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NEPHROLOGY FORUM

Interaction of renal disease and pregnancy

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Case presentation

A 25-year-old woman in labor was admitted to the Yale-New Haven Hospital. Ten years earlier, 3+ proteinuria was noted on a routine physical examination. At that time there were no abnormal physical findings, including no evidence of edema. Her blood pressure was 115/70 mm Hg (sitting). The hematocrit was 40%; BUN, 11 mg/dl; and serum creatinine, 0.6 mg/dl. Urinalysis disclosed 10 to 15 red blood cells and 6 to 8 white blood cells per high-power field and an occasional granular cast. An antinuclear antibody study was negative; C3 was 30 mg/dl (normal, 65–120 mg/dl); total serum protein, 4.5 g/dl; and serum albumin, 2.5 g/dl. A urine culture was negative. An intravenous pyelogram was reported as normal. Percutaneous renal biopsy demonstrated mesangiocapillary glomerulonephritis.

Approximately 5 years before admission, the patient noted intermittent dependent edema, and furosemide was prescribed. Her blood pressure at that time was in the range of 150/100 mm Hg, and antihypertensive treatment was instituted with propranolol and hydralazine. Two years earlier an obstetrician whom she had consulted about the possibility of pregnancy referred her to the Yale-New Haven Hospital. At that time her blood pressure was 130/90 mm Hg and there were no abnormal physical findings. She reported swelling in her lower extremities, below mid-calf, at approximately 2- to 3-week intervals; the edema promptly subsided after a single dose of furosemide, 40 mg. She was taking propranolol, 40 mg, and hydralazine, 25 mg, both twice daily on a regular basis. Pertinent laboratory findings included: hematocrit, 38%; BUN, 12 mg/dl; serum creatinine, 0.9 mg/dl; serum albumin, 2.5 g/dl; urine protein, 4.0 g/24 hr; and creatinine clearance, 115 ml/min. She and her husband were advised that pregnancy was likely to be complicated by increased edema formation and that control of hypertension might become more difficult. She also was told that there was a good chance, however, for her carrying the pregnancy to term, although gestation would require close medical supervision. In addition, because of the progressive nature of her glomerulopathy, she was advised to attempt conception, if she chose to do so at all, while her renal function was normal rather than at a later time.

Throughout the pregnancy, propranolol and hydralazine were continued in the same doses as before conception; blood pressure was recorded twice daily at home and was maintained in the range of 120–150/80–95 mm Hg. A low-sodium diet was instituted in the first trimester, 1500 mg/24 hr, in an effort to blunt the expected rate of edema formation. At approximately 20 weeks gestation, she developed edema in her legs; the edema partially responded to intermittent doses of furosemide, 160 mg. The diuretic was used to reduce edema to a level that decreased discomfort, but no attempt was made to eliminate the edema entirely. In the third trimester, edema was more refractory to diuretics; bed rest at home was prescribed and she was encouraged to lie on her side. Laboratory studies demonstrated: hematocrit, 32%; serum creatinine, 1.2 mg/dl; serum albumin, 1.5 g/dl; urine protein, 12 g/24 hr. Physical examination and ultrasound examination revealed normal fetal growth, and the patient experienced spontaneous labor in the 38th week of gestation; she delivered per vagina a 3100 g male infant. At delivery the Apgar score was 9 and no developmental abnormalities were noted.

Discussion

DR. JOHN P. HAYSLETT (*Chief, Section of Nephrology, and Professor of Medicine, Yale University School of Medicine, New Haven, Connecticut*): This patient illustrates many of the issues that confront the physician managing a woman with renal disease who wishes to become or is already pregnant. The patient usually wants to know whether pregnancy will influence the natural course of her underlying renal disease and/or whether gestation will cause new complications. Certainly she wishes to know her chances for delivering a healthy baby. The physician may be confronted with the problem of diagnosing the cause of renal dysfunction during pregnancy and selecting a treatment regimen most likely to promote the viability and development of the fetus. I should like to discuss salient information on the physiologic alterations that occur during normal pregnancy, because these changes have a direct bearing on the detection and evaluation of renal disease during pregnancy. In addition, I will review new information related to the effect of pregnancy on the course of renal disease and the effects of renal disease on pregnancy and fetal outcome.

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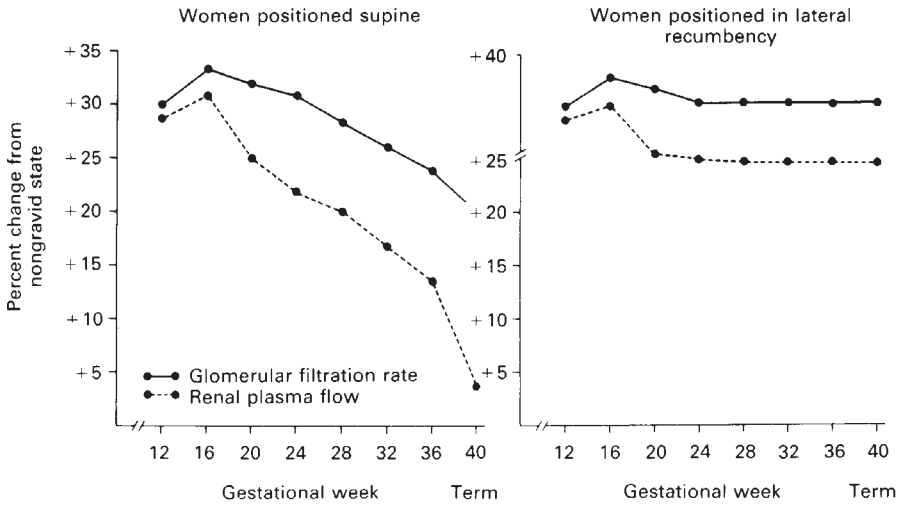

Fig. 1. *Early increment in glomerular filtration rate and effective renal plasma flow is position dependent and is sustained if subjects are studied in lateral recumbency.* (Adapted from Peppig L: Clinical aspects of renal disease in pregnancy. *Med Hyg* 27:181–192, 1969, in Lindheimer MD, Katz AI: *Kidney Function and Disease in Pregnancy.* Philadelphia, Lea & Febiger, 1977.)

