Renal

UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL SCHOOL
INTERNAL MEDICINE GRAND ROUNDS

# PREGNANCY IN THE SETTING OF KIDNEY DISEASE

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## Introduction

Traditionally, pregnancy has been discouraged in women with antecedent renal disease. Early reports indicated that maternal and fetal morbidity were prohibitive in such cases. This view has been significantly altered over the past two decades, primarily as a result of careful clinical studies carried out by both obstetricians and nephrologists. There is also no doubt that important advances in prepartum management have altered the morbidity associated with such high risk pregnancies. A clearer understanding of the normal physiological changes in pregnancy and the mechanisms and management of renal diseases has made successful pregnancy a possibility for many such women.

The discussion today will focus first on the physiological changes which accompany pregnancy, and then the impact of pregnancy on renal disease, followed by the management of such pregnancies and finally some suggestions regarding the assessment of risk in such patients.

## PART I: PHYSIOLOGICAL CHANGES ACCOMPANYING PREGNANCY

### Anatomic changes in the genitourinary system

The microscopic appearance of renal tissue is not altered by pregnancy. However, there is a general consensus that renal size is increased during gestation. Intravenous pyelograms performed in first week following delivery consistently show kidneys which are larger than predicted by standard height-weight nomograms (1). Further, when pyelograms are repeated six months after delivery, there is an average 1 cm decrease in renal length. Studies involving pregnant rodents (2) and autopsies of women dying during or shortly after gestation (3) have demonstrated an increase in renal weight. In the case of the animal studies, both wet and dry weight were increased. However, other groups (4) have found no biochemical markers of renal growth in rodents and thereby conclude that the increase in renal weight observed in pregnancy is likely the result of increased water content.

The most impressive morphological changes in pregnancy occur in the collecting system (calyces, pelvis and ureters). These changes, usually greater on the right, may be present as early as the first trimester, and are present in over 90% at term (5). Both mechanical and hormonal factors may participate in the collecting system changes. While some have argued an obstructive etiology (6), still others have pointed out that the ureters remain dilated despite catheterization (7) and that such dilation may be produced by estrogen administration to nonpregnant primates (8,9). Nonetheless, there is evidence which supports a role for obstruction. Rubi and Sala (10) have shown a marked increase in intraureteral pressure when near-term gravidas are in a standing or supine position. The pressure is significantly reduced by moving the subject into a lateral recumbent position. Interestingly, the intraureteral pressure was elevated only above the pelvic brim. Independently, Dure-Smith found that ureteral dilatation terminates at the true bony pelvic brim, at a point where the ureter is crossed by the iliac artery (10). Intravenous pyelograms performed during or shortly after pregnancy may show a cut-off or filling defect in the ureters at the point where they are crossed by the iliac artery; i.e. the so-called "iliac sign".

The dilation of the collecting system during pregnancy may be of considerable clinical significance. First, the presence of dilated ureters and calyces may give the false impression of pathological obstruction. Second, the diagnosis of true obstruction is obviously complicated by this "physiological" hydronephrosis. Finally, the increase in urinary "dead" space and subsequently increased urinary drainage time may contribute to the increased incidence of urinary tract infection in pregnant women; especially those who exhibit chronic bacteriuria prior to pregnancy. The urinary stasis and dilated collecting system may also promote serious errors in clinical tests which depend on timed, complete urine collections (e.g., creatinine, protein,

estriol). Such errors can be minimized by water loading to produce a brisk, dilute urine flow and by maintaining the subject in a lateral recumbent position. Finally, because the kidneys are increased in length (by an average of 1 cm) during pregnancy, a reduction in renal length during the weeks or months following delivery may be mistaken for a pathological change.

**Changes in Volume Homeostasis Accompanying the Normal Pregnancy**

Normal individuals, in steady state, control their extracellular volume (ECF) within very narrow limits. The mechanisms by the ECF is regulated are complex and involve interrelated regulation of both volume and osmolality. Volume is a sodium-dependent concept, whereas osmolality is more related to water. In this way, an increase in ECF sodium content results in thirst, drinking and an increase in the excretion of sodium and water. Water excess results in an increase in solute-free urine, whereas water loss results in thirst and an antidiuresis.

In contrast, pregnancy cannot be regarded as an ordinary steady state condition. The average primigravida gains 12 Kg during gestation, whereas multiparous women gain about 11 Kg. (11,12). Approximately 80% of this weight (9.5 Kg) is gained after the 20th week, and just under 50% of the weight gained is salt and water (13). Hytten (14) has analyzed the weight gain of pregnant women throughout gestation and has approximated the distribution of the added mass as shown in Table 1.

**Table 1**

**Weight Gain Accompanying Normal Pregnancy**

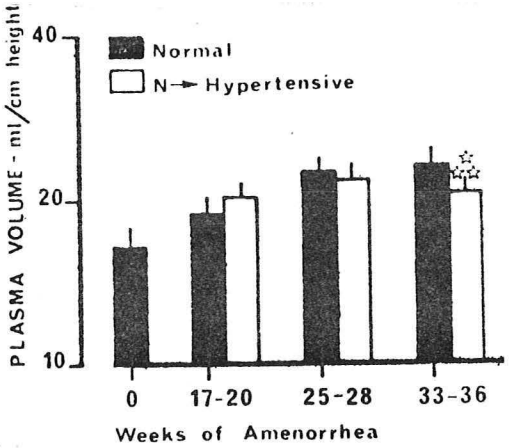
| Tissue | 10 Weeks | 20 | 30 | 40 |
|---|---|---|---|---|
| Fetus | 5 | 300 | 1500 | 3400 |
| Placenta | 20 | 170 | 430 | 650 |
| Amniotic Fluid | 30 | 350 | 750 | 800 |
| Uterus | 140 | 320 | 600 | 970 |
| Mammary Gland | 45 | 180 | 360 | 405 |
| Blood | 100 | 600 | 1300 | 1250 |
| Extravascular Fluid | 0 | 30 | 80 | 1680 |
| Total | 340 | 1950 | 5020 | 9155 |
| Unaccounted Weight | 310 | 2050 | 3480 | 3345 |
| Total Gain | 650 | 4000 | 8500 | 12500 |

(All weights in grams. Table adapted from Hytten (14) and Lindheimer and Katz (5))

It should be noted that the 12 Kg weight gain (quoted from the British literature, Ref. #11) was based on women who were edema-free during the course of their pregnancy.

Lindheimer (5) has pointed out that the 12 to 13 Kg figure is considerably greater than values reported earlier. He notes that the early studies included women with abnormal pregnancies, women observing strict dietary limitations and many observations of less than two trimesters. He further points out that the 12 Kg figure is an average, not an upper limit, and that greater gains may be entirely normal.

To the physiologist, it is most interesting that the maternal weight gain (about 7 Kg of which is salt and water) is a state of physiological hypervolemia. Volume receptor mechanisms apparently sense this increase as normal, and when pregnant women are treated with either salt restriction or diuretics, their response may be similar to that of volume depleted non-pregnant subjects.




Plasma volumes during pregnancy in normotensive (black bars) and women who developed hypertension in the third trimester (open bars) (13).

Equally confounding is the fact that proportionately more water than sodium is retained resulting in modest hyponatremia and hypoosmolality. On average, plasma osmolality decreases by 10 mOsm/Kg during a normal pregnancy. Such a fall in plasma osmolality, combined with an increase in plasma volume would ordinarily suppress secretion of antidiuretic hormone (ADH) and result in a prompt water diuresis. Nevertheless, pregnant women do not experience such an effect. Despite basal plasma osmolarities 8 to 10 mOsm less than in the nonpregnancy state, ADH rises if plasma osmolarity is increased, and decreases if a water load is administered (15). That is, the ADH response to osmolarity is apparently normal, but **reset** to operate from a lower baseline. Volume receptors for ADH secretion also appear to be reset by pregnancy. Plasma volume, increased 30% to 40% over the non-pregnant state is rigidly maintained. Animal experiments have shown that decrements in plasma volume of as little as 1% result in increased circulating ADH (16). Although some authors have suggested that pregnant women excrete a water load less efficiently than non-pregnant controls (17), these observations may have been an effect of the supine position.

