

METRONIDAZOLE AND PREGNANCY*

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Since metronidazole is so widely used, it is important to know whether there is any risk from giving the drug during pregnancy. Many drugs are now withheld during early pregnancy, unless their administration is considered essential. There are, however, patients to whom drugs are given before the existence of pregnancy is recognized. In such cases there may be risks of foetal malformations.

Apart from the study by Scott-Gray (1964), there have been few reports of the outcome of pregnancies in which metronidazole was given to the mother in the first trimester. The present report describes some findings at The London Hospital which, although limited as regards numbers, were thought worth reporting in the hope that others would record their own experiences.

Material and Methods

During 1961 and 1962, 78 pregnant patients received metronidazole in doses of 200 mg. three times daily for 7 days. Most were attending the Whitechapel Clinic but a small number were treated at the ante-natal clinic. Most of the babies were delivered at hospitals other than The London Hospital and information regarding the pregnancies and babies was obtained from the records at these hospitals or by visiting the patients. The duration of pregnancy when the drug was given was dated from the first day of the last menstrual period. In 1962 and subsequently, comparatively few patients were given the drug because it became the policy of the clinic to avoid its use during pregnancy until more information about its effects was available.

Results

The outcome of the pregnancy was known in 61 cases. The remaining seventeen women could not be traced. The stage of pregnancy when treatment was given in the 61 cases is shown in Table I. Ten received the drug in the first 8 weeks of pregnancy.

57 patients gave birth to living full-term infants with no congenital malformations.

TABLE I
STAGE OF PREGNANCY OF 61 PATIENTS

Trimester			Number		
1st	..	4 wks .. 5-8 wks .. 9-12 wks ..	3 7 3	13	
2nd			29
3rd			19

Three gave birth to premature stillborn infants but none showed any malformations. In two instances the stillbirth occurred 8 weeks and 6 months respectively after treatment with metronidazole. In the other, a retroplacental haemorrhage occurred 3 days after starting metronidazole, but the patient had hypertension and was also receiving intravenous iron injections.

One patient, who was treated in the fifth month of pregnancy, gave birth to a full-term infant who suffered from white asphyxia and could not be resuscitated. No malformations were found *post mortem*.

Discussion

Although several workers have mentioned that they have given metronidazole to pregnant patients without ill-effects, relatively few have mentioned the stages of pregnancy at which the drug was given. Trials undertaken in ante-natal clinics are likely to include patients mainly in the second and third trimesters of pregnancy. Scott-Gray (1964) reported a large series in which 79 patients were treated in the first trimester, but did not state how many of them were treated in the first 8 weeks which is the period in which organogenesis takes place.

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The results reported by various workers are shown in Table II. In no instance could any congenital malformation be attributed to the drug and the incidence of malformations was no higher than that expected by chance. However, there is no information about effects, such as deafness, which would not be detected until some time after birth.

Animal experiments performed by Cosar, Ganter, and Julou (1961) failed to show any deleterious effects on the foetuses of rats given 50 to 100 mg. per kg. metronidazole daily by mouth. Ingham (1963), using rabbits and rats, also failed to show any teratogenic action.

Summary

No instance of congenital malformation was observed in the infants of 61 mothers who received metronidazole during pregnancy; thirteen mothers were given the drug in the first 12 weeks of pregnancy.

Sufficient evidence is available to indicate the safety of metronidazole when given in the second and third trimesters of pregnancy. Although there is no evidence of deleterious effects of the drug when given in the first trimester, there are as yet too few reported cases to be certain of its safety. It is hoped that other workers will report their findings.

TABLE II
OUTCOME OF PREGNANCY IN PATIENTS TREATED WITH METRONIDAZOLE

Authors	Date	Daily Dose (mg.)	Days of Treatment	Total Treated	No. in first Trimester	No. with known Outcome	Foetal Death or Abnormality
Robinson and Johnston ..	1961	500	10	100	Not stated	93	1 with hydrocephalus 1 with umbilical hernia 1 with skin tag on ear
Watt and Jennison	1962	600	7	23	Not stated	19	1 with anencephaly 1 non-surgical abortion
Schram and Kleinman ..	1962	500	10	26	Not stated	26	1 stillbirth 5 weeks after treatment
Williams	1962	1000	10	14	Not stated	*?14	None
Zacharias, Salzer, Gunn, and Dierksheide	1963	1000	10	39	Not stated	34	1 stillbirth (Rh. incompatibility)
Monroe	1963	100-1000	10	25	10	?25	None
Lyon, Sinykin, and Barr ..	1963	500-750	10	11	3	9	None
Perl and Ragazzoni ..	1963	750	10	100	6	49	None
Andrews and Andrews ..	1963	500	10	27	7	19	2 abortions
Narang, Bhargava, Chohan, and Rao	1963	600	7	14	Not stated	?14	None
Whitelaw, Fox, and Schlichting	1963	750	10	5	1	5	None
Csonka	1963	600	7-10	21	Not stated	7	None
Gardner and Dukes	1964	1000	5	18	Not stated	?18	None
Pereyra and Lansing	1964	750	3-10	42	None	?42	None
Kotcher, Frick, and Giesel ..	1964	1000	10	36	None	35	1 with "crooked feet" (mother treated in third trimester) 1 abortion (foetal heart not heard for 1 month before treatment)
Scott-Gray	1964	600	7	295	79	290	1 with anencephaly } All mothers 1 with microcephaly } treated in 1 with multiple defects } late pregnancy 1 with hydrocephalus } 2 non-surgical abortions (1 mother had Rh. incompatibility and 1 had heart disease) 6 stillbirths (2 cord strangulation, 3 pre-eclampsia, 1 anencephaly)
Parker, Thomas, and Jones ..	1965	500-750	10	36	Not stated	?36	None
Rodin and Hass	Present study	600	7	78	18	61	3 stillbirths (none showed malformations)

* ? Before a number indicates that it is not clear from the report that all these patients were followed.

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La metronidazole et la grossesse

RÉSUMÉ

Aucun cas de malformation congénitale n'a été observé chez les bébés de 61 mamans qui avaient reçu de la métronidazole pendant la grossesse; 13 mamans avaient pris le médicament pendant les premières douze semaines de la grossesse.

Il y a suffisamment de preuve pour indiquer que la métronidazole peut être donné sans risque pendant le second et le troisième trimestre de la grossesse. Quoiqu'il n'y ait pas de preuve d'un seul effet nuisible quand le médicament est donné pendant les premiers trois mois de la grossesse, il y a jusqu'à présent trop peu de cas rapportés pour être certain de son innocuité. Il est à souhaiter que d'autres observateurs publieront leurs conclusions.