CHOLERA IN PREGNANT WOMEN

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Summary The records of 60 pregnant patients with cholera admitted to the Pakistan-SEATO Cholera Research Laboratory ward were reviewed and compared with those of 100 non-pregnant controls. There was no maternal mortality. Cholera in the third trimester was associated with significantly greater dehydration and stool output than in the second trimester, or in non-pregnant controls. 18 of 36 third-trimester patients had stillborn infants early in the course of the disease. Fetal deaths were attributed to the effects of hypoxia and acidosis. Fetal wastage due to cholera can probably be effectively reduced only by preventing maternal infection.

Introduction

THE occurrence of cholera in a pregnant woman is a situation "fraught with particular danger". So concluded Pollitzer from his review of the world literature (1959), noting that most 19th and 20th century observers reported a high incidence of stillbirths as well as an unusually high maternal morbidity. These observations were made before the therapeutic concept of quantitative intravenous replacement of stool water and electrolyte losses was introduced (Watten et al. 1959), which reduced the mortality of treated cholera to less than 1% (Bullock and Phillips 1965, Carpenter et al. 1966a, Lindenbaum, Akbar, Gordon, Greenough, Hirschhorn, and Islam 1966). In order to determine the risks to mother and fetus in patients treated with modern methods, we analysed the records of pregnant women with cholera treated on the ward of the Pakistan-SEATO Cholera Research Laboratory (P-SCRL) over four and a half years.

Patients and Methods

We reviewed the records of women admitted to the P-SCRL ward with diarrhœa associated with cultures positive for *Vibrio choleræ* from December, 1962, up to the end of March, 1967. 69 were in the second or third trimester of pregnancy when admitted with cholera (since pelvic examinations were not done routinely, first-trimester pregnancies were not identified with certainty and are excluded from this report; no first-trimester abortions were seen, however). 9 patients (4 third and 5 second trimester) who did not miscarry during their admission for cholera were lost to follow-up. In the remaining 60 the outcome of pregnancy was determined; the records of these patients were analysed in this study. 100 non-pregnant women of child-bearing age (twelve to forty-five) admitted with documented cholera during the same period served as a control group. Their records were selected from each annual epidemic in numbers proportional to the distribution of pregnant women by dividing the total number of eligible controls by the number desired in each time-period, and then systematically sampling to achieve the desired number; this ensured that the sample of control records was drawn proportionately from the entire study period.

The methods of diagnosis and therapy used have been described elsewhere (Greenough 1965, Lindenbaum et al. 1965). 46 pregnant patients and 70 controls received tetracycline or chloramphenicol; 14 and 30, respectively, were given intravenous fluids only. Total stool output was measured over eight-hour periods until the end of diarrhœa. The total output for the first two full eight-hour periods after admission was used to calculate initial stool-rate (expressed as millilitres per hour).

Results

The patients can be divided into four groups:

Group A: 18 patients—third trimester with stillbirths after onset of cholera.

Group B: 18 patients—third trimester with live births during or after cholera.

Group C: 24 patients—second trimester with stillbirths (2) and with live births (22).

Group D: 100 patients—non-pregnant (age twelve to forty-five).

The pregnant patients had slightly lower mean plasma-protein levels and hæmatocrits after recovery from cholera than the non-pregnant controls (table I). None of the pregnant women was overtly malnourished, hypoproteinæmic, or severely anæmic.

TABLE I—DATA ON STATE OF NUTRITION (MEANS ± S.E.)

