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TRICHOMONAS VAGINALIS IN PREGNANCY THE RESULTS OF METRONIDAZOLE THERAPY ON THE MOTHER AND CHILD

BY

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ONE hundred and twenty-five years ago Donne (1836) the French investigator, first described the *Trichomonas vaginalis*. Hoehne (1916) eighty years later adopted the view that *Trichomonas vaginalis* was an aetiological factor in vaginitis. Little progress, when compared with other organisms, has been made in its biological, biochemical and epidemiological history. Recent conventions in Paris, Montreal and London have contributed to a more widespread knowledge of the organism and its clinical significance. Improved cultural techniques have aided human and animal experimentation. It has been proved that the organism remains viable outside the host over longer periods than were previously considered possible. Burch and his colleagues (1959) cultured the organism from damp infected towels up to twenty-five hours. Whittington (1957) cultured the protozoa from infected bakelite lavatory seats after forty-five minutes at room temperature.

The pathogenicity of the organism is still debatable. Many investigators regard it as non-pathogenic, in view of its recovery from normal vaginas in asymptomatic cases, pathogenicity developing under certain conditions. Moore and Simpson (1954) regarded emotional upsets of great importance. Other suggested factors are intercurrent infections, hormonal changes and trauma either from the use of contraceptives or sexual intercourse. Spontaneous clinical cures are known to occur.

INCIDENCE IN PREGNANCY

Most investigators agree that the incidence of infection is higher in the pregnant than the non-

pregnant woman. Trussell (1947) found 28.9 per cent of 433 pregnant women infected, compared with 17.9 per cent of 703 non-pregnant cases. In pregnancy the higher incidence is probably due to: discontinuation of contraceptives, many of which are trichomonocidal (Whittington, 1951), a tendency for more frequent sexual intercourse in the early months of pregnancy (especially amongst prostitutes), local hormonal changes and the emotional upsets in unwanted pregnancies. The trichomonas has not in the past been considered as a cause of abortion. However, studies of aborted women and the products of abortion might prove interesting. The trichomonas-foetus occurring in cattle may cause a balanitis in bulls, and pyometra, abortion and sterility in cows. Although estimated to affect less than 0.5 per cent of cattle, this organism has been demonstrated in the amniotic fluid of the aborted calf.

The protozoa have been reported far more commonly in coloured patients, either pregnant or non-pregnant. This higher incidence may be due to overcrowding, sexual promiscuity and the lack of contraception.

COMPLICATIONS ASSOCIATED WITH TRICHOMONIASIS OF PREGNANCY

Psychological

Many women may develop a fear of venereal disease, or that their pregnancy is not proceeding normally.

Clinical

(1) Widespread condylomata acuminata due to a virus may develop as a result of the

hyperaemia and moisture of the trichomonal infection.

(2) A blood-stained discharge may develop due to an acute vaginitis or an acute cervical erosion.

(3) Urethritis and an associated cystitis may be responsible for increased frequency of micturition and lower abdominal discomfort. The protozoa have been demonstrated in the pelvis of the kidney; extension to the renal pelvis would be more prone to occur if a physiological hydro-ureter of pregnancy existed.

(4) Painful urethral carunculosis may accompany the urethritis.

Seitz (1919) and Carretti (1938) suggested that the presence of the trichomonad increased the puerperal morbidity rate. Neumann (1926), Crown (1933) and Trussell *et al.* (1942) have not confirmed this. This infection should however be considered in cases of pyrexia associated with a foul lochial discharge developing three to four weeks after confinement.

TECHNIQUE OF DIAGNOSIS

Trichomonas vaginalis is the only flagellated protozoon known to occur in the vagina. Diagnosis may be made by the immediate examination of wet preparations, by culture or by stained films. Wet preparations are prepared by mixing a little of the vaginal discharge with a small amount of normal saline, and examining under the 1/6 lens. To facilitate recognition of the organism Safranin dye may be added to the normal saline to make an 0.1 per cent final dilution. The discharge is collected from the posterior vaginal fornix and the vaginal mucosa in its vicinity, either by a probe, platinum loop, pipette or spoon. Warming of the slide will enhance motility of the organism if the latter is sluggish. Cultural methods may be employed where facilities for immediate examination are not available, in the transport of specimens to a central laboratory or to confirm doubtful cases. A sterile probe may be dipped in the discharge and put directly into Stuart's carrying media, whence later it will be transferred to the special media, or put immediately into the special media such as Whittington's. The staining of smears is time-consuming and requires a great

deal of practice to get good results. The best results are obtained by making a very fine film of diluted discharge on a warm slide, or by fixing the smear with Osmic acid vapour (which is expensive) or by using Meyer's egg albumin. The smear can then be stained later by Leishman's or Giemsa's method.

