# Effect of oral antihypertensive drugs on the fetal and Uteroplacental blood flow

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- "I certify that this material has not been published previously and is not under consideration by another journal. I further certify that I have had substantive involvement in the preparation of this manuscript and am fully familiar with its content."

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**Running title**

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The study's protocol was approved by Institutional Review Board and ethical committee of faculty of Medicine, Menoufia University.

**Consent to participate**

Written informed consent was taken from all participants.

Data availability: available.

## Abstract

**Background:** PIH Complications may be related to placental insufficiency can be detected through uterine and umbilical arteries Doppler.

**Objective:** Was postulated to detect the impacts of α-Methyldopa and Labetalol on Doppler flow in fetal umbilical arteries and maternal Uterine arteries in females with gestational hypertension.

**Patients and methods:** 176 pregnant women with gestational hypertension who required oral antihypertensive drugs. underwent thorough history taking, physical examination and lab investigations. Obstetric ultrasound with Doppler ultrasound assessment of S/D ratio, Resistive index (RI) and Pulsatility index (PI) in both uterine and umbilical arteries was done as baseline before and after treatment.

**Results:** mean Uterine arteries RI, systole /diastole ratio showed a significant decrease while PI didn't show a significant difference. Umbilical artery RI showed a significant decrease, systole /diastole ratio and PI didn't show a

significant difference before and after treatment with Labetalol Mean Uterine arteries RI, systole /diastole ratio showed a significant decrease while PI didn't show a significant difference. Umbilical artery RI showed a significant decrease, systole /diastole ratio and PI didn't show a significant difference before and after treatment with α- methyl dopa.

**Conclusion:** Doppler studies of uterine and umbilical arteries revealed a significant decrease in RI and S/D ratio in uterine arteries blood flow with labetalol and methyl dopa therapy and a significant decrease in RI in umbilical artery blood flow after Labetalol and methyl Dopa treatment, these changes may be related to the vasodilatory effect of the antihypertensive drugs.

**Keywords:** Gestational hypertension, doppler, Labetalol, α- methyl dopa.

## Introduction

Gestational hypertension is known to be a systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg after twenty gestational weeks without proteinuria in previously normotensive pregnant female while chronic hypertension predates pregnancy. [1]

Pregnancy induced hypertension (PIH) includes 3 items, mainly gestational hypertension, pre-eclampsia and eclampsia. PIH may be complicated by Intra uterine growth restriction (IUGR), early neonatal deaths, intraventricular and pulmonary hemorrhage, periventricular leukomalacia, necrotizing enterocolitis and hypoxic ischemic encephalopathy. [2]

Complications may be related to placental insufficiency that can be detected by assessment of fetal and uteroplacental blood flow through uterine and umbilical arteries Doppler velocimetry study. [3]

Labetalol and α- methyl dopa are commonly used drugs for treating hypertension in pregnancy, their potential side effects are less clear. In-utero exposure to these agents has been associated with preterm labor, low birth weight and other perinatal morbidities. However most published studies are biased so fetal safety needs to be confirmed. [4,5]

## Objective

This study was designed to assess the impacts of orally administered antihypertensive drugs (α-Methyldopa, Labetalol) on Doppler flow in fetal umbilical arteries and maternal Uterine arteries in females with gestational hypertension.

## Subjects and Methods

This was a prospective observational study that was performed at the Department of Obstetrics and Gynecology in the University Hospital in Menoufia after obtaining institutional review board approval under number 2/2023OBSG20-1. Study started at February 2023 and ended in December 2024. All patients signed informed consent.

The study included 194 patients ;18 cases were dropped out, the remaining 176 pregnant women with gestational hypertension who required oral antihypertensive drugs with variable doses based on patients' blood pressure readings, patients were divided randomly by computer generated program into 2 groups

Group (I): 88 patients with gestational hypertension received oral α-methyldopa. Doses ranged between 500 mg and 3 gm daily.

Group (II): 88 patients with gestational hypertension received oral Labetalol. Doses ranged between 200mg and 800 mg daily.

**Sample size calculation**

Was calculated depending on previous studies, at 80% power, 95% CI, it was 88 subjects for each group.

