PREGNANCY AND RENAL DISEASE

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PREGNANCY AND RENAL DISEASE

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DEFINITIONS

Toxemia - Proteinuria and/or edema and/or hypertension occurring after the sixth month (24 weeks) of the first pregnancy and all abnormalities disappearing after delivery.

Classification on Toxemia of the American Committee on Maternal Welfare (modified)

I. Acute Toxemia of Pregnancy (onset after the 24th week)

A. Pre-eclampsia

1. Mild

2. Moderate

3. Severe

B. Eclampsia - (convulsion or coma has occurred)

II. Chronic Hypertensive Vascular Disease or Renal Disease with Pregnancy

A. Hypertension and/or Renal Disease known to antedate the pregnancy

1. With acute toxemia

2. Without acute toxemia

B. Hypertension and/or Renal Disease discovered in pregnancy

1. With acute toxemia

2. Without acute toxemia

Bacilluria - presence of > 100,000 organisms/ml in a mid-stream urine (two successive positive mid-stream collections have a 96% chance of a third being infected)

Fetal Prematurity - < 2500 grams birth weight

Roll-over Test - In primigravida patients, a stable blood pressure is obtained in the left lateral position supine. The patient is then asked to "roll over" on her back and her blood pressure is re-taken. An increase of > 20 mm Hg in the diastolic reading is POSITIVE. This is said to be the earliest sign of pre-eclampsia in 83% of primigravidas.

NORMAL CHANGES IN PREGNANCY

Anatomical

Size - The kidneys increase in length approximately 1 cm during pregnancy. Such enlargement is thought to be due to increased blood flow and not true hypertrophy (1).

Ureters - Dilatation of the uretus begins as early as 10 weeks after gestation. There are two major etiological mechanisms considered to play a part in this change.

1. Hormonal - Postmenopausal females treated with ovarian hormones and men treated with estrogens have both shown a tendency to dilate the ureter. However, this mechanism does not explain why it is always more marked on the right side and always above the pelvic brim.

2. Mechanical - Since the dilatation appears as early as the 10th. week, it cannot be due to obstruction by the uterus. Recent studies suggest any obstruction is probably a combination of:

   a. The ovarian venous plexus around the ureter.

   b. The iliac artery compressing the ureter as it crosses at the pelvic brim (2).

2.9 ↘

Reflux - 29% of cases studied show ureteric reflux. It is very questionable if there is an increased incidence of true reflux in pregnancy despite the presence of dilatation. Most authors believe that it does not increase the incidence of infection.

All cases due to pregnancy should reverse post-delivery.

- 60% by 2 weeks

- essentially all by 12 weeks

The entity of persistent ureteric dilatation secondary to pregnancy is questioned by most urologists.

THE ABOVE IS WHY INTRAVENOUS PYELOGRAPHY IS UNINTERPRETABLE BEFORE AT LEAST 6 WEEKS POST-DELIVERY.

1. Bailey, R.R. and Rolleston. Kidney length and ureteric dilatation in the puerperium. J. Obstet. and Gyn. Brit. Commonwlth. 78:55, 1971.

2. Dure-Smith, P. Pregnancy dilatation of the urinary tract. The iliac sign and its significance. Radiology 96:545, 1970.

Physiological

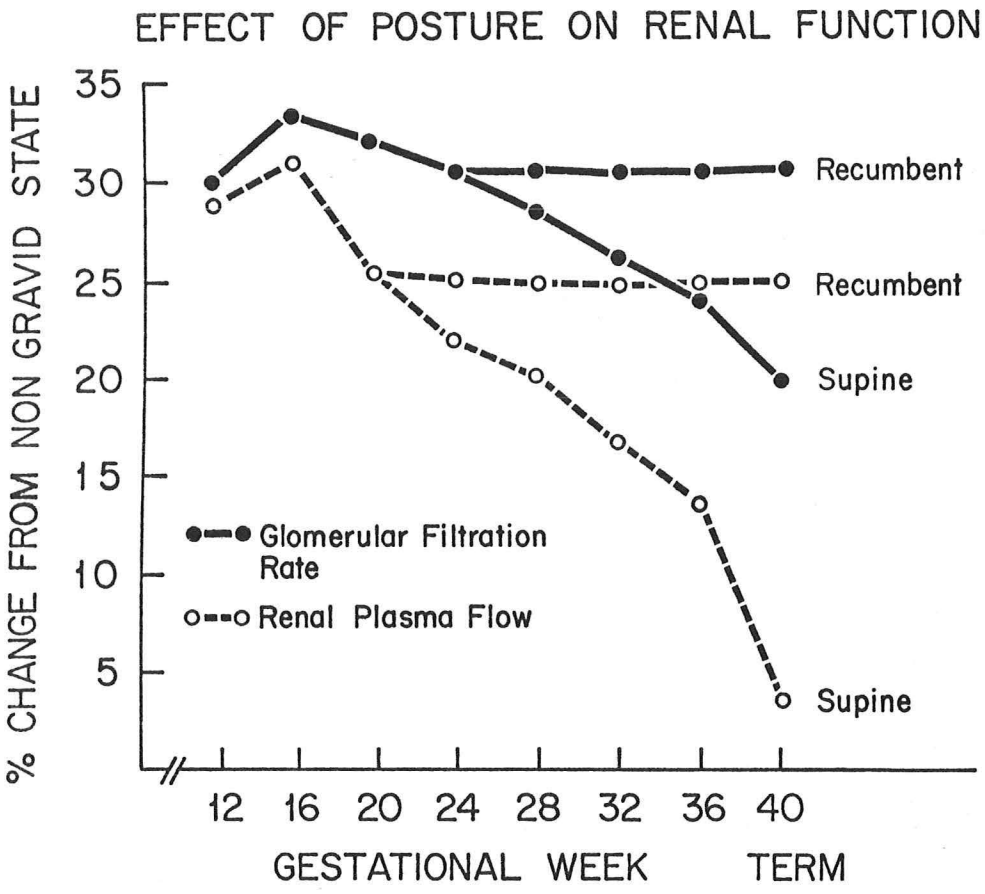
Renal Plasma Flow - Increases early in pregnancy and probably remains elevated through pregnancy.

Glomerular Filtration Rate - Increases between 30-50% above the non-pregnant level providing renal function is relatively normal (3) (Cr < 1.2%). Clearance of creatinine in pregnancy increases from 80-125 ml/min/1.73 M^2 to 125-200 ml/min/1.73 M^2 (5).

Figure 1 illustrates the above changes and in addition demonstrates the artifactual effect position can make in such studies.

Perhaps the most outstanding physiological adaptation of pregnancy is that of blood pressure and peripheral vascular resistance. Both factors decrease despite a 50% increase in vascular volume and a 40% increase in cardiac output. These changes are displayed in Figure 2.

THIS MARKED DROP IN BLOOD PRESSURE MAY MASK MILD UNDERLYING HYPERTENSION IN THE FIRST AND EVEN SECOND TRIMESTERS.



Modified from Chesley

Figure 1

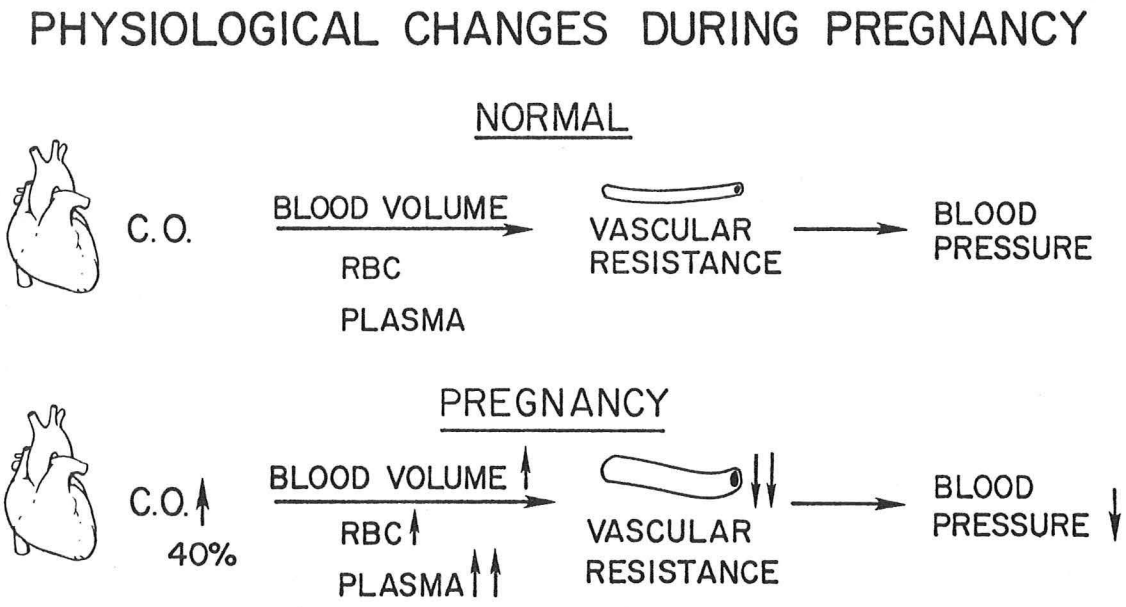

PHYSIOLOGICAL CHANGES DURING PREGNANCY
NORMAL
C.O.
BLOOD VOLUME
RBC
PLASMA
VASCULAR RESISTANCE
BLOOD PRESSURE
PREGNANCY
C.O. ↑
40%
BLOOD VOLUME ↑
RBC ↑
PLASMA ↑↑
VASCULAR RESISTANCE
BLOOD PRESSURE ↓

Figure 2

3. Chesley, L.C. and Arretto, J.E. Pregnancy in the patient with hypertensive disease. Am. J. Obstet. & Gyn. 53:372, 1947.

