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# The Use of Verapamil for the Prevention and Treatment of Hypertensive Complications of Pregnancy and Its Effect on Cardiohemodynamic Indexes

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A study is performed of the efficacy of verapamil for the prevention and treatment of late toxemia of pregnancy. The preparation is shown both to produce a therapeutic effect in developed pathology and to prevent the development of severe forms of hypertensive complications in women with high-risk pregnancies.

**Key Words:** *verapamil; hypertensive complications of pregnancy*

At present calcium antagonists are widely used in the treatment of arterial hypertension [2,3,5]. Hypertension in pregnancy develops mainly due to a change of calcium metabolism in membranes of platelets and vascular cells [7].

Calcium ions in the circulatory bed serve as a main second messenger transmitting the signal from a surface membrane receptor into the cell. The activity of calcium channels is controlled by hormones and transmitters regulating the exchange of phosphoinositides in membranes of platelets and vascular smooth muscle cells. Activation of vascular cells by vasopressive transmitters causes an excessive influx of calcium ions into the cell, structural changes of vessels, and an increase of the total peripheral vascular resistance (TPVR). The early detection of altered vessel reactivity in women predisposed to develop hypertension in pregnancy offers the opportunity to take timely measures to forestall the development of a pathological process. One possible way of preventing hypertensive complications is to stimulate the production of endothelial relaxation factors (prostacyclin and nitric oxide), thereby restoring the balance between intracellular cAMP and cGMP and phosphoinositide signal-transduction systems [4].

We used verapamil, a blocker of calcium-ion entry into vascular cells and platelets which acts to dilate peripheral vessels and inhibit platelet aggregation, to prevent severe hypertensive complications and treat pregnant women with arterial hypertension. Isoptin-retard-240 (sustained-release verapamil) (Knoll) was used in combined therapy and did not affect the hemodynamics.

The aim of the study was to examine the cardiohemodynamic effects of verapamil in pregnant women at high risk for late tox (LT) as well as in women with hypertension and with developed LT. The body-turn test is the most practical one for identifying women at high risk of developing severe hypertensive complications of pregnancy [6].

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## MATERIALS AND METHODS

Clinical observations were performed on 53 women aged from 17 to 42 years at 26-38 weeks of gestation. Verapamil was prescribed to 21 women to prevent the development of LT and to 32 women to treat LT and hypertension.

The first group consisted of 21 preventively treated women who had displayed a positive body-turn test in the second trimester of pregnancy. Extragenital pathology in this risk group was as follows: mixed hyperandrogeny (6 women), hyperfunction of the thyroid (3 women), type II diabetes mellitus controlled by diet (4 women), and the rest with stages I-II of obesity. The course of pregnancy in 14 women was complicated with threatened abortion.

Verapamil with sustained release was prescribed to pregnant women of the at-risk group at 120 mg *per os* once a day in the morning for 14.2±2.6 weeks.

Pregnant women with hypertensive complications were given verapamil at 240 mg twice a day during 6.5±1.2 weeks. Twelve women with stage I hypertension and without clinical manifestations of LT before verapamil treatment formed the 2nd group. The 3rd group consisted of 20 women with developed LT against the background of stage I-II hypertension, including 16 women with stage I and 4 women with stage II nephropathy. One in three women of this group had obesity. The course of pregnancy in 5 women was complicated with threatened premature labor.

Examination of the women included blood pressure recording (Korotkov method) and central rheography. The central hemodynamics was studied with a PA-9-01 polyanalyzer with subsequent calculation of the stroke volume (using Kedrov's formula), minute volume of the circulation, TPVR (according to the Frank-Poiseuille formula), and of the cardiac index. The mean hemodynamic pressure (MHP) was computed from Chickem's formula [1]. The women were examined in the fasting state in the half-sitting posture. The central hemodynamics was recorded prior to verapamil treatment, on the 10th-12th day of treatment, and before delivery.

## RESULTS

Indexes of the central hemodynamics prior to verapamil treatment, on the 10th-12th day of treatment, and before delivery are presented in Table 1. We see that the indexes of heart activity were lowered on the 10th-12th day of verapamil treatment in the 1st group. By the time of delivery the stroke volume had decreased by 15%, the heart rate by 18%, the cardiac index by 23%, and the minute volume by 16%. In this group the cardiohemody-