Others (18) have shown that when studied in the lateral recumbent position, pregnant women exhibit normal diluting capacity. The puzzle of osmolar and volume regulation in pregnancy was further compounded in 1962 by the finding of an enzyme in the blood of pregnant women, presumably of placental origin, which deactivates oxytocin and vasopressin. This enzyme, an aminopeptidase called vasopressinase, has greatest plasma activity late in the third trimester. There have been conflicting reports regarding the renal response to exogenous vasopressin during pregnancy (19-21). Further, there has been some question regarding the vasopressin requirements of pregnant women with diabetes insipidus, although the bulk of data seem to support the view that their requirements increase (22). Nevertheless, even if exogenous vasopressin resistance were proven, it might well be due to factors other than vasopressinase, such as altered volume of distribution or metabolic clearance of the hormone. In this respect, animals which produce no vasopressinase (goats and rats) also demonstrate vasopressin resistance during pregnancy (23,24).

**Changes in Blood Pressure Regulation During Pregnancy**

Mean arterial pressure decreases during the first trimester with diastolic pressures averaging as much as 15 mmHg less than postpartum levels. In the second and third trimesters, the mean arterial pressure gradually rises but does not reach prepregnancy levels. Cardiac output mirrors blood pressure, rising in the first trimester, then remaining relatively constant until term. Because mean pressure is decreased during gestation, some women with preexistent hypertension may display near normal blood pressure values in the first trimester and subsequently be labelled as preeclamptic in the second trimester when abnormal pressures are recorded. It has been recommended that 75 mmHg in the second and 85 mmHg in the third trimester be considered the upper limit of normal for the diastolic blood pressure (25).

Reduced peripheral vascular resistance is the underlying mechanism of the hemodynamic changes in pregnancy. The reason for this reduction in PVR is somewhat uncertain but has been the subject of a great deal of investigation. Pregnancy is accompanied by marked increases in circulating renin, renin substrate and angiotensin II (26-30). However, pregnancy is also associated with marked rsistance to the effects of angiotensin (30). Levels of estrogens and progesterone are certainly increased during gestation and are responsible for smooth muscle relaxation in a number of organs. One might suspect that the action of these hormones is responsible for the decrease in PVR; i.e., arteriolar relaxation. However, these steroids reach their maximum concentrations during the latter half of pregnancy, when mean arterial pressure is increased in comparison with the first trimester. Catecholamine metabolism is apparently unaffected by pregnancy (31). Recently, considerable attention has been directed toward vasodilating prostaglandins, principally of the E series (32-35). Presumably produced by the

utero-placental complex, the urinary excretion of $PGE_2$ and $PGF_2$ is markedly increased during gestation. Pedersen and his associates (36) have recently shown that preeclampsia is accompanied by a decrease in urinary $PGE_2$ excretion to a level equivalent to that observed in the nonpregnant state, suggesting that pregnancy-induced hypertension (preeclampsia) may be a state of prostaglandin ($PGE_2$) deficiency. Differences in urine volume between the preeclamptic and normotensive women were not sufficient to account for the difference in $PGE_2$ excretion.

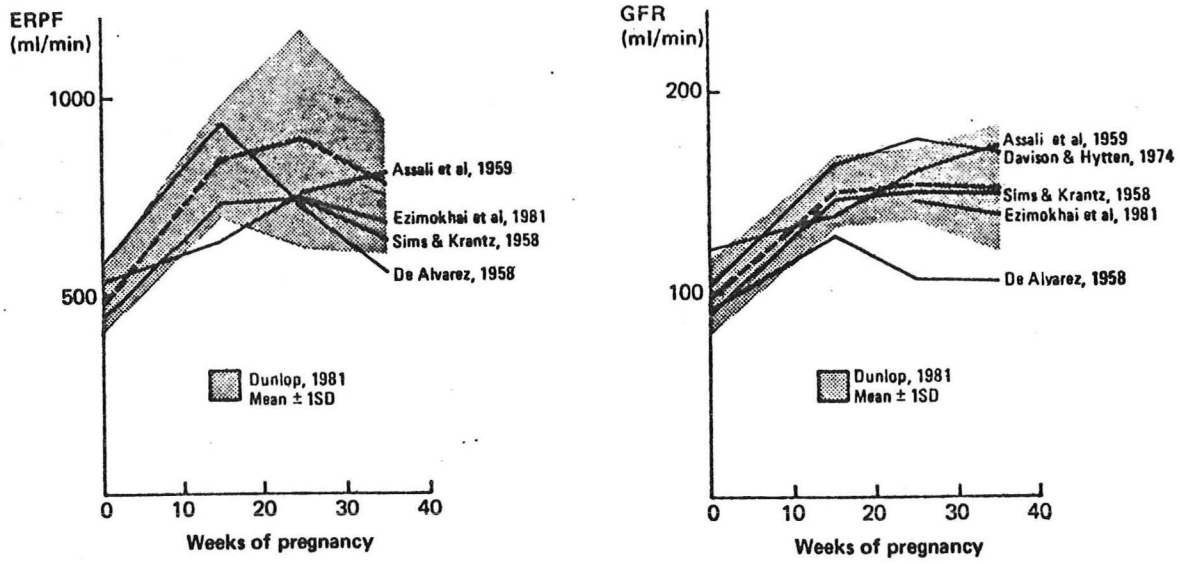
It has been suggested that the metabolites of progesterone are responsible for the increased production of vasodilating prostaglandins (37). These prostaglandins may then exert their effect directly on the vascular smooth muscle, either by altering angiotensin receptors or by altering the cellular environment in such a way that response to angiotensin is altered (13). Further work will be needed to establish the role of prostaglandins in the reduced PVR of pregnancy.

## Glomerular Filtration and Renal Tubular Function in Pregnancy

For many years, the effect of pregnancy on renal plasma flow (RPF) and glomerular filtration (GFR) was controversial. The confusion was principally the result of methodological problems, small sample size and comparisons between women in different stages of pregnancy.

More recent studies, though not perfect, have resulted in relative agreement on several important issues. Most authors agree that GFR increases early in pregnancy and remains elevated until at least the ninth month. The clearance of creatinine is increased as early as one month following conception, and peaks at 40 to 50% higher than non-pregnant levels at about twelve weeks of gestation. The increased clearance is sustained to near term (36th week) when it may actually decrease slightly (38,39). Three months postpartum, creatinine clearance has returned to prepregnancy values (40).

RPF also increases dramatically during gestation and rises to values as great as 50 to 80% greater than prepregnancy levels during the first and second trimester (40). Near term, RPF seems to decrease by approximately 25%, but remains above prepregnancy values (39-41). Lindheimer and Katz (5) have pointed out that there remains some question about the validity of the decrease in RPF near term. They point out that para-aminohippurate infusions (used to measure RPF) are subject to considerable variation.