4. Chesley, L.C. and Sloan, D.M. The effect of posture on renal function in late pregnancy. Am. J. Obstet. & Gyn. 89:754, 1964.

5. Lindheimer, M.D. and Katz, A.I. Renal function and disease in pregnancy. The Kidney 5(3):1972.

Biochemical Changes

Serum Creatinine - Due to the increase in G.F.R. the following values should be considered normal during pregnancy.

	NON-PREGNANT	PREGNANT - Trimester		
		1st.	2nd.	3rd.
Cr. mgm%	.83	.73	.58	.53

BUN - Likewise, falls from 13 ± 3 mgm% to 8.7 ± 1.5 mgm% in normal pregnancy.

Uric Acid - Initially, falls like creatinine in response to increased G.F.R. but late in the 3rd. trimester it increases for unknown reasons even in normal pregnancies.

	NON-PREGNANT	PREGNANT - Trimester		
		1st.	2nd.	3rd.
Uric Acid mgm%	3.86	2.72	2.6	3.61

Sodium - Despite their expansion during normal pregnancy, women can handle an acute sodium load (6). Also their capacity to conserve sodium when challenged with a low sodium intake (10 mEq) is normal (7).

6. Sarles, H.E., et al. Sodium excretion patterns during and following intravenous sodium chloride loads in normal and hypertensive pregnancies. Am. J. Obstet. & Gyn. 102:1, 1968.

7. Lindheimer, M.D. and Katz, A.I. Renal function in pregnancy. Obstet. Gyn. Ann. 1:139, 1972.

A good basic review.

Water - Early in pregnancy there is a resetting of the "osmostat" with a resulting decrease in serum osmolarity by 5-10 millimoles. The cause of this resetting is not clear (8).

In addition, studies from Aberdeen by Hytten and others (9) show a marked increase in unaccounted for water in the 3rd. trimester. Their work would suggest 90% of women develop some swelling. They believe the extra fluid is stored in either maternal fat or connective tissue under the influence of estrogens. See *Figure 3*.

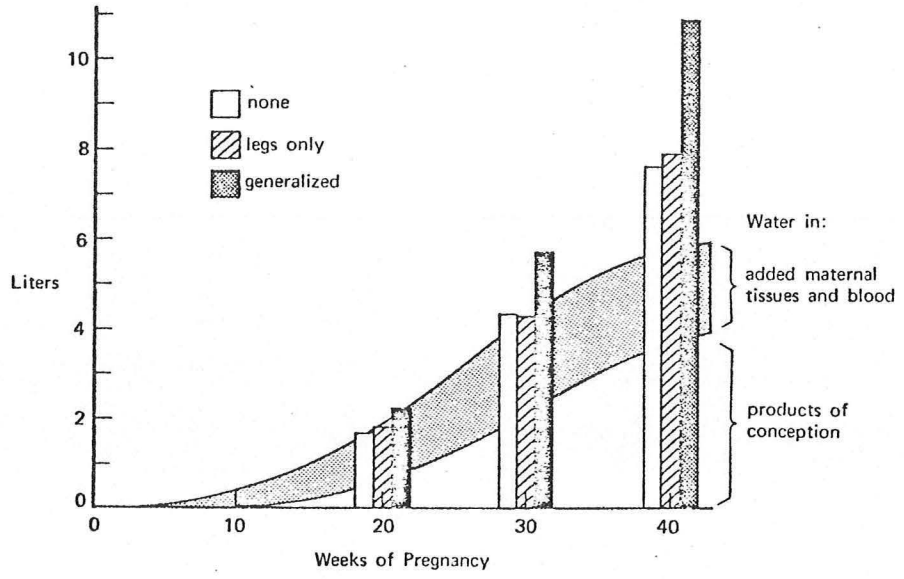


Figure 3

8. Robertson, E.G. and Gheyne, G.A. Plasma biochemistry in relationship to oedema of pregnancy. J. Obstet. & Gyn. Brit. Commonwlth. 79:769, 1972.

9. Hytten, F.E. and Thomson, A.M. Weight gain in pregnancy. *In* Hypertension and Pregnancy. M.D. Lindheimer, Ed. Wiley Med. Press, p.179, 1976.

An excellent overview of this problem and the changing emphasis.

Glucosuria - The presence of glucose in the urine is common with pregnancy. If over 100 mgm of glucose per 24 hrs. is taken as abnormal, then up to 70% of pregnancies in one study show glucosuria. These etiologies have been proposed (11).

1. A lower threshold and a decreased TM. (tubular maximum)

2. A higher filtered load because of ↑ G.F.R.

3. Increased "Splay" in the excretion curve secondary to volume expansion (12).

In two reported papers, Hytten and his groups have suggested that none of these theories apply (13,14). Their argument is that

a. the infusion method influences renal function, and

b. in several studies there was a reduced ability to reabsorb glucose under infusion conditions when the same woman became pregnant.

This group has also shown that pregnant women with the greatest glucosuria also have abnormal reabsorption patterns but not glucosuria when not pregnant. Regardless of what view one holds, all agree that the presence of glucosuria and even the quantity bear little relation to blood glucose levels.

This whole subject becomes more important when one realizes that the only long term follow-up of pregnancy shows diabetes mellitus is two and a half times more common in the primiparous eclamptics and four times more common in multiparous "eclamptic women" (10). No study as yet has tried to correlate this finding with glucosuria during pregnancy.

10. Chesley, L. The remote prognosis of eclamptic women. Am. Heart. J. 93(3):407, 1977.

In this and listed papers, the author has the best long term study of pre-eclamptic patients.

11. Fine, J. Glycosuria in pregnancy. Brit. Med. J. 1:205, 1967.

12. Robson, A.M. and Bucker, N.J. Influence of saline loading on glucose reabsorption in the rat. J. Clin. Invest. 47:329, 1968.

13. Davison, J.M. and Hytten, F.E. Carbohydrate metabolism in pregnancy and the newborn. Churchill, Livingston. Edenburgh, 1974.

14. Ibid. Brit. J. Obstet. & Gyn. 82:374, 1975.

Amino Aciduria - Increased in pregnancy probably due to the effect of increased levels of plasma cortisol on the renal tubule (15).

15. Burke, C.W. and Roulet, F. Brit. Med. J. 1:657, 1970.

Hormones - A reset system exists as shown in Table 1 modified from Weir (18). This system is responsive but at higher levels to changes in posture, volume changes, and other stimuli.

These hormonal levels are raised by the interaction of a number of stimuli (18).

1. Estrogen induced stimulation of renin substrate
2. Various hemodynamic and renal changes.
   a. ↓ BP
   b. Dilatation of the vascular bed
   c. Naturetic action of progesterone.
3. Trophoblastic tissue renin (the activity of the substance is unclear at present).

It is of interest that despite the high aldosterone levels, pregnant women do not become hypokalemic. Ehrlich and Lindheimer postulate that the high level of progesterone make them virtually refractory to potassium wasting (16).

16. Ehrlich, E.N. and Lindheimer, M.D. Effect of administered mineralocorticoids on ACTH in pregnant women. J. Clin. Invest. 51:1301, 1972.

17. Kaplan, N. Hypertension with pregnancy and the pill. Chapter 11. Med. Com. Series. In press.

18. Weir, R.J. et al. Studies on the renin-angiotensin in aldosterone system, cortisol, DOC and ADH in normal and hypertensive pregnancy. In Preeclampsia and Hypertension. Wiley Med. Press. p.251, 1976.

TABLE 1

RENIN ANGIOTENSIN VALUES: NORMAL PREGNANCY AND PREGNANCY WITH HYPERTENSION AND PROTEINURIA VERSUS NON-PREGNANT CONTROLS

	Normal Non-pregnant Range	Normal Pregnancy	Hypertension and Proteinuria
Renin (μ units/ml)	20-105	230 ± 20	161 ± 17
Renin Substrate (μm)	.45-128	3.73 ± .36	2.76 ± .22
Angiotensin (pg/ml)	5-35	78 ± 24	14.9 ± 2.1
Aldosterone (mg/100 ml)	<18	51 ± 15.8	23 ± 3.8
DOC (mg/100 ml)	4.1-13.5	20.4 ± 2.5	10.2 ± .7
Cortisol (μg/100 ml)	6-20	18.7 ± 1.4	23.6 ± 2.3
Corticosterone (μg/100 ml)	.13-2.3	.91 ± .13	81 ± .08
ADH (pg/ml)	4-8	9.7 ± .9	11.5 ± .9

Clotting Factors - Extensive changes occur throughout the system. Plasma fibrinogen doubles with even greater increases in Factors VII, VIII, and X. The fibrinolytic side also undergoes changes. With a two-fold increase in plasminogen accompanied by a marked drop in plasminogen activator in the circulating plasma and in the venous endothelium (20).

These changes in pregnancy appear to alter the system toward a state of enhanced capacity to produce fibrin with a diminished ability to remove it from the system. This may be necessary to maintain the uteroplacental circulation in normal pregnancy with a localized intravascular coagulation process (19).

19. Sheppard, B.L. and Bonnar, J. The ultrastructure of the arteriol supply of the human placenta in early and late pregnancy. J. Obstet. Gyn. Brit. Commonwlth. 81:497, 1974.

20. Bonnar, J., Redmon, C.W.G. and Denson, K.W. The role of coagulation and fibrinolysis in pre-eclampsia. *In* Hypertension in Pregnancy. Wiley Medical Press. p. 85, 1976.

A detailed and fair presentation of the changes involved in normal pregnancy and extreme far advanced toxemia. The authors view toward a heparin trial must be looked on with caution.