Renal function and extracellular volume status during pregnancy

Normal pregnancy is characterized by a gradual, cumulative retention of 500 to 900 mEq of sodium and 6 to 8 liters of water, which are distributed between the maternal extracellular fluid and the fetoplacental unit. Plasma volume rises by 30% to 45%; this change in volume status, marked in the second trimester, is sustained to term. Despite the increase in extracellular volume, blood pressure falls owing to a decrease in peripheral vascular resistance.

Changes in renal function during gestation occur against this background of alterations in extracellular volume. The glomerular filtration rate (GFR) begins to rise soon after conception and achieves a level 30% to 50% above control by the twelfth week of gestation. Similar changes occur in renal plasma flow. The elevation in GFR is sustained until term, after which the GFR rapidly falls to nongravid levels [1, 2], as shown in Figure 1. This figure also shows that GFR and renal plasma flow are markedly influenced by position in late pregnancy. When a pregnant woman changes from lying on her side to an upright or supine position, renal plasma flow and GFR immediately decrease. Unless GFR is measured in a lateral decubitus position, the intrinsic level will be underestimated. During pregnancy, plasma levels of BUN and serum creatinine are reduced below nonpregnant values because of the increase in filtered load and the dilutional effect of expansion of the extracellular fluid [3]. It has been suggested that values of blood urea nitrogen above 13 mg/dl and serum creatinine levels above 0.8 mg/dl should alert the physician to the possibility of renal insufficiency [4].

The demonstration that GFR increases during the first and second weeks of pregnancy in the rat has prompted studies into the factors responsible for these changes. In the rat, gestation lasts 21 to 22 days. Recent studies have shown that GFR is increased by day 5 or 6 and that it rises still further by day 10 or 11 [5]. This change in GFR is associated not only with the increase in extracellular fluid volume that I mentioned, but also with an approximately 10% increase in the length of the proximal tubule [6]. Micropuncture studies have indicated that single-nephron GFR correlates with glomerular plasma flow rate, and not with other determinants of ultrafiltration [7]. Similar changes in renal function and volume status have been observed in pseudopregnancy, that is, in studies in which female rats were mated with vasectomized males [8]. Therefore, it is unlikely that the fetoplacental unit is required for pregnancy-induced changes in renal function. Further studies suggest that neither progesterone nor estrogen are causative factors [8], although prolactin has not been excluded from contributing to changes in renal function and structure during pregnancy [9].

The retention of sodium by the gravid female appears to represent a normal physiologic response mediated by factors controlling extracellular volume status. Clinical studies have demonstrated similar responses both to acute volume expansion with sodium salts and to acute restriction in sodium intake during gestation and in nonpregnant women [10, 11]. On the basis of these observations, there is no rationale for reducing dietary sodium intake in normal pregnancy.

In addition to changes in GFR and renal handling of sodium, plasma osmolality regularly falls to about 270 mOsm/liter in normal pregnancy. In an elegant study in the rat, Durr, Stamoutsos, and Lindheimer showed that this gestation-induced effect on osmolality is secondary to a resetting of the osmostat [12]. Plasma bicarbonate also falls during pregnancy from 26 to 28 mEq/liter to approximately 20 mEq/liter, owing to a mild, progesterone-induced respiratory alkalosis.

Urinary protein excretion is not increased in normal pregnancy; therefore, daily excretion rates above 200 mg should be regarded as abnormal. The urinary excretion of glucose and amino acids, however, can increase in the absence of an increase in plasma levels, apparently because of a change in binding affinity of proximal tubular cells or because of a saturation of maximal transport capacity for these substances [13].

An understanding of these physiologic changes in normal pregnancy has important clinical implications, because the detection of renal disease and the evaluation of patients with established renal disease must take into account the expected physiologic alterations in renal function. An evaluation of GFR, for example, should compare observed measurements with expected values in pregnancy and not with the normal range

found in the nonpregnant state. It is of interest that a recent analysis of 33 women with various types of primary renal disease and a moderate decrease in GFR before pregnancy disclosed a similar increment in GFR and effective renal plasma flow as that observed in normal gravidas [14].

Diagnosis of renal dysfunction during pregnancy

An important clinical question in many patients with proteinuria during pregnancy is whether the renal abnormality is a manifestation of preeclampsia or whether it results from another cause of renal disease. Because preeclampsia does not occur before the twentieth week of gestation (except in hydatidiform mole or multiple gestational pregnancies), the differential diagnosis is simplified if signs of renal disease were present before conception or in the first trimester. When proteinuria is first discovered after the twentieth week of pregnancy, however, one often has difficulty distinguishing between underlying renal disease and preeclampsia, because the clinical features—proteinuria, hypertension, edema, and renal insufficiency—occur in both settings.