In female clinics the organism may be demonstrated from the vagina, urethra, Skene's or Bartholin's glands and from urinary sediment after careful centrifuging. Allen and Butler (1946) demonstrated the organism in urine in 21 per cent of 234 cases of female trichomoniasis. Failure to examine extra-vaginal foci is responsible for many clinical relapses. Ideally, all male partners should be examined and treated, in some circumstances empirically. In men the organism may be found in the following sites: the urethra, sub-preputial sac, prostate gland, bladder, and occasionally in the seminal fluid.

TREATMENT PAST AND PRESENT

Local therapy has been the standard treatment in the past. Results were good where the trichomonad was confined to the vagina. Where other foci were involved re-infection of the vagina was common. Many of the preparations formerly used contained Acetarzone, an arsenical derivative. Pregnant women are known to be sensitive to arsenic. It was found that many cases treated by these drugs developed either a local or generalized dermatitis, the latter occasionally simulating German measles. Cases of encephalitis have also been described. Male partners in some instances developed local reactions to the pessaries.

An effective systemic treatment, whereby all foci of infection would benefit, is undoubtedly the answer to the problem. Recently surveys have been conducted in this country and abroad, using the new oral drug Metronidazole. The consensus of opinion is that it is an excellent preparation, although it is not an invariable cure. The majority of the female cases were non-pregnant.

CHEMICAL COMPOSITION OF METRONIDAZOLE

Metronidazole, now designated Flagyl, is a nitro-derivative of imidazole with a formula of

1-B hydroxyethyl-2 methyl-5 nitroimidazole. It is supplied in tablets containing 200 mg. of metronidazole. As it is a nitroimidazole the drug was given initially to non-pregnant patients. In the labour survey it was found that there was increased absorption of the drug in those patients in whom gastric lavage had been previously carried out before oral treatment was commenced (MG-N, G-N, P-R, R-G). Tablets were given after meals to the pregnant women.

In vivo studies of Flagyl on the *Treponema pallidum* were done in the department, in view of the increase of acute infectious syphilis in this country. The drug appears to have no treponemacidal properties.

SURVEY

PART I. ANTENATAL SERIES

Flagyl has no contraceptive action. Pregnancies have occurred during the observation periods following upon therapy; in 2 cases of previous sterility conception took place at 6 and 8 weeks respectively after the completion of the course of tablets. Examinations of seminal fluid, conducted in the male department on men receiving therapy, showed normal spermatogenesis.

In all, 65 pregnant women suffering from trichomoniasis have been treated with Flagyl and 16 of these patients have now had normal confinements with healthy babies. One patient had a seven-month baby which lived three days. Death occurred as the result of oesophageal atresia and cerebral haemorrhage. In this case Flagyl was administered for seven days at the fifth month of pregnancy; but it was not considered to be the cause of the congenital condition.

No serious toxic effects have been noted, and no skin eruptions have been encountered. In two cases therapy was discontinued, one because of profuse vomiting, the other because of acute abdominal pain. Both conditions subsided when the drug was stopped. Minor upsets occurred as follows: 5 cases of nausea, 3 of lower abdominal pain (one had loose motions), 2 cases of bitter taste in the mouth, and 3 patients reported with dirty furred tongues. Yeasts were

cultured from all affected tongues. Flagyl is secreted in the saliva and it is possible it may precipitate a fungoid condition.

The vaginal flora was graded as recommended by Schroeder.

Grade	Vaginal Smear	No. of Cases
I	Lacto-bacilli present	2
II	Lacto-bacilli and other bacteria	19
III	Bacteria other than lacto-bacilli	44

Regime of Survey

A general medical overhaul was carried out in all cases, including blood tests, urine and blood analyses and followed by a genital examination to exclude any concomitant infection.

Any patient with a past or present history of renal infection, low haemoglobin estimation or a previous history of eclampsia was excluded. Full co-operation of the patient in taking the tablets as advised, and the need for regular attendance were also stressed. Two patients were given 21 Flagyl tablets, one tablet three times daily for seven days. They were re-examined at the end of treatment and whenever possible at 2, 3, 4, 6, 8, 12, 16 and 20 weeks after their initial attendance. In some instances attendances were more frequent because of some other complicating factor. Intercourse was discouraged or the use of a sheath advised. Patients were advised to report back immediately if they developed symptoms of severe nausea, mouth or throat infections or any febrile condition which might suggest an agranulocytosis.

A significant study was only applicable in 40 of the cases, either through default, irregular attendances change of address or transference to other clinics or to their own doctor's care.