Table 2

PHYSIOLOGICAL AND BIOCHEMICAL

	Normal	Pregnancy
BUN	13	8.7
Creatinine	.60	.46
Blood Pressure	110/70	103/56
Uric Acid	5	3
Na		↓*
H_2O^+		↑↑
Amino Acids Reabsorption		↓
Glucose Threshold	194	155
T_{M_G}	366	378 (Non glucosuria)
		310 (Glucosuria)
HCO_3		↓*
Albumin		↓*
Calcium		↓*

* related to H_2O

BACILLURIA

Bacilluria (defined as > 100,000 organisms per ml) is found without symptoms in somewhere between 4 and 7% of females at their first visit to an obstetrician following conception. Most of these women will retain this infection throughout the pregnancy. In addition, another 1-2% will develop asymptomatic bacilluria as the pregnancy progresses (21,27).

The following conditions are said by varying authors to cause an increased incidence of asymptomatic bacilluria above the baseline 4-7% (24).

1. Increasing age
2. Increasing parity
3. Lower socio-economic level
4. Glucosuria
5. Sicle-cell trait
6. Underlying renal disease
7. Blood group B

It should be noted that bacilluric pregnant females have a significant impairment in urinary concentrating ability and this is probably reversible with eradication.

Pyelonephritis

This complication only occurs in 1-2% of all pregnancies, however, it developes in at least 1/3 of asymptomatic bacturetics (21). Pyelonephritis is rare in the first trimester (5%) and becomes progressively more common - 35% in the second trimester and 60% in the third trimester (22). It is more common in primiparas. If unilateral, it is more common on the right (the side with the most marked so-called "physiological dilatation"). But this is not thought to be a signficant association

Kincaid-Smith states even intermittent bacilluria is associated with an increased incidence of pyelonephritis in the third trimester (23). Pyelonephritis in the third trimester can be a very severe complication. As term is approached, premature labor can be induced probably by the non-specific effect of fever and/or toxins. At term, we have seen, in the absence of obstruction, complete anuria in three patients. In 1975,

Drs. Whalley, Cunningham, and Martin (22) showed clearly the depressive effect on renal function of pyelonephritis at any time in pregnancy. Figures 4 and 5 show the marked depression and the recoverying of function after treatment.

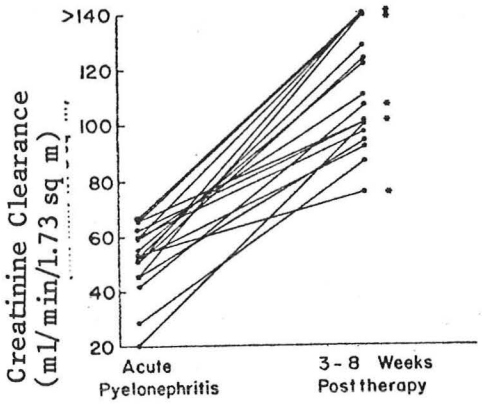


Figure 4

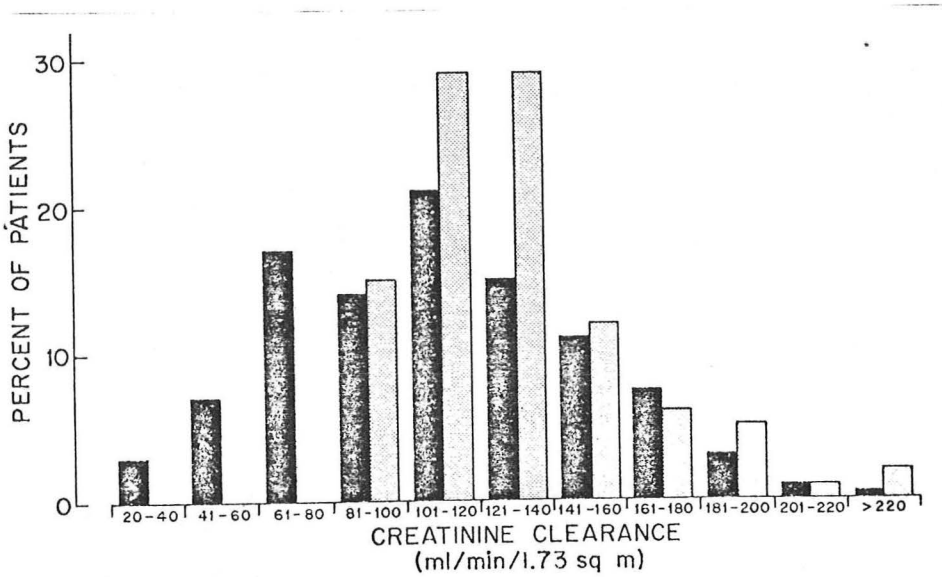


Figure 5

Black bars = pyelonephritis patients
Grey bars = controls

Prematurity and/or Pre-eclampsia

There is a questionable association of these two events with either bacilluria or pyelonephritis. A review of the literature is shown in Table 3 taken from Kincaid-Smith (23). One can see that the findings vary from study to study with questionable significance. What has not been done in these studies is to try and differentiate the upper urinary tract infections and the difficult to eradicate ones. If that group was isolated, a study could show treatment of these reduces the incidence of prematurity. Table 4 is a modification of the original work of Turck, Ronald and Petersdorf (26) showing ways that one might be able to recognize infections in the kidney.

Kincaid-Smith (who may see a different population than the rest of the world because of analgesics) suggests that it is not the bacilluria per se that causes the problems in pregnancy but the high association of bacilluria with underlying renal defects or diseases (23). She believes unlike most authors that there is an increased incidence of prematurity and it is due to the underlying renal problem.

One author has summarized asymptomatic bacilluria as follows (24):

1. If there is a cause and effect relationship between asymptomatic bacilluria and prematurity it must account for only a small percentage of premature births.

2. The successful eradication of bacteriuria reduces only minimally the <u>overall</u> rate of prematurity.

3. Bacteriuric patients who fail to clear with treatment or recur after treatment probably have higher rates of prematurity than do other bacteriuremic who clear with treatment or non-bacteriuremic women.

Almost no one believes that bacilluria or the resultant pyelonephritis causes an increased incidence of toxemia.

TABLE 3

BACTERIURIA AND PREMATURITY

Reference	Bacteriuric Total	Bacteriuric Premature (no.)	Bacteriuric Premature (%)	Nonbacteriuric Total	Nonbacteriuric Premature (no.)	Nonbacteriuric Premature (%)
Little	265	23	8.7	4735	360	7.6
Kincaid-Smith and Bullen	240	32	13.3	500	25	5.0
Whalley	176	26	15	100	14	7
Norden and Kilpatrick	114	17	15	100	7	7
Sleigh, et al.	100	7	7	100	7	7
Kass	95	26	27	1000	88	9
Stuart, et al.	88	20	23	729	83	11
Low, et al.	80	5	6	690	49	8
Layton	63	10	17	114	10	9
TOTALS	1221	166	13.6	9953	657	8.2

TABLE 4

SITE OF BACILLUIRA (BLADDER VERSUS KIDNEY)

	Bladder	Kidney
Concentrating ability	N	↓
Antibody coating	No	Yes
Recurrent infection	Delayed	Rapid
Organism	New	Same
Response to Tx.	Good	Fair
Serum antibody titre	Absent	Present
Premature delivery	N	?↑
I.V.P.	No	? Abn.

Treatment of Asymptomatic Bacilluria

While there is general agreement that such patients should be treated, the method is debated. Kass (27) and Kincaid-Smith (25) have stated that long term suppression for the duration of the pregnancy is necessary to protect from pyelonephritis. Kass's data is shown in Table 5 below. Other workers (24) have suggested that antibiotics eradicate other organisms that we normally miss on routine cultures and that these organisms cause pyelonephritis at term. This is an attempt to explain the lower incidence of pyelonephritis in the treated group as compared to the non-bacteria controls.

TABLE 5

EFFECT OF TX OF BACILLURIA ON COMPLICATIONS OF PREGNANCY

	Pyelonephritis Pyelonephritis	Prenatal Mortality	Prematurity
Bacteriuric	% of Total		
TX	0	0	7.5
Placebo	26	9.7	15.3*
Non Bacteremia	1.4	2.6	11.5*

* twins not included

In March of this year, Dr. Whalley and Dr. Cunningham (28) published their paper on the short term treatment of bacilluria at Parkland Memorial Hospital. Figure 6 shows the response to reported short term oral agents either sulfa or madrodantin. Specific other antibiotics were used for second and third challenges. Table 6 shows the comparison in Drs. Whalley and Cunningham's study of long term treatment versus short term in the same population at Parkland Memorial Hospital.