Fisher and associates have provided information about the relative incidence of the causes of proteinuria and hypertension during gestation in a series of 176 patients who underwent renal biopsy within 6 days of delivery [15]. Renal biopsy was an important feature of this analysis, because glomerular capillary endotheliosis is thought to be specific for preeclampsia and is invariably present, even in mild cases [16]. Among primigravidas, the incidence of preeclampsia was 83%; intrinsic renal disease (excluding preeclampsia), 12%; and hypertensive glomerulosclerosis, 5%. In multiparous patients, in contrast, preeclampsia occurred in only 38% of patients, whereas intrinsic renal disease accounted for 26%, and hypertensive renal disease for 26%. Preeclampsia was superimposed on one of the other renal parenchymal lesions in 10% of patients. Prior to delivery, preeclampsia was the primary diagnosis in nearly all patients. This analysis demonstrates that the diagnosis of preeclampsia cannot be made with certainty on clinical grounds alone, particularly in multiparous patients and in those with coexistent renal disease.

Effects of pregnancy on renal disease and of renal disease on the outcome of pregnancy

Patients whose renal function is sufficiently impaired to raise serum creatinine above 2 to 3 mg/dl are usually infertile. Therefore data bearing on the effect of pregnancy on the course of underlying renal disease principally involves patients with only mild to moderate reductions in renal function. Although a few reports suggest that pregnancy leads to progressive deterioration of renal function [17, 18], the majority of investigations indicate that pregnancy does not influence the natural course of renal disease, if renal function is relatively well preserved and hypertension is absent at conception [14, 19, 20].

Katz and associates at three centers provided new insights into this relationship in a combined prospective and retrospective study of 121 pregnancies (between 1959 and 1979) in 89 women with renal disease [14]. The women were included in the study only if renal tissue was available for examination and if pregnancy continued at least through the first trimester. Their clinical course was studied through subsequent pregnancies, if any, and for periods of varying length. Pregnancies ending in therapeutic abortion were not included. These women had a variety of renal diseases: chronic diffuse glomerulonephritis in 26, focal glomerulonephritis in 12, membranous nephropathy in 7, and interstitial nephritis in 21. Prior to conception, hypertension was present in 20%, but it was mild in most. Proteinuria was found in one-third of women, but exceeded 1 g/24 hr in less than one-half, and in all patients the serum creatinine level did not exceed 1.4 mg/dl.

During the course of pregnancy, shown in Figure 2, hypertension was noted in 23% of gestations, but in one-half blood pressure was elevated before conception. Renal function decreased in 16% of all pregnancies in this series, most often in women with diffuse glomerulonephritis (11 of 19). In general, the reduction in renal function was mild to moderate, and renal function returned to pregestational levels after delivery. In 2 cases, marked deterioration of renal function was due to acute tubular necrosis, and in 3 women pregnancy seemed to occur in the downhill phase of the disease, which eventually progressed to renal failure. Increased proteinuria was the most common adverse renal effect of gestation, occurring in 47% of pregnancies. In 39 pregnancies, the rate of protein excretion exceeded 3 g/24 hr. During follow-up, which ranged from 3 months to 23 years, and which averaged 62 months, the changes in renal function and blood pressure observed during pregnancy usually remitted. Moderately severe hypertension was present in only one patient; 7 others had mild hypertension, but 4 of them were hypertensive before pregnancy. Although abnormal protein excretion was present in 23 women at the end of follow-up, it exceeded 3.0 g/day in only 5 patients. Renal function was reduced in 10 patients at the end of follow-up. One-half of these patients progressed to end-stage renal failure; in the remaining 5 patients, shown in Figure 2, renal function was only moderately reduced (serum creatinine $\leq$ 1.7 mg/dl). Because the onset of end-stage renal failure varied between several weeks and more than 8 years after delivery, the authors concluded that there was no evidence that pregnancy accelerated the rate of progression of the underlying renal disease.

Other workers also have reported an increase in protein excretion during pregnancy, often to nephrotic levels [20–22]. As expected, this complication usually occurs in patients with glomerulopathies, not tubulointerstitial diseases. The rate of protein excretion falls in most subjects to preconception levels following delivery. Heavy proteinuria and nephrotic syndrome also can occur in preeclampsia, and therefore the magnitude of proteinuria does not distinguish patients with underlying renal disease from those with preeclampsia. In a recent report of 23 women with biopsy-proven preeclampsia and nephrotic syndrome, protein excretion at follow-up (average, 36 months) was mildly abnormal in only 2 patients, and only one patient with polycystic kidney disease had an elevated serum creatinine level [23].

The outlook for the fetus in women who become pregnant despite the presence of renal disease seems favorable as long as significant hypertension is absent and renal function is not severely reduced. In an analysis of 8 series of pregnancies in women with renal disease, Ferris reported no maternal deaths and a fetal survival rate of 93% in 176 normotensive mothers [24]. In contrast, a fetal survival rate of only 55% was found in women with renal disease and hypertension. In the series of 121 pregnancies reported by Katz and associates, the fetal survival