Group	Age (yr.)	No. of pregnancies	Admission weight (kg.)	Convalescent plasma-protein (g./100 ml.)	Convalescent hæmatocrit (%)
A	22·9 (±2·3)	3·6 (±0·6)	38·2 (±1·0)	7·3 (±0·2)	32·3 (±0·2)
B	23·3 (±1·1)	3·2 (±0·6)	41·1 (±1·0)	6·8 (±0·2)	32·0 (±0·9)
C	26·0 (±2·1)	4·2 (±0·7)	39·0 (±1·2)	7·2 (±0·1)	32·0 (±1·6)
D	26·5 (±0·5)	..	...	7·7 (±0·1)	34·1 (±0·7)

Severity of Cholera

None of the patients in the pregnant or non-pregnant groups died (1 patient in group A, however, required cardiopulmonary resuscitation on admission). Two indices of the severity of cholera are shown in table II: the difference between admission and convalescent plasma-protein concentrations (indicating the severity of dehydration at admission), and the initial stool-rate after admission. Cholera was more severe in the third trimester (groups A and B) than in the second trimester (group C) or non-pregnant patients (group D): groups A and B were significantly more dehydrated and had greater initial stool-rates than groups C and D (table II). The duration of vibrio excretion did not differ significantly among the groups.

TABLE II—SEVERITY OF CHOLERA (MEANS ± S.E.)

Group	Admission minus convalescent plasma-protein concentration (g. per 100 ml.)	Initial stool-rate (ml./hr.)	Total stool output (litres)*	Duration of vibrio excretion (days)*
A+B	3·9 (±0·3)	336 (±32)	11·7 (±1·5)	2·6 (±0·3)
C	2·7 (±0·3)	251 (±34)	9·9 (±1·8)	3·0 (±0·3)
D	3·0 (±0·2)	258 (±24)	10·4 (±0·8)	2·3 (±0·2)
Statistical comparisons:				
A+B v. C	P<0·01	N.S.	N.S.	N.S.
A+B v. D	P<0·025	P<0·05	N.S.	N.S.

N.S. = not significant. * Antibiotic-treated patients only.

Fate of the Fetus

There were 20 stillbirths. They occurred one to seventeen days after onset of illness. Significant associated hæmorrhage was present in a single patient. Fetal heart-sounds were absent on admission in all but 2 of the patients who later miscarried. Some degree of maceration was seen in most of the stillborns. Necropsies, performed on 4 fetuses, revealed maceration, organ and placental autolysis, and serosal petechiæ; cultures of placenta, fetal blood, and amniotic fluid were negative for *V. choleræ*. The findings were compatible with an estimated occur-

rence of fetal death before admission to hospital, soon after the onset of diarrhœa.

18 (50%) of 36 women in the third trimester, but only 2 (8%) of 24 in the second trimester, miscarried ($P < 0.001$). The severity of dehydration on admission was significantly greater in third-trimester patients who miscarried (group A) than in those who did not (group B), as shown in table III. Severity of dehydration was clinically apparent at the outset. 16 (89%) of 18 patients in group A had an absent or thready radial pulse. This finding was present in 12 (67%) of 18 patients in group B and 13 (54%) of 24 patients in group C. The likelihood of miscarriage could have been determined on admission by assessment of the radial pulse: 18 (44%) of 41 patients with absent or thready pulse had stillbirths; only 2 (11%) of 19 with a normal pulse miscarried, Groups A and B did not differ in initial stool-rate (table III). None of the patients who miscarried had a rectal temperature greater than 100·6°F (38·1°C) during their stay in hospital. The time-interval between onset of symptoms and arrival at hospital was similar in all groups; 85% of pregnant and 77% of non-pregnant patients were admitted less than 24 hours after onset of diarrhœa. 15 of 18 in group A and 14 of 18 in group B received antibiotic therapy.

TABLE III—SEVERITY OF CHOLERA IN THIRD-TRIMESTER PATIENTS WHO MISCARRIED (GROUP A) AND WHO DID NOT MISCARRY (GROUP B) (MEANS ± S.E.)

Group	Admission minus convalescent plasma-protein concentration (g. per 100 ml.)	Initial stool-rate (ml./hr.)	Total stool output (litres)*	Duration of vibrio excretion (days)*
A	4·5 (±0·5)	338 (±49)	13·4 (±2·5)	2·5 (±0·4)
B	3·3 (±0·3)	334 (±46)	9·8 (±1·6)	2·7 (±0·4)
P value	<0·05	N.S.	N.S.	N.S.

N.S. = not significant. * Antibiotic-treated patients only.

