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Impact of Pregnancy on Underlying Renal Disease

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Abstract

Normal pregnancy involves marked renal vasodilation and large increases in glomerular filtration rate (GFR). Studies in rats reveal that the gestational renal vasodilation is achieved by parallel reductions in tone in afferent and efferent arterioles so GFR rises without a change in glomerular blood pressure. There is some evidence from animal studies that increased renal generation of nitric oxide (NO) may be involved. Although chronic renal vasodilation has been implicated in causing progression of renal disease in nonpregnant states by glomerular hypertension, there are no long-term deleterious effects of pregnancies on the kidney when maternal renal function is normal because glomerular blood pressure remains normal. When maternal renal function is compromised before conception, there are no long-term adverse effects on renal function in most types of renal disease, providing that the GFR is well maintained before conception. When serum creatinine exceeds ~ 1.4 mg/dL, pregnancy may accelerate the renal disease increases and when serum creatinine >2 mg/dL, the chances are greater than 1 in 3 that pregnancy will hasten the progression of the renal disease. The available animal studies suggest that glomerular hypertension does not occur despite diverse injuries. Thus, the mechanisms of the adverse interaction between pregnancy and underlying renal disease remain unknown.

Index Words

Glomerular filtration rate; renal vasodilation; animal models; primary glomerular disease; diabetes

There are profound hemodynamic changes in normal pregnancy including increases in plasma volume, red blood cell volume, and hence blood volume. Both stroke volume and heart rate increase leading to ~40% elevations in cardiac output, despite which, blood pressure (BP) falls because of large reductions in total peripheral vascular resistance (TPVR).¹⁻³ In addition to peripheral vasodilation, a vascular refractoriness to a variety of administered vasoconstrictors including angiotensin II develops quite early.²⁻⁴ Striking changes also occur in kidney function, with an early increase in glomerular filtration rate (GFR), which is first detectable within 3 to 4 weeks after conception (Fig 1).⁵ GFR continues to rise to a maximum of 40% to 50% above nonpregnant values by the end of the first trimester, and this increase is maintained throughout most of the pregnancy, although a fall in GFR occurs in the few weeks before delivery.⁶ An optimal increase in GFR is a good prognosticator for a successful pregnancy outcome. As shown in Figure 1, in a serial study of normal pregnant women, 2 women who failed to show the early rise in GFR subsequently underwent early spontaneous abortion.⁵

The rat is an excellent animal model for study because it exhibits systemic and renal hemodynamic changes during normal pregnancy that are similar to humans and the total gestation period in rats is only 22 days (Fig 2). During pregnancy, there is a progressive plasma

volume expansion (which can reach 100% above the nonpregnant rat value) followed by a fall in blood pressure (although this is not evident until close to term) and a midterm rise in GFR of approximately 30% (which falls toward nonpregnant values soon before delivery).⁷ The changes in GFR are paralleled by renal plasma flow (RPF), which is the result of a marked renal vasodilation. We have conducted a series of glomerular micropuncture studies in the pregnant rat at different stages of pregnancy. These studies reveal that both afferent and efferent arteriolar resistances (R_A and R_E) relax in parallel, and this relaxation allows a selective increase in glomerular plasma flow to occur with no change in the other determinants of single nephron GFR.⁷ Importantly, parallel reductions in R_A and R_E allow the kidney to vasodilate and permit increases in RPF and GFR without an increase in glomerular blood pressure (P_{GC}). As shown in Figure 3, there is no increase in P_{GC} at any stage in rat pregnancy despite the variations that occur in R_A and R_E . Roberts et al⁸ have used an indirect approach to estimate the impact of normal pregnancy on glomerular hemodynamics in normal pregnant women. They measure renal hemodynamics and neutral dextran sieving curves (over a wide molecular weight range) that, with certain assumptions based on the rat data, allows modeling of the single nephron determinants of GFR. Much like the rat, the majority of the increased GFR in pregnant women is because of increased RPF, although a small component may be because of falls in plasma protein concentration (and hence colloid osmotic pressure of blood entering the glomerulus). There is no evidence that the P_{GC} increases during pregnancy, suggesting that parallel relaxation of R_A and R_E also occurs in normal pregnant women. This finding has important implications for the long-term effects of pregnancy on renal function (see later).

