

BACTERIURIA IN RELATION TO RENAL DISEASE IN ADULTS

With Special Reference to Women of Childbearing Age

WILLIAM BRUMFITT

BACTERIURIA IN PREGNANCY

It has been known for many years that pregnant women were liable to have large numbers of bacteria in their urine even though they have no symptoms. Dodds appreciated that technical problems in collection and examination of urine made interpretation of "positive" results difficult.¹ She reported that of 793 urine specimens collected during pregnancy and puerperium six per cent grew pure cultures of *E. coli* and five per cent grew gram-positive organisms. In a postpartum follow-up study of 84 patients with antenatal infections Dodds found that 49 per cent had sterile urine, 35 per cent evidence of chronic pyelonephritis and 16 per cent were still infected.²

During the last decade a revival of interest in the bacteriuria in pregnancy resulted from the application of quantitative techniques to the problem.³⁻⁵ Many studies have been made worthless by the failure to apply the correct procedures to the collection, transport and examination of urine specimens. Indeed some of the studies in which contamination of the urine has been interpreted as significant bacteriuria have confused thought on the relation of true bacteriuria to organic disease. Suitable methods for the detection of significant bacteriuria have recently been reviewed in detail by Brumfitt and Reeves⁶ and Norden and Kass.⁷

ACUTE PYELONEPHRITIS IN PREGNANCY

Kass reported that acute pyelonephritis of pregnancy was found in 40 per cent of pregnant women and did not occur in patients who did

not have bacteriuria.^{3,5} Subsequently, his own work on larger numbers⁸ and that of others has shown that a smaller percentage of untreated patients developed the complication. Some of the newer data, shown in Table 1, indicate that approximately 25 per cent of untreated pregnant women with bacteriuria develop pyelonephritis later in pregnancy. Two other points have emerged: first, although treatment greatly reduces the incidence of pyelonephritis the complication cannot be prevented entirely (Table 1) and, second, some women who do not have infection at the first antenatal screening subsequently develop bacteriuria and this may progress to acute pyelonephritis. Thus the hope that screening of all antenatal patients at their first visit would allow eradication of bacteriuria at an asymptomatic stage and so eliminate acute pyelonephritis in pregnancy has not been entirely realized although the incidence can be greatly reduced.

Factors Influencing the Prevention of Acute Pyelonephritis

If patients are given an eight to ten day course of treatment for bacteriuria of pregnancy the patients can be classified (Table 2) into those who succeed (Group I) and those who fail (Group II). Group II can be further divided into those who respond to a second course of treatment (Group IIA) or fail (Group IIB). Patients who responded to a first course of treatment were less likely to develop acute pyelonephritis (1.4 per cent) than those who failed and needed further treatment (6.6 per cent).^{9, 10} In a different study 23.3 per cent of 86 patients who were given placebo developed acute pyelonephritis.¹¹ Of the 87 patients treated 10.3 per cent developed pyelonephritis, but in this particular group the number of primary treatment failures was high. It is important to note, therefore, that none of the patients who responded to primary treatment developed pyelonephritis. Furthermore, five of the nine patients who developed this complication had an

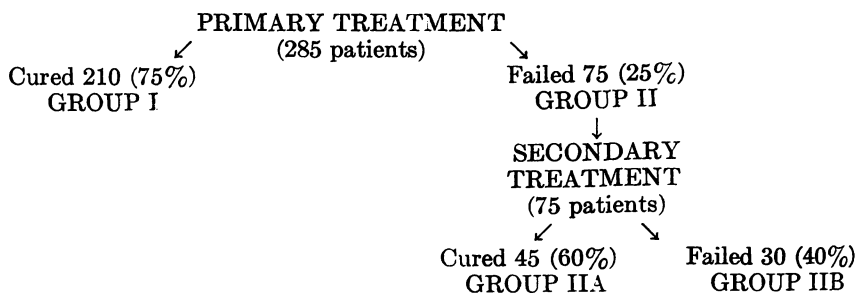
TABLE 1. INCIDENCE OF PYELONEPHRITIS IN PREGNANCY

	Bacteriuria in Pregnancy	
	Treated	Untreated
Brumfitt, <i>et al.</i> ⁹	8/285 (2.8%)	
Condie, <i>et al.</i> ¹¹	9*/87 (10.3%)	20/86 (23.3%)
Savage, <i>et al.</i> ⁸	0/75 (0%)**	26/198 (26.4%)
Little ¹²	4/124 (3.2%)	35/141 (24.8%)

* Five were treatment failures.