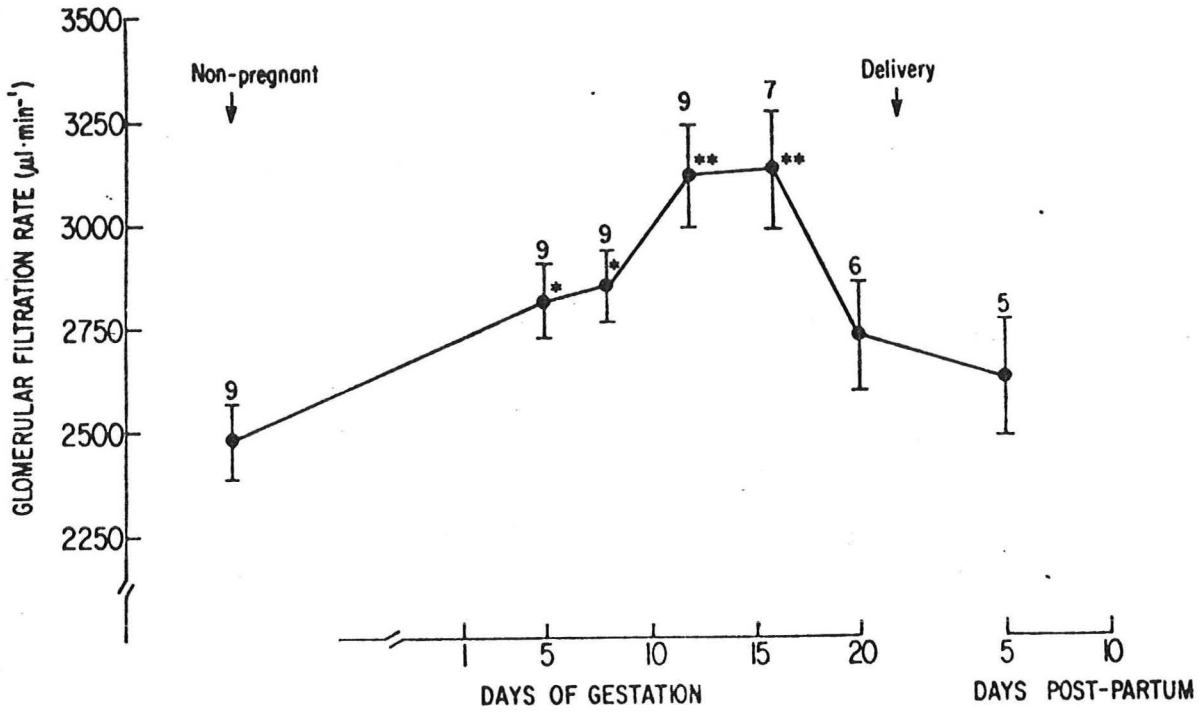



Changes in effective renal plasma flow (figure left) and GFR (figure right) throughout the course of pregnancy. Results are not corrected for body surface area (40).

The mechanisms responsible for these remarkable changes in renal hemodynamics remain unsettled. As discussed earlier, cardiac ouptut increases significantly early in pregnancy, and together with the decrease in plasma oncotic pressure may enhance GFR. Certainly the volume expansion experienced by pregnant women might contribute to increases in both RPF and GFR, but the greatest increment in plasma volume does not occur until after the 13th week, when the increase in GFR is already established (42).

Endocrine changes during gestation include sharp increases in circulating aldosterone, progesterone, cortisol and parathyroid hormone. All these hormones are thought to have some effect on renal function, but clearly none are known to have actions sufficient to be responsible for the hemodynamic changes observed in pregnancy.

Similar to the changes in humans, rats (43), rabbits (44), dogs (45), and sheep (46) all show changes in renal hemodynamics during normal pregnancy.




Measurements of GFR before and during gestation and post partum in female Long-Evans rat.
*p<0.05, **p<0.01 (from C. Baylis, Sem. Neph. Vol.4, 1984)

Garland and Green (47) have suggested that there is a redistribution of blood flow to juxtaglomerular nephrons which have higher clearance rates than cortical nephrons.

Interestingly, Baylis (48) has reported that many of hemodynamic changes which occur in rats during the course of a normal pregnancy also occur with pseudopregnancy. Such findings suggest that the hemodynamic and GFR changes are independent of the products of conception The increase in GFR (and creatinine clearance) are reflected in the plasma creatinine and BUN, which decrease during pregnancy. Early work by Sims and Krantz (49) indicated that the average plasma creatinine in non-pregnant women of childbearing age was 0.67 ± 0.14 mg/dL and 0.46±0.13 in pregnant cohorts. Other authors have found that plasma urea nitrogen, which averages 12.1 mg/dL during the postpartum period is 9.2±2.1 mg/dL during pregnancy (50). Lindheimer and Katz (5) recommended that concentrations of plasma creatinine and urea nitrogen exceeding 0.8 mg/dL, and 13 mg/dL (respectively) during pregnancy should alert the physician to the possibility of intrinsic renal disease.

## Renal Tubular Function in Pregnancy

### Uric Acid Clearance

The plasma concentration of uric acid decreases during normal pregnancy. At approximately eight weeks of gestation, the

plasma uric acid is about 29% lower than during the non-pregnant state (51), but rises once more during the third trimester, ultimately reaching pregestational levels at term (52). It is likely that this pattern of events is the result of altered tubular handling of uric acid. Uric acid is freely filtered, but is actively reabsorbed and only about 10% of the filtered load appears in the urine. It is, therefore, impossible to conclude whether the changes observed in pregnancy are the result of altered secretion or reabsorption (51,52).

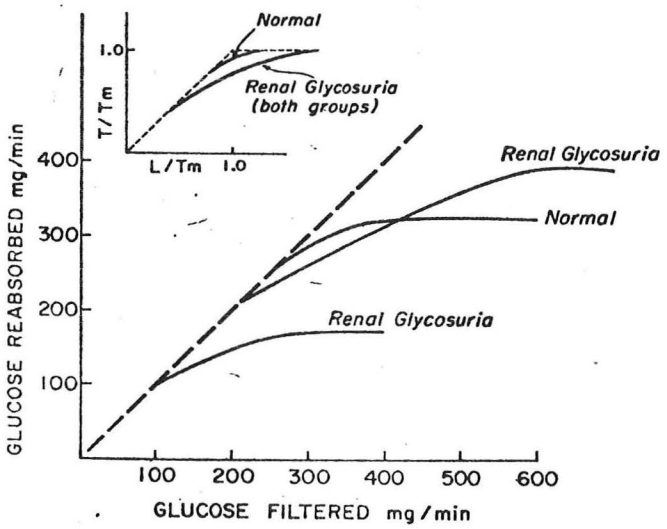
The clinical significance of uric acid in pregnancy is the relation it bears to preeclampsia (pregnancy-induced hypertension). Relative hyperuricemia correlates with the severity of this condition (53,54) and, in some studies, fetal outcome (55,56). The changes in urate clearance which occur in both normal and preeclamptic pregnancies are not precisely understood. Despite the decrease in plasma albumin concentration and increase in the total pool of uric acid, decreased protein binding of uric acid is generally held not to be responsible for these changes (57). Rather, most work implicates changes in maternal ECF volume as the primary factor affecting uric acid clearance (5,57,58). As discussed previously, posture may have significant effects on clearance measurements performed late in pregnancy. Lindheimer (59) has suggested that posture may have introduced artifacts into studies which show that urate clearance decreases near term.

**Glucose**

Normal, nonpregnant women excrete less than 100 mg glucose/day into the urine. Glucosuria during normal pregnancy was first noted almost a century ago. In 1972, Lind and Hytten (60) reported serial observations on 30 healthy women throughout their pregnancies. All had normal glucose tolerance. Each women regularly collected 24 hour urine samples from early in the first trimester until 6 weeks post partum. Urinary glucose was measured by an enzymatic (glucose oxidase) method to avoid artifacts introduced by other reducing sugars. Prior to pregnancy, all women excreted less than 100 mg glucose per day. During pregnancy, 26 women (86%) experienced a significant increase in glucose excretion. Twelve women (40%) excreted 500 mg or less, four (13%) excreted more than 500 mg but less than 1.0 gm, while ten (33%) excreted more than 1.0 gm/day. Most striking was the variability of glucose excretion by a particular patient. In most, glucosuria was only intermittently present and was unrelated to either blood glucose concentration or state of gestation. Pregnancy-associated glycosuria reverts to normal within one week following delivery (61).

