Tivortin® in the therapy of placental dysfunction

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The issue of placental dysfunction has been a current problem in modern Obstetrics for a several decades already.

Currently, both in the society and in healthcare, there is a paradoxical situation in place. On the one hand, we have a technical possibility to prove the presence of foeto-placental problems (conventional ultrasound, Doppler ultrasound) and at least a partial understanding of pathogenesis in such problems. On the other hand, we refuse to respond with pharmacological prevention and therapy, while termination of pregnancy is used as the only way to solve these problems. The paradox lies in the fact that we are instructed to watch foetal deterioration passively and only when it reaches its climax (that is, the brink of foetal loss), we induce labour or otherwise deliver the foetus regardless of the gestational age [1]. When one considers the high cost of care in preterm neonates (especially at Weeks 22–32) and the rejection of mere efforts to manage circulatory disorders in the foeto-placental system (given the availability of positive therapeutic experience in our country), an idea suggests itself that this paradox might be explained by the lobbying of the corporate interests of large commercial medical centres.

Abnormalities at the stage of trophoblast invasion are known to be the principal pathogenetic mechanism behind placental dysfunction [2]. The related disruptions in the architectonics of the spiral artery walls causes the so-called flow mediated dilatation (FMD), a flow of mediated dilation responsible for increasing peripheral vascular resistance and blood flow disorders in the placental complex [3]. It is logical to assume that normalisation of peripheral vascular resistance will allow restoring the disrupted blood flow or will at least prevent further advancement of the process.

One more mechanism responsible for impaired haemodynamics in the maternal-placental-foetal circulation system is the emergence of endothelial dysfunction due to increasing serum levels of asymmetric dimethylarginine (ADMA), an inhibitor of nitric oxide [4].

The nitric oxide (NO), synthesised by endothelial cells, has been proved to be a regulator of vascular tone and an inhibitor of platelet aggregation [5]. Multiple studies from the viewpoint of evidence-based medicine, conducted by the cardiologists, neurologists, pathophysiologists and other researchers, have demonstrated the significance and efficacy of normalisation of NO levels for restoration of blood flow (both microcirculation and macrocirculation) [6].

There is ample experimental and clinical evidence suggesting that even minor changes in ADMA levels may considerably affect the vascular tone, systemic peripheral resistance and renal function. Elevated ADMA levels are found in hypertension, ischaemic heart disease, chronic vascular insufficiency, diabetes, hyperhomocysteinaemia, hypercholesterolaemia, gestational hypertension, pre-eclampsia and other conditions [7, 8].

On a practical level, not only NO levels, but also ADMA levels are important. Elevated ADMA levels may cause relative L-arginine deficiency even in normal levels of this amino acid in the blood (this phenomenon is referred to as the arginine paradox). Additional supply of L-arginine will restore the physiological status by virtue of normalisation of the L-arginine/ADMA ratio (the normal ratio is 50–100:1). The L-arginine/ADMA ratio is considered the most accurate instrument to measure the endogenous substrate for NO synthesis. This ratio increases in L-arginine intake regardless of initial ADMA levels [7, 8].

The clinical effect of L-arginine is explained by restoring the endothelial NO synthesis to normal

The changes of maternal and foetal haemodynamics before and after therapy with Tivortin®

Vessels investigated		Terminal velocity of diastolic blood flow, cm/sec	Systolic/ diastolic ratio	Resistance index
Uterine artery	Before treatment	42.3±2.14	2.47±0.32	0.65±0.08
	After treatment	60.9±2.46*	1.54±0.34*	0.35±0.21*
Placental artery	Before treatment	62.3±4.3	3.67±0.32	0.79±0.25
	After treatment	73.8±3.35*	2.34±0.45*	0.65±0.05*

Note: * is a significant change ($p < 0.05$)

levels, which will ensure the restoration of vascular function.

When L-arginine (a natural NO substrate) enters the body, there is no excessive vasodilating effect beyond the normal range [7, 8]. In other words, administration of L-arginine does not cause any excessive hypotensive effects, orthostatic deregulation or reflex-driven tachycardia. Unlike exogenous NO donor substances (nitrates), L-arginine intake does not cause drug tolerance and is not associated with oxidative stress in the arterial wall.

Since this amino acid (arginine) is the only endogenous donor substance of NO radical in human body, using L-arginine products in therapy of placental dysfunction appears to be very promising. A domestic product of L-arginine, Tivortin® has attracted our attention since its efficacy has been demonstrated in cardiologic patients and it has been approved for use in pregnancy.