BACTERIURIA IN PREGNANCY

(Short Term Oral Antibiotics)

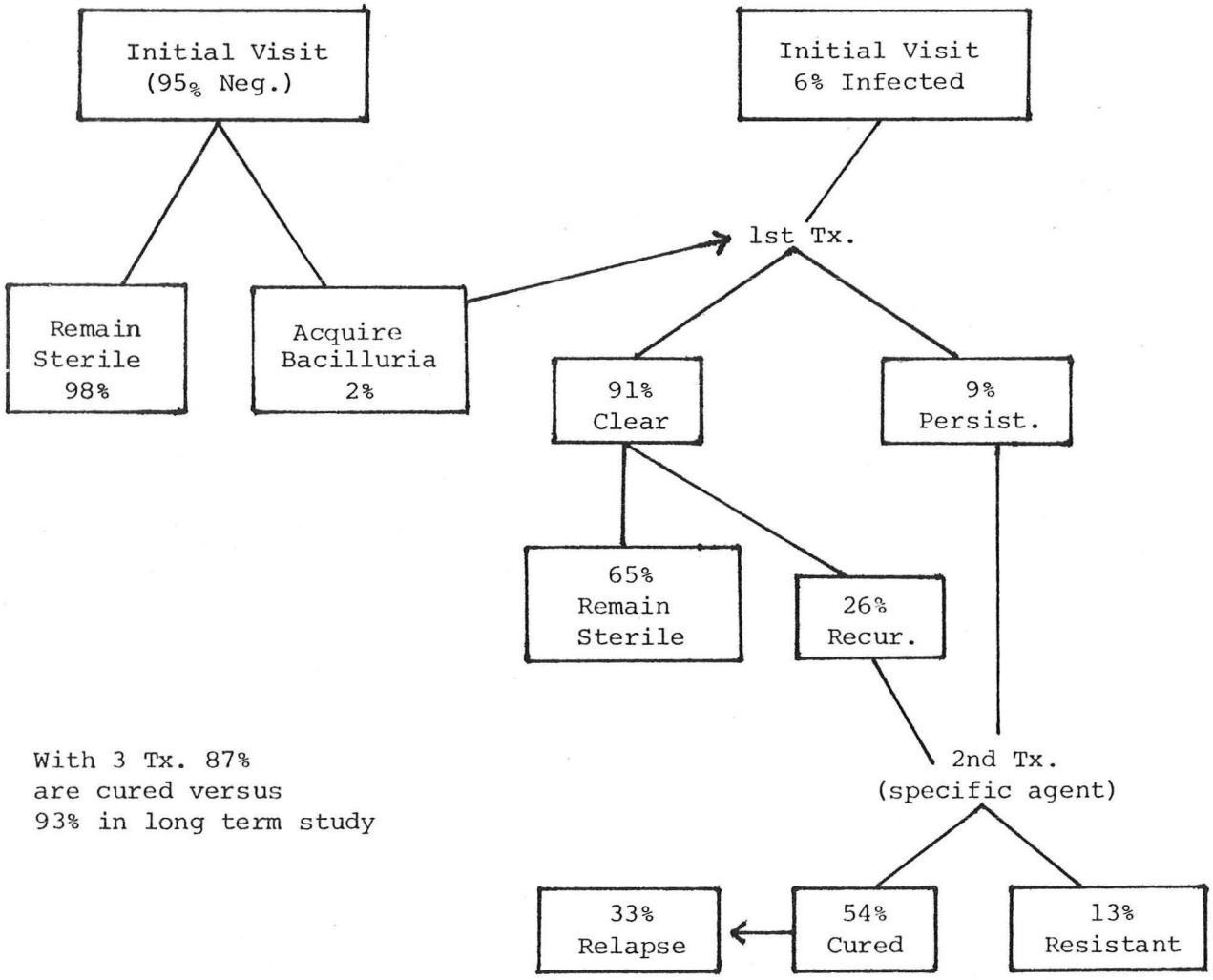


Figure 6

TABLE 6

RESPONSE OF MATERNAL BACTERIURIA TO THERAPY WITH SHORT-TERM AND CONTINUOUS ANTIMICROBIAL ADMINISTRATION

Therapy	Total	Cured*	Not Cured		
			Relapse	Reinfection	No Response
Short Term					
First course	199	129	47	5	18
Second course	70	38	23	---	9
Third course	32	6	18	---	8
TOTAL		173 (87%)			
Continuous					
First drug	95	83	3	2	7
Second drug	12	5	3	---	4
TOTAL		88 (93%)			

*for remainder of gestation

Problem Agents

Table 7 lists some antibiotics that may cause problems in the mother or the fetus. Some are only a problem close to term.

TABLE 7

PROBLEM AGENTS

ANTIBIOTIC	MOTHER	INFANT
Choramphenical	Marrow Suppressive	Circulatory Collapse
Gentamycin/Kanamycin	Nephrotoxicity	Ototoxicity
Macrodantin		Hemolysis*
Sulfas		Hemolysis* Kernicterus
Tetracyclines	Liver	Abnormal Teeth

*G-6-P-D deficiences

SUMMARY

Treatment of asymptomatic bacilluria with antibiotics controls the infection in 90% of cases. Such suppression decreases the incidence of pyelonephritis of pregnancy from 25% to 2%. This reduction in pyelonephritis probably produces a significant decrease in perinatal mortality in this group. It is questionable if it effects prematurity in the overall population. There is no evidence to suggest that such treatment prevents pre-eclampsia.

21. Whalley, P.J. Bacilluria of pregnancy. Am. J. Obstet. Gyn. 97: 723, 1967.

22. Whalley, P.J., Cunningham, G.F. and Martin, F.G. Transient renal dysfunction associated with acute pyelonephritis of pregnancy. Obstet. and Gyn. 46:174, 1975.

23. Kincaid-Smith, P. *In* Progress in Pyelonephritis. E.H. Kass, Ed. F.A. Davis & Co., Philadelphia, p.11, 1965.

24. Mead, P.B. and Gump, D.W. Asymptomatic bacteruria in pregnancy. *In* The Kidney in Pregnancy. R.R. deAlvarez, Ed. Wiley Medical Press, p.45, 1976.

A good general reference. The best source for details of the various techniques utilized in bacilluric studies.

25. Kincaid-Smith, P. and Bullen, M. Bacteriuria in pregnancy. Lancet 1:395, 1965.

26. Turck, M., Ronald, A.R. and Petersdorf, R.G. Relapse and reinfection in chronic bacteruria. New Eng. J. Med. 278:422, 1968.

27. Kass, E.H. Bacteriuria and pyelonephritis of pregnancy. Arch. Int. Med. 105:194, 1960.

28. Whalley, P. and Cunningham, G.F. Short term versus continuous antimicrobial therapy for asymptomatic bacteriuris in pregnancy. Obstet. and Gyn. 49:262, 1977.

Best study on effects of short term treatment with oral antibiotics.

PREVIOUS RENAL DISEASE

There are two questions asked by women with underlying renal disease or their family.

1. Does underlying renal disease increase the morbidity or mortality to the mother and/or the fetus?

2. Does the progression of renal disease accelerate during pregnancy?

These questions are very difficult to answer because we have only one study with repeat biopsies before, during and after pregnancy (31). Available studies suggest that in clinical renal disease, if the serum creatinine is between 1 and 1.5 mgm%, the "normal" physiological increase in G.F.R. does not occur. However the renal function (measured by serum creatinine) does not deteriorate. If the serum creatinine is > 1.5 mgm% before pregnancy then one is likely to see deterioration in renal function as pregnancy progresses (30). It seems unlikely that we will ever be able to determine the incidence of early fetal loss in mild renal disease. Without this information, one cannot be sure what effect impaired renal function has on conception.

The studies that we do have would suggest that underlying renal disease causes major problems with the fetus.

In a series of eight studies of mostly biopsy-proven renal disease reviewed by Ferris (32) and shown as Table 8, we see an obvious effect on the fetus. Please note that 11% for toxemia was chosen as an average figure from this group of studies by me to allow a comparison. It would appear that blood pressure is much more significant as a prognostic sign than azotemia or proteinuria. This point becomes clear in an old (1963) but well regulated study by Mackay (29) outlined in Table 9.

Therefore, one can answer the first question positively, underlying renal disease does increase fetal morbidity and mortality and increases maternal morbidity.

TABLE 8

UNDERLYING MILD RENAL DISEASE

	# Patients	# Of Deliveries	Fetal Loss %	Toxemia %
All Cases	365	406	23	15
Proteinuria Alone		176	7	17
Proteinuria + ↑ BP		123	45	57
Normal			2	11

TABLE 9

MODERATE RENAL DISEASE

	# Of Cases	Fetal Loss %	Toxemia %
Normal		2	11
Proteinuria only	46	17	35
Azotemia/BP < 175/100	38	40	50
Azotemia/BP > 175/100	25	60	100

In regard to the second question and the progression of renal failure, most authors would agree with Studd and Blainey (33). Their data suggests no rapid acceleration in progression of renal disease. Unfortunately the only well studied group, 45 women with biopsy proven disease reported by Kincaid-Smith (31) does not support the "No Progression" theory. Her data is shown in Table 10. It strongly suggests that in 7 of 22 patients in the last three groups, there was sudden unexpected and irreversible deterioration. The Melbourne group believe this was directly related to the pregnancy and furthermore is not predictable in the individual patient. Their summary states that this makes glomerulonephritis a justifiable indication for termination of a pregnancy.

HISTOLOGY IS NOT AN INDICATION FOR ABORTION AT PARKLAND.

Other Forms of Renal Disease

Polycystic renal disease, collagen vascular disease including systemic lupus erythematous and even diabetes should be evaluated on the basis of renal function and hypertension. If the parents <u>really</u> want the child, there is probably little increase in maternal and slight fetal risk if renal function is normal and the mother is followed closely. However, once deterioration in renal function starts, complications rise rapidly.

SUMMARY

Patients with underlying renal disease but relatively normal function can delivery normal children safely but there is definitely an increased risk. The factors to judge the increased risk relative to increased morbidity and mortality are listed below in increasing order of significance.

1. PROTEINURIA - Mild contraindication
2. AZOTEMIA - Serious contraindication (Cr > 1.5 mgm%)
3. HYPERTENSION - Probably an absolute contraindication
4. PROGRESSION OF 2 OR 3 - Absolute contraindication

TABLE 10

RENAL BIOPSY OF PROTEINURIC PATIENTS DURING PREGNANCY

		Successful Pregnancy		Unsuccessful Pregnancy			
Biopsy Diagnosis	No.	Normal Renal Function	Post Partum Deterioration	Normal R.F.	Toxemia	Deterioration in R.F.	Maternal Death
Lupus Glomerulonephritis	12	10			1		1
Mild Proliferative Glomerulonephritis	11	8		1	2		
Diffuse Glomerulonephritis Focal Fibrin and Crosants	9	5	1			2	
Membranous Glomerulonephritis	7	4	2		1		
Mesangiocapillary Glomerulonephritis	6	1		1	2	2	1

TOXEMIA DEVELOPING IN THE FIRST OR SECOND TRIMESTER OR IN OTHER THAN THE FIRST PREGNANCY IS STRONG SUGGESTIVE EVIDENCE OF UNDERLYING RENAL DISEASE OR ESSENTIAL HYPERTENSION.