**Inclusion criteria:**

Pregnant women suffering from gestation-

al hypertension between 28-32 gestational weeks were recruited. Gestational hypertension was diagnosed when systolic (≥ 140 mm Hg) and or diastolic (≥ 90 mm Hg) blood pressure persistently without proteinuria.

Singleton pregnancy, Live fetus with Intact chorio-amniotic membranes.

**Exclusion criteria:**

Medical diseases with pregnancy as pre-eclampsia, chronic hypertension, DM.

Twin pregnancy, Patients in active labor, Patients with premature rupture of membranes.

Intrauterine growth restriction (IUGR) and Fetuses with structural abnormalities.

## Methods

176 pregnant women with gestational hypertension who required oral antihypertensive drugs. All the included participants underwent thorough history taking, physical examination and lab investigations (CBC-Liver and Kidney Functions-Prothrombin time and urine analysis).

Obstetric ultrasound with Doppler ultrasound assessment of S/D ratio, Resistive index (RI) and Pulsatility index (PI) in both uterine and umbilical arteries was done as baseline before receiving the medications and after 1 week of receiving the medications when blood pressure readings became normal.

## Technique of scanning

A single operator did all examinations to prevent interobserver variability. Pregnant women were examined lying down in the prone position with a slight tilt to their left side, after 15 minutes of rest measurements were taken during fetal inactivity and apnea. Grey scale fetal biometry was obtained initially using B mode2-Dconvex probe, the fetal position was located, fetal biometry was done. Then color Doppler duplex was performed, measurements were done with by obtaining consecutive similar waveforms. Both the grey scale and color doppler duplex were performed using the convex abdominal probe with an ultrasonic machine (Voluson p6 color Doppler ultrasound diagnostic instruments, GE Healthcare, Fairfield, US) with an abdominal probe using frequency of 3.5 ~ 5 MHz; with the insonation angle as close to zero as possible. Machine Software measured the S/D ratio, RI and PI automatically.

**Uterine Artery:** examinations were done when patients were full bladder. Uterine artery was evaluated near the internal os crossing vertically 0n external iliac artery. Then Doppler velocimetry measurement was done. After obtaining multiple similar waveforms the image was frozen. The Resistance index, Pulsatility index and S/D ratio were obtained, the same was repeated with the other uterine artery then the mean was calculated. [2,6,7]

Umbilical artery: examinations were done at a free - floating loop of umbilical cord or at the site of insertion of the cord at the placenta to obtain the best quality signals from umbilical artery. The Resistance index, Pulsatility index and S/D ratio were measured.

## Statistical analysis

Was done with a personal computer of IBM with Statistical Package of Social Science (SPSS) version 20 (IBM Corporations, 2011), Armonk, NY and Epi Info 2000 programs, Data were collected, tabulated, statistically analyzed using the following statistics.

**a- Descriptive statistics:** quantitative data were presented as mean ($\bar{X}$), standard deviation (SD), range, median and interquartile range, and qualitative data were presented as numbers and percentages (%) Kolmogorov-Smirnov test and Shapiro-Wilk test were used to test the normality.

**b- Analytical statistics:**

**Wilcoxon test:** was used to compare different readings of not normally distributed data in the same group

## RESULTS

176 pregnant women were randomly allocated to daily treatment with α- Methyl Dopa (n. 88) group (I) or Labetalol (n. 88) group (II).

The reference values for Doppler indices of the Uterine Artery (UA) and umbilical artery were determined in normotensive pregnant women and significantly higher levels were seen in patients with Pregnancy Induced Hypertension (PIH). The reference values vary according to gestational age, with abnormal values detected when exceeding 95th percentile for the corresponding gestational age, for the gestational age 28-32 weeks, mean uterine artery PI was 0.72, mean RI was 0.48 and s/d ratio < 3. mean umbilical artery PI was 1.2, mean RI was 0.7 and s/d ratio < 2.8. [2]

Table 1: shows the characteristics of the recruited patients.

Mean maternal age was 29.7±6.1years, mean body mass index 26.5±4.2(Kg/m2) mean Gestational age (in weeks) was 30.3±1.3

Table 2: shows mean Uterine arteries (Rt and Lt) doppler indices before and after treatment with α- methyl dopa.

