

## METHYLDOPA IN HYPERTENSION OF PREGNANCY

by

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The advent of powerful and effective hypotensive drugs has made it relatively easy to control the systemic hypertension associated with pregnancy toxæmia. In spite of good control of blood pressure, the perinatal mortality in toxæmic women has remained well above the normal value, although usually less than in untreated patients. Recently, favourable reports have appeared on the use of methyldopa, either alone or in combination with a thiazide drug, in hypertensive pregnant women (Hans and Kopelman, 1964; Kincaid Smith *et al*, 1966; Leather *et al*, 1968). Harley (1966) opined that it is possible that the use of hypotensive drugs other than methyldopa may actually have a deleterious effect on the foetus.

In India, the perinatal mortality in toxæmia of pregnancy is even higher than it is in Western countries. We thought it worthwhile therefore to

study the therapeutic efficacy of methyldopa in hypertension associated with toxæmia of pregnancy.

### *Material and Methods*

The series consisted of 25 women who were found to have a diastolic blood pressure of 90 mm. Hg. or above, when examined at the antenatal clinic. All patients were admitted to hospital and put on complete bed rest and were sedated with phenobarbitone, 30 mg. three times a day. Patients were accepted for the study only if the diastolic blood pressure remained at 90 mm. or at higher level 24 hours after admission.

Blood pressure readings were recorded by the same observer throughout the entire study in all the patients. At all stages only the blood pressure in the sitting position was estimated. It was taken every morning at approximately the same time during the in-patient phase of therapy. The patients' weights were recorded every third day and the urine tested for albumin every day while they were in the ward, and at every weekly visit during the out-patient phase of treatment.

Methyldopa administration was begun the day after admission in a dosage of one tablet (250 mgm. each)

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twice a day. If the fall in blood pressure was inadequate, the dose of methyldopa was increased at two or three day intervals until a satisfactory blood pressure level was attained. After the blood pressure had remained under proper control for a week or more, patients were discharged and seen every week at the antenatal clinic. Ten patients were treated thus and were readmitted for delivery. The other 15 patients delivered while under treatment in the ward. All were closely followed during labour, and for a period of six weeks to six months post-partum subsequent to discharge.

All patients were maintained on a salt poor diet. Hydrochlorothiazide, 50 mg. daily or on alternate days, was given to 14 patients in whom a considerable degree of oedema persisted after several days of therapy with methyldopa, salt restriction and bed rest. Guanethidine was used in one patient who continued to have a high blood pressure in spite of 2 gms. of methyldopa daily.

Investigations done on admission included blood N.P.N., E.C.G., X-ray chest, fundoscopy and liver function tests.

Of the 25 patients, 10 were primigravidae, and of the 15 multiparous patients, 6 had a history of oedema during previous pregnancies. Their ages ranged from 18 to 35 years

(average 26 years). (Table I and II). The patients were grouped as mild, moderate and severe when the diastolic blood pressure was above 90 mm., between 90 and 100 mm. and above 100 mm. of Hg. respectively.

TABLE I  
*According to parity*

	Blood pressure		
	Mild	Moderate	Severe
Primigravidae	2	6	2
Gravida I to IV	-	3	1
Above V	2	5	4

TABLE II  
*Severity according to age*

	Blood pressure		
	Mild	Moderate	Severe
Upto 20	2	4	1
20-35	-	9	6
Above 35	-	3	-

None of our patients were first seen earlier than the twentieth week of gestation, so that it is not known which of them had elevated blood pressure during the earlier months of pregnancy, nor was any information available as to whether hypertension existed previous to the pregnancy, except for 2 patients who were known hypertensives (Table III).

TABLE III  
*Onset at weeks of gestation*

	Mild	Moderate	Severe
At & below 24 weeks	-	2	1
24 to 36 weeks	3	6	3
At and above 36 weeks	-	7	3



On admission, 17 patients had proteinuria, 7 of these had only a trace of albumin in the urine, and six patients had marked albuminuria, in 30 of which the diastolic B.P. was above 100 mm. Hg.

Eighteen patients had oedema, which was of marked degree in fifteen.

Fifteen had both proteinuria and oedema. The systolic blood pressure just before start of therapy varied from 130 to 180 mm. Hg. and the diastolic from 90 to 120 mm. Hg. The effect of other antihypertension drugs on foetal survival was compared with these patients in identical groups of severity of toxæmia.

## Results

### Hypertension

The average blood pressure before treatment, during treatment and after delivery was not significantly different in the group of patients treated with Methyldopa alone and in the group where hydrochlorthiazide was supplemented (Table IV).

The hypertension responded adequately to methyldopa (supplemented by hydrochlorthiazide in 14 patients). 24 of the 25 patients, could

be stabilized on a constant dosage, 17 patients required only 0.5 gm. of methyldopa daily while the other 7 received 0.75 to 1 gm. daily. The hypertension in one patient was partly refractory to methyldopa; even in a daily dose of 2 gm. adequate control was obtained in this case only after guanethidine, 10 mg. daily, was added to the methyldopa-hydrochlorthiazide regime.