Follow-up of Live Births

Of the 40 live-born children in this study, 3 were born at full-term while on the ward, and appeared to be normal. 3 children died shortly after birth at home after discharge from hospital (one hour, and seven and eight days, respectively). 17 other children returned for at least one follow-up visit within the first two years of life: 1 had a history of seizures at birth; 2 were severely spastic (the mothers of these, one with third, the other with second trimester cholera, had been severely dehydrated, with admission-minus-convalescent plasma-protein concentrations of 3·7 and 4·3 g. per 100 ml. respectively); the remainder were grossly normal compared to other children in our hospital who were born of normal pregnancies. The balance of the group (17 children) not seen by one of us were observed to be alive by our visiting nurse.

TABLE IV—DISTRIBUTION OF PREGNANT PATIENTS (2ND AND 3RD TRIMESTERS ONLY) AMONG WOMEN, AGE TWELVE TO FORTY-FIVE, ADMITTED WITH ACUTE DIARRHŒA FROM DECEMBER, 1962, TO MARCH, 1967

Diarrhœa	April–September	October–March*	Overall†
Choleraic:			
With pregnancy ..	8 (*14%*)	61 (*13%*)	69 (*13%*)
Total	59	474	533
Non-choleraic:			
With pregnancy ..	8 (*2%*)	13 (*4%*)	21 (*3%*)
Total	347	354	701

* Late autumn and winter epidemics of cholera in these years.
† Difference in numbers with pregnancy in those having choleraic and non-choleraic diarrhœa: $\chi^2 = 43$, $P < 0.0005$.

Association of Cholera and Pregnancy

The incidence of an associated pregnancy among all female patients of childbearing age admitted to our hospital with acute diarrhœal illnesses during the period of the study is shown in table IV. An associated pregnancy was significantly more common in the choleraic than in the non-choleraic group. The association was present during epidemic as well as non-epidemic periods.

Discussion

19th and early 20th century clinicians generally found that cholera in pregnant women had an unusually severe course, in most cases resulting in the death of both mother and fetus (Pollitzer 1959). In our study of patients treated with therapeutic techniques introduced during the past decade, there was no maternal mortality, but earlier observations of increased severity of cholera and high fetal wastage were confirmed. The increased severity of diarrhœal disease, as indicated by greater dehydration on admission to hospital and greater initial stool-rate as compared with non-pregnant controls, was evident only in third-trimester patients. Cholera in the second trimester was no worse than in the non-pregnant state.

Associated with the greater severity of third-trimester cholera was a much greater stillbirth rate (50%) as compared with the second trimester (8%). The absence of fetal heart-sounds on admission to hospital in patients who subsequently miscarried, and the finding of extensive maceration of the delivered fetuses, suggest that fetal death occurred early in the course of the disease, probably before arrival at hospital and initiation of therapy. The status of the patient at the time of admission, as indicated by circulatory changes evident clinically, and degree of hæmoconcentration, was more important in predicting fetal death in third-trimester patients than the stool-rate after admission to hospital (table III), again suggesting irreversible fetal damage before intravenous therapy could be initiated.

The association of fetal wastage with more intense dehydration and circulatory embarrassment, our inability to culture *V. cholerœ* from stillborn babies of infected mothers, and the usual absence of septicæmia in cholera (Lindenbaum et al. 1965), suggest that intrauterine death was not due to fetal infection, but was a consequence of metabolic and circulatory changes in the mother. Of these the most important may well have been the effects of the profound hypovolæmic shock of cholera on the placental circulation. It is estimated that a 3 kg. full-term fetus requires a uterine blood-flow of 150–350 ml. per minute (Brown 1967), roughly 3–6% of maternal cardiac output (Kerr 1968). Cardiac output in untreated cholera patients may be less than 2 litres a minute (Harvey et al. 1968), and placental blood-flow in severely dehydrated women may well fall below a critical level. Fetal ischæmia may be further aggravated by the slight but definite decrease in maternal arterial oxygen saturation (Harvey et al. 1968). Fetal acidosis may be an added detrimental factor: the arterial pH of cholera patients in shock is often in the 7·0–7·2 range (Carpenter et al. 1966b, Harvey et al. 1968), and maternal acidosis may produce a disproportionate lowering of fetal pH (Goodlin and Kaiser 1957).

