4].

Renal haemodynamics in experimental models

Changes in renal haemodynamics during gestation have been documented in various animal species. The animal model that has been most extensively studied
is the pregnant rat. Figure 2 summarizes measurements of GFR (both in the whole kidney and in single nephrons) that have been performed in the pregnant rat in the last four decades. It is evident that GFR was found to be increased in most of the studies, especially in the middle week of gestation (pregnancy lasts three weeks in the rat). There are some notable exceptions, however, mainly in early and late pregnancy. As emphasized by Baylis, who has recently and exhaustively reviewed the literature on renal haemodynamics in the pregnant rat, much of the discrepancy is accounted for by methodological differences, such as diverse extracellular fluid volume status, the effects of anaesthesia, or surgery [5]. These sources of artificial variations have been recently circumvented by Conrad, who has developed a model consisting of conscious, chronically

Figure 1. Relative changes in renal haemodynamics in human pregnancy (reproduced by permission from Kidney International [2]).
catheterized, normovolaemic rats, trained to clearance studies [6]. Longitudinal measurements of GFR and ERPF in these rats during pregnancy have shown that both increase significantly as early as day five of gestation. GFR and ERPF attain their maximum increase of about 30 per cent at days 16 and 12, respectively, then decrease to pre-gestation values at day 20 [6]. The results of Conrad, therefore, as well as most previous studies indicate that similar renal haemodynamic changes occur in the rat and human, at least in the stage of human gestation from the fourth to the seventh month, corresponding to days 10 to 16 in the rat.

The pregnant rat is an invaluable experimental model in that it can be used in renal micropuncture studies. Until now, glomerular haemodynamics in the pregnant rat has been the object of micropuncture studies by Baylis [7], and by our group [8]. Baylis studied 12-day pregnant rats and found a 30 per cent increase in single nephron GFR (SNGFR) that was accounted for entirely by a proportional increase in glomerular plasma flow (GPF). No change was found in the other determinants of ultrafiltration, that is effective filtration pressure (EFP) and the ultrafiltration coefficient (Kf, an index of hydraulic permeability and area of the filtering surface) (Figure 3). Unfortunately, Baylis did not report data on arteriolar resistances, but total glomerular resistance was probably decreased, because glomerular blood flow was increased and renal perfusion pressure was unchanged [7]. In 15-day pregnant rats, SNGFR was increased by 40 per cent. The increase in SNGFR was largely due to an increase in GPF, but
in part it was secondary to increased EFP (Figure 3). In turn, the rise in EFP was accounted for by increased hydrostatic pressure in glomerular capillaries [8]. In 15-day pregnant rats, Kf was moderately but significantly decreased. Should Kf fall further in the last days of gestation, this would account for the decrease in GFR shown by Conrad at day 20 [6]. In 15-day pregnant rats we could calculate the resistance of single afferent (Ra) and efferent arterioles (Re). Ra was halved, and also Re was significantly reduced, by 40 per cent. In conclusion, micropuncture studies have indicated that an afferent arteriole dilatation is the primary renal haemodynamic event in gestation, allowing more blood (and plasma) to flow and more pressure to be transmitted within glomerular capillaries. The decrease in Re may be a secondary phenomenon, due to moderate dilatation of this very elastic and compliant vessel while receiving increased blood flow rate [9].

Renal haemodynamics in chronic hypertension in pregnancy

In man, the information available is very scanty, and limited to cross-sectional measurements of GFR and ERPF in third-trimester patients. Lindheimer and Katz found average values of both GFR and ERPF close to the upper limits of normal in patients with sustained hypertension [10]. In contrast, Sarles et al found that both GFR and ERPF were consistently lower in hypertensive patients.
than in normal subjects [11]. Clearly, these discrepant results may well be due to the variable degree to which renal function may be affected by chronic hypertension. Serial studies will be necessary in the future to distinguish the changes in renal haemodynamics that are secondary to pregnancy from those due to hypertension that pre-existed pregnancy.