Mean Uterine arteries resistance index showed a significant difference (0.89±0.25 and0.69±0.12). mean systole /diastole ratio also showed a significant difference (2.45±0.47 and 2.1±0.11) while Mean Pulsatility Index didn't show a significant difference (0.79±0.129 and 0.78±0.16).

Table 3: shows Mean Uterine arteries (Rt and Lt) doppler indices before and after treatment with Labetalol.

Mean Uterine arteries resistance index showed a significant difference (0.88±0.26 and 0.70±0.11) mean systole /diastole showed a significant difference (2.49±0.44 and 2.2±0.098) while mean Pulsatility Index didn't show a significant difference (0.79±0.13 and 0.78±0.13).

Table 4: shows Umbilical artery doppler indices before and after treatment with α- methyl dopa.

Umbilical artery resistance index showed a significant difference (0.63±0.05 and 0.48±0.13). systole /diastole ratio didn't show a significant difference (2.45±0.33 and2.49±0.31) also Pulsatility Index didn't show a significant difference (0.77±0.16 and 0.77±0.14).

Table 5: shows Umbilical artery doppler indices before and after treatment with Labetalol.

Umbilical artery resistance index showed a significant difference (0.63±0.05 and0.42±0.09) systole /diastole ratio didn't show a significant difference (2.45±0.34 and2.47±0.31) also Pulsatility Index showed No significant difference (0.79±0.15 and 0.77±0.15).

## DISCUSSION

Hypertension during pregnancy is mostly related to vasospasm and defective trophoblastic penetration of spiral arteries leading to increasing the resistance of uterine artery and impedance to the blood flow in uterine arteries with impaired placental circulation. [4]

Uterine and umbilical artery doppler indices were found to be impaired in patients with PIH than in normotensive pregnant females as stated in Saleh et al., [6] and Aharwal et al. [ 2]

α-methyldopa therapy is sympatholytic agent that mediates its action through binding to alpha 2 adrenergic receptors inhibiting its action and reducing the vasoconstrictor signals. Also, it reduces the stiffness of the maternal arterial system as detected through pulse-wave analysis. [7]

Labetalol is a non-selective adrenergic blockade drug that has a direct vasodilatory effect leading to a decrease in peripheral vascular resistance. [8]

In This study the participants mean age was 29.7±6.1 years, mean gestational age for participants was 30.3±1.3 weeks, the mean BMI was 26.5±4.2 (Kg/m2).

In This study Doppler indices in Uterine arteries (Rt and Lt) were represented as mean

values by adding both measures in Rt and Lt branches then dividing by two.

mean Uterine arteries resistance index showed a significant decrease, systole /diastole ratio showed a significant decrease while pulsatility index PI didn't show a significant difference before and after treatment with Labetalol as shown in table 3.

These results agree with Baggio et al., [9] study which showed that the use of labetalol improved the blood flow in uterine artery due to a reduction of its PI and RI.

On the contrary, other previous studies didn't show any significant difference before and after Labetalol use. As in Yashodhara et al., [10] PI and RI of uterine artery insignificantly decreased after treatment with labetalol.

Lunell et al., [8] and Pirhonen et al., [11] studied the effect of labetalol on uteroplacental flow in patients with PIH. Doppler indices showed no change.

In this study Umbilical artery resistance index showed a significant decrease, systole / diastole ratio and PI didn't show a significant difference before and after treatment with Labetalol as shown in table 5.

On contrary, Mahmoud et al., [12] study showed no significant changes in color Doppler indices in umbilical artery after one week of labetalol use. Also, Yashodhara et al [10] stated that PI and RI of umbilical artery were insignificantly increased after labetalol use.

In this study, Uterine arteries (Rt and Lt) doppler indices before and after treatment with α- methyl dopa. revealed that mean Uterine arteries resistance index showed a significant decrease, systole /diastole ratio also showed a significant decrease while PI didn't show a significant difference. As shown in table 2.

These results agree with the study by Rey [13] he treated the patients with a dose of 750 mg α-methyldopa daily for 7 days and found a significant reduction of uterine artery PI.