The findings therefore indicate that most fetal deaths in cholera patients occur within the first twenty-four hours of the onset of illness, when fulminating watery diarrhœa

leads to profound hypotension and acidosis. The fetal wastage associated with cholera probably cannot be significantly reduced by therapy in the hospital. Prevention of the disease in the mother, either by vaccination, a safe procedure in pregnancy (Freda 1956), or by antibiotic prophylaxis in epidemic situations (McCormack et al. 1968), seems to be the only effective way of reducing fetal losses. Our observations also indicate that little would be gained by induction of labour or therapeutic abortion, as has been suggested in the past (Pollitzer 1959), since maternal mortality should be negligible with intravenous therapy alone.

Data based on admissions to our hospital over four and a half years indicate that an associated pregnancy was more common in cholera patients than in those with non-choleraic diarrhœas. While it is possible that pregnancy enhances susceptibility to infection with *V. choleræ*, incidence data based on hospital admissions are often biased, and observations based on surveillance of entire population groups will be required to verify whether a significant association exists.

The causes of the increased severity of cholera in the third trimester of pregnancy and the possible increased incidence of cholera in pregnancy are obscure. Many profound anatomical, physiological, hormonal, and immunological changes take place in pregnancy. The effect of any or several of these changes in combination on cholera is not known. Studies of experimental cholera infection in pregnant animals have not (to our knowledge) been performed.

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IMMUNE COMPLEXES IN THE NEPHROTIC SYNDROME OF AFRICAN CHILDREN

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Summary Renal-biopsy specimens from Nigerian children with the nephrotic syndrome were studied by fluorescence microscopy after staining with fluorescein isothiocyanate-labelled antibodies against human immunoglobulins and complement (β-1-C). In all patients bound immunoglobulin and complement were observed, characteristically in the form of granular deposits along the glomerular capillary walls. Electron microscopy showed deposition of immune complexes along the epithelial side of the glomerular basement membrane, and reactive changes in epithelial and endothelial cells. Antibody eluted from the kidney of one patient gave precipitates with preparations containing *Plasmodium malariæ* antigens, but no reaction with *P. falciparum* or normal kidney antigens. Immune complexes containing *P. malariæ* antigen are thought to play a causal role in the ætiology of the nephrotic syndrome of African children.

Introduction

ALTHOUGH the nephrotic syndrome of African children has been well characterised from the clinical and pathological viewpoints (Hendrickse and Gilles 1963, Hendrickse 1966, Edington and Mainwaring 1966, Kibukamusoke and Hutt 1967), and its association with *Plasmodium malariæ* infection has been established (Giglioli 1962 a, b, Gilles and Hendrickse 1963, Kibukamusoke et al. 1967), the pathogenesis of the renal lesion is still imperfectly understood.

It is widely believed that human glomerulonephritis is an immune disorder, and animal experiments have revealed two distinct mechanisms by which antibody in the host can cause glomerular damage (Unanue and Dixon 1966). The first is based on the production by the host of antibodies capable of reacting with its own glomerular basement-membrane antigens. The second depends on the formation by the host of antibodies that can react with non-glomerular endogenous or with exogenous antigens to form circulating antigen-antibody complexes which are trapped in the glomerular capillary walls. Either of these processes concentrates an antibody-antigen reaction in glomeruli, where in the presence of an amplifying mechanism—often involving complement and polymorphonuclear leucocytes—it can produce inflammation and injury. In laboratory animals glomerulonephritis of the immune-complex type is characterised by the presence of host immunoglobulin and complement in a characteristic distribution in the glomeruli, where they are recognisable by fluorescence microscopy with the appropriate fluorescein-labelled antisera (Unanue and Dixon 1966).

Sera of animals and man with acute malarial infections often have "soluble" antigens demonstrable by precipitation in agar—e.g., the antigens described in African children with *P. falciparum* malaria (McGregor et al. 1968). These serum antigens are probably of parasite