Possible Causes of the Gestational Rise in GFR

We know that maternal factors initiate the gestational renal events because renal vasodilation and increases in GFR and RPF occur in pseudopregnant rats in which fetoplacental tissue is absent.⁹ In addition, both the peripheral vasodilation and plasma volume expansion that attend normal pregnancy are evident in pseudopregnant rats.¹⁰ In pregnant women, renal and peripheral vasodilation begins before complete placentation,¹¹ suggesting that the fetoplacental unit is not necessary for the initiation of the increase in GFR and/or the volume expansion of pregnancy, and thus this time course of vasodilation points to a maternal stimulus.

A number of vasoactive factors have been investigated as likely mediators of the gestational renal vasodilation, including increased activity of the prostaglandins and/or atrial natriuretic peptide, reduced angiotensin II actions, and so on.^{2,7} However, nitric oxide (NO), which plays an extremely important, physiologic role as a renal vasodilator,¹² has been implicated as an important mediator of the gestational fall in renal vascular resistance (RVR). Both plasma and urinary levels of inorganic nitrite and nitrate (NO_x ; oxidation products of NO) and cyclic guanosine monophosphate (cGMP) (a major second messenger of NO) increase during pregnancy in rats,¹³⁻¹⁵ suggesting an increase in total systemic NO production is occurring. In women, 24-hour urinary excretions of cGMP and plasma cGMP increase in normal pregnancy,^{16,17} although the persistence of this increased cGMP excretion long after delivery¹⁶ may reflect the prolonged postpartum rise in plasma atrial natriuretic peptide,¹⁸ rather than stimulation by NO. The findings with plasma and urinary NO_x excretions have been more variable,¹⁹ and the only study conducted using a controlled low NO_x intake (a requirement for interpretation of NO_x values in the context of NO activity²⁰) reported no elevation in plasma or 24-hour urinary NO_x excretion in late pregnancy versus the nonpregnant state.²¹ Of note, renal NO generation represents only a small percentage of the total NO_x production²⁰; thus, a local increase in renal NO production could still occur in pregnant women.

We have reported an increase in the NO synthase activity in vitro of both renal cortex and medulla in the pregnant rat, which is in phase with the renal vasodilation. Interestingly, this effect is confined to the soluble fraction that houses predominantly the neuronal and inducible

nitric oxide synthesis (nNOS and iNOS), whereas membrane fraction NOS activity (predominantly endothelial [eNOS]) actually falls at midterm.²² This agrees with a report of increasing renal nNOS and iNOS protein during pregnancy in rat kidney but a decline in the abundance of eNOS.²³ Functional studies confirm an important role for NO. Danielson and Conrad²⁴ have reported that low-level, acute (nonselective) NOS inhibition can reverse the pregnancy-induced rise in GFR without affecting the value in nonpregnant rats. We reported that chronic nonselective NOS inhibition prevents the gestational rise in GFR and the renal vasodilation²⁵ (Fig 4) and causes systemic hypertension. According to our *in vivo* and *in vitro* studies, the NOS isoform responsible has characteristics of both nNOS and iNOS.^{22,26} It is thus possible that a novel cytosolic NOS is upregulated in the rat kidney during pregnancy, as suggested by Singh et al.²⁷ Unfortunately, there are no clinical studies that address the role of NO in the gestational renal vasodilation of normal women.

If increased renal NO generation is the mechanism by which the pregnancy related renal vasodilation occurs, what is the trigger? We know that this is a maternal signal and estrogens have been suggested because they have a widespread stimulatory action on the NO system in the nonpregnant female.²⁸ Estrogens, however, are unlikely to provide the stimulus to renal vasodilation because in rats estrogen levels fall throughout pregnancy, increasing only just before term when the renal vasodilation is waning.²⁹ A novel and exciting possibility was raised by Danielson et al³⁰ recently; he suggested that the ovarian hormone, relaxin, might provide the trigger. Relaxin release is stimulated by pregnancy (via chorionic gonadotrophin), and relaxin has a selective renal vasodilatory action in nonpregnant female rats that is NO dependent.³⁰ No direct link, however, has yet been established between relaxin and renal vasodilation in pregnancy.

In summary, the animal literature suggests that NO plays an important role in mediating the gestational rise in GFR, although there are no data currently available in normal women. Whether or not defects in the renal NO system are involved in situations in which pregnancy has an adverse effect on renal function also remains to be determined.