Also Study done by Gunenc et al., [14] showed that uterine artery RI and PI were significantly reduced after methyldopa treatment.

On contrary Montan et al., [15] and Adiga et al., [16] Khalil et al. [7] studied Doppler flow before and after one week of methyldopa treatment, there was no change in uterine artery doppler indices.

In this study, Umbilical artery doppler indices before and after treatment with α- methyl dopa. RI showed a significant decrease, systole /diastole ratio and PI didn't show a significant difference as shown in table 4.

On contrary Study done by Gunenc et al., [14] showed no significant difference in PI and RI of umbilical artery after treatment with methyldopa, Montan et al., [15] showed no change umbilical artery indices after one week of methyldopa treatment. also, Yashodhara et al., [10] showed no significant doppler changes with methyl dopa.

The results of this study may be explained by the vasodilatory effect of antihypertensive dugs which relieve the uterine artery vasospasm which improve the uteroplacental blood flow and reduce the risk of severe hypertension leading to improvement in maternal outcomes.

This study results is contradictory to some of previous studies which evaluated the effect of methyl dopa and labetalol in patients with PIH this may be attributed to the difference in studied population as in this study only patients with gestational hypertension were included while patients with chronic hypertension and preeclampsia were excluded as the pathology may be more vigorous in cases with preeclampsia where there is intense failure of trophoblastic invasion and vascular lesions are more prominent than the situation in patients with gestational hypertension. Also, some previous studies were evaluating the effect of antihypertensives used through IV route during management of acute severe hypertension.

Advantage of this study is its dealing with patients with gestational hypertension only excluding cases with preeclampsia and eclampsia with the more severe pathological vascular changes. This makes the results of doppler changes mostly related to the effects of the studied drugs.

The limitation of this study is the assessment of uterine and umbilical arteries only without assessment of other fetal vasculature, also no follow up of patients was done to evaluate pregnancy outcome.

## CONCLUSION

Doppler studies of uterine and umbilical arteries revealed a significant decrease in RI and S/D ratio in uterine arteries blood flow with labetalol and methyl dopa therapy and a significant decrease in RI in umbilical artery blood flow after Labetalol and methyl Dopa treatment, these changes may be related to the vasodilatory effect of the antihypertensive drugs.

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**Table 1: Descriptive data of the recruited participants (no= 176)**

| Item | Frequency(no=176) | Percentage |
|---|---|---|
| **Age (in years)** | | |
| Mean ± SD<br>Min- max<br>Median (IQ) | 29.7±6.1<br>20-40<br>29.5(24-35) | |
| **Body mass index (Kg/m$^2$)** | | |
| Mean ± SD<br>Min- max<br>Median (IQ) | 26.5±4.2<br>19-33<br>27(23-30) | |
| **Gravidity** | | |
| Primigravida<br>Multigravida | 74<br>102 | 42.0<br>58.0 |
| **Gestational age (in weeks)** | | |
| Mean ± SD<br>Min- max<br>Median (IQ) | 30.3±1.3<br>28-32<br>30(29-31) | |
| **Medication** | | |
| Methyl dopa<br>Labetalol | 88<br>88 | 50.0<br>50.0 |

**Table 2: Mean Uterine arteries (Rt and Lt) doppler indices before and after treatment with α- methyl dopa. (no=88)**

| Items | Before | After | Test of significance and p-value |
|---|---|---|---|
| **Uterine artery systole /diastole** | | | |
| Mean ± SD<br>Min- max<br>Median (IQ) | 2.45±0.47<br>2-3.6<br>2.21(2.1-2.7) | 2.1±0.11<br>2-2.37<br>2.1(2.09-2.2) | Wilcoxon = 4.81<br>P =0.00** (≤ 0.001) |
| **Uterine artery resistance index** | | | |
| Mean ± SD<br>Min- max<br>Median (IQ) | 0.89±0.25<br>0.50-1.5<br>0.84(0.72-1.07) | 0.69±0.12<br>0.50-0.88<br>0.69(0.57-0.805) | Wilcoxon = 4.95<br>P =0.00** (≤ 0.001) |
| **Uterine artery PI** | | | |
| Mean ± SD<br>Min- max<br>Median (IQ) | 0.79±0.129<br>0.5-1.03<br>0.82(0.72-0.88) | 0.78±0.16<br>0.5-1.03<br>0.83(0.62-0.91) | Wilcoxon = 1.16<br>P =0.115 (> 0.05) |

