Homocysteinaemia during pregnancy and placental disease

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Summary

Objective: Hyperhomocysteinaemia, due to enzymatic defects or to the lack of some vitamin cofactors (vit. B6, vit. B12, folic acid), could be associated with obstetric disease. The aim of this study was to investigate placental disease in women with mild-moderate hyperhomocysteinaemia.

Materials and Methods: Blood samples of seven pregnant women with severe early onset preeclampsia were assessed for hyperhomocysteinaemia. The obtained values were compared with those of a control group. In all cases, tissue samples obtained from the placenta, umbilical cord and membranes were studied. One of the patients was treated empirically with folic acid during a subsequent pregnancy.

Results: Patient homocysteine plasma levels were higher than in the control group. In all cases several placental abnormalities were found. The patient treated with folic acid had a good pregnancy outcome.

Conclusion: Hyperhomocysteinaemia during pregnancy could be responsible for placental abnormalities. Treatment with folic acid could improve pregnancy outcome in women with homocysteine metabolism abnormalities.

Key words: Hyperhomocysteinaemia; Placental disease; Homocysteine; Folic acid.

Introduction

The amino-acid homocysteine plays an important role in cell metabolism. It participates in the remethylation pathway maintaining adequate cellular levels of methionine or is catabolized by transsulphuration [1]. Both homozygosity and heterozygosity for hereditary defects in the enzymes involved in homocysteine metabolism can be associated with high, moderate or mild hyperhomocysteinaemia [2]. This metabolic disorder can also be associated with a low intake of the vitamin cofactors of the enzymes (vit. B6, vit. B12, folic acid) [1].

Hyperhomocysteinaemia is diagnosed through the determination of plasma homocysteine levels both in the fasting state (normal level: 5-12 μmol/L) and six hours after the ingestion of a methionine load (0.1 g/kg) [3].

Defects in the enzymes or in the cofactors (vit. B12, folic acid) involved in remethylation result in hyperhomocysteinaemia found in the fasting state. Hyperhomocysteinaemia found after methionine loading seems to be due to defects in the enzymes or in the cofactor (vit. B6) involved in transsulphuration [3].

Several authors have reported that mild or moderate hyperhomocysteinaemia could be associated with some obstetric diseases, such as unexplained recurrent abortion [4], intrauterine growth retardation (IUGR), intrauterine foetal death (IUD), placental abruption, placental infarction [5] and severe early preeclampsia [6].

Hyperhomocysteinaemia may result from low folic acid intake. Several studies [7, 8] demonstrated significantly that homocysteine plasma levels could be higher in women carrying an affected foetus (particularly neural tube defects) than in control women and that these defects can be prevented by a sufficiently large dose of folic acid.

The aim of this study was to investigate placental disease in women with mild-moderate hyperhomocysteinaemia.

Materials and Methods

Subjects of this study were seven pregnant women presenting to the Department of Obstetrics-Gynaecology, Urological Science and Reproductive Medicine at the "Federico II" University of Naples. They gave informed consent before participating in the study.

The patients were diagnosed retrospectively as having hyperhomocysteinaemia, following a recent history of severe early onset preeclampsia, with or without IUD, IUGR or premature placental abruption. None of the women had a history of hypertension or thromboemolic disease before pregnancy.

In three cases pregnancies concluded with IUD, associated in one case with IUGR. All the other four pregnancies were complicated by IUGR and premature placental abruption (at 32 weeks in two cases, at 34 weeks in another and at 36 weeks in the last case).

Patient blood samples were assessed for hyperhomocysteinaemia in the fasting state using RIA.

Homocysteine plasma levels were compared with those of 18 women at 28 weeks of gestation. The mean obtained from these control samples was 5.1 μmol/L, SD=1.1, range=3.4-9.6 μmol/L, $3.03<IC<7.16$ μmol/L, $\alpha=3\%$.

Clinical information and outcome of pregnancies are presented in Table 1.

In all cases, tissue samples obtained from the umbilical cord, membranes, placental foetal and maternal side were treated with hematoxylin-eosin and histologically studied (Table 2).

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The woman whose pregnancy concluded with IUGR and placental abruption at 34 weeks was treated empirically with folic acid (0.4 mg/die) during a subsequent pregnancy. The outcome is presented in Table 3.

Results

All patient homocysteine plasma levels were higher than in the control group.

Most of the placental findings indicated abnormal placentation but these were not specific to maternal hyperhomocysteinaemia nor found in every case.

In the pregnancies concluding with IUD at 34 and 36 weeks, histology showed multiple infarctions and accelerated villous maturity; placental were also small for gestational age.