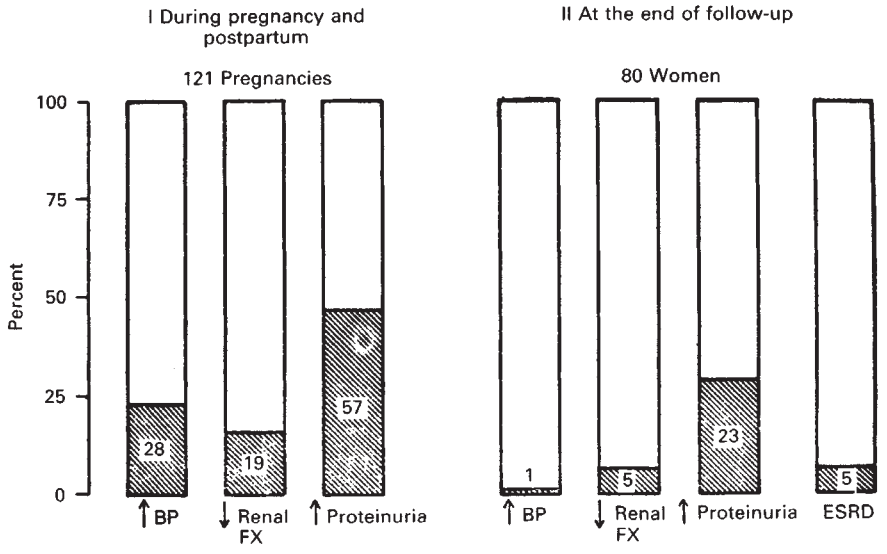

Fig. 2. *Course of renal disease in 89 women during gestation and the puerperium* (3 bars on the left) *and in 80 women followed after pregnancy* (4 bars on the right). Numbers within bars are individual pregnancies (on the left) and individual women (on the right). BP refers to blood pressure; ESRD refers to end-stage renal disease; FX refers to function. (Reproduced with permission from LINDHEIMER MD, KATZ AI: Maternal and fetal prognosis in women with chronic renal disease, in *Fetal Growth Retardation*, edited by VANASSCHE FA, ROBERTSON WB, Edinburgh, Churchill Livingstone, 1981, p 146.)

rate was 94% [14]. It should be noted, however, that 20% of deliveries were preterm and that 27 of 111 infants whose birth weights were known (24% of all live births) were small for gestational age. These data therefore indicate that the likelihood of prenatal survival is only slightly reduced by the presence of primary renal disease with normal to moderately reduced renal function but that the incidence of retarded fetal growth is increased. In contrast, the relatively few patients with advanced renal failure who do become pregnant experience a live birth rate of only about 20% to 50% and a high frequency of fetal growth retardation [25].

Regarding women who have systemic diseases affecting the kidney, there is a paucity of data except for those with diabetes mellitus and systemic lupus erythematosus (SLE). Sims reported that pregnancy did not worsen renal function in 8 patients with diabetic glomerulosclerosis (and normal renal function prior to pregnancy), even in women with severe, long-standing diabetes mellitus [26]. Kitzmiller and associates reported their experience with 26 women with diabetic nephropathy who attained 24 weeks gestation [27]. Eight of these women had a creatinine clearance less than 70 ml/min (average, 43 ml/min) when they conceived; in the group as a whole, renal function generally remained stable throughout pregnancy and to the end of follow-up (9 to 35 months later). Proteinuria increased dramatically in the majority of patients, however, exceeding 6 g/day in 58% of patients. As in patients with primary renal disease, protein excretion fell to pregestational levels following delivery. Perinatal survival was 89% in this series of diabetic patients but, as expected, the rate of fetal growth retardation was high, 20.8%; macrosomia was observed in 12.5%.

Restrospective analyses of large series of women with SLE disclose that pregnancy can induce the disease in some patients with a predisposition for SLE, and it can exacerbate the disease in some patients with established SLE. In most studies of 20 or more patients with both pregnancy and SLE, the disease first appeared during gestation in about 10% of patients [28]. In addition, the rate of relapse and exacerbations of clinical activity in patients with an established diagnosis prior to conception appears to increase during pregnancy and postpartum. A recent report by Hayslett and Lynn, using data from 13 nephrology groups in the United States and Canada, analyzed the clinical course of SLE during 65 pregnancies in 47 patients with lupus nephropathy [29]. A renal biopsy specimen was available in 77% of the patients, and on the basis of the selection criteria it seemed likely that bias in selection favored inclusion of those whose lupus nephropathy was more severe. This analysis indicated that signs of extrarenal activity and/or renal disease before conception correlated with clinical activity during pregnancy and postpartum in 43 women (56 pregnancies) whose SLE was manifest before pregnancy. Of 31 pregnancies characterized by complete clinical remission (including signs of renal disease) for at least 6 months before conception, remission persisted throughout pregnancy in two-thirds, whereas in one-third the pregnancy was complicated by clinical relapse, including 3 patients with nephrotic syndrome and 3 with moderately severe renal insufficiency. In all instances, however, a complete or partial remission occurred after delivery and, excluding therapeutic abortions, the incidence of live births was 88%. Of 25 pregnancies associated with preceding signs of disease activity, including either extrarenal or renal involvement, SLE activity was unchanged or improved in 52% but worsened in 48%. Exacerbations were more severe in this group, and increased disease activity persisted postpartum in one-fourth of patients. The live birth rate in this cohort was 64%. A history of severe systemic disease or renal disease in the remote past did not correlate with the course or outcome of pregnancy. The live birth rate did, however, correlate with the level of renal function during pregnancy; the rate of live births was reduced 50% in 10 noninterrupted pregnancies in patients with a serum creatinine of 1.5 mg/dl or more. The results of this analysis of SLE and pregnancy have been corroborated by other recent reports (see Ref. 28 for review).

Nephrotic syndrome in pregnancy

The nephrotic syndrome is a common problem among pregnant women with glomerulopathies due to primary renal disease or systemic disease; in such patients, fluid retention often worsens during late pregnancy, often coexisting with a further reduction in plasma albumin concentration. In addition, retention of fluid can aggravate hypertension. Nevertheless, in most

series more than 90% of patients with normal or only slightly impaired renal function give birth to live babies. Although a low birth weight was said to correlate with a low plasma albumin level in one study [21], this finding has not been confirmed in others [20].

In summary, the current data suggest that pregnancy does not accelerate the course of renal disease, except in patients with SLE in whom the systemic disease may become exacerbated during pregnancy. In most reports the live birth rate is approximately 90% in patients who have neither severe renal insufficiency nor severe hypertension at conception. In the presence of either of these features, the likelihood of a successful outcome is reduced substantially. Women with renal disease who become pregnant, however, are at higher risk for developing nephrotic syndrome and have a higher incidence of preterm and small-for-gestational-age babies.