**TABLE 1.** Changes of Central Hemodynamic Indexes in Women Examined ($M \pm m$)

| Group of women | Before verapamil treatment | 10th-12th day of treatment | Prior to delivery |
|---|---|---|---|
| *MHP, mm Hg* | | | |
| 1st | 88.9±1.3 | 84.2±2.1 | 82.4±2.4 |
| 2nd | 96.9±1.4 | 93.6±1.9 | 87.2±1.6 |
| 3rd | 117.4±3.3 | 105.8±3.1 | 100.4±2.9* |
| *Heart rate, beats/min* | | | |
| 1st | 79.4±3.3 | 72.8±3.6 | 64.9±1.1* |
| 2nd | 82.2±2.2 | 71.3±3.1 | 72.4±4.3 |
| 3rd | 94.6±2.9 | 88.4±1.5 | 84.7±4.1 |
| *TPVR, dyn×sec×cm$^{-5}$* | | | |
| 1st | 1264.3±142.6 | 1328.2±86.4 | 1298.3±117.2 |
| 2nd | 1448.6±206.3 | 1011.3±78.2* | 964.2±108.7* |
| 3rd | 1772.4±109.1 | 1549.8±112.8** | 1428.4±93.5** |
| *Stroke volume, ml* | | | |
| 1st | 68.4±3.2 | 65.7±2.9 | 58.4±3.4* |
| 2nd | 69.4±2.4 | 62.5±4.3 | 62.8±3.3 |
| 3rd | 60.2±3.9 | 64.8±3.7 | 71.4±4.1* |
| *Minute volume of circulation, ml/min* | | | |
| 1st | 5882.7±168.4 | 5532.6±149.2 | 5192.1±154.2* |
| 2nd | 5996.4±172.2 | 5648.9±161.7 | 5321.8±133.7* |
| 3rd | 4832.2±201.7 | 5311.1±127.8 | 5612.1±154.2* |
| *Cardiac index, liters/min×m$^2$* | | | |
| 1st | 3.52±0.17 | 3.08±0.12* | 2.72±0.14** |
| 2nd | 3.62±0.09 | 3.27±0.08 | 3.12±0.11* |
| 3rd | 2.54±0.13 | 2.86±0.16* | 3.40±0.15** |

**Note.** *$p<0.05$, **$p<0.001$ as compared to the baseline values.

namic indexes dropped to the greatest extent in cases of hyperandrogeny and diabetes. In the majority of women MHP and TPVR did not change against the background of verapamil.

During the course of verapamil treatment of women of the 2nd group at the end of the third trimester, MHP dropped by 10%, the heart rate by 12%, and TPVR by 34%. Stroke volume, minute volume, and cardiac index decreased by 11.8% on average.

In the case of LT-complicated pregnancy in the 3rd group verapamil improved the indexes of heart activity by the 10th-12th day of treatment. At the end of the third trimester the stroke volume increased by 17%, the minute volume by 16%, and the cardiac index by 34%. Verapamil treatment lowered the heart rate by 11.8%, MHP by 14.5%, and TPVR by 19.5%. This effect was greater in women who had been suffering from hypertension for less than 3-5 years and less pronounced in patients with hypertension from a young age who, in addition, were overweight.

The comparison of the central hemodynamic indexes shows that verapamil affected them differently in women with hypertension and in women with LT. The hemodynamic indexes were lowered in women of the at-risk group with hypertension but without clinical manifestations of LT, whereas in LT stroke volume, minute volume, and cardiac index tended to rise. MHP decreased in all women and TPVR decreased predominantly in LT patients. Ultimately, all verapamil-treated women exhibited normalization of hemodynamic indexes by delivery.

At this time they had variously pronounced symptoms of LT. For example, 14 weeks after verapamil treatment (just before delivery) moderate edema was noted in 8 women and systolic pressure rose to 140 mm Hg in 2 women with diabetes mellitus in the group at risk. There was no proteinuria in this group. Thus, at the end of the third trimester stage I nephropathy had developed in 2 women treated with verapamil to prevent LT and 6 women had edema.

Among the 12 women with previous hypertension 5 had moderate edema by delivery. blood pressure had normalized in all of them.

All women with LT had edema before verapamil treatment, but it was most pronounced in 2 women with stage II hypertension. With verapamil treatment edema was preserved in all women, being increased in 2 women with stages I and II hypertension. Proteinuria was initially noted in 9 women, and in 4 of them with stage II nephropathy it was preserved at the time of delivery. The hypotensive effect of verapamil was most pronounced. Blood pressure had normalized in the 16 pregnant women with stage I nephropathy and had stabilized at the level of 140-150/90 mm Hg in 4 women with stage II hypertonic disease.

All pregnant women treated with verapamil successfully delivered. Among the deliveries 45 were full-term, 8 were induced prematurely at 36.12±1.27 weeks in view of the long-lasting combined LT, and 11 were by cesarean section. The mean weight of newborns was 3373.2±158.1 g in full-term births and 2891.3±102.6 g for premature deliveries. The state of all newborns was assessed as 7-8 points of the Apgar score. Perinatal mortality was zero.

Thus, verapamil prevents the development of severe forms of LT in women with a positive body-turn test and has a therapeutic effect in developed LT, namely it lowers blood pressure and TPVR, and normalizes the cardiohemodynamic indexes. In addition, verapamil sometimes promotes liquid retention in the organism.

Verapamil is more effective in cases where LT has developed against the background of hypertension. Verapamil with sustained release (Isoptin-retard-240) is effective at small doses given 1-2 times per day, a feature which is important for long pharmacotherapy of pregnant women at high risk for hypertensive complications.

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