**Table 3: Mean Uterine arteries (Rt and Lt) doppler indices before and after treatment with Labetalol.**
**(no=88)**

| Items | Before | After | Test of significance and p-value |
|---|---|---|---|
| **Uterine artery systole /diastole** | | | |
| Mean ± SD<br>Min- max<br>Median (IQ) | 2.49±0.44<br>2.1-3.6<br>2.3(2.2-2.6) | 2.2±0.098<br>2-2.37<br>2.1(2.1-2.2) | Wilcoxon = 6.93<br>P =0.00** (≤ 0.001) |
| **Uterine artery resistance index** | | | |
| Mean ± SD<br>Min- max<br>Median (IQ) | 0.88±0.26<br>0.50-1.5<br>0.85(0.69-1.07) | 0.70±0.11<br>0.50-0.88<br>0.71(0.61-0.805) | Wilcoxon = 6.02<br>P =0.00** (≤ 0.001) |
| **Uterine artery PI** | | | |
| Mean ± SD<br>Min- max<br>Median (IQ) | 0.79±0.13<br>0.5-1.03<br>0.80(0.69-0.89) | 0.78±0.13<br>0.5-1.03<br>0.81(0.69-0.89) | Wilcoxon = 0.594<br>P =0.552 (> 0.05) |

**Table 4: Umbilical artery doppler indices before and after treatment with α- methyl dopa.(no=88)**

| Items | Before | After | Test of significance and p-value |
|---|---|---|---|
| **Uterine artery systole /diastole** | | | |
| Mean ± SD<br>Min- max<br>Median (IQ) | 2.45±0.33<br>1.9-3.0<br>2.4(2.2-2.7) | 2.49±0.31<br>1.9-3.0<br>2.5(2.3-2.7) | Wilcoxon = 1.19<br>P =0.233 (> 0.05) |
| **Uterine artery resistance index** | | | |
| Mean ± SD<br>Min- max<br>Median (IQ) | 0.63±0.05<br>0.54-0.70<br>0.63(0.59-0.67) | 0.48±0.13<br>0.28-0.70<br>0.48(0.36-0.59) | Wilcoxon = 6.92<br>P =0.00** (≤ 0.001) |
| **Uterine artery PI** | | | |
| Mean ± SD<br>Min- max<br>Median (IQ) | 0.77±0.16<br>0.5-1.10<br>0.73(0.64-0.91) | 0.77±0.14<br>0.5-1.10<br>0.73(0.65-0.90) | Wilcoxon = 0.054<br>P =0.957 (> 0.05) |

**Table 5: Umbilical artery doppler indices before and after treatment with Labetalol. (no=88)**

| Items | Before | After | Test of significance and p-value |
|---|---|---|---|
| **Uterine artery systole /diastole** | | | |
| Mean ± SD<br>Min- max<br>Median (IQ) | 2.45±0.34<br>1.9-3.0<br>2.4(2.2-2.8) | 2.47±0.31<br>1.9-3.0<br>2.5(2.3-2.7) | Wilcoxon = 0.501<br>P =0.616 (> 0.05) |
| **Uterine artery resistance index** | | | |
| Mean ± SD<br>Min- max<br>Median (IQ) | 0.63±0.05<br>0.54-0.70<br>0.63(0.59-0.67) | 0.42±0.09<br>0.28-0.66<br>0.43(0.34-0.48) | Wilcoxon = 7.97<br>P =0.00** (≤ 0.001) |
| **Uterine artery PI** | | | |
| Mean ± SD<br>Min- max<br>Median (IQ) | 0.79±0.15<br>0.5-1.10<br>0.75(0.67-0.92) | 0.77±0.15<br>0.5-1.10<br>0.73(0.64-0.91) | Wilcoxon = 0.502<br>P =0.616 (> 0.05) |