Management of pregnant patients with renal disease

Pregnant women with renal disease are in a high-risk category and preferably should be managed in centers with facilities for accurate and close fetal monitoring and with personnel experienced in treating the complications encountered in patients with renal disease. Because pregnancy does not adversely affect renal disease, the primary aim of management is to maintain pregnancy until fetal maturity is assured by sensitive monitoring techniques.

Hypertension is a common complication of renal insufficiency and often is exacerbated by pregnancy; therefore hypertension should be anticipated, and if it occurs it should be treated effectively. I will discuss the use of antihypertensive agents in pregnancy momentarily. Generally, hematocrit values should be maintained above 25%, and intermittent transfusions should be given if necessary. It is our view that glucocorticoids and cytotoxic agents, including azathioprine and cyclophosphamide, should be employed in pregnant patients with active SLE, systemic vasculitis, and similar diseases. Because clinical studies to date have not found that these agents induce developmental abnormalities in the fetus, the threat of the underlying disease to maternal health and fetal viability is regarded as being greater than the potential risk of fetal drug toxicity. The management of patients with diabetic glomerulosclerosis requires special efforts to maintain blood glucose levels within a normal range, as in pregnant diabetic patients in general. The principles and practical aspects of prenatal care of this group of patients are described elsewhere [30].

Although renal biopsy has been performed successfully during pregnancy and has important implications in establishing the cause and severity of renal injury, limited experience with this technique during gestation in most centers should, in our judgment, preclude its use until after delivery. If the diagnosis of preeclampsia is an important diagnostic consideration, renal biopsy should be performed within approximately 7 days after delivery, because the finding of glomerular capillary endotheliosis is thought to be pathognomonic for preeclampsia, and the abnormality resolves soon after delivery [16].

The use of diuretics for control of hypertension and edema in pregnant patients is controversial. Concern exists that these agents may reduce placental blood flow and hence threaten fetal survival. Reports of fetal complications related to the use of some antihypertensive agents also have generated concern. Much of the concern about diuretics is based on studies by Gant and colleagues, who reported a reduced metabolic clearance rate of dehydroepiandrosterone sulfate (DHEA) in patients treated with either thiazides or furosemide [31]. Since approximately 40% to 50% of the total metabolic clearance rate of DHEA reflects placental conversion of the substance to estradiol, a fall in its metabolic clearance rate is thought to represent a decrement in uterine blood flow and placental metabolic competence. It is of interest, however, that in a randomized, double-blind study of early and continuous use of 50 mg of hydrochlorothiazide in 1030 obstetric patients, no significant difference in birth weight was found between control and thiazide groups [32]. Until the question of whether diuretic agents reduce placental blood flow is resolved, these drugs should be used judiciously in selected patients. In addition to diuretics, beta-adrenergic antagonists, such as propranolol, have been reported to cause intrauterine growth retardation and neonatal hypoglycemia and bradycardia [for review, see Ref. 33]. Other antihypertensive agents, including guanethidine, rauwolfia alkaloids, clonidine, captopril [34], and diazoxide, have not been recommended either because of maternal and fetal complications, or because of inadequate evaluation in pregnant patients.

There is no generally accepted technique for treating hypertension in the pregnant patient. Some authorities recommend continuing the same regimen during pregnancy that has proved effective prior to conception, including the use of thiazide diuretics [33]. Methyldopa and hydralazine are preferred in patients who become hypertensive after conception because extensive experience during pregnancy has failed to indicate significant maternal or fetal complications. Thiazide diuretics should be added to the regimen only after methyldopa and hydralazine have proved inadequate. Criteria for initiating treatment recently has shifted to higher diastolic levels because of increasing concern about adverse effects of drugs on the fetus. Feitelson and Lindheimer define moderate hypertension in pregnancy as a diastolic blood pressure greater than 100 mm Hg in the second trimester or 110 mm Hg in the third trimester [35]. We now believe that therapeutic measures should be introduced to prevent the level of diastolic blood pressure from exceeding 95 mm Hg at any time during pregnancy.

In patients with the nephrotic syndrome, we recommend that sodium restriction be initiated before edema develops. Because pregnant women can absorb sodium avidly, negative sodium balance should not occur. In most patients with nephrotic syndrome, sodium restriction and frequent periods of bed rest prevent anasarca. When this regime has proved inadequate, we have employed diuretics, including furosemide, on an intermittent basis to avoid excessive edema formation. The goal of therapy is maintaining the level of edema at a tolerable level by inducing weight decrements of 2 to 3 lbs with each course of treatment; the regimen does not attempt to eliminate all edema.

Dialysis and renal transplantation

Both peritoneal dialysis and hemodialysis have been used successfully in pregnant patients with acute and chronic renal failure. Most reports of hemodialysis, however, involve single case reports or small series. Nissenson reviewed the accumulated literature consisting of 20 pregnant women, and reported that fetal survival was approximately 50%, with a high incidence of

preterm delivery [36]. He reported that hypotension and vaginal bleeding were frequent complications in patients treated with hemodialysis, and that premature contractions or labor often occurred during or immediately after treatment. There is no evidence that early hemodialysis treatment in this group of patients promotes increased fetal survival. Also, no substantial experience with peritoneal dialysis has been reported, and I am unable to comment about its potential usefulness. On the basis of available data, I believe that dialysis should be instituted according to the same criteria used for nonpregnant individuals. There is no evidence that the potential benefits of earlier treatment outweigh the risk of dialysis-induced complications.