29. Mackay, E.U. Pregnancy and renal disease. A 10 year survey. Aust. NZJ Obstet. Gyn. 3:21, 1963.

A good review of the association of various degrees of renal disease with "complications" in pregnancy.

30. Bear, R.A. Pregnancy in patients with renal disease. A study of 44 cases. Obstet. & Gyn. 48:13, 1976.

A recent review suggesting some markers in renal function as a guide to complications.

31. Fairley, K.F., Whitworth, J.A. and Kincaid-Smith, P. *In* Glomerulonephritis. Wiley Interscience, p.997, 1972.

The only study with kidney biopsies before, after, and sometime during pregnancy.

32. Ferris, T.F. Medical complications during pregnancy in renal disease toxemia. Saunders and Co., Philadelphia, 1975.

33. Studd, J.W. and Blainey, J.D. Pregnancy and the nephrotic syndrome. Brit. Med. J. 1:276, 1969.

ACUTE RENAL FAILURE

Acute renal failure associated with pregnancy tends to assume a bimodal distribution. Figure 7 as modified from Smith (33).

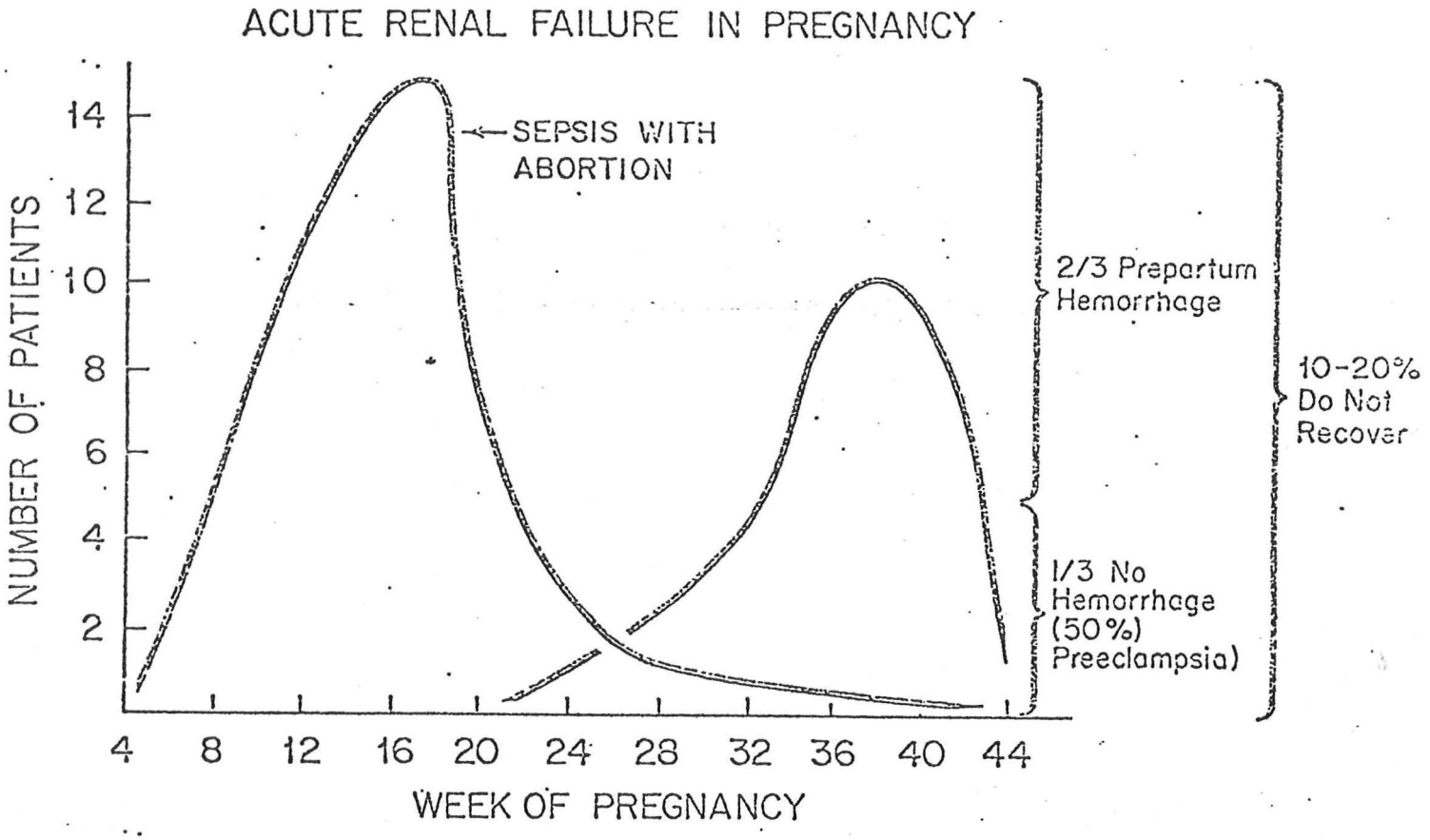


Figure 7

The first peak is in the early week of pregnancy and probably relates to induced abortion. Sepsis and nephrotoxins make up the largest part of this group. Recovery is usually dependent on controlling the sepsis and preventing surgical intervention. Mortality can run as high as 25% usually because in the past, patients sought medical attention late because of legal fears.

The second peak occurs around term. Two-thirds of the cases are associated with prepartum hemorrhage. The remaining one-third have no hemorrhage but up to 50% of this group may have had pre-eclampsia.

Volume depletion secondary to the bleeding or the use of diuretics are major factors in the etiology. If volume is not replaced rapidly, and/or intravascular coagulation occurs (usually a late event) a signifi-

cant percentage can develop bilateral cortical necrosis. Such cases probably account for the 10 to 20% of the second peak that do not recover renal function.

33. Smith, K. et al. Renal failure of obstetric origin. Brit. Med. Bull. 24:49, 1968.

ACUTE CORTICAL NECROSIS (A.C.N.)

In two early series of A.C.N. pregnancy accounted for 48/71 (67%) (34) and 86/149 (57%) (35). In the later study by Wohle, 51 of the 86 pregnant cases were complicated by abruptio placenta. These two reports have sometimes been overlooked because of the monumental and classic monograph describing some 700 cases published by Sheehan and Moore (35). Their paper was the ultimate reference on the subject; however, in 1974 Heptinstall added an excellent overall review (42). Heptinstall reported only 23 cases of A.C.N. out of 11,800 autopsies and not one was associated with abruptio. In addition, he excluded patients with necrosis due to known arterial disease, e.g. polyarteritis, scleroderma or malignant hypertension. Besides abruption there appears to be a higher incidence in pregnancy if volume depletion and/or infection is present. This same combination is also noted in non-pregnancy related A.C.N., e.g. cholera.

Pathology

The description from Sheehan and Moore still provides the best view of the varied involvement of this entity. It must be remembered that their material was all observed at autopsy and that artifical kidneys and dialysis were not available. Today, some of their patients would probably have survived and perhaps recovered various degrees of function.

Classification from Sheehan and Moore:

FOCAL C.N. - Individual glomeruli and areas up to .5 mm in diameter. Proximal tubules are always necrosed.

MINOR C.N. - Areas up to 3 mm in diameter. The center of the necrotic areas are pale with a red congested rim. Arterioles, arteries and glomeruli contain thrombi. Extensive proximal tubular necrosis is found in the rest of the cortex.

PATCHY C.N. - Most of the width of the renal cortex is necrosed with a zone of congestion around the periphery. This may involve up to 2/3 of the cortex. All structures within the necrotic area were dead.

GROSS C.N. - The whole cortex is necrosed except for a thin surviving area under the capsule and another area at the cortical medullary junction.

One can readily see how at least the first two types and perhaps the third type could, with dialysis support, recover function. Indeed, there are now a number of reports of biopsy proven cases that have recovered enough function to be removed from dialysis.

Diagnosis

Complete anuria for more than a few days was once considered pathognomonic but since the advent of adequate dialysis, this sign is no longer reliable. If biopsy is not undertaken, then a diagnosis may sometimes be made in more extensive cases by x-ray. A rim of calcium will appear where the blood supply approaches the necrotic area (37,38).

Pathogenesis

Sheehan and Moore believe it is due to intermittent vasospasm with poor flow following the initial spasm. If good flow is reestablished, simple tubular necrosis or a milder form of cortical necrosis results. This intermittent vasospasm and flow is outlined below.

ACUTE CORTICAL NECROSIS

MECHANISM

1. INITIAL ISCHEMIC PERIOD (4-6 hrs) - producing death of tubular and glomerular cells in the cortex.

2. RETURN OF BLOOD FLOW THROUGH THE ISCHEMIC AREA (6-12 hrs) - fibrin thrombi are formed at this time.

3. SECOND PERIOD OF ISCHEMIA - "Operative Spasm" of intratubular arteries (0-8 hrs or longer).

4. BRIEF SECOND PERIOD OF RETURN OF FLOW - Dilation of glomeruli and arterioles with thrombi formation in the dead tissue.

Experimental studies appear to support this view. It has been noted that the vasculative in pregnancy is sensitive to vasoconstruction. In further studies, Byron injected oxytocin with female hormones and produced cortical necrosis (40).

The possible association of A.C.N. with the Shwartzman reaction has been raised by a number of authors and will be discussed later. Workers have continually looked for fibrin thrombi in glomeruli and results are variable. In abruption where a clotting abnormality can occur, this may be an initiating force since volume depletion is already present.