Normally, glucose is filtered at a rate of up to 160 mg/minute (GFR X plasma glucose concentration) and is entirely reabsorbed in the nephron. As the filtered load increases from 160 to about 350 mg/minute, both urinary excretion and reabsorption of glucose increases. All filtered glucose in excess of 350 mg/minute appears in the urine. Therefore, 160 mg/min is

referred to as the **threshold**, and 350 as the **tubular maximum** ($T_M$). It is important to recognize that $T_M$ may increase as GFR increases. In a study by Welsh and Sims (62), the GFR of a group of pregnant women did not differ, but the $T_M$ for glucose was lower in those with glucosuria. However, because postpartum measurements were made in only three subjects one cannot positively conclude the possibility that pregnancy lowers the $T_M$ for glucose. More recently, Davison and Hytten (63) have also observed decreased resorptive capacity for glucose in pregnancy. They were able to show that with a filtered load of 300 mg/minute, pregnant women would reabsorb between 50 and 80%, while males and nonpregnant women reabsorbed 90%. Still others have not been able to show any change in either $T_M$ or renal glucose threshold with pregnancy, and suggest that the "splay" is altered by pregnancy (relatively more glucose is excreted in the range between threshold and $T_M$) (64).




Titration curves of glucose reabsorption in renal glycosuria. Normal individuals and two groups of patients with glycosuria are represented.

Volume expansion is known to increase the splay in glucose excretion in otherwise normal rats (65) It is relatively well-established that glucose can be reabsorbed in nephron segments other than the proximal tubule (66,67). In fact, using free-flow micropuncture techniques, it has been shown that the proximal nephron of the pregnant rat can reabsorb more glucose than that of the nonpregnant animal (68). This may offset any increase in filtered load resulting from an increase in GFR. Thus, gestational glycosuria probably results from defective reabsorption of glucose which escapes proximal reabsorption. Glucose can be reabsorbed in distal nephron segments, but there is also potential for passive back-leak.

There is no evidence to suggest that gestational glycosuria is a forerunner of diabetes mellitus or that it is associated with perinatal complications. It should be noted that diabetic women regularly experience increased glycosuria during pregnancy. For these reasons, the routine use of random urinary glucose measurements may be misleading and harmful. The daily loss of glucose into the urine is usually small and will not adversely affect maternal nutritional status. However, this

phenomena may offer an explanation for the increased number of hypoglycemic episodes known to occur early in the pregnancy of diabetic women.

## Amino Acids

The urinary excretion of amino acids is increased with pregnancy. In fact, at one time, urinary histidine was used as a test to detect pregnancy. A failure of tubular reabsorption has been postulated, but because the filtered load of amino acids is also increased, the mechanism is not clear. Very little information is available concerning the effect of pregnancy on amino acid threshold and $T_M$. Amino aciduria may reach 2 gms per day and may pose a real threat to women with poor nutritional status prior to pregnancy.

## Potassium

Theoretically, pregnant women should waste potassium into the urine. The factors leading to such a position are (a) increased GFR, (b) elevated circulating aldosterone and (c) a tendency to develop bicarbonaturia at lower plasma bicarbonate concentrations than nonpregnant cohorts. Nevertheless, there is no tendency to waste potassium, rather there is a cumulative retention of about 350 mEq. Moreover, pregnant women are resistant to the kaliuretic effect of exogenous mineralocorticoids and high sodium diet (69). The ability to resist the kaliuretic effects of potent mineralocorticoids may be due to the high circulating levels of progesterone which accompany pregnancy. Lindheimer (69) has shown that the administration of $9\alpha$-fluorocortisol (Florinef acetate, 1.6 mg/day) to a healthy, pregnant young woman, resulted in sodium retention, but no increase in urinary potassium. This remained true even when sodium intake was abruptly increased. Others have noted that women with Bartter's Syndrome (a condition associated with urinary potassium wasting) exhibit a decrease in urinary potassium during pregnancy (70). Conversely, it has been proposed that women with disorders which impair potassium excretion may be at increased risk to develop hyperkalemia during pregnancy (5).

## Acid-Base Status

Pregnancy is accompanied by a modest increase in blood pH, typically about 0.04 pH units (7.38-7.40, nonpregnant to 7.42-7.44 in gestation) (71,72). Because the level of plasma bicarbonate is slightly lower in pregnancy, the possibility that hydrogen ion secretion may be abnormal has been considered. Lim and his associates (73) have shown that bicarbonate reabsorption is probably normal and increases as the plasma concentration is increased to as high as 31 mEq/L. It is now accepted, if not established, that the modest reduction in plasma bicarbonate is due to a mild, chronic respiratory alkalosis, probably an effect of progesterone (72).

**Sodium**

Pregnancy is accompanied by the retention of 500 to 850 mEq of sodium. Edema occurs in at least 33% of pregnancies (74) although some reports put this figure at closer to 90% (75). Such data indicate that edema cannot be regarded as a pathological sign. Furthermore, both pregnant women (76) and animals (77) excrete an acutely administered sodium load in a manner similar to nonpregnant cohorts. However, the absolute capacity to conserve sodium during dietary restriction may be impaired (76). It would appear that pregnancy resembles a form of "mineralocorticoid escape". During both mineralocorticoid escape and normal pregnancy, ECF volume is increased and sodium balance is established at a new steady state. The capacity to excrete an acute sodium load is not impaired by this new steady state, and the expanded ECF could account for the modest defect in conservation capacity. Space does not permit a detailed discussion of all the factors that influence salt (sodium) retention and excretion. However, the following table lists those factors and highlights the diverse mechanisms involved.

**Factors Influencing Renal Sodium Handling in Pregnancy**

**Factors Enhancing:**

| **Sodium Retention:** | | **Sodium Excretion** | |
|---|---|---|---|
| Increased: | Aldosterone<br>Estrogen<br>Cortisol<br>Ureteral pressure<br>Filtration fraction | Increased: | GFR<br>Progesterone<br>Vasopressin<br><br>Atrial Natriuretic Factor |
| | | Decreased: | Renal Vascular Resistance |
| Posture | | | Plasma Albumin |
| Placental A-V Shunting | | | |

(Modified from Berl, T., and Schrier, R. Renal and Electrolyte Disorders 2nd Edition. Little, Brown, Boston 1984)

## PART II: THE INTERACTION OF PREGNANCY AND RENAL DISEASE

### Primary Renal Disease with Preserved GFR

The possibility of pregnancy in women with chronic renal disease poses important questions for both patient and physician:

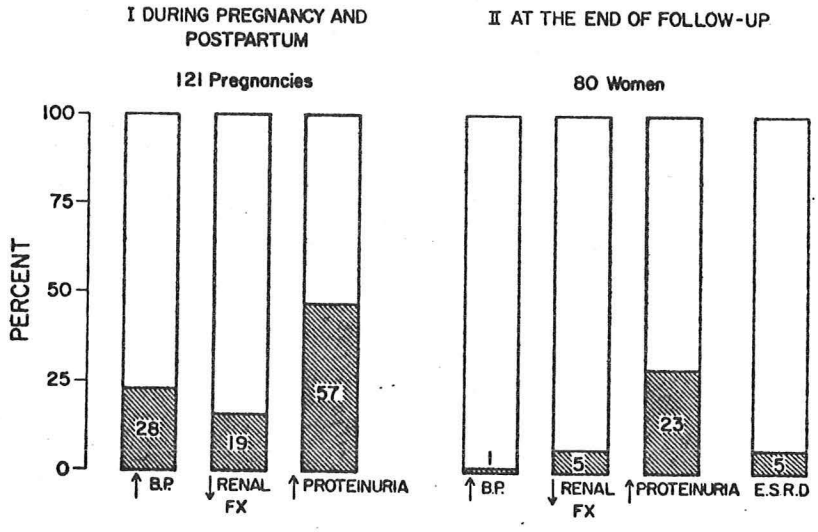
a) Will pregnancy adversely affect maternal renal function?
b) Will pregnancy increase the risk for a nonrenal complication of pregnancy?
c) Will renal disease affect fetal morbidity?