The aim of the work was to assess the clinical efficacy of 4.2% solution of L-arginine hydrochloride (Tivortin®) at the dose of 100 mL, administered as an intravenous infusion once a day in a 5-day regimen for pharmacological correction of placental dysfunction.

MATERIALS AND METHODS

We have observed 21 gravidae (gestational age 35–37 weeks) with impaired haemodynamics in the maternal-placental-foetal circulation system. To assess the functional condition of the foeto-placental complex, we have used ultrasound foetometry and placentometry, Doppler ultrasound assessment of blood flow in the maternal-placental-foetal circulation system and foetal biophysical profile.

RESULTS AND DISCUSSION

The mean age of pregnant women was 24.3±1.3 years. In 2 patients (9.5%) placental dysfunction has developed in the setting of type 1 diabetes; in 2 patients (9.5%) the condition has emerged in the setting of chronic pyelonephritis; one patient (4.8%) had a history of natural sterility and one more patient (4.8%) had antiphospholipid syndrome. In 2 patients (9.5%) the course of pregnancy has been complicated by mild degree pre-eclampsia, one patient (4.8%) had severe pre-eclampsia; 12 pregnant women (57.1%) were found to have oligohydramnios and 6 patients (28.6%) had intrauterine growth restriction.

When studying the peculiarities of haemodynamics in the maternal-placental-foetal circulation system, isolated changes of blood flow in uterine arteries were found in 10 (47.6%) women; these changes were accompanied by reduction of the diastolic component, the terminal diastolic blood velocity (TDBV) to 42.3±2.14 cm/sec and by the increase of the resistance index (RI) to 0.65±0.08 and of the systolic/diastolic ratio (SDR) to 2.47±0.32.

Impaired foeto-placental blood flow was found in 8 patients (38.1%); furthermore, 6 of these patients had impaired blood flow in one of the umbilical arteries with TDBV reduced to 62.3±4.3 cm/sec, RI increased to 0.79±0.25 and SDR increased to 3.67±0.32. Only 3 patients had their blood flow impaired in both utero-placental and foeto-placental circulation (see Table).

All patients received Tivortin® at the dose of 100 mL as an intravenous infusion once a day in a 5-day regimen as a therapy for the above disorders. Monitoring of foetal well-being in course of treatment was performed by measuring the foetal biophysical profile (BPP) at Day 3 and at Day 6 from

the onset of treatment. At Day 3 of treatment, dubious BPP of 6 points was found only in 2 patients (those with haemodynamic abnormalities both in the maternal and the foeto-placental circulation). No abnormal or dubious BPPs were found after completion of Tivortin® therapy.

At the completion of therapy (see Table), there was a clinical improvement of general well-being of the pregnant women, as well as stabilisation of blood pressure in 2 patients with mild degree pre-eclampsia. Repeated Doppler ultrasound assessment of blood flow in the maternal-placental-foetal circulation system has demonstrated high clinical efficacy of Tivortin® for correction of haemodynamic abnormalities in both the uterine arteries and in foetal circulation. Seven of the 10 gravidae (70%) were found to have normalised haemodynamic indices in the territory of uterine arteries. Thus, there was a significant increase in TDBV (to 60.9±2.46 cm/sec); RI decreased to 0.35±0.21 ($p<0.05$) and SDR decreased to 1.54±0.34 ($p<0.05$). In 4 of the 6 patients (66.7%) with abnormal haemodynamics in the umbilical artery, there was a significant decrease of SDR (to normal values, that is, to less than 3). The gravidae with blood flow impairments in both uterine and foetal vessels has a significant decrease of RI in both uterine arteries (0.42±0.12; $p<0.05$) and in the umbilical arteries (RI 0.65±0.05; $p<0.05$).

CONCLUSIONS

Therefore, haemodynamic abnormalities in the foeto-placental circulation can and must be corrected, which is true of other organs and systems in the human body. Any instances of ineffective or scarcely effective correction may not be the reason to reject the treatment as such (just as mortality occurring during the therapy of heart failure cannot be a cause to reject the treatment).

Tivortin®, being a donor substance of NO, exerts a marked influence on the vascular tone of both uterine arteries and umbilical arteries, which promotes normalisation of haemodynamics in the maternal-placental-foetal circulation system.

Tivortin® has promising obstetric perspectives, being one of the few pharmaceuticals approved for use in pregnancy. However, full elucidation of its therapeutic potential calls for further research.

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