Unilateral cortical necrosis has been reported (41). In all cases, there is obstruction to blood flow or urine output on the protected side.

Parkland Experience

Studies at Parkland show that if the patient is treated initially in Parkland for abruptio they never develop A.C.N. It is in the patients transferred from elsewhere in whom we see the cases of A.C.N. It is possible that the use of massive fluid and blood infusions prevents the low flow state and secondary vasospasm.

34. Duff, G.L. and Murray, E.D.G. Bilateral cortical necrosis of the kidneys. Am. J. Med. Sci. 201:428, 1941.

35. Sheehan, H.L. and Moore, H.C. Renal cortical necrosis and the kidney of concealed accidental hemorrhage. Oxford Blackwell, 1952.

The definitive reference on this subject.

36. Wohle, G.H., Jr. and Muerhead, E.E. Bilateral cortical necrosis in a child associated with incompatible blood transfusion. Tex. J. Med. 49:770, 1953.

37. Effersøe, P., Roaschow, F., and Thomsen, A.C. Bilateral cortical necrosis: A patient followed up over 8 years. Am. J. Med. 33:455, 1962.

A good review of recovery as reported in the literature up to this time.

38. Alwall, N. et al. Two cases of gross renal cortical necrosis with roentgerotogical studies. Acta Med. Scand. 161:93, 1958.

39. Phillips, M.J. Bilateral cortical necrosis associated with calcification. J. Clin. Path. 15:31, 1962.

40. Byrom, F.B. and Prati, O.E. Oxytocin and renal cortical necrosis. Lancet 1:753, 1959.

41. Blair, E.B. et al. Unilateral renal cortical necrosis. Case report and experimental evaluation. Am. J. Dis. Child. 122:31, 1971.

42. Heptinstall, R. *In* Pathology of the Kidney. Little, Brown Co., p.235, 1974.

The most recent overview with excellent references.

TOXEMIA

The definition (a triad of increased blood pressure, edema and proteinuria occurring in the third trimester of a primigravida) is not adequate. However, through the years a more useful term has not evolved. As to what it is not, I would refer you to an address given by Leon Chesley (43). Table 11 is a modification of the American Committee on Maternal Welfare that tries to differentiate between underlying renal disease and toxemia.

TABLE 11

I. Acute Toxemia of Pregnancy (onset after 24th week)

   A. Pre-eclampsia

      1. Mild

      2. Moderate

      3. Severe

   B. Eclampsia - (convulsion or coma has occurred)

II. Chronic Hypertensive Vascular Disease or Renal Disease with Pregnancy

   A. Hypertension and/or Renal Disease Known to Antedate the Pregnancy

      1. With acute toxemia

      2. Without acute toxemia

   B. Hypertension and/or Renal Disease Discovered in Pregnancy

      1. With acute toxemia

      2. Without acute toxemia

While this table is helpful with large groups, it may not be too useful in individual patients at the time of their pregnancy. This is particularly true when no studies are available from before the patient becomes pregnant.

In reviewing the literature in regard to making the diagnosis of pre-eclampsia, I believe one can make the following statements.

1. A renal biopsy before or very shortly after delivery will allow one to make the diagnosis.

2. Long term follow-up is necessary without a biopsy before the diagnosis can be confirmed.

3. Cases early in pregnancy and in pregnancies other than the first are suspect and most likely some other etiology is present.

Verification of this last point is again supplied by Chesley (44) who has the best and longest follow-up of toxemics. His life survival figures are shown in Figure 8.

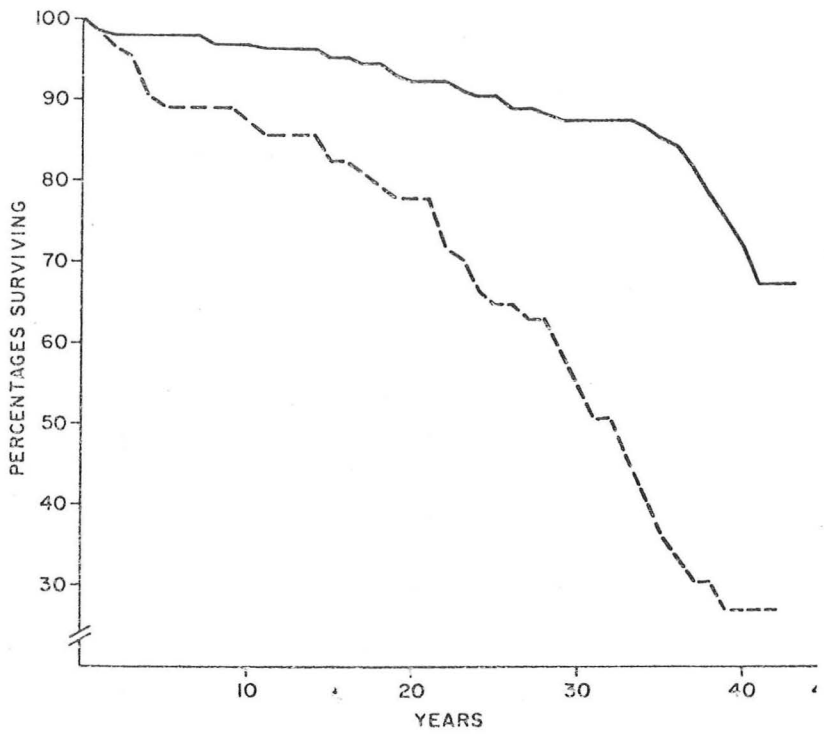


Figure 8

Diagnosis

In addition to the points made above there are some additional diagnostic aids. Figure 9 is an attempt to display the diagnostic criteria in regard to hypertension.

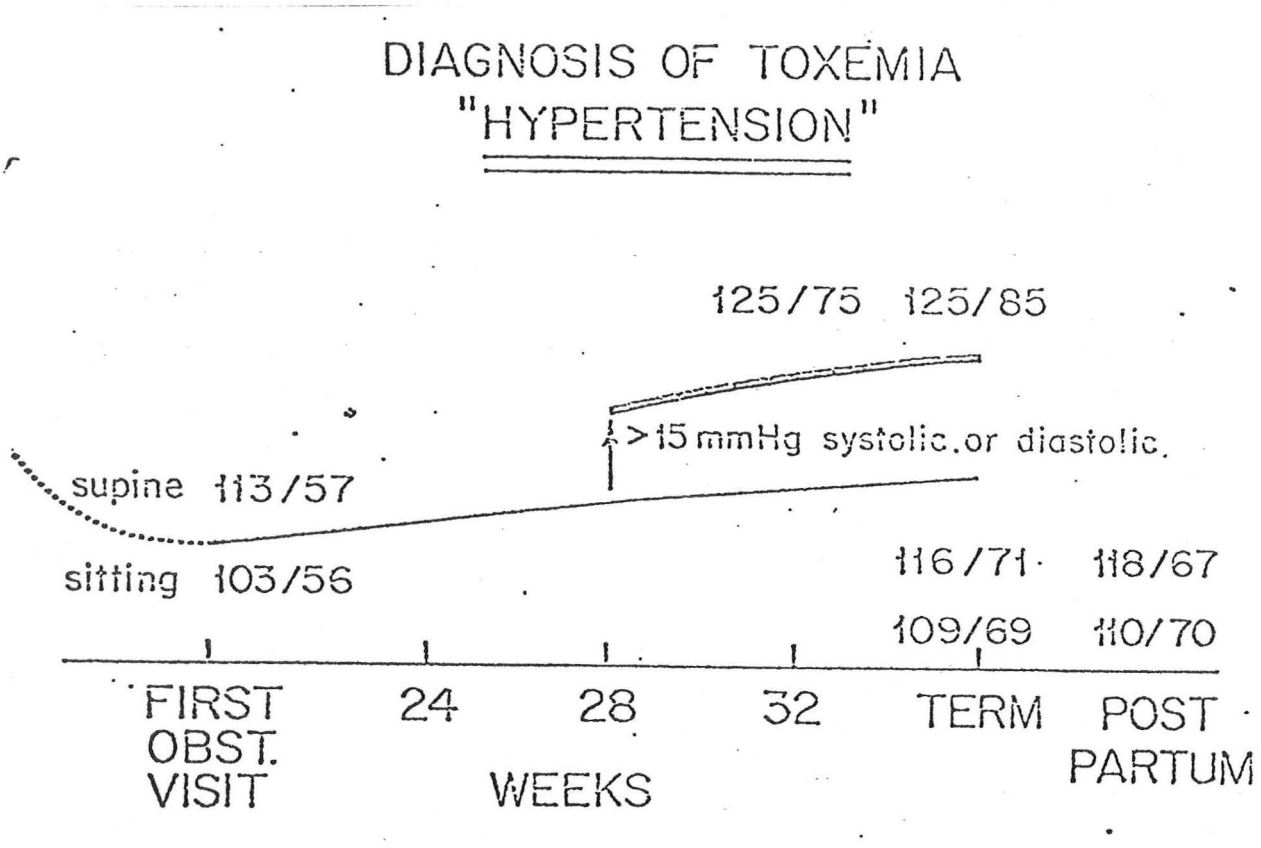


Figure 9

In addition, two other changes should be looked for.

1. Sudden gain in weight in the third trimester.

2. Elevation of the serum uric acid (46) from the low levels of pregnancy to pre-pregnancy range or above.

Etiology

There are any number of factors that are said to influence the development of pre-eclampsia. However, none appears to stand alone. Some of the more significant associated findings are listed below but as time passes, questions have been raised about each (43).

1. Environment
2. Lower socioeconomic status
3. Age of mother
4. Poor nutrition
5. Familial tendencies
6. Large weight gains
7. Coagulation problems

A recent review of a possible immunological basis has been suggested by Beer (51).