The answers to these questions have been controversial owing primarily to the nature of the available data. For all practical purposes, there are no experimental models and thus, all available information has come from clinical surveys. The majority of this literature consists of series that were retrospective, contains small numbers of cases, or both. Many such case series, especially those published prior to the past decade, failed to identify the renal disease, or to include the degree of renal function impairment at the time of conception. In addition, it should be noted tha most retrospective series reported before 1975 involve patients managed prior to the advent of potent antihypertensive drugs and modern methods for managing high risk prenancies. Though a consensus of opinion is still lacking, the divergency has narrowed in the past ten years. It is now evident that the most important determinants of the effect of pregnancy on renal disease (and vice-versa) are: (a) the level of renal function at the time of conception and (b) the nature of the renal lesion.

In 1963, McKay (73) reported the results of a ten year survey which included 46 pregnancies in women with persistent proteinuria (8 were nephrotic), normal renal function and blood pressure early in pregnancy. Renal function remained normal throughout pregnancy in all cases, although one third experienced "preeclampsia". In the same year, Johnson (79) described 29 pregnancies in ten women with preexistent nephrosis (histology unknown). In five of the 29 episodes of pregnancies, blood pressure and urea nitrogen rose, but returned to prepregnancy levels after delivery.

In the late 1970's Katz and associates (80) undertook a combined retrospective/prospective study to examine the effects of pregnancy on antecedent renal disease. This study involved three medical centers, and included women from varying racial, geographic and economic backgrounds. Criteria for inclusion in the final report included a biopsy proven diagnosis and continuation of the pregnancy beyond the first trimester. All women had plasma creatinine concentrations <1.4 mg/dL. Proteinuria was present in one third and 20% were hypertensive (mild in most cases). Women with lupus nephropathy were analyzed in a separate report (81).

The results of this study (121 pregnancies in 89 women) are represented in the Figure below:

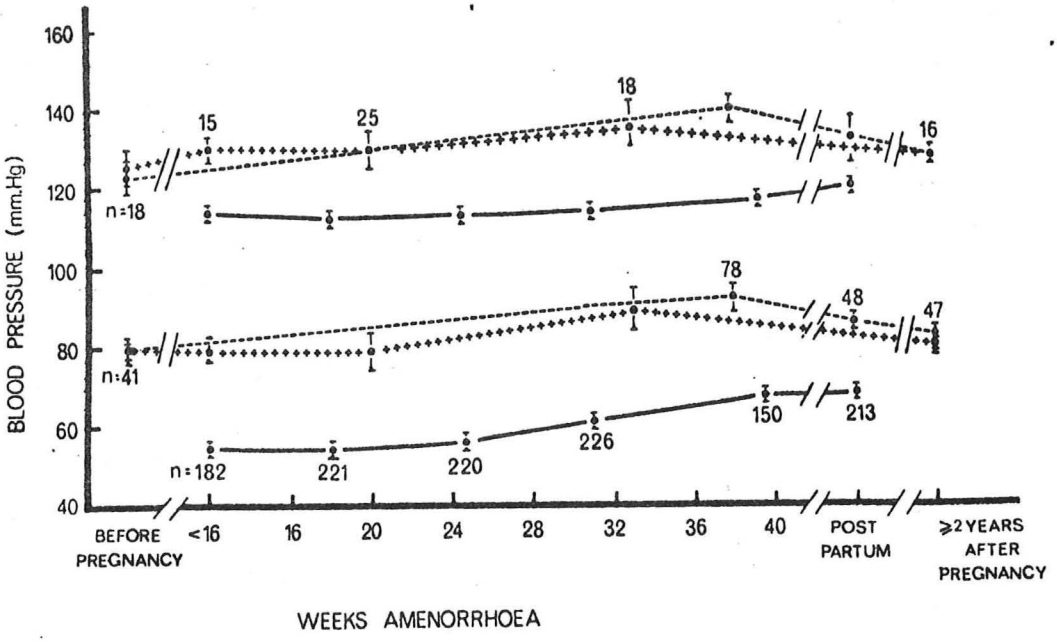



The course of renal disease during pregnancy (n=89) and after follow-up (n=80). FX= function, ESRD= end stage renal disease (80).

Measurements were obtained before and during the pregnancy, as well as in the immediate postpartum period and finally at 3 months to 23 years (mean = 62 months) after delivery.

Diffuse and focal glomerulonephritis (GN) accounted for 49% of all cases, whereas chronic interstitial nephritis accounted for 21%. The remainder were distributed among membranous nephropathy (8%), nephrosclerosis (7%), lipoid nephrosis (5%) and other, less common, renal lesions (10%). During the course of the pregnancy and the immediate post-partum period renal function declined (creatinine rose to frankly abnormal levels) in 16%, most often in those with diffuse GN, but most returned to prepregnancy levels following delivery. In two of these cases, the decline in GFR was due to acute tubular necrosis.

Significant hypertension (Bp= 140/90-160/110) occurred in 23% of all pregnancies. Half occurred de novo. It was most common and severe in those with diffuse GN. Blood pressure elevations were particularly common among black patients. The most severe elevations in blood pressure occurred shortly before or after delivery.




Mean blood pressure levels in normal pregnancy (n=92) contrasted with patients with glomerulonephritis (n=64). Solid lines = normal pregnant patients. Crossed and dotted lines, two geographically separated groups of patients with glomerulonephritis) (90).

Proteinuria occurred in 47% of all pregnancies and exceeded 3 gms/day in 32%, often resulting in marked edema. Nephrotic range proteinuria occurred in all types of renal disease except interstitial nephritis and appeared for the first time during gestation in a substantial number of women.

Of the 80 women available for followup, 5 (6%) reached end stage renal function, the same number showed a decline in GFR (creatinine >1.7 mg/dL) while 23 women had continuing proteinuria, although milder than during pregnancy. Only one woman was significantly hypertensive at the conclusion of the study period.

Among all the pregnancies, seven (6%) ended in fetal death, either spontaneous abortion (beyond the first trimester) or stillbirth. Of these, five were in women with diffuse GN. There were six (5%) neonatal deaths, equally distributed in all renal diseases. Twenty-four deliveries were preterm (<36 weeks), almost half among those with diffuse GN Twenty-seven live births were small for gestational age, the majority of which were delivered at term.

In summary, these results indicate renal disease may first become apparent, or worsen during gestation. However, it is also apparent that the natural history of the disease (at least in those who have normal GFR at conception) is affected little,

if at all. It is noteworthy that the five women who reached end stage all had diseases associated with relentless progression (i.e., amyloidosis, polycystic kidneys, focal glomerulosclerosis, and diffuse GN). Clearly, this was not a perfect study, but its results are indeed encouraging for women with mild renal disease at the time of conception.

More recently, Surian and associates (82) followed 123 pregnancies in 89 women. Unfortunately, their results were not strictly comparable to those of Katz (81) in that there were no data concerning renal function at the time of conception and the most common underlying renal diseases were IgA nephropathy and Allport's Syndrome. Renal function deteriorated in ten women, but reversed after delivery in six. Of those who suffered a fixed reduction in GFR, two had membranoproliferative GN, one each had amyloidosis and Allport's Syndrome. Twenty-four pregnancies were complicated by significant hypertension which reversed in thirteen. The authors concluded pregnancy did not alter the course of most glomerular diseases, but cautioned that women with MPGN were at higher risk for deterioration of renal function and that those with IgA nephropathy were more likely to develop persistent hypertension.

**Diabetes**

Because diabetes is relatively common in the obstetric population, it is important to examine the effects of gestation on these women as a separate group. Early studies (83,84) indicated that pregnancy adversely affected renal function in diabetic women. These results may have been influenced by salt restriction, diuretics and more than trivial renal dysfunction at the time of conception. Diabetic women of child-bearing age usually have Type I diabetes and have had the disease long enough to produce kidney lesions. Nevertheless, recent data as well as the general experience indicate that renal complications of such pregnancies are unusual. Sims (85) and Kitzmiller, et al (86) have studied the effect of pregnancy on renal function and blood pressure in diabetic women. Both groups found that hypertension and nephrotic range proteinuria were present in as many as two-thirds in the third trimester, but both resolved after delivery. GFR remained generally stable and the rate of GFR decline after delivery was similar to that expected for diabetic women.