### Proteinuria

Of the 17 patients with proteinuria a gradual reduction in urinary protein loss was observed in 12. Four of the remaining 5 patients who did not have any reduction in proteinuria delivered still-born babies.

### Oedema

In all but three patients the oedema gradually disappeared under therapy.

### Duration of pregnancy

Seven patients delivered at term, 12 at 36 to 38 weeks, 3 at 34 weeks one at 33 weeks, and 2 at 30 weeks.

### Foetal mortality

Twenty of the 25 patients delivered live babies, all of whom were alive

TABLE IV

Drug Therapy	No. of patients	Mean blood pressure			Foetal outcome
		Before treatment	During treatment	After treatment	
Methyldopa	11	140	137	121	2 S.B.
		100	90	83	
Methyldopa with Hydrochlorthiazide	14	150	136	115	3 S.B.
		93	90	77	

[illegible]



eclamptic fit, despite the fact that her blood pressure had been controlled at 140/90 just before the onset of labour. She delivered a still-born baby on the same day and for 4 days thereafter her blood pressure fluctuated between 140/90 and 200/120. One week after delivery the blood pressure had fallen to 140/80 and 6 weeks after delivery it was 130/80.

Another patient experienced a precipitous fall in blood pressure to 80/? mm.Hg. She subsequently suffered acute renal failure due to acute tubular necrosis from which she made a complete recovery.

### Discussion

Kincaid Smith's series (1964) of 32 hypertensive pregnant women consisted almost entirely of patients with more severe grades of hypertension who were known to have been hypertensive previous to the pregnancy. The blood pressure of these patients was adequately controlled throughout the entire period of gestation and this probably accounts for the fact that only 3 perinatal deaths occurred in the series. Kincaid Smith *et al* (1966) used methyldopa in a dose of 0.5 to 4 gm. daily. Seven patients also received chlorothiazide or reserpine.

Leather *et al* (1968) recently published the results of a controlled trial of methyldopa and bendrofluazide combination therapy in hypertension of pregnancy. Forty-eight patients were untreated controls, while 52 were treated with methyldopa, 0.5 to 2 gm. and bendrofluazide, 5 to 10 mg. daily. Leather *et al* (1968) classified 20 of his treated patients as 'moderate' (diastolic pressure 90 to 99 mm.

Hg.) and the other 32 as 'severe' (diastolic pressure 100 mm. Hg. or above).

There were 5 abortions and 4 perinatal deaths in the control group and 6 perinatal deaths (no abortion) in the Methyldopa group. Their results suggested (a) that hypotensive therapy improved the chances of a successful outcome to pregnancy in patients developing hypertension prior to the twentieth week of pregnancy while in late pregnancy hypertensives the benefit was minimal, (b) that proteinuria was a more important prognostic guide than the level of blood pressure.

All our pregnant hypertensives could be classified as 'mild to moderate' in severity according to Leather *et al* classification, since their diastolic blood pressure fell within the 90 to 110 mm.Hg. range. A large proportion of our charitable hospital class of pregnant women do not attend antenatal clinic at all while the rest usually make only a few antenatal visits during the later months of pregnancy. We are, therefore, unable to distinguish between early and late pregnancy hypertensives.

We found that the lowering of blood pressure levels to the desired range was usually easily accomplished with methyldopa (supplemented by hydrochlorothiazide in 14 patients). The therapeutic fall in blood pressure was usually prompt, occurring within 48 hours. When the initial dosage had to be increased, the increments could be made repeatedly at 2 or 3 days' intervals so that in nearly 11 cases the optimum blood pressure levels were attained within a week of admission.

There was no evidence of ill effects on the foetus in patients treated with methyldopa. The perinatal mortality rate was not reduced significantly in the group treated by methylopa as compared to the group treated with Methyldopa together with hydrochlorothiazide. It was seen that when the toxæmia was associated with proteinuria, the incidence of prematurity was increased and the birth weight of the baby was reduced. Leather *et al* (1968) opine that in hypertension in late pregnancy there is a negligible difference in length of gestation between treated and control group. This is also our observation. The vitality and neonatal progress of the babies of treated women was the same as those of the babies born of non-toxaemic mothers. Most of the stillbirths were associated with mothers having proteinuria. So it seems that more than treatment, the association of proteinuria influences the mortality and morbidity of the foetus.

Though the blood pressure was effectively controlled foetal salvage could not be improved. However, this cannot be considered conclusive as most of our cases came for treatment in late pregnancy.

### Summary

Methyldopa was used to treat the late pregnancy toxæmia in 25 women. The blood pressure could be efficiently controlled. There was no adverse reaction on the mothers or the babies.

The foetal salvage was not appreciably changed because of the treatment.

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