At present, the greatest interest appears to be focused on coagulation factors. The literature is divided with one group finding abnormalities both in

a. the clotting factors and fibrin degradation products in serum, and

b. fibrin deposited in the kidney.

Figures 10 and 11 are modified from Mackay (47) who is probably one of the most vociferous advocates of this theory.

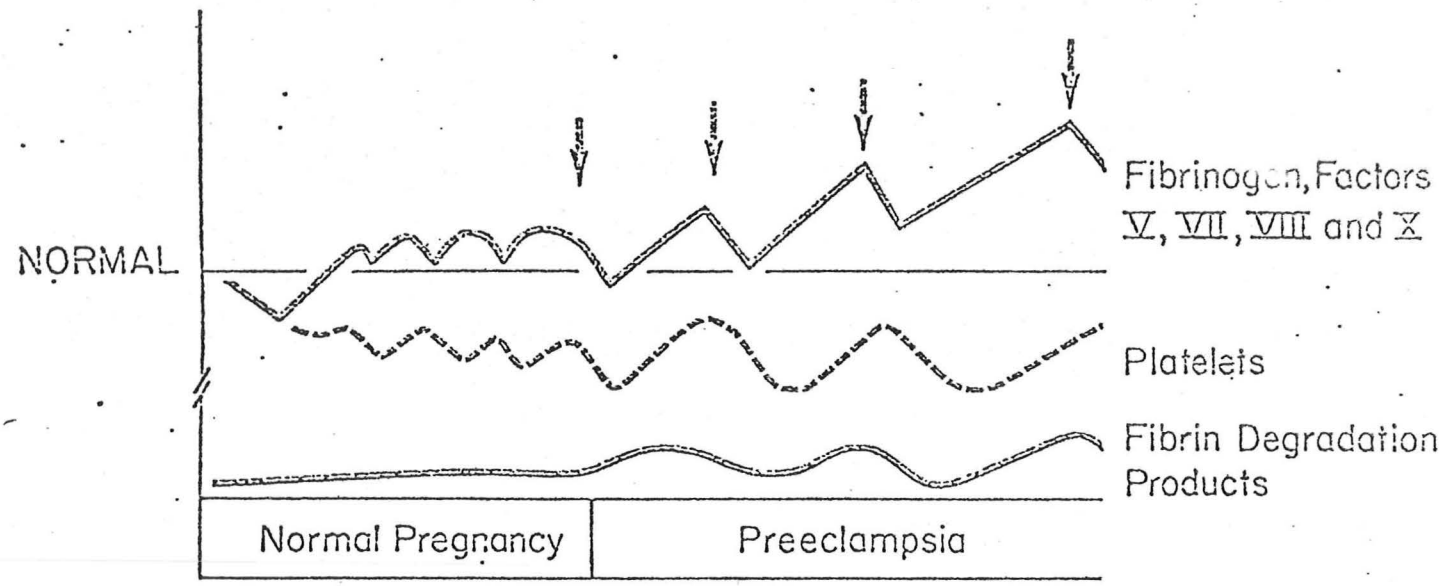
This view holds that there is always a chronic intravascular coagulation at the uteroplacental junction but that in normal pregnancy it is "localized". In pre-eclampsia for some reason the process is triggered in bursts, perhaps by small placental infarcts, to become more generalized. This results in the changes noted in the right part of Figure 10. As pre-eclampsia progresses this process increases. The occurance of seizures (eclampsia) is said to be due to fibrin depositing in other organs - in this case the brain. The final step would be as shown in Figure 11 with perhaps abruption. There would be massive release of thromboplastin into the already primed system and disseminated intravascular coagulation results with concomitant renal shut down.

There is little doubt as one surveys the literature that this can be shown. The major question is whether this is the primary initiating event or a secondary phenomena. Many of the studies come from Australia and the British Isles, few from the U.S.A. This raises the possibility that people might be describing events at different stages in the course of the same disease. Support for this interpretation is clearly shown in a paper from Glasgow by Howie (48) describing coagulation abnormalities in "severe" pre-eclampsia but not normal pregnancy. Figure 12 is one of a series from his paper. This one shows levels of fibrin degradation products. Fortunately, he displayed mild pre-eclampsia which shows no change from normal. This misinterpretation appears to be at the base of these two theories. The people who treat "severe" pre-eclampsia or observe patients after convulsions in attempts to control the process see coagulation problems.

Diuretics

Another variable that may play a part in pre-eclampsia and actually make the syndrome worse is diuretics. Dr. Gant (40) has shown that diuretics or low salt diets usually cause more problems in uterine placental flow and metabolic clearance even when the mother appears to improve.

PREGNANCY AND CHRONIC INTRAVASCULAR COAGULATION

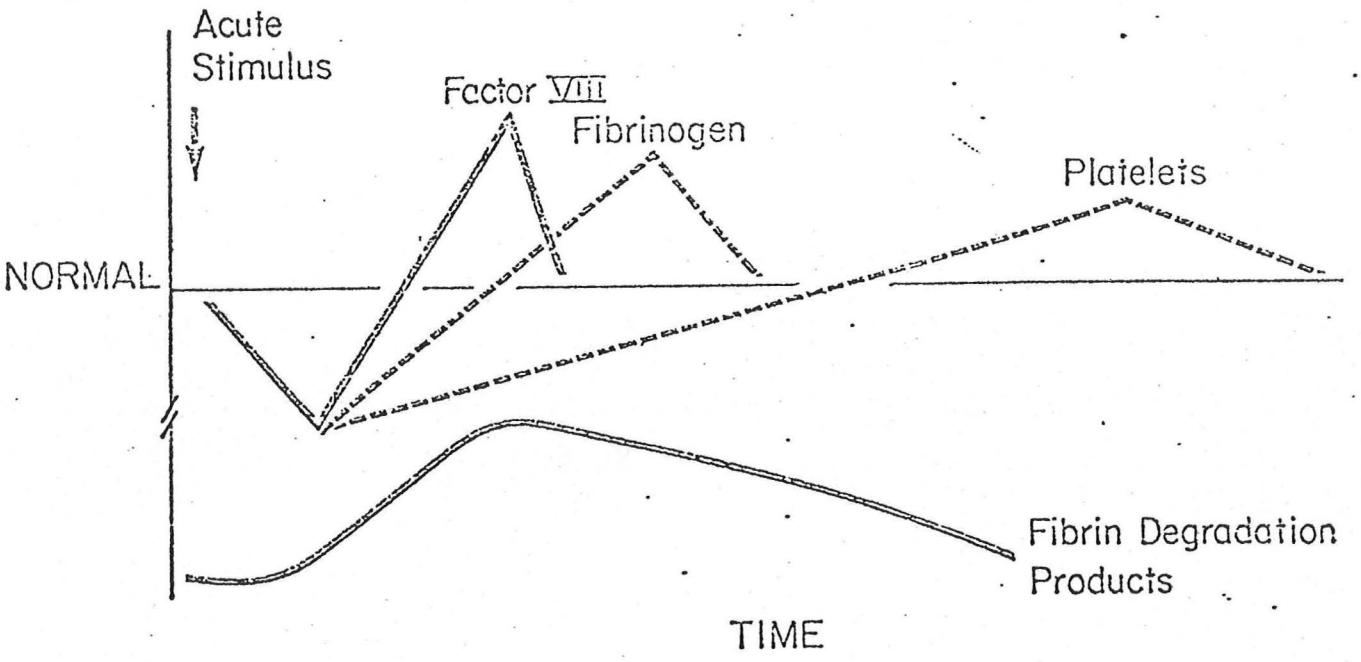


Repeated activation of coagulation mechanism

Modified from McKay

Figure 10

ACUTE MASSIVE DISSEMINATED INTRAVASCULAR COAGULATION



Modified from McKay

Figure 11

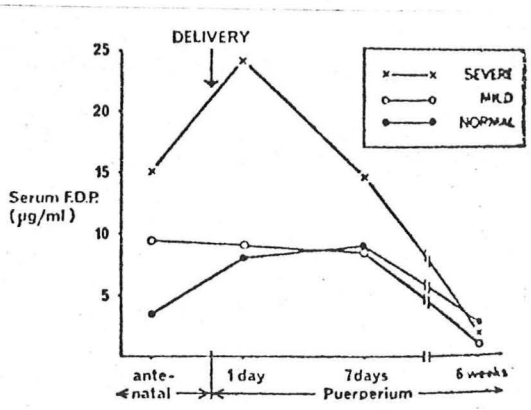


Figure 12

In summary, it seems that if the patient is not treated early and volume given and maintained, that progression to eclampsia and secondary intravascular coagulation will occur with marked maternal and fetal complications. Decreased uterine placental flow is probably the basic problem but pathophysiologic reasons for this are not clear at present.

Pathophysiology

Biopsy findings during pregnancy and up to four days post partum by a number of groups show a mixed group of lesions (45). If vascular changes of increased blood pressure and true underlying renal disease are omitted, we can probably summarize the biopsy findings of pre-eclampsia as follows:

1. Swelling and probably slight proliferation of endothial cells.

2. Increase in mesangial cells and matrix.

3. Abnormal granular, fibrillary, and basement membrane-like deposits between and within endothial cells, in mesangial matrix, and often in continuity with the endothial aspect of the basement membrane.

These lesions tend to disappear within twelve weeks post delivery. Some authors feel that the swelling is the normal reaction of the encothial and mesangial cells as they try and phagocytize fibrin-fibrinogen breakdown particles that have become trapped in the glomerular filter. While such swelling may indeed decrease the GFR it is more difficult to think of the associated proteinuria being a mere mechanical reaction as cells are "lifted" from the basement membrane by the swelling as has been proposed.