**Lupus Erythematosis**

Systemic lupus erythematosis (SLE) is primarily a disease of women of child-bearing age. The relationship of pregnancy to SLE has been the subject of considerable controversy and debate (81,87-90). Nevertheless, the available data do allow several conclusions on which there appears to be agreement.

It appears that the most important determinant of the clinical course is the status of disease (SLE) activity at the time of conception. Both Kincaid-Smith (89) and Hayslett (81) have found that those patients who become pregnant following remission of all SLE symptoms for at least 6 months have the best prognosis. In 25 such pregnancies, Hayslett (81) found that 30% experienced an exacerbation of SLE symptoms, and 10% experienced significant morbidity. Most experienced a reversal of symptoms following delivery. The incidence of fetal loss (one therapeutic abortion) was not statistically greater than that experienced in the general population.

In twenty-five pregnancies, there was evidence of SLE activity in the 6 month interval prior to conception. During the pregnancy, SLE manifestations remained unchanged in 10 (40%), improved in only 3 (12%) and became worse in 12 (48%). These 25 pregnancies resulted in only 16 live births. There was a single maternal death among this group which was attributed to adrenal failure precipitated by abrupt steroid withdrawal. Serological studies (complements and anti-native DNA) performed in the six month period prior to conception were not helpful in predicting disease activity during gestation.

In summary, the course of pregnancy in women whose SLE is active at or shortly before conception, is problematic. There is a 50% incidence of morbidity (severe hypertension, proteinuria, reduced GFR) during gestation, 35% fetal loss, and a 4% maternal death rate. When SLE was first diagnosed during pregnancy or at the postpartum period, the results were very similar. In nine such patients, renal involvement with SLE became evident during the pregnancy in five and during the postpartum period in the remaining four. Excluding a single elective abortion, the live birth rate was 63%. There was a single maternal death, 18 months after delivery. (Death occurred as a result of pancreatitis, and was associated with persistent clinical activity of SLE). Despite this relatively severe course, clinical remission occurred in 7 patients after delivery and 5 subsequently became pregnant again.

Kincaid-Smith and her associates (89,90) have similar results, and feel that inactive SLE is not a contraindication to pregnancy. However, this group of investigators generally require renal biopsy proof of SLE inactivity. On the other hand, any sign of disease activity at the time of conception is thought sufficient risk as to recommend elective abortion.

**Primary Renal Disease and Moderate Renal Insufficiency**

The effect of pregnancy on the course of renal disease in women with preconception plasma creatinine between 1.5 and 5.0 mg/dL is less certain. Women with this degree of renal insufficiency are usually hypertensive which itself may have a deleterious effect on renal function. Kincaid-Smith and associates (91) have reported on eleven women with BUN greater than 50

mg/dL who became pregnant. In six of the eleven, renal function deteriorated (as judged by BUN) during the pregnancy. Virtually all experienced severe hypertension. However, fetal survival was rather high (nine of eleven). More recently, Hou et al, (92) have described the results of 23 pregnancies in women whose plasma creatinine was equal to or greater than 1.4 mg/dL at the time of diagnosis of the pregnancy. The majority of these cases were obtained by questionnaires to several medical centers. In 14 of these women, renal function either remained stable or declined to a degree thought consistent with the primary disease. In contrast, seven experienced greater deterioration of function than expected in the natural progression of their disease. The occurrence of hypertension to moderately severe levels (9 of 25) was an important associated complication. The authors concluded that pregnancy may accelerate the course of renal insufficiency in some women with moderate impairment of GFR.

It is apparent from the small number of such cases available that definitive conclusions regarding the effect of pregnancy on moderate renal insufficiency (and vice-versa) are not possible. It is equally obvious, however, that the presence of moderate renal insufficiency may indicate a very difficult pregnancy. It is possible that the observed deterioration in renal function is a result of accelerated hypertension. Recent animal studies indicate that hypertension accentuates glomerular lesions and accelerates the rate of decline in GFR (93). Studies addressing the role of hypertension in such cases may be difficult because of the conservative approach to blood pressure control taken by most contemporary obstetricians.

## PART III: MANAGEMENT OF PREGNANT PATIENTS WITH RENAL DISEASE

As outlined in the preceding section, pregnancy in women with renal disease is a high risk situation, and should be managed in centers with adequate facilities for close maternal and fetal monitoring.

### Renal Biopsy in Pregnancy

There is no real consensus regarding the indications for and advisability of closed renal biopsy during pregnancy. The enthusiasm for biopsy is usually a function of how enthusiastic the author is about biopsies in general. Hayslett (94) and others (95) suggest that renal biopsy is seldom necessary during the course of pregnancy, and point out that limited experience with biopsy technique during pregnancy should preclude its use until after delivery. Kincaid-Smith (90), however, argues that biopsy is safe and is essentially the only way to accurately determine diagnosis and is helpful in managing severe hypertension in second and third trimesters (primary renal disease vs. preeclampsia). This same author points out, however, that almost all such biopsies in their medical center are performed

by a single individual who has carried out over 65 such procedures in the previous 15 years. These authors agree that the discovery of a severe glomerular lesion must raise the question of termination of the pregnancy.

**Hypertension**

Hypertension is common in pregnancy, and is probably the rule in patients with renal disease. Although most common with women who were hypertensive prior to conception, women who are normotensive at conception are clearly at risk to develop the problem (92,94). Whether worsening hypertension represents superimposed preeclampsia in an individual patient is difficult to determine. Preexisting renal disease may give rise to all the features of preeclampsia, including proteinuria and hyperuricemia. Fisher and his associates (96) have examined renal biopsies from women who were diagnosed as preeclamptic and found that the clinical impression was borne out by the histology in only 25% of multigravidas, and only 50% of primigravidas. However, biopsy is rarely necessary to distinguish between preeclampsia and hypertension due to renal disease. The decision to deliver or terminate the pregnancy is based on the severity and ability to control the blood pressure (95). Because hypertension may occur abruptly in those with renal disease, the blood pressure should be monitored biweekly. In as many cases as possible, the patient should be trained to measure her blood pressure at home, and instructed to do so daily.

The management of hypertension has been the subject of a great deal of literature (Reviews: 97-100), much of which has come from the Department of Obstetrics at this institution. Though it is not the intent of this discussion to review the management of preeclampsia (pregnancy-induced hypertension) in the absence of known renal disease, a few words are necessary, as renal disease and preeclampsia may occur in the same patient (as discussed above). Gant and Pritchard (98) have classified pregnancy-induced hypertension according to the magnitude of the blood pressure and either end-organ effects or effects on the fetus.