A substantial number of women with renal transplants have successfully conceived and sustained pregnancies. Penn, Makowski, and Harris reviewed the course of 56 pregnancies in 37 women; of the 44 live-born neonates, 70% were normal and 30% had one or more complications, including respiratory distress and seizures [37]. Only 6 of these 44 neonates were small for gestational age, but 4 had congenital abnormalities. Labor and delivery were uncomplicated. It should be noted that approximately 50% of the patients who had impaired graft function at conception developed evidence of preeclampsia during pregnancy; preeclampsia also occurred in 5 patients who had normal graft function. The European Dialysis and Transplantation Association reported 110 live deliveries in 97 transplant patients; the total number of conceptions and the level of basal renal function were not reported [38]. Twenty-one patients had evidence of a decline in renal function in association with pregnancy, and the incidence of small-for-gestational-age infants and preterm deliveries was increased above the rate in normal subjects.

I have summarized the salient physiologic changes in renal function and volume status that occur in pregnancy, and pertinent data on the course of pregnancy in women with renal disease. It is my view that the patient and spouse ultimately have responsibility for deciding whether to conceive or to continue a pregnancy. The physician's role is to provide data on the risks and chances for a successful outcome, to interpret these data for the patient and her spouse, and to provide close supervision for women who decide to conceive or complete a pregnancy. The goal of treatment is to prevent maternal complications and maximize the chance of a live birth.

Questions and answers

DR. JOHN T. HARRINGTON: We know that GFR increases markedly immediately after conception in rats. When does this occur in humans?

DR. HAYSLETT: The rise in GFR occurs very soon after conception. Davidson has shown that the GFR is significantly increased by the eighth week of gestation, and that it reaches maximum levels within another 4 weeks [1].

DR. HARRINGTON: You mentioned that proximal tubule length increases by 10% in the pregnant rat. Does that 10% increase in length translate to an increase in volume of the proximal nephron sufficient to account for reabsorption of the increase in sodium load, or does the increase in sodium reabsorption require changes in distal tubular function as well?

DR. HAYSLETT: Micropuncture studies in the rat have shown that fractional reabsorption of sodium in the proximal convolution does not differ at 6 and 12 days of gestation between pregnant and control animals, despite the increase in filtered load [39]. I am unaware of studies designed to examine your specific question, that is, is the apparent luminal surface area increased to match the change in filtered load of sodium?

The change in renal growth in pregnancy is reminiscent of compensatory growth after loss of renal mass. Studies from my laboratory several years ago demonstrated that the luminal volume of the proximal tubule paralleled the compensatory rise in glomerular filtration rate after uninephrectomy [40]. Structural changes included a 35% increase in length and a 17% increase in luminal diameter. Under these conditions there was a rise in absolute sodium absorption in the proximal tubule in the absence of a change in fractional reabsorption.

DR. JEROME P. KASSIRER: I agree with your view that the husband and wife must take substantial responsibility for deciding whether to have a child, and that the physician's role is to provide data and advice. Except for patients with active lupus, are there any circumstances in which you strongly advise against attempting pregnancy? Are there any circumstances in which the danger is sufficient to justify recommending therapeutic abortion?

DR. HAYSLETT: I think patients should be discouraged from becoming pregnant or continuing pregnancy in the early stages of gestation if a high likelihood exists that maternal health will be impaired if the pregnancy is carried to term, and if there is a reduced outlook for a live birth. These patients generally are those with severe hypertension, especially if they have a poor response to drug therapy. In the third trimester, deterioration of renal function due to presumed preeclampsia is an indication for termination of pregnancy.

Also, I believe that patients and their spouses should consider their responsibilities towards child rearing as well as child bearing. This issue is especially important in patients with congenital renal disease and when rapid progression to end-stage renal failure seems certain. For patients with a congenital lesion, such as polycystic kidney disease, counseling by a clinical geneticist is often helpful. In the final analysis, however, the patient and spouse have the responsibility for determining the course of the pregnancy, and I believe that the physician should support their decision.

DR. KASSIRER: Several factors have changed my approach to these patients in the past 10 to 15 years. First, the risks to the mother and fetus in the patient with renal disease are less than earlier estimates led us to believe. Second, patients are more willing to take risks because adoption is more difficult now that fewer babies are available. Third, we are substantially less paternalistic now than before for a number of appropriate reasons. Do you find it easier or more difficult now to counsel such families? Are we justified in discouraging patients from becoming pregnant?

DR. HAYSLETT: As you know, most patients today expect to share in decisions involving diagnostic and therapeutic plans. I don't think that issues related to pregnancy are different from those in other areas of medicine, and I believe that the quality of patient care is enhanced if the patient-doctor relationship is viewed as one in which both parties assume an active role. Because I have always tried to practice medicine along these lines, I have not experienced any personal difficulty with the recent tendency of patients to want more information and to

participate in a more active manner in decisions that affect their health care.

Regarding the question of whether we are justified in discouraging patients from becoming pregnant, I don't think that, in principle, this issue is any different than our efforts to encourage patients to avoid other factors that can adversely affect their health, such as cigarettes, alcohol, or emotionally stressful circumstances. I assume that whenever a physician provides advice that touches on an important area of life, such as having children or the patient's occupation, the doctor speaks from an informed position and is free of personal bias.

DR. ANDREW S. LEVEY (*Division of Nephrology, NEMC*): What causes the increase in proteinuria during pregnancy in women with preexisting renal disease?