** In a random series of nonbacteriurics the rate of symptomatic disease was 1.4 per cent.

TABLE 2. BACTERIURIA IN PREGNANCY, CLASSIFICATION ACCORDING TO RESULT OF TREATMENT



infection that resisted multiple courses of treatment. The latter findings reemphasize the need for care in assessing the value of preventive medicine programs. For example, unusually large numbers of patients with organic disease of the urinary tract together with the choice of a less efficient antimicrobial substance for primary therapy can prejudice unfavorably the outcome of such programs.

It is apparent, therefore, that eradication of bacteriuria, which can usually be achieved in the majority of patients, reduces the incidence of subsequent pyelonephritis to low levels. When treatment fails, the incidence of pyelonephritis is significantly higher so that when reporting on the effectiveness of treating bacteriuria in pregnancy it is important to analyze the results in terms of those patients in whom treatment has succeeded and those in whom it has failed. Unfortunately, a number of workers have neglected to make this distinction and have merely compared all patients treated with a control untreated group.

The value of treatment has also been clearly established by the large series of Little, in which treatment was given for 30 days,¹² and Savage, in which treatment was given until the 32nd week of pregnancy.⁸

Another important question is how many women whose urine was sterile at the first antenatal visit subsequently develop bacteriuria, and how many of these progress to pyelonephritis? Unfortunately little information is available on this point although Little found that 19 (0.4 per cent) of 4735 women without bacteriuria at the first antenatal visit later developed acute pyelonephritis.¹² Further studies are needed that involve repeated urine examination on pregnant women who are nonbacteriuric at their first antenatal visit.

Prematurity and Low Birth Weight

An association between acute pyelonephritis and premature delivery has been known for a long time.² Kass found that 24 per cent of a group of women with asymptomatic bacteriuria delivered babies weighing less than 2,500 grams, whereas, in a similar group in whom the infection had been eradicated, the incidence fell to ten per cent, a level similar to the nonbacteriuric patients.⁵ Le Blanc and McGanity¹³ and Stuart, Cummins and Chin¹⁴ confirmed this finding but many others were unable to find a significant association with bacteriuria.^{12, 15-20} Kincaid-Smith and Bullen agreed that the risk of prematurity was increased in bacteriuric patients, but found that the prematurity rate was uninfluenced by successful treatment.²¹ These workers used continuous chemotherapy throughout pregnancy and subsequently found that the frequency of radiologic abnormalities on intravenous pyelography and blood urea levels was significantly higher in bacteriuric than in nonbacteriuric women. Discussions on the possible reasons for failure to confirm the relation of bacteriuria in pregnancy to prematurity have recently been reviewed.⁷

Findings in two different studies have supported the observations of Kass relating bacteriuria to prematurity (Tables 3 and 4).⁹⁻¹¹ However, it can be seen in Table 3 that despite adequate courses of chemotherapy birth weights of infants of bacteriuric patients were significantly lower than in control patients without bacteriuria. Persistent infection increased the risk (Group II) and the smallest infants were

TABLE 3. PREMATURETY AND MEAN BIRTH WEIGHTS

	<i>Control</i> (uninfected)	<i>Group I</i>	<i>Group II</i>	
			<i>A</i>	<i>B</i>
Number of births	507	201	40	25
Mean birth weights	7 lb. 6 oz.	7 lb. 3 oz.	7 lb. 0 oz.	6 lb. 5 oz.
Premature births	28 (5.5%)	11 (5.4%)	3 (7.5%)	5 (20%)

TABLE 4. PREMATURETY AND BACTERIURIA*

	<i>Bacteriuria</i>	<i>Uninfected Controls</i>
Total patients	180	180
Premature babies**	23 (12.8%)	9 (5%)

* Condie, *et al.*¹¹

** 2,500 g. or less at birth.
($p < 0.001$).

TABLE 5. INCIDENCE OF FETAL MORTALITY*

	Group I	Group II
Number of infants	208	71
Number of "unexplained" deaths	5	6
Incidence	2.4%	8.5%

* Brumfitt, *et al.*,⁹ and Grüneberg, *et al.*¹⁰

TABLE 6. FETAL MORTALITY AND BACTERIURIA*

	Bacteriurics	Controls
Total cases	180	180
Stillbirths	2	0
Neonatal deaths	4	1
Abortions	3	1

* Condie, *et al.*¹¹

born to women whose infection failed to respond to multiple courses of antibacterial therapy (Group IIB).