In the survey of the 40 patients, 8 were found to have concomitant gonorrhoea (20 per cent), 12 moniliasis and 6 condylomata acuminata. The oldest patient was aged forty years, the youngest sixteen. The average age was twenty-six years. There were 21 married and 19 single girls.

Previous pregnancies	0	1	2	3	4	5	8
Number of cases	17	7	6	6	1	2	1

Duration of Pregnancy at Commencement of Treatment		Number of Cases
1 week	2
6 weeks	2
2 months	6
3 months	3
4 months	3
5 months	5
6 months	7
7 months	2
8 months	6
8+ months	4

Special Investigations

Estimations of the drug in serum and urine were only performed in a few cases; the results closely resembled those found in non-pregnant women.

White blood counts were not routinely carried out in Survey I or II, as it was discovered that the counts were too variable to be of any value, especially on the out-patients. In pregnancy the white count is complicated by the fact that a leucocytosis of 12–15,000 per c.mm. is common but not constant. At parturition the count often rises to 25,000. High counts are usual in primiparae, especially in the last month of pregnancy. On the first day after delivery the count may be 17,000 per c.mm. and within a week fall to 10,000. A digestion leucocytosis is said not to occur during pregnancy.

Results of Treatment

There was no apparent relationship between parity or the duration of pregnancy and the subsequent clinical response. An excellent response after one course of treatment was obtained in 32 patients (80 per cent). The overall cure rate after three patients responded to a second course of tablets was 88 per cent. Spermatozoa were carefully looked for where the response to treatment was poor.

Re-infection was probably the cause of failure in 4 of the patients, 2 prostitutes who always demonstrated spermatozoa in their smears, and 2 married women who continued to have regular marital intercourse. Unfortunately both husbands refused examination or empirical treatment. Two patients with associated massive condylomata acuminata, responded to treatment only after their warts had been surgically removed. It is possible in these cases that the protozoa hide deep in the clefts of the warts and escape contact with the drug. Associated urethral warts may be responsible for re-infection of the vagina.

One patient with severe nausea and vomiting was a clinical failure due to non-absorption of the drug.

Two other failures were noted in patients with a concomitant heavy vaginal moniliasis. These cases were subsequently treated by painting the genitalia internally and externally with gentian violet and using Penotrane pessaries locally. Both drugs have trichomonocidal properties so further assessment in respect of Flagyl was invalid. On examining mixed cultures I have demonstrated in one instance trichomonads adhering by their axostyles to mycelia. It may well be that those protozoa resist or escape treatment. Where yeasts are abundant, it might be advisable to clear up this condition before commencing treatment with Flagyl which has no effect on the *Candida albicans*. Scott Gray and Murrell (1961) suggested that there might be a tendency to a slight increase of moniliasis with this drug.

A delayed clinical response was noted in one patient exhibiting an extensive acute bleeding cervical erosion. After painting the cervix with iodine and alcohol the response was good.

Observation Period

In December, 1960 only 26 patients in this survey were able to attend the clinic; others were recently confined or unfit to travel. The observation period of these patients was as follows:

Time in months	2	3	4	5	6	7
Number of cases	8	9	4	3	1	1

PART II. FLAGYL AND THE BABY

When this survey was conducted a few months ago, the effect of Flagyl on the foetus and the breast-fed infant was not known. No animal experimentation had been performed to determine whether a placental barrier to the drug existed. In view of the composition of the drug, this survey was considered advisable. The paediatricians were also interested as this drug, if used carelessly, might be responsible for unexplained cases of icterus gravis occurring in hospital or general practice.

Twenty-six women admitted to hospital either in the early or late stages of labour were given Flagyl, one tablet three-hourly until delivery. No side-effects were noted in any of the mothers. Maternal blood and urine were

collected towards the termination of labour. Blood was immediately collected from the umbilical cord and baby urine was collected by means of plastic bags as soon as possible after birth.

Estimations of urine and blood levels were performed on 24 patients on specimens collected during labour; estimations were purposely delayed in 2 cases for 24 and 36 hours after confinement. A careful watch was kept on these patients and their infants while in hospital and later as out-patients.