DR. HAYSLETT: There is no answer to your question at present. It seems likely, however, that the increased filtered load of protein, which is due to the rise in GFR, plays an important role in the increase in proteinuria that is regularly observed in pregnant proteinuric patients. Recent work suggests that the reabsorption of albumin by the proximal tubule might approach the maximum transport rate under control conditions; therefore, changes in the filtered load in patients with preexisting proteinuria would be expected to influence protein excretion rates.

DR. LEVEY: If that were the only explanation, one would expect the rise in urinary protein excretion to parallel the rise in glomerular filtration rate during pregnancy. Yet the data you reported for women with diabetic nephropathy indicate that the magnitude of proteinuria does not increase until the third trimester, although glomerular filtration rate increases during the first trimester.

DR. HAYSLETT: I agree with your suggestion that the further rise in protein excretion in the last trimester of pregnancy implies that the mechanism for the change in protein excretion is multifactorial.

DR. SUSAN HOU (*Division of Nephrology, NEMC*): Since you believe that pregnancy does not hasten the decline in renal function in women with renal disease, if a woman wanted to become pregnant but was infertile because of renal insufficiency, would you be willing to try to induce fertility with drugs?

DR. HAYSLETT: I haven't been confronted with that problem, although if I were I probably would apply the same principles as I would with a woman who already had the capacity to conceive. I would discuss the likelihood of her having a successful pregnancy and the potential risk to her if she became pregnant. As I mentioned before, I think couples who are likely to be confronted with major health problems also should consider the question of their ability to raise a child under the conditions of increased physical and emotional burdens.

DR. KASSIRER: Dr. Hou, does clomiphene work in patients with moderate to advanced renal disease? Second, how does renal insufficiency prevent a patient from becoming pregnant?

DR. HOU: Clomid has been given to only a few patients whose serum creatinine levels approximate 2 mg/dl, so we do not know the answer to your first question. The mechanism for infertility in renal failure is not known. Although hyperprolactinemia is common in dialysis patients, we have found elevated prolactin levels in only one-fourth of patients with serum creatinines between 2 and 8 mg/dl (unpublished observations).

DR. JERRY MCCAULEY (*Nephrology Division, NEMC*): As you pointed out, pregnant women are slightly hypoosmolar. Is this because of alterations in ADH secretion or metabolism, or because of a resetting of the osmostat? Is this effect centrally mediated?

DR. HAYSLETT: Rat studies performed in Marshall Lindheimer's laboratory showed that the fall in serum osmolality during pregnancy was centrally mediated. The osmostat responds normally to small changes in osmolality, but at a lower absolute value than in the nonpregnant state.

DR. MARTIN GELMAN (*Renal Division, St. Elizabeth's Hospital, Boston*): Are data on the natural history of proteinuria and the glomerular lesion in preeclampsia well documented?

DR. HAYSLETT: Most workers agree that glomerular endotheliosis is specific for preeclampsia. The question of whether the lesion is present in all patients with preeclampsia, including those with mild clinical disease, remains unsettled. Sheehan recently reviewed this topic [16].

DR. GELMAN: You mentioned that the glomerular endotheliosis that occurs with preeclampsia resolves shortly after delivery. Do you ever biopsy patients with postpartum proteinuria? If so, how long after delivery do you allow for the proteinuria to clear before proceeding with biopsy?

DR. HAYSLETT: It is generally assumed that the clinical manifestations of preeclampsia completely resolve within 6 weeks after delivery. The persistence of proteinuria beyond 6 weeks postpartum strongly suggests another cause for the proteinuria. In attempting to distinguish between preeclampsia and a primary glomerulopathy, we usually wait 6 weeks postpartum. If proteinuria disappears, we assume the cause was preeclampsia. If proteinuria persists, we evaluate the patient further, including renal biopsy, using the same criteria for study that we usually apply to nonpregnant individuals.

DR. WARREN GOORNO (*Staff Nephrologist, Emerson Hospital, Concord, Mass.*): What is the incidence of congenital anomalies in children born to immunosuppressed women who have received a renal allograft?

DR. HAYSLETT: Penn, Makowski, and Harris at the University of Colorado compiled data on children born to women with renal allografts [37]. Fifty-six pregnancies resulted in 44 live births and 4 congenital abnormalities. The authors concluded that the incidence of congenital abnormalities was no greater than that expected in a normal population. But I regard this question as unsettled at present because of the relatively small number of patients studied.

DR. HOU: First, are you aware of any experience with pregnancy in renal transplant patients treated with cyclosporin? Second, do you know of any long-term follow-up data on children of mothers treated with azathioprine? Do these offspring have a higher-than-average risk of childhood malignancy?

DR. HAYSLETT: I know of no clinical experience in which pregnant women have been treated with cyclosporin, nor am I aware of long-term studies of children whose mothers were treated with immunosuppressive agents during pregnancy. Obviously these are important questions, and information on these issues is critical if we are to discuss the risks of pregnancy in women treated with these agents during pregnancy.

DR. HARRINGTON: Dr. Hou, does the literature about hepatic transplantation contain information about the teratogenic potential of cyclosporin?

DR. HOU: Three pregnancies have occurred in women with liver transplants [41]. One woman had a therapeutic abortion. A second had two uncomplicated and successful pregnancies, one induced by clomiphene. She took azathioprine and prednisone during both pregnancies.

DR. LEVEY: Until the safety of cyclosporin during pregnancy is verified, it might be preferable if azathioprine were substituted for cyclosporin after transplantation in women wishing to conceive. Experience in several U.S. centers suggests that this substitution rarely leads to graft rejection after successful transplantation.

DR. MARY D'ALTON (*Department of Maternal-Fetal Medicine, St. Margaret's Hospital for Women, Boston, Mass.*): Would you please comment on the mode of delivery in renal transplant recipients and on the value of renal echogram during labor to detect compression of the kidney? Do you think this is a valid approach?