In both studies fetal loss was greater in patients with bacteriuria and this was enhanced if the infection was refractory to treatment (Tables 5 and 6).

Time of Acquisition of Bacteriuria in Pregnancy

It has been suggested by several workers that bacteriuria becomes established early in pregnancy. However, more recent evidence indicates that bacteriuria is equally common in nonpregnant women of child-bearing age. Sleigh found that eight per cent of 397 women attending an infertility clinic in Edinburgh had bacteriuria compared with 6.6 per cent of 1,684 pregnant women.¹⁶ However, patients with infertility are liable to have undergone pelvic manipulations, including catheterization, and probably are not representative of the population in general. Nevertheless, population studies in Jamaica, Japan and South Wales have shown that significant bacteriuria is present in three to seven per cent of adult women.²²⁻²⁴

A study has also shown a prevalence of 5.4 per cent in 1,506 new nonpregnant patients attending a gynecologic clinic.²⁵

It seems that a number of women acquire bacteriuria relatively early in life; Kunin found that 1.2 per cent of apparently healthy schoolgirls had bacteriuria.²⁶ However, as stated above, the prevalence

probably increases after marriage and evidence indicates that this may be associated with intercourse because in nuns of childbearing age the prevalence was similar to that found in schoolgirls.²⁷

RELATION OF ASYMPTOMATIC BACTERIURIA TO CHRONIC PYELONEPHRITIS

One of the most fundamental yet difficult problems awaiting solution is the relation of asymptomatic bacteriuria to chronic pyelonephritis. Kass suggested that asymptomatic significant bacteriuria represents an early stage of the natural history of urinary tract infection and that these infections may lead to acute infections, chronic infections and eventual death from renal failure.^{22, 28} In children strong evidence has been found that relates urinary infection to chronic pyelonephritis.^{26, 29, 30} In adults the situation is less clear because, with the exception of certain patients such as those with neurogenic bladder, progression to chronic pyelonephritis has not been observed.

Bacteriuria and Chronic Active Pyelonephritis

It is becoming apparent that patients with asymptomatic bacteriuria may also have asymptomatic infection of the kidney (asymptomatic pyelonephritis). For example, evidence based upon ureteric catheterization,³¹ raised serum antibody titers against the infecting organism³² and impaired concentrating ability³³ has shown that 30 to 45 per cent of patients with bacteriuria of pregnancy have renal tissue involvement.

This silent renal infection is important because the patients so affected are more resistant to treatment. It has been shown that patients with renal involvement are less likely to respond to chemotherapy.³⁴⁻³⁶

Pregnant women also show a relation between failure to respond to treatment and acute symptomatic complications, low birth weight of the infant and the presence of urinary tract abnormalities.^{9, 10, 37} In a prospective study 157 women who had bacteriuria of pregnancy were followed for two to four years. All of these patients had been treated and all had sterile urine on discharge from the postnatal clinic, but at long-term follow-up 43 (27 per cent) were again found to have bacteriuria. These patients could be divided into two groups according to whether they had responded to a course of chemotherapy (as discussed previously). Infection was more than twice as likely to be present in the group who had failed treatment than in those who had

responded (Table 7). Intravenous pyelography on 71 of the 157 women showed an abnormality in 23 (37 per cent) and these abnormalities also correlated with difficulty in eradicating infection during pregnancy (Group I, 23 per cent abnormal; Group IIA, 35 per cent abnormal and Group IIB, 65 per cent abnormal). Furthermore, the lesions in Group II were more severe than those found in Group I, definite evidence of chronic pyelonephritis being found in a total of 11 women, ten of whom were in Group II (Tables 8 and 9).