Some information on renal haemodynamics in chronic hypertension in pregnancy are obtainable from animal models. Recently, we have developed an animal model in female rats made hypertensive by clipping the right renal artery, mated three weeks after clipping. Pregnant hypertensive rats have been compared with both non-pregnant hypertensive and pregnant normotensive rats. Non-pregnant normotensive rats were used as control of basal renal haemodynamic conditions [12]. Renal micropuncture studies of the left (non-clipped) kidney were performed at day 15 of gestation and showed that hypertension was not associated with a rise in $R_A$ in pregnant rats as great as in non-pregnant rats. Therefore, glomerular autoregulation was impaired in pregnant hypertensive rats. Consequently, the increased renal perfusion pressure raised GPF in pregnant hypertensive rats. The increase in GPF was associated with a reduction in filtration fraction [13].

Possible effects of changes in renal haemodynamics on renal salt handling

The changes in renal haemodynamics in normal pregnancy and hypertensive pregnancy have the potential for influencing salt excretion. Increased GFR, in fact, will increase the filtered load of salt. The reduction in filtration fraction will be associated with decreased oncotic pressure within peritubular capillaries and this will reduce the net physical force modulating proximal tubular reabsorption [14]. Finally, it is reasonable to believe that glomerular autoregulation is not effective in juxtamedullary nephrons, similarly as in cortical nephrons (micropuncture has been performed only in the latter). Juxtamedullary nephrons, in fact, are not well autoregulated even in the normal (non-pregnant) condition [15]. Impaired autoregulation of juxtamedullary nephrons could be associated with increased haemodynamic pressure within vasa recta, and this would reduce salt reabsorption in Henle’s loop [16]. Indirect evidence that the last mechanism occurs in hypertensive pregnancy has been recently given in man. Conte et al have measured free-water clearance ($CH_2O$) during maximal water diuresis in hypertensive pregnant women and in hypertensive non-pregnant women of similar age and blood pressure. $CH_2O$ was significantly lower in pregnant than non-pregnant hypertensive women, both in the basal condition and after saline loading [17]. Since free-water is generated by salt reabsorption in Henle’s loop, these studies strongly suggest that salt reabsorption is decreased in pregnant hypertensive patients.

Evidence for a salt-losing disposition in pregnancy

Undoubtedly, normal pregnancy is associated with net salt retention, which is necessary for both fetal growth and expanding maternal ECV. Nevertheless,
pregnancy has been compared to a subtle salt-wasting condition, because of the ease by which the pregnant subject comes into a relative salt deficiency [13]. Experimental studies suggest that in pregnancy the kidney has a salt-losing disposition. In the normal pregnant rat urinary salt excretion is increased, at least in the first two weeks of gestation [18]. Urinary loss of salt with reduced net salt retention occurs in the experimental model of pregnant rats with renal hypertension [18]. Increased salt excretion is difficult to prove in steady-state conditions in hypertensive pregnant patients. Even if a relative loss of salt occurred in any stage of gestation, this would raise salt-retentive stimuli and a new state of salt balance would take place, interrupting the loss of salt. 'Memory' of these events, however, should remain in a reduced content of salt in the body (Figure 4). If this hypothesis obtains, one expects a relative decrease in ECV

![Diagram](image_url)

Figure 4. Postulated effects of a relative loss of salt in any stage of gestation

and plasma volume in patients with pregnancy hypertension. It is quite impressive, therefore, that Gallery et al, who measured plasma volume in a large group of such patients, found a highly significant inverse relation between plasma volume and diastolic blood pressure [19], suggesting that a relative salt depletion occurs whose extent depends on the level of blood pressure. The finding of Gallery et al fit very well with our results in the pregnant rat with renal hypertension. Rats with malignant hypertension, in fact, lost more and retained less salt than rats with benign hypertension [18]. Evidence for a salt-losing disposition in patients with pregnancy hypertension has recently come from studies of Conte et al, who showed a greater natriuretic effect of acute saline loading in hypertensive pregnant patients than in non-pregnant women of similar age and blood pressure levels [17].

Conclusions

In conclusion, both clinical and experimental studies indicate that relevant renal haemodynamic changes occur in gestation. These changes impair the ability of
the kidney to autoregulate and dispose to salt excretion, especially in hypertensive pregnancy. Great caution is, therefore, necessary in reducing salt intake, or causing salt depletion by diuretics in hypertensive pregnant patients [20].

References

2. Davison JM, Dunlop W. Kidney Int 1980; 18: 152
4. Davison JM, Dunlop W. Seminars in Nephrology 1984; 4: 198
5. Baylis C. Seminars in Nephrology 1984; 4: 208
7. Baylis C. J Physiol 1980; 305: 405