**Classification of Pregnancy-Induced Hypertension**

| Sign | Mild | Severe |
|---|---|---|
| Diastolic blood pressure | <100 mmHg | >110 mmHg |
| Proteinuria | Tr - 1+ | >2+ (persistent) |
| Plasma creatinine | normal usually <0.7mg/dL) | elevated |
| Plasma AST (SGOT) | minimal elevation | significant elevation |
| Plasma bilirubin | normal | elevated |
| Platelet count | normal | low |
| Fetal growth retardation | absent | present |
| Headache | absent | present |
| Visual disturbances | absent | present |
| Convulsions | absent | present |
| Oliguria | absent | present |

(Adapted and Modified from Gant and Pritchard, Ref #98)

The object of treatment in either pregnancy-induced, or renal disease associated hypertension is (a) to prevent hypertensive damage to the mother i.e., cerebral hemorrhage or fixed renal damage, and (b) preserve placental blood flow. Recognizing that any therapy may compromise one or the other objective, a degree of controversy still exists regarding the most appropriate course of therapy. The more conservative approach is characteristic of the obstetric department at Parkland Memorial Hospital. As outlined in numerous reviews (97,98, representative articles, not complete bibliography), these authors recommend the induction of labor if the fetal age is sufficient. When fetal age does not allow delivery, bed rest, preferably in a hospital is recommended. These authors recommend hospitalization for women with systolic pressure greater than 140 mmHg or a diastolic pressure of 90 mmHg or greater. If enforced bed rest results in lower blood pressure, the regimen is continued until delivery can be safely accomplished. When the blood pressure elevation is severe (diastolic >110 mmHg), magnesium sulfate is given parenterally (to prevent seizures) and delivery is undertaken as soon as possible. Gant and Pritchard (98) point out that the temptation to forestall delivery in order to enhance fetal maturation may be unjustified in severe preeclampsia or

hypertension. They feel that the probability for fetal survival may be greater in a modern neonatal intensive care unit than **in utero** if hypertension is severe.

Others believe that drugs may be useful as short-term management pending delivery (100). These groups recommend parenteral hydralazine, and diazoxide as an alternative. A number of drugs have been tried, including sodium nitroprusside (101,102), nifedipine (103) and labetalol (104,105). In each case, undesirable and even frankly dangerous effects have been observed.

Methyldopa (Aldomet) has been used extensively in Europe in both mild (106) and severe (107,108) hypertension. One study (109), which employed methyldopa without a diuretic, showed that the incidence of severe hypertensive episodes was reduced among the treated group and that fetal deaths were significantly reduced when compared to a control (no drug) group. However, the authors were unable to attribute the improved fetal outcome to the antihypertensive effect of the drug. In particular, midtrimester abortions were confined to the control group and none were related to maternal hypertension.

In the past, diuretics have been used extensively both to treat and prevent hypertension in pregnancy. However, all adequately controlled studies (110-114) agree that neither perinatal mortality or the incidence of preeclampsia is altered by the prophylactic use of diuretics. Further, there is no evidence that diuretics are beneficial in the treatment of established preeclampsia. In fact, these agents tend to aggravate the hypovolemia associated with preeclampsia and may precipitate iatrogenic renal failure (115).

Much of the concern regarding diuretics is based on studies by Dr. Gant and his associates (116) which have shown that the metabolic clearance of dehydroepiandrosterone sulfate (DHEA) is decreased in patients treated with either thiazide or loop diuretics. Because 40 to 50% of the metabolic clearance of DHEA is a result of placental conversion of DHEA to estradiol, a fall in clearance is thought to represent a decrease in uterine blood flow. It is interesting, however, that a randomized, double blind trial of 50 mg per day of hydrochlorothiazide in 1030 obstetric patients found no significant difference in birth weight between thiazide and control groups (112). Until such time that the issue of placental blood flow is resolved, diuretics should probably be reserved for life-threatening situations such as pulmonary edema.

## Antihypertensive Drugs and Pregnancy: Potential Side Effects

| | |
|---|---|
| **Diuretics** | Volume depletion<br>Renal failure<br>Compromised placental blood flow<br>Neonatal hemolysis and thrombocytopenia |
| **Methyldopa** | Fetal hypotension<br>Neonatal tremors |
| **Beta-adrenergic antagonists** | Fetal bradycardia |
| **Alpha-beta adrenergic antagonists (labetalol)** | Fetal inability to maintain blood pressure during hypoxemia (in sheep) |
| **Calcium channel antagonists** | Myometrial relaxation<br>Cardiac failure<br>(potentiated by magnesium) |
| **Sodium nitroprusside** | Cyanide toxicity |
| **Diazoxide** | Ischemia<br>Uncontrolled hypotension |
| **Hydralazine** | Headache and epigastric pain mimicking impending eclampsia<br>Reduced placental blood flow in those with chronic hypertension |

## Systemic Lupus Erythematosis

Because complete suppression of SLE activity increases the likelihood of an uncomplicated pregnancy, appropriate treatment should not be withheld from women with SLE who become pregnant. Further, there is no apparent evidence to indicate that the use of glucocortocoids or cytotoxic agents increase the incidence of developmental abnormalities among the off-spring of women treated during pregnancy. There seems to be a consensus among clinicians who have considerable experience with SLE patients that patients with signs of active disease (either clinically or by renal biopsy) should undergo treatment before considering pregnancy (81,90,94). It has not been the practice of most groups to increase steroid or cytotoxic therapy during pregnancy unless complications arise. Active SLE at the time of conception, or the onset of active SLE during gestation indicate a stormy course which may include an irreversible deterioration in renal function, a high incidence of fetal loss and an increase in maternal death rate. For these reasons, termination of the pregnancy may be a consideration.

## Nephrotic Syndrome

As indicated earlier, the development of the nephrotic syndrome is a common transient complication of pregnancy in women with renal disease. Although nephrosis may contribute to overall morbidity, there are no data to indicate that heavy proteinuria affects the course of the renal disease (117). In both membranous nephropathy (118) and minimal change nephropathy (NIl lesion) (119), proteinuria is increased during pregnancy but does not appear to affect the overall course of the disease. Further, the proteinuria tends to return to prepregnancy levels following delivery.

In most patients with nephrotic syndrome, moderate sodium restriction and periods of bed rest will prevent anasarca. Because pregnant women can avidly absorb sodium, negative sodium balance is unlikely.

When bed rest and dietary restriction have proven inadequate, some invetigators have used small doses of diuretics on an intermittent basis to reduce edema (94). The goal of such therapy is to reduce edema to a tolerable level by lowering body weight by 2 to 3 lbs. with each treatment course. At no time should one attempt to eliminate all edema.

## Dialysis in Pregnant Patients

Both peritoneal and hemodialysis have been employed in pregnant patients with acute and chronic renal failure. Nissenson (120) has reviewed most of the literature concerning hemodialysis in pregnancy (approximately 20 cases) and found

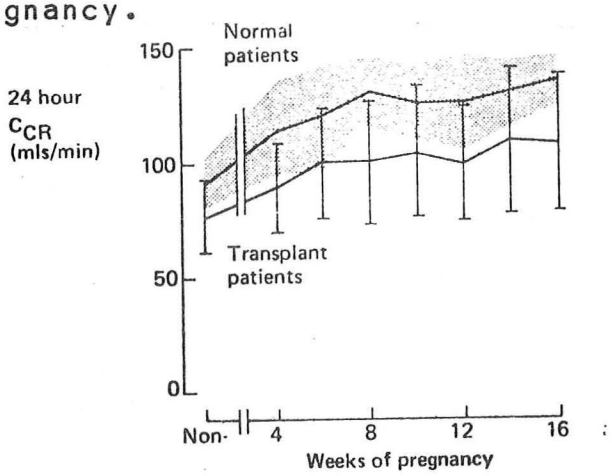
that fetal survival was 50%, with a high incidence of preterm delivery. He reported a high incidence of vaginal bleeding and hypotension as well as premature labor often occurring shortly after dialysis.

Most women with severe renal insufficiency are amenorrheic or experience anovulatory cycles. Nevertheless, pregnancies do occur, and an incidence of one in 200 patients has recently been quoted (121). However, the true frequency is unknown because most pregnancies in such patients likely end in spontaneous abortion. The incidence of conception may increase as chronic ambulatory peritoneal dialysis (CAPD) gains popularity. CAPD is associated with an apparent resumption of reproductive capacity in a high percentage of uremic women (122).

There are no firm guidelines to assist the physician with the dialysis prescription for pregnant patients. In an early report of a successful pregnancy, the frequency of dialysis was increased to maintain BUN levels near 30 mg/dL (123). However, others have recommended that dialysis be started when the BUN is between 80 and 100 mg/dL (95). Late in pregnancy, monitoring fetal heart rate during hemodialysis appears advisable.