Thus, patients who responded to chemotherapy were less likely to have radiologic abnormalities and when present these were less severe than in patients resistant to therapy. Consequently, patients with bacteriuria in pregnancy cannot be regarded as a homogeneous group of patients, but as a mixed one containing some with presumably simple infections that can easily be eradicated and that are of less sinister prognostic significance. On the other hand patients who have

TABLE 7. URINARY INFECTION AT LONG-TERM FOLLOW-UP IN 157 WOMEN

	<i>Total</i>	<i>Group I*</i>	<i>Group II*</i>
Number of women	157	109	48
Significant bacteriuria at follow-up	43 (27%)	21 (19%)	22 (46%)

* Group I responded to one course of chemotherapy during pregnancy. Group II required two or more courses of chemotherapy during pregnancy.

TABLE 8. RESULTS OF RADIOLOGIC EXAMINATION IN 71 WOMEN

	<i>Total</i>	<i>Group I</i>	<i>Group II*</i>	
			<i>A</i>	<i>B</i>
Number of women examined	71	31	23	17
Abnormal I.V.P.	26 (37%)	7 (23%)	8 (35%)	11 (65%)

* Group IIA responded and Group IIB failed to respond to a second course of treatment with ampicillin.

TABLE 9. RADIOLOGIC ABNORMALITIES IN 26 WOMEN

<i>Abnormality</i>	<i>Total</i>	<i>Group I</i>	<i>Group II</i>	
			<i>A</i>	<i>B</i>
Chronic pyelonephritis	11	1	6	4
Duplex system	6	3	1	2
Abnormal dilatation	5	2	1	2
Calculus	4	1	0	3

infections resistant to treatment are more likely to have underlying urinary tract abnormalities. The possibility that some of these patients have a progressive disease that originated in childhood and may eventually lead to renal failure deserves consideration. Similar findings in gynecologic outpatients with asymptomatic bacteriuria that related resistance to treatment and symptomless but serious renal diseases were reported by Williams.²⁵

Sussman carried out a study on a group of 107 nonpregnant bacteriuric women and 88 controls in Cardiff.²⁴ Radiologic abnormalities were found in 32 of 93 (34 per cent) bacteriuric patients, but only six of 50 controls (13 per cent). This difference is highly significant and establishes that radiologic abnormalities are found more commonly in bacteriuric subjects than in uninfected controls.

THE VALUE OF DETECTION AND TREATMENT OF ASYMPTOMATIC BACTERIURIA

The value of presymptomatic detection of urinary infection in children seems to be beyond doubt.^{26, 30} Similarly the substantial reduction in the complications to the mother during pregnancy and to the baby both during pregnancy and after delivery seems to justify screening the urine for bacteriuria at the first antenatal visit. In the pregnant woman the use of short-term therapy seems to be a useful method of defining those patients needing further investigation after pregnancy.

Screening the nonpregnant female population for significant bacteriuria has been the subject of debate. According to Sussman it is not worthwhile because it fails to detect urinary infection at an early and reversible stage of its natural history and, furthermore, treatment suitable for use on a large scale fails to halt its progress.^{24, 40} The study was only continued for one year and the authors admit that the relation to the ultimate development of scarring and contraction of the kidney and renal failure remains to be defined.

A group of 96 females with chronic bacteriuria were studied who had an average duration of infection of 12 years.³⁸ These patients were highly susceptible to reinfection and were chronically unwell. About half of the patients had renal damage as judged by radiology and the creatinine clearance was reduced in 28 per cent. Fifty per cent of patients had evidence of chronic active pyelonephritis. Reasonably good results were obtained by short-term curative treatment followed by long-term prophylaxis.³⁹

Therefore, the conclusion of the Cardiff group that attempts to detect and treat bacteriuria in the nonpregnant adult female are not justified is unproven. Morbidity resulting from infection and the progression of renal damage can be measured only by controlled studies continued over many years. Furthermore, long-term investigations are needed to determine the value of treating bacteriuric women by adequate and properly controlled therapy. A program to detect bacteriuria and follow up the results of therapy would enable those women most liable to recurrent infection, and possibly progressive renal damage, to be defined and given appropriate treatment and supervision.

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