DR. HAYSLETT: Patients with renal allografts usually experience no unusual problems with vaginal delivery, because the kidney lies in the false pelvis. Ultrasound studies could be important in planning delivery if the anatomic placement of the kidney was abnormal.

DR. RONALD PERRONE (*Division of Nephrology, NEMC*): Why was sodium restricted in this patient from the beginning of her pregnancy?

DR. HAYSLETT: Patients with heavy proteinuria prior to pregnancy, as exemplified by this patient, generally experience increasing edema during gestation. We initiated a low-sodium diet early in pregnancy to blunt the rate of edema formation. Because pregnant women conserve sodium normally, we ran no apparent risk of inducing volume depletion by this measure. We aim to reduce edema formation in an attempt to provide greater comfort to the patient, and to reduce the effects of volume expansion on hypertension.

DR. GELMAN: You alluded to the animal model of pseudopregnancy and said that during this condition sodium balance and GFR can mimic those of the pregnant state. Can you explain these most interesting findings?

DR. HAYSLETT: Pseudopregnancy in the rat, produced by breeding normal females with vasectomized males, is characterized by the renal changes and the extrarenal physiologic characteristics of normal pregnancy. This model should provide an exciting experimental paradigm by which we can explore the factors that cause the well-known physiologic changes of pregnancy.

DR. DAVID CAHAN (*Chief of Nephrology, Faulkner Hospital, Boston, Mass.*): In preeclampsia, are the epithelial foot processes well preserved?

DR. HAYSLETT: In preeclampsia the foot processes are not effaced as in lipoid nephrosis. This finding suggests that the mechanism of proteinuria involves a loss of size as well as, possibly, of charge selectivity. I am not aware of any formal investigations of the mechanism of proteinuria in preeclamptic women, but methods are available that would make such a study feasible.

DR. HARRINGTON: How accurate is the DHEA method for measuring arterial perfusion? My own bias is that it is not a valid index.

DR. HAYSLETT: The DHEA method is not a direct measure of placental blood flow, but rather an index of a metabolic function of the placenta that is thought to correlate with blood flow. Because of the great concern about the effect of a variety of therapeutic agents on placental blood flow, and hence on fetal viability, noninvasive methods that accurately reflect placental blood flow are urgently needed.

DR. HARRINGTON: Could one examine arterial blood flow in experimental models of preeclampsia such as that described in sheep by Ferris?

DR. HAYSLETT: Unfortunately, no experimental model of toxemia, including the one used by Dr. Ferris in sheep [42], closely approximates the human syndrome. The lack of an experimental model of toxemia has created increased difficulties in attempts at unraveling the cause and pathogenesis of toxemia.

DR. HOU: You mentioned that Feitelson and Lindheimer [35] define moderate hypertension in the third trimester as a diastolic blood pressure of greater than 110 mm Hg. When such a blood pressure is secondary to preeclampsia, prompt delivery is often instituted. What are your guidelines for delivering a pregnant woman with renal disease and worsening hypertension?

DR. HAYSLETT: In preeclampsia, delivery is an effective means of controlling accelerated hypertension. When hypertension is caused by severe renal parenchymal disease, it is not clear that termination of pregnancy will reduce hypertension. Because diastolic blood pressures of 110 mm Hg and above are associated with significant maternal cardiovascular complications, vigorous efforts should be undertaken to prevent blood pressure from persisting at that level. This type of intervention may include therapeutic agents that are potentially harmful to the fetus. If all measures failed to control accelerated hypertension, termination of pregnancy would be an acceptable alternative.

DR. HOU: If a patient's renal function worsens in the absence of hypertension prior to assumed fetal viability, would you advise terminating the pregnancy?

DR. HAYSLETT: Because no evidence exists that pregnancy affects the course of underlying renal disease, except in preeclamptic women, there is usually no reason to interrupt pregnancy. Attempts should be made to closely monitor fetal maturity, and delivery should be performed when fetal viability seems likely.

DR. LEVEY: Why do women hyperventilate during pregnancy?

DR. HAYSLETT: Women hyperventilate during the latter stages of pregnancy because the enlarging uterus elevates the diaphragm. As I mentioned earlier, elevated levels of progesterone also can contribute to hyperventilation. Detailed evaluation of this phenomenon has been reported [43].

DR. MCCAULEY: What is the importance of the 30% to 50% increase in GFR in normal pregnancy? In patients with chronic glomerulonephritis, and in other states in which intravascular volume is effectively lower, might one expect to see a difference in the outcome of pregnancy?

DR. HAYSLETT: The importance of the increase in GFR in normal pregnancy is, of course, unknown. This change might simply reflect the generalized decrease in vascular resistance that characterizes pregnancy. In patients with a chronic reduction in GFR that is due to renal disease, the small increment in GFR provides a higher absolute GFR during gestation that

intuitively might prove advantageous to the patient. A reduction in GFR to levels below the normal, nonpregnant value has been associated with fetal growth retardation.

DR. MCCAULEY: Is there an increased risk to the mother or child if the GFR does not increase during pregnancy?

DR. HAYSLETT: This might be a question that can be addressed in the rat model of normal pregnancy.

DR. HARRINGTON: Brenner and others have argued that increased GFR per residual nephron can lead to focal sclerosis. Does the pseudopregnant rat manifest any changes that mimic focal sclerosis?

DR. HAYSLETT: I am not aware of studies in which glomerular histology has been carefully studied after single or consecutive pregnancies in animals or humans. Pregnancy, because of the remarkable sustained increases in GFR, could provide an interesting model for examining whether persistent elevations in glomerular capillary flow lead to glomerular histopathologic changes.

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