Long-Term Effects of Pregnancy on Maternal Renal Function When Renal Function Is Normal

In nonpregnant patients, prolonged periods of renal vasodilation in some types of chronic progressive renal disease (CRD) can lead to increased P_{GC} , which in turn contributes to the further progression of the renal disease.³¹ In these settings, the renal vasodilation is predominantly of R_A , which exposes the fragile glomerulus to an elevated P_{GC} . Although the kidney is vasodilated throughout a normal pregnancy, there is no increase in P_{GC} during a single gestation period in the rat or in women because of the parallel reduction in tone in R_A and R_E (Fig 4). Also, in contrast to CRD, pregnancy is a physiologic condition not associated with loss of nephron number or underlying disease, and the vasodilation reverses after delivery.

Pregnancy-induced renal vasodilation might therefore have benign long-term effects on the kidney, and we conducted studies on normal Munich Wistar rats to test this possibility. Female rats were subjected to 5 successive closely spaced pregnancies and compared with age-matched virgins at the age of ~1 year. The kidney's of the repetitively bred rats were vasodilated because of pregnancy/lactation for approximately 40% of their life. We found that repeated pregnancies had no adverse effects on kidney function or structure compared with age-matched virgin females and that there was no chronic elevation in P_{GC} despite the persistent renal vasodilation.³² The only systematic clinical study looking at long-term effects of pregnancy in normal women was reported by Davison.³³ Ten women with an average of 2.5 ± 1 pregnancies showed stable GFR and no proteinuria over 17 years, and similar findings were noted at 23 years of follow-up (Danson, unpublished data, 2000). Also, normal women showed no tendency for

GFR to decline during the reproductive years; in fact, they showed less of an age-dependent decline in GFR than men.³⁴ It should be noted that these studies were conducted on women from Western countries with access to good antenatal and postnatal care, and the multiparous women had only a modest number of pregnancies. Whether or not women in third-world countries also fare as well, given that they may become pregnant every 1 to 2 years during their reproductive lives and that they lack access to adequate medical care, is unknown. Based on the animal and clinical data available, however, multiple pregnancies have no long-term damaging effects on the maternal kidney when renal function is initially normal.

Glomerular Hemodynamics During Compromised Pregnancies

There are increased risks for women with underlying renal disease who become pregnant. For instance, the incidence of preeclampsia is elevated, and in some situations, the superimposition of pregnancy has been reported to accelerate the rate of loss of renal function.³⁵ What predicts those women with CRD who are at risk for pregnancy-induced complications? Women with a variety of mild underlying primary renal diseases (serum creatinine <1.4 mg/dL) often show increases in GFR during pregnancy (Fig 5), although of smaller magnitude than seen in normal pregnant women.³⁶ Increased proteinuria often occurs but abates after delivery in most women with mild renal disease; indeed, a small increase in protein excretion is also a function of normal pregnancy.³⁷ Of note, renal transplant recipients also show a substantial increase in GFR during pregnancy provided that there is no underlying graft rejection.³⁷ The increase in GFR follows a similar time course to that seen in normal pregnant women (Fig 6). The persistence of this gestational renal vasodilation in transplant recipients is remarkable, given that the transplants are hypertrophied, denervated, and ectopic, and many of the transplanted kidneys are from male cadaveric donors.

In women with elevated serum creatinine because of primary renal disease before conception, there is a decline in the frequency of a gestational fall in creatinine.³⁸ The gestational rise in GFR becomes compromised as the severity of the underlying disease worsens, and in 1 study, only ~50% of women with moderate and none with severe chronic renal disease showed any rise in GFR during pregnancy.³⁹ Providing that the preconception serum creatinine is <1.4 mg/dL and that hypertension and/or heavy proteinuria are absent, the obstetrical outcome, in terms of a healthy baby, is good.³⁵

The pattern is quite similar in women with renal disease secondary to type 1 diabetes, who usually also show a gestational rise in GFR, providing that the renal function is near normal preconception.⁴⁰ With more severe diabetic nephropathy, abrupt falls in GFR can occur during the pregnancy. Although this can also occur in the nonpregnant woman with diabetic nephropathy, a careful serial study suggests that an acute loss of renal function directly attributable to pregnancy does occur.⁴¹

In rats the effects of superimposed pregnancy on glomerular hemodynamics is highly variable and depends on the model of underlying renal disease (Table 1). In gentamicin-induced acute renal failure, the spontaneously hypertensive rat (SHR) and the rat subjected to chronic NOS inhibition, there is no midterm rise in GFR or renal vasodilation.^{25,42-44} Rats with the FX1A model of membranous glomerulonephritis (GN) respond to pregnancy with renal vasoconstriction by an unknown mechanism and GFR falls, but because the rise in RVR is localized at R_A , the P_{GC} actually goes down.⁴⁵ In this situation, pregnancy acutely impairs maternal renal function. In all of these animal models of renal disease, there was only mild functional impairment at the time of conception.