Biopsy studies here as elsewhere show a poor correlation between clinical and histological material (45). This is probably influenced by the time the biopsy was done post delivery and the degree of severity of the toxemic process.

Treatment

Pre-eclampsia - as treated in Parkland Memorial Hospital (52)

Once the diagnosis is made the patient should be placed at limited bed rest, preferably in an obstetrical high risk observation ward.

Free ambulation and a regular hospital diet produce a lowering of blood pressure in 85% of cases.

Serial serum creatinines and weekly creatinine clearances are used to monitor renal function.

Blood pressure is recorded four times per day.

Weight is recorded three times per week.

Fetal growth is measured by sonography every three weeks.

Sedation and antihypertensives are not used.

Delivery is effected if:

1. Blood pressure cannot be controlled.
2. Rapid weight gain occurs.
3. Significant proteinuria developes.
4. Fetal growth retardation is shown by sonography.
5. Severe headaches or scotomata develope

Eclampsia - as treated in Parkland Memorial Hospital (53)

1. Patients are admitted to the labor and delivery area for treatment.
2. Control of convulsions with MAGNESIUM SULPHATE:

   4 gms I.V. over 3 minutes

   5 gms in each buttock

   5 gms alternately injected in the buttock q4h depending on:

-urine flow (> 100 ml)

-respirations - not depressed

-patellar reflexes present

3. Antihypertensive therapy: Apresoline I.V. to lower diastolic pressure to 100 mmHg (usually 5-20 mgm of Apresoline give control).

4. Diuretics were not used nor were hyperoncotic fluids.

5. Fluids: D_5W up to 2 liters in the absence of hemorrhage or hyponatremia at the rate of 60-125 ml/hr. There-Thereafter Ringers lactate was used.

6. Delivery was undertaken as soon as the patient regained consciousness and was oriented to time and place.

7. Hemorrhage or hypotension post delivery was considered to be volume depletion and was treated with blood and Ringers lactate.

Results of Treatment

Pre-eclampsia

Groups	Perinatal Mortality
Treated patients	9/1000
Patient who left hospital (AMA)	154/1000
P.M.H. obstetric population	29/1000

Eclampsia

No maternal deaths

Perinatal mortality 15.4

43. Chesley, L. False steps in the study of pre-eclampsia. *In* Hypertension and Pregnancy. M.D. Lindheimer, Ed. Wiley Med. Press. p.1, 1976.

Excellent review of the mistakes made in the interpretation of the cause of toxemia.

44. Chesley, L. Remote prognosis after eclampsia. *In* Hypertension and Pregnancy. M.D. Lindheimer, Ed. Wiley Med. Press. p.31, 1976.

45. Pollak, V.E. and Nettles, J.B. The kidney in toxemia of pregnancy: A clinical and pathological study based on renal biopsies. Medicine (Balt.) 39:469, 1960.

46. Chesley, L. Simultaneous renal clearances of urea and uric acid and the differential diagnosis of late toxemias. Am. J. Obstet. Gyn. 59:960, 1950.

47. MacKay, D.G. Blood coagulation and toxemia of pregnancy. *In* Glomerulonephritis. P. Kincaid-Smith, Ed. Wiley Med. Press, p.963, 1972.

48. Howie, P.W., Prentic, C.R.M. and McNicol, G.P. Coagulation, fibrinolysis and platelet function in pre-eclampsia, essential hypertension and placiatel insufficiency. J. Obstet. Gyn. Brit. Commonwlth. 78: 992, 1971.

A good comparison of coagulation changes related to severity of toxemia.

49. Gant, N.J., Worley, R.J. and McDonald, P.C. The clearance rate of maternal plasma prehormones of placental estrogen formation. *In* Hypertension and Pregnancy. M.D. Lindheimer, Ed. Wiley Med. Press. p.309, 1976.

A good review to become familiarized with the techniques of measuring uterine placental flow and clearance.

50. Pritchard, J.R., Cunningham, F.G. and Mason, R.A. Does coagulation have a causation role in eclampsia. *In* Hypertension and Pregnancy. M.D. Lindheimer, Ed. Wiley Med. Press. p.95, 1976.

51. Scott, J.R. and Beer, A.A. Immunologic aspect of pre-eclampsia. Am. J. Obstet. Gyn. 125:418, 1976.

A basis for a possible immunological etiology for pre-eclampsia.

52. Hauth, L.C., Cunningham, F.G. and Whalley, P.J. Management of pregnancy-induced hypertension in the nullepara. Obstet. and Gyn. 48:253, 1976.

Excellent review of conservative management of pre-eclampsia

53. Pritchard, J.R. and Pritchard, S.R. Standardized treatment of 154 cases of eclampsia. Am. J. Obstet. Gyn. 123:543, 1975.

Best study with the lowest mortality figures using simple standard therapy.

POST PARTUM RENAL FAILURE

In 1968 Robson (53) described four cases of post partum renal failure (adult hemolytic uremic syndrome). Subsequently, a number of papers including five cases from here were reported.

Presentation

Patients generally sought medical attention three days to ten weeks post partum. Initial complaints included general malaise, abdominal pain or vaginal bleeding. Renal failure was usually far advanced at the time of presentation and progressed to shut down in most cases.

While none of the patients gave a hypertensive history and most did not present with increased blood pressure all developed it.

In none of the reported cases was toxemia of pregnancy diagnosed.

Anemia was common at admission. Distorted red blood cell morphology and reticulocytosis was usually present when it was looked for.

Biopsies

Were described as resembling scleroderma or acute vascular transplant rejection. As Heptinstall (42) has pointed out, this means they had areas of severe necrosis and microinfarction. In the collected series by Lawrence (54) three cases did show microcortical infarcts. Serial biopsies showed progression to tubular death and vessel thrombosis.

Etiology

The cause is not known although a number have been proposed. Because cases were all reported over a short period of time (1967-1971) infections and drug etiologies (55) have been suggested but not confirmed.

Treatment

In the literature, heparin is considered the treatment of choice - especially early in the course. Luke (55) reported one case that appeared to respond. We also have one case that responded but in long term follow-up this partial recovery of function was paid for by a severe uncontrollable malignant hypertension.

It is our impression now that if the patient is shut down then heparin probably has no place. If the patient is seen early with good urine output, heparin might be tried if a biopsy is obtained first. Once one has accepted renal failure as permanent then bilateral nephrectomy should be done to control the blood pressure and the patient considered for transplantation.

53. Robson, J.S. et al. Irreversible postpartum renal failure. Quart. J. Med. 147:423, 1968.

54. Clarkson, A.R., Meadows, R. and Lawrence, J.R. Postpartum renal failure - the generalized Shwartzman reaction. A review. Aust. Ann. Int. Med. 18:209, 1969.

A good overall review of the subject with reference to the Shwartzman reaction.

55. Luke, R.G. et al. Heparin treatment for postpartum renal failure with microangiopathic hemolytic anemia. Lancet 2:750, 1970.

PREGNANCY FOLLOWING CHRONIC RENAL FAILURE

Dialysis

A number of cases have been reported of patients who either had chronic renal failure or developed failure during pregnancy and required support by dialysis.

Schriener (56) has reviewed the data from Europe and North America over the last number of years. There appears to be a 50% chance of spontaneous abortion. In the remaining 50% that carried the babies to term, 2 of 14 had congenital abnormalities.

It would appear as Schreiner states that "optimal dialysis" is still not optimal for the fetus.

Transplant

Penn's review (57) of the Colorado results suggests that male transplant recipients can father children with little fear. Of the 39 deliveries (fathered by transplanted males) to date, there have been two abortions and one congenital defect which was quite severe.

In the female transplant recipient the results are not as encouraging. There have been 31 pregnancies completed resulting in 22 live births. The remainder were made up of 1 stillborn, 1 ectopic and 7 abortions. Of greater concern is what happened to the 22 live births. Only 9 of the group had an uncomplicated neonatal course. The remaining 13 had one or more complications. These are listed below.

Respiratory distress syndrome	4
Adrenocortical insufficiency	2
Septicemia	2
Seizures	1
Congenital abnormalities	3
Less than 36 weeks gestation	10

Surprisingly the delivery does not seem to be affected by the transplanted kidney. None of the transplanted mothers in the Colorado group have shown alteration in renal function associated with pregnancy.

Our own experience at Parkland Memorial Hospital is shown in Table 12.

TABLE 12

DALLAS TRANSPLANTS AND PREGNANCY

Transplanted Parent		Aborted	Pregnant	Normal Child
Women	5	2	1	3
Males	5	0	0	7

One of the patients who aborted developed severe jaundice of pregnancy.

IN SUMMARY

While the risk in all series to the mother and the transplanted kidney are small, the results in the children are significant. One must council very carefully female transplant patients who wish to get pregnant. The transplanted father seems to present much less risk to the child. This is probably due to the normal environment once conception has taken place.

56. Schreiner, G.E. Dialysis and pregnancy. J. Am. Med. Assoc. 235:1725, 1976.

57. Makowski, E.L. and Penn, I. Parenthood following renal transplantation. *In* The Kidney in Pregnancy. Wiley Med. Publications. p.215, 1976.

Largest series of well followed-up patients.

General References

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The Kidney in Systemic Disease. W. Suki and G. Eknoyan, Ed. Wiley and Sons, New York, 1976.

Glomerulonephritis. P. Kincaid-Smith, Ed. Wiley Med. Press, New York, 1973.

The Kidney in Pregnancy. deAlvarez, Ed. Wiley Med. Press, New York, 1976.

Hypertension in Pregnancy. M.D. Lindheimer, A.I. Katz and F.P. Tuspon, Ed. Wiley Med. Publications, New York, 1976.

Medical Complications During Pregnancy. G.N. Burrow and T.F. Ferris, Ed. Saunders, Philadelphia, 1975.