In the pregnancy with IUGR and IUD at 21 weeks, we found no trophoblast-induced physiological vascular changes.

Table 1. — *Clinical information and pregnancy outcome.*

Cases	Age	Clinical information	Homocysteine plasma levels (μmol/L)*
1	26	PE, IUD at 36 weeks	12
2	25	PE, IUD at 34 weeks	13.1
3	31	PE, IUGR, IUD at 21 weeks	14.3
4	29	PE, IUGR, PPA at 32 weeks	12.2
5	32	PE, IUGR, PPA at 32 weeks	12.9
6	27	PE, IUGR, PPA at 34 weeks	13.4
7	29	PE, IUGR, PPA at 36 weeks	14.1

* Homocysteine plasma levels in the control group (μmol/L): mean=5.1, range=3.4-9.6, 3.03 IC <7.16, α=3%.
PE=preeclampsia; IUD=intrauterine foetal death; IUGR=intrauterine growth retardation; PPA=premature placental abruption.

Table 2. — *Histological findings.*

Cases	Findings
1	Multiple infarctions, accelerated villous maturity, small for gestational age placenta
2	Multiple infarctions, accelerated villous maturity, small for gestational age placenta
3	Absence of trophoblast-induced vascular changes, small for gestational age placenta
4	Retroplacental haemtoma, accelerated villous maturity, small for gestational age placenta
5	Retroplacental haematoma, multiple infarctions, small for gestational age placenta
6	Retroplacental haematoma, accelerated villous maturity, small for gestational age placental
7	Retroplacental haematoma, multiple infarctions, accelerated villous maturity, small for gestational age placenta

Table 3. — *Case treated with folic acid.*

Age	27
Homocysteine plasma level at 28 weeks	8.5 μmol/L
Pregnancy outcome	Caesarian section at 37 weeks, newborn SGA with Apgar score = 7 at 1 min and = 9 at 5 min
Histological findings	Small for gestational age placenta

In pregnancies with IUGR and premature placental abruption we found retroplacental haematoma formations and accelerated villous maturity.

Histological findings included atherosis of the maternal placental side in all the cases.

Pregnancy of the woman treated with folic acid concluded at 37 weeks. The foetus was SGA, with an APGAR score of 7 at one minute and 9 at five minutes and had a very good outcome. Placental histological findings indicated a small for gestational age placenta without other significant alterations.

Discussion

The most specific discovery among our histological findings seems to be the absence of throphoblast-induced physiological vascular changes. Acute atherosis and thrombosis of the maternal placental side could be responsible for the accelerated villous maturity and the multiple infarctions. A weakening of the arterial wall could predispose to premature placental abruption.

These observations and hypotheses, like several literature reports, seem to support the role of hyperhomocysteinaemia in causing described placental pathologies.

Chambers *et al.* [9] demonstrated that hyperhomocysteinaemia could cause some endothelial dysfunctions, such as endothelial cell damage, smooth muscular cell proliferation, thrombogenesis and NO activity reduction. These reports suggest a responsibility of maternal hyperhomocysteinaemia for the patterns of placental atherosis and thrombosis found by histology.

Harpel *et al.* [10] suggested that homocysteine could inhibit several anticoagulant mechanisms mediated by the vascular endothelium. Homocysteine also interferes with the fibrinolytic properties of the endothelial surface, inhibiting the binding of tissue plasminogen activator to endothelium [11]. The processes of implantation and placentation are both dependent on the invasion and remodelling of the uterine endometrium and vasculature by trophoblasts through a plasmin-mediated mechanism [11]. If homocysteine inhibits plasmin production, it could cause the patterns of inadequate placentation found by histology.

Pregnancy increases folic acid needs. Low folic intake, just enough to prevent the clinical onset of hyperhomocysteinaemia in non-pregnant women, becomes insufficient during pregnancy, thus making clinical signs of hyperhomocysteinaemia worse. This fact could have an important therapeutic implication [12]. The improved pregnancy outcome of our patient treated with folic acid seems to support the hypothesis of the role of homocysteine in some pregnancy complications.

Conclusion

The histological findings reported suggest that hyperhomocysteinaemia could be in part responsible for several placental diseases. In this study, the diagnosis of hyperhomocysteinaemia was made after pregnancy

disease onset. It is possible, however, that placental alterations are the first signs of subclinical hyperhomocysteinaemia; this eventuality should be considered and thus placental histological exams shoud become routine.

The results also suggest that adequate folic acid intake during pregnancy could improve the outcome in women with homocysteine metabolism abnormalities. If further randomised controlled trials confirm these findings, folic acid supplementation could be used in preventing complications in pregnant women with hyperhomocysteinaemia.

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