In an anti-glomerular basement membrane model of GN associated with an elevated P_{GC} , the kidney is able to vasodilate at midterm so that GFR increases. Although in this model, the P_{GC} is maintained (ie, P_{GC} does not increase further as a result of the pregnancy).⁴⁶ The most

remarkable example of the robust nature of the gestational renal vasodilatory signal is found in the 5/6 renal ablation model. Despite severe reduction of functional renal mass and marked compensatory hypertrophy of the remnant kidney, the remnant kidney vasodilates during pregnancy so that GFR increases. Yet surprisingly, P_{GC} goes down in this model because pregnancy also has a markedly antihypertensive effect.⁴⁷ Another unusual characteristic of this model is that the gestational renal vasodilation persists until close to term RVR is reached.⁴⁷ In the rat with early type 1 diabetes, a gestational rise in GFR is seen that is additive to the diabetic hyperfiltration.⁴⁸ In addition, in a rat model of hyperinsulinemia (without hyperglycemia), the renal hemodynamic response to pregnancy is normal.⁴⁹ Unfortunately, there have been no glomerular micropuncture studies in these animal models.

In summary, there is a very variable pattern of possible glomerular hemodynamic responses to pregnancy in the presence of underlying renal disease. Of note, we found no situation in any of our studies in which pregnancy leads to increases in P_{GC} . Thus, we conclude that when pregnancy does result in a long-term, damaging effect on residual renal function, this most likely occurs by nonhemodynamic mechanisms.

Long-Term Effects of Pregnancy on the Kidney When Maternal Renal Function Is Compromised

The preconception level of renal function is again a significant indicator of the long-term prognosis. Normal women with single kidneys removed because of kidney donation do well in the long-term. There is a minimal incidence of hypertension and proteinuria in women ~20 years after kidney donation, and this is lower than in male kidney donors.⁵⁰ Although the parity of the female subjects in this study was not reported, it is likely that many underwent 1 or more pregnancies.⁵⁰ In another study, all indices of renal function were normal 8 years after kidney donation and after an average of 2 pregnancies.⁵¹ Although after 17 years and an average of 2 pregnancies, Davison³³ reports a slight (~10%) decline in GFR in women who had donated kidneys.³³ There is evidence that renal transplant recipients showed no adverse long-term effects after 2 pregnancies (variable intervals after transplant), providing that the graft function was well preserved at conception.⁵²

There have been several long-term studies in women with CRD. Jungers et al⁵³ have reported findings from patients up to 30 years from the clinical onset of renal disease because of primary GN. All of these patients had normal renal function at the time of the first conception and one or more pregnancies did not accelerate the disease. This was true for both women who remain normotensive and those who were hypertensive, although both parous and nulliparous hypertensives had a greater rate of progression of CRD (Fig 7).⁵³ Jones and Hayslett published a study on the effect of pregnancy in patients with primary GN, on “long-term” (1 year after pregnancy) maternal renal function, which stratifies women into three groups according to their initial level of renal function.³⁸ Providing serum creatinine is <2 mg/dL in the first or second trimester, most subjects show stable renal function up to 12 months postpartum with only 2% showing an accelerated rate of decline in function. In women whose serum creatinine is >2 mg/dL, ~33% showed sustained loss of renal function during or immediately after the pregnancy (Fig 8). These findings are in agreement with the observations of Becker and colleagues who point out that pregnancy can accelerate the course of renal failure when renal function is significantly diminished before pregnancy.⁵⁴ Although severe loss of renal function compromises fertility, conception can occur, even in women with end stage renal disease who are on dialysis. In this population, the chances of a live birth are only ~20% to 50% and there is a risk of severe maternal consequences, particularly, uncontrolled hypertension,^{35,55}

Women with type 1 diabetes respond similarly to those with primary renal disease in terms of the impact of pregnancy on long-term renal function. When there is minimal renal impairment

before conception (serum creatinine <1.4 mg/dL = 124 μ mol/L), it is generally considered that pregnancy does not influence the course of diabetic nephropathy. When there is moderate to severe preexisting renal functional impairment, however, pregnancy has a $>40\%$ chance of acutely accelerating the rate of progression to end-stage disease.⁴¹ In a long-term follow-up study (16 years), pregnancy was found to have no adverse renal effects in women with normal renal function before conception.⁵⁶ Although type 2 diabetes is now appearing in the teens and twenties, there have as yet been no studies on the impact of pregnancy on renal function in this population.