This survey shows that there is no placental barrier to the drug. The rates of clearance in both mother and child were rapid. Within twenty-four hours the concentration level was minimal and complete clearance had occurred in

TABLE I

Case Record	Maternal				Baby				
	Age	No. Tablets Taken	Specimen Collection Times	Polarographic Assay g.		Sex	Polarographic Assay g.		
				Serum	Urine		Serum	Urine	
T-S ..	35	5	Labour	6.4	850	F	4.3	60	
W-N ..	27	6	36 hours A-L	0	0	M	0	0	
N-S ..	25	6	28 hours A-L	0	0	M	0	5	
T-L ..	36	6	24 hours A-L	1.0	5	F	1.2	—	
C-N ..	30	4	Labour	6.6	440	F	6.0	40	
MD-L ..	26	2	Labour	2.9	340	M	2.8	—	
C-S ..	20	2	5 hours A-L	4.3	75	F	3.7	—	
MGN-N ..	31	6	Labour	9.4	820	F	10.5	40	
G-N ..	24	6	Labour	18.0	860	F	16.6	100	
L-Y ..	39	3	Labour	7.5	90	F	5.4	—	
O-T ..	30	4	Labour	3.6	100	F	2.3	—	
C-L ..	22	5	Labour	3.7	350	F	4.5	—	
S-N ..	27	2	3 hours A-L	—	50	F	—	—	
A-I ..	18	3	Labour	4.5	410	F	4.5	—	
B-W ..	20	2	Labour	4.1	30	F	2.5	15	
D-E ..	27	2	Labour	4.9	140	F	5.9	—	
P-R ..	25	6	Labour	19.5	530	M	16.9	430	
PQR ..	23	8	10 hours A-L	5.4	No spec.	M	9.2	No spec.	
DN-N ..	29	4	2 hours A-L	6.3	410	M	5.2	10	
R-G ..	23	4	Labour	22.7	70	M	20.2	—	
F-T ..	30	9	Labour	5.1	430	M	5.2	—	
R-Y ..	25	4	Labour	7.4	450	F	10.7	90	
C-E ..	27	12	Labour	5.6	500	M	3.0	140	
R-D ..	24	33	Labour	9.5	No spec.	M	6.8	No spec.	

M=Male. F=Female. A-L=After labour. No spec.=No specimen.

thirty-six hours. Many of the baby urines, because of natural delay in their collection, showed no concentration of the drug, although the initial foetal serum level had been high.

It was of particular interest to observe with what ease the drug was absorbed during labour, as I had been informed by senior obstetrical colleagues that very little absorption occurs during labour with some drugs taken by mouth.

The results of treatment had no relationship to the patients' age (oldest 39 years, youngest 18 years), parity or sex of child. The confinements were all normal with healthy babies.

The concentration results are presented in Table I.

In view of the above findings it is unlikely that any damage to the child would take place after birth as the drug was excreted rapidly by the infant.

Serum bilirubin estimations were carried out in some cases. The average maternal level was 0.6 mg. per cent, the average baby level being 0.9 mg. per cent. Those levels were well within the safety zones. A trace of urobilinogen was found in most of the maternal and baby urines.

Macroscopic placental examinations were normal in all cases. Three placentas were histologically examined. The chorionic villi were found to be normal in size, but in one case it was noted that the capillaries were more numerous and congested. Further histological examinations are required to show if this finding is of any significance.

Flagyl and Breast-Feeding

I have proved in a recent series that Flagyl is secreted in breast milk—these results are being published at a later date. The amount absorbed by the infant is being personally investigated.

Puerperal Vaginitis

Many women report with a trichomonal vaginitis after a recent confinement. The onset of clinical symptoms in a previously asymptomatic case may be due to the presence of the lochia acting as a good culture medium, or to the resumption of sexual intercourse.

SUMMARY

Metronidazole is a new oral trichomonacide of undoubted value. In a survey of 40 pregnant women the cure rate was 88 per cent. This percentage could be raised if all the male partners were examined and treated simultaneously with their female contacts. It is specific for *Trichomonas vaginalis*. The drug has no contraceptive and no apparent treponemacidal action. A definite diagnosis of *Trichomonas vaginalis* must be made before commencing treatment.

In view of the absence of a placental barrier, and the high concentrations sometimes found in the newborn child, this drug must be used with care and under medical supervision. Courses of treatment should never be prolonged beyond ten days. A second course may be considered in certain cases of failure.

Indiscriminate use of the drug may cause severe toxic symptoms, the formation of resistant strains of the protozoa and lack of faith in a specific trichomonacidal drug. In my series and routine clinical treatments, I have encountered no such toxic symptoms.

In these two separate surveys all confinements up to date have been normal and the babies healthy. Special attention must be paid to the drug when the mother is breast-feeding.

Flagyl has many advantages over local therapy. In the later stages of pregnancy there may be difficulty in inserting pessaries; also there may be risk of introducing infection. When a co-existing gonorrhoea is present, there is greater risk of spreading infection to others or to the eyes if pessaries are used.

The 96 patients involved in these surveys preferred oral treatment to local pessaries, although Flagyl is not an invariable cure. Patients were advised to swallow the tablets whole, as mouth symptoms were more prone to develop if they disintegrated.

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