**Renal Transplantation**

There have now been approximately 1200 reported pregnancies among female renal transplant recipients. Approximately four of every five pregnancies has occurred in women with cadaveric grafts (124). In this series, 30% of pregnancies were electively terminated (reasons included unplanned pregnancy, psychosocial problems and unstable renal function) and spontaneous abortion occurred in 13%. Therefore, 40% of conceptions did not progress beyond the first trimester. However, of the remaining 60%, almost all (90%) ended successfully. When renal function was adequate (plasma creatinine <2.0 mg/dL) at conception, GFR was usually maintained throughout the gestation. In most cases, GFR increases as would be expected during normal pregnancy.




Changes in 24 hour creatinine clearance in healthy women (upper line) and ten renal allograft recipients (lower line) (124).

About 15% of the women experienced a decline in GFR which persisted after delivery. However, because a gradual decline in function is experienced with allografts, it is difficult to relate this directly to the gestation.

The incidence of renal allogrft rejection during pregnancy is about 9%, a figure not significantly different from that predicted in nonpregnant graft recipients (125).

The ideal timing of pregnancy in women with renal allografts is between two and five years post-transplantation. At this time renal function has usually stabilized and immunosuppressive medication has been reduced to minimum levels. As discussed earlier, immunosuppressive drugs apparently offer minimal teratogenic risk to the fetus. Azathioprine (Imuran), cyclophosphamide (Cytoxan) and corticosteroids (prednisone and prednisolone) have all been used with successful pregnancies. However, in one survey (124) only 60% of the infants born to transplant recipients experienced no problems. In the same series, preterm deliveries and small-for-dates infants were common (45 to 60% and 15 to 20% respectively). Though the incidence of congenital malformation is low, the **in utero** exposure to immunosuppressive agents may result in neonatal problems ranging from adrenal insufficiency to immunodeficiency. The incidence of such problems is less than 10%. Some of the more common problems are listed below:

Preterm delivery
Respiratory distress
Adrenal insufficiency
Septicemia
CMV infection
$Hb_SAg$ carrier state
Thymic aplasia
Depressed hematopoiesis
Reduced lymphocyte PHA reactivity
Chromosome abnormalities in lymphocytes
Reduced T cells
Reduced immunoglobulins

Unfortunately, there is virtually no literature regarding the use of Cyclosporin A in pregnant women with renal allografts. There are three reported pregnancies in women with liver transplants who had been maintained prior to conception on Cyclosporin A. One woman underwent elective abortion, while the second patient had two successful pregnancies. However, in both cases, azathioprine and prednisone were used during the pregnancies (126). It has been suggested that until its safety in pregnancy is established, that Cyclosporin A not be used in pregnant renal transplant recipients (94). It is not known how **in utero** exposure to immunosuppressive drugs will eventually affect the reproductive function of the off-spring.

The transplanted kidney is most often located in the false pelvis. However, mechanical interference between the uterus and

the graft is unusual. The mode of delivery therefore, should be determined on obstetric criteria. Finally, the steroid dose should be increased to cover the stress of delivery.

## PART IV: ASSESSING THE RISK OF PREGNANCY IN WOMEN WITH RENAL DISEASE

As emphasized by the preceding discussion, pregnancy in women with renal disease is a high risk endeavor. Nevertheless, a successful pregnancy is possible in many cases and careful medical management can significantly increase this prospect. Appropriate pregestational counseling is an integral part of the management of women with renal disease and if such a patient chooses to become pregnant, the pregnancy should be planned and managed at an adequately equipped medical center with close collaboration between obstetrician, nephrologist and pediatrician.

The ability to conceive and carry a pregnancy to term or near-term appears to depend on the following factors:

a) Level of renal function
b) Nature of the renal lesion (histological diagnosis)
c) Activity of associated or primary disease
d) Pregestational blood pressure

### Minimal Renal Dysfunction

As previously noted, women with primary renal disease who have normal or nearly normal renal function at the time of conception have a very good chance of carrying a pregnancy to a successful outcome with minimal risk to the mother or fetus. The literature (81,82) indicates that deterioration of renal function most frequently occurs in women with proliferative glomerular lesions and may be safer in those with more benign renal histology (membranous nephropathy and Nil lesion). However, because this assessment is based on only a few studies, counseling must be conservative. Nevertheless, because the available data indicate a relationship between the renal lesion and the course and outcome of pregnancy, a renal biopsy might be advisable in women who contemplate pregnancy. The question of biopsy in women who are pregnant has been addressed above. The procedure appears to be benign, or at least to carry no increased risk in the hands of experienced individuals (90). Nevertheless, the decision to biopsy a pregnant woman should be based on the absolute need to know the renal histology and the biopsy experience of the nephrologist. In the event that a biopsy is deemed necessary, it should be performed under sonographic (rather than x-ray) guidance.

Women with established renal disease should be advised that nephrosis (proteinuria and edema) and hypertension are likely problems and that hospitalization may be necessary during the latter portion of pregnancy. Further, if hypertension cannot be

controlled by conservative measures, early, induced delivery may be necessary. The risk of fetal loss (excluding first trimester abortion) during such pregnancies is between 5 and 10%.

**Collagen-Vascular Diseases**

Women with collagen-vascular diseases (SLE, mixed connective tissue disease and scleroderma) represent a special subset. The literature is most helpful with regard to those with SLE. If there has been no clinical disease activity during the six months prior to conception, approximately one third of such patients will experience an exacerbation of symptoms, but most will resolve after delivery. The statistical risk to the fetus is essentially the same as the general population. If, however, SLE has been clinically active during the six months prior to conception, or is active during the pregnancy, half of such women will experience significant morbidity and the risk of fetal loss is about 35%.

Patients who require immunosuppressive medication to maintain remission of SLE activity should continue such drugs during the pregnancy. They should be advised that there appears to be no added tetratogenic effects of such drugs but that the risk of neonatal infection and adrenal insufficiency is increased. Further, the long-term effects of **in utero** exposure to immunosuppressive and cytotoxic agents is not known.

The patient with scleroderma should be advised that pregnancy is thought to adversely affect renal function in 40% (90) and that both malignant hypertension and death have been reported in significant numbers of such women.

**Moderate to Severe Renal Insufficiency**

Because pregnancy is unusual, if not rare, in those with moderate to severe renal insufficiency, statistics are almost meaningless. Nevertheless, the available data indicate that such pregnancies carry great risk, both to mother and fetus, and probably should not be encouraged. The same is true for patients requiring regular dialysis therapy.

**Transplant Patients**

Because renal transplantation has been in widespread use for only about 25 years, there are few long-term studies on which to base any advice regarding pregnancy. Because graft survival beyond two years indicates about an 80% 5 year graft survival rate, it appears wise to advise such patients to wait at least 24 months before attempting conception.

The following criteria appear to predict a successful outcome of pregnancy with minimal maternal risk:

(a) Good health for two years after transplantation.
(b) No proteinuria (<250 mg/day).
(c) Normotensive with minimal medication.
(d) Normal urinary collecting system by sonogram or IVP.
(e) Plasma creatinine <2.0 mg/dL, preferably <1.5 mg/dL.
(f) 15 mg/d prednisone or less
    2 mg/Kg/d azathioprine or less.
(g) Stature compatible with good obstetric outcome.

**Summary**

Successful pregnancy is possible in women with significant renal disease and the risks to both mother and fetus may be assessed and minimized by careful medical surveillance. In those with minimal reduction in GFR, or normally functioning renal allografts, the outlook is indeed good. Systemic disease activity and/or significant impairment of GFR herald a stormy course for both mother and infant. It is probably not wise for the physician to either recommend or discourage child-bearing. Nevertheless, patients should be given the best possible advice and information concerning the risks or pregnancy.

Finally, emphasis in the future should focus on improving prepregnancy assessment criteria and reassessing the rationale and implications of the treatment of pregnancy-related complications and monitoring the remote outcome of pregnancy on maternal renal function and the offspring.

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