In conclusion, there is considerable evidence that in most types of renal disease, pregnancy has no long-term adverse effects on the maternal kidney providing that preconception renal function is close to normal. There is also clear evidence that pregnancy is damaging to the long-term health of the kidney when maternal renal function is already compromised. The likelihood of pregnancy-induced damage is apparently related to the initial level of renal dysfunction more than to the specific disease. The mechanism by which pregnancy accelerates progression in moderate to severe renal disease remains unknown. Multiple pregnancies in rats with 1 kidney and fed a high-protein diet have no long-term effect on P_{GC} nor do they worsen the structural damage to the kidney.⁵⁷ Also, long-term studies in the spontaneously hypertensive rat show that repetitive pregnancies do not lead to increased P_{GC} and have no long-term deleterious effects on the kidney.⁴⁴ Thus, there is no evidence from animal studies of a hemodynamic basis for pregnancy-associated worsening of renal disease.

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Figure 1.

Changes in 24-hour creatinine clearance measured weekly before conception and through to uncomplicated spontaneous abortion in 2 women. The solid line represents the mean and the stippled area the range for 9 women with successful obstetric outcome. MP, menstrual period; LMP, last menstrual period. (Reprinted with permission.⁵)

Figure 2.
Time course of the changes in GFR, plasma volume, and mean arterial BP in the normal pregnant rat. (Data from⁷.)

Figure 3. Summary of mean arterial BP, glomerular capillary blood pressure (P_{GC}), and the transglomerular hydrostatic pressure gradient (ΔP ; P_{GC} , proximal tubule pressure) in Munich Wistar rats in the virgin state and throughout normal pregnancy. Gestation lasts for 22 days in the rat. (Reprinted with permission.⁷)

Figure 4.

Time course of the change in GFR in normal conscious rats during pregnancy (solid circles) and during low-dose NOS inhibition (50 mg/L L-nitro-arginine methyl ester, drinking water; open circles) and high-dose NOS inhibition (100 mg/L L-nitro-arginine methyl ester, closed triangles) given chronically from days 3 to day 19 of pregnancy. *A significant difference in the normal pregnant rats from the virgin value. †A difference between normal midterm or late pregnant rats versus rats receiving chronic NOS inhibition. (Data from²⁵.)

Figure 5. GFR estimated from serial 24-hour creatinine clearances (mean) in 10 normal women (upper curve) and in 26 women with mild underlying primary glomerular disease (mean $\pm$ 1 standard deviation). (Reprinted with permission.³⁶)

Figure 6.

Impact of pregnancy on GFR during 10 pregnancies in 8 renal transplant recipients (lower curves ± 1 standard deviation). Serial GFR measurements were determined both from the 24-hour creatinine clearance and from the inulin clearance (C_{IN}) during infusion studies. The upper curves and shaded areas give the mean ± 1 SD for a group of 10 women with normal renal function. (Reprinted with permission.³⁷)

Figure 7.

Kaplan Meier renal survival curves for women with primary glomerular disease followed over 30 years. The upper lines show data for women who remained normotensive and experienced 1 or more pregnancies (solid line) or no pregnancies (dotted line). The lower lines show data for women who became hypertensive with 1 or more pregnancies (dash line) and those who never became pregnant (dot-dash line). (Reprinted with permission.⁵³)

Figure 8.

Figure to show the predictive effect of the preconception serum creatinine on renal function during and after pregnancy in women with primary renal disease of varying severity. (Reprinted with permission.³⁸)

Table 1

Summary of the Impact of Superimposed Pregnancy on RVR, RVR GFR, and Glomerular Blood Pressure (P_{GC}) in Normal Rats and in Rats With Various Forms of Underlying Renal Disease

	RVR	GFR	P_{GC}
Normal preconception P_{GC}			
Normal controls ^{7,9}	↓	↑	→
Gentamicin-induced ARF ⁴²	→	→	→
High preconception P_{GC}			
Anti-GBM GN ⁴⁶	↓	↑	→
Fx1a, membranous GN ⁴⁵	↑	↓	↓
High preconception P_{GC} and BP			
5/6th renal ablation ⁴⁷	↓	↑	↓
SHR ⁴⁴	→	→	→
Chronic NOS inhibition ¹⁵	→	→	→

Abbreviation: GBM, glomerular basement membrane.