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Original Article

# Homocysteine and folate plasma concentrations in mother and baby at delivery after pre-eclamptic or normotensive pregnancy: Influence of parity

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ABSTRACT

Pre-eclampsia affects between 2% and 7% of all pregnant women, contributing to perinatal and maternal morbidity. There are conflicting data on plasma homocysteine and folate in pre-eclampsia, and little about fetal concentrations.

*Objectives:* Firstly, to compare the concentrations of homocysteine and folate in maternal and paired fetal (umbilical venous) plasma samples from normotensive or pre-eclamptic pregnancies at delivery; secondly, to identify any effect of parity on these concentrations.

*Study design:* Hospital based cross-sectional study consisting of 24 normotensive and 16 pre-eclamptic pregnant White European women from whom maternal and fetal plasma samples were collected at delivery.

*Main outcome measures:* Maternal and fetal plasma homocysteine and folate concentrations between normotensive and pre-eclamptic pregnancies with varying parity.

*Results:* There were no significant differences in either maternal or fetal plasma homocysteine or folate concentrations between normotensive and pre-eclamptic pregnancies, or between homocysteine and folate. In both the normotensive and pre-eclamptic women, plasma folate concentration was higher in paired fetal compared to maternal plasma ($P < 0.001$ and $P = 0.047$, respectively). With regards to homocysteine, only the normotensive samples had higher fetal concentrations ($P = 0.002$). Both maternal and fetal plasma folate concentrations were lower in parous women ($P = 0.001$ and $P = 0.017$, respectively), the lowest concentrations being in pre-eclamptic parous women ($P = 0.004$), but homocysteine concentrations were similar ($P > 0.4$ for both).

*Conclusions:* The low plasma folate in parous women is an interesting finding and, when intake is also low, may contribute to adverse pregnancy outcomes, particularly in relation to pre-eclampsia.

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## 1. Introduction

Pre-eclampsia is estimated to occur in 2–7% of all pregnancies and is a leading cause of maternal and perinatal mortality and morbidity in the Western world [1]; together with other hypertensive disorders of pregnancy it

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**Table 1**
Maternal and fetal venous plasma homocysteine and folate and participant details.

| Parameter | Normotensive pregnant ($n = 24$) | Pre-eclampsia ($n = 16$) |
|---|---|---|
| Maternal age (years)[a] | 29 ± 6.6 | 31 ± 5.8 |
| Booking body mass index (kg/m$^2$)[a] | 25.9 ± 5.6 | 25.7 ± 3.8 |
| Primipara, *n* (%) | 15 (62.5) | 11 (68.8) |
| Max. systolic blood pressure (mm Hg)[a] | 116 ± 4.3 | 157 ± 7.4[#] |
| Max. diastolic blood pressure (mm Hg)[a] | 76 ± 2.5 | 98 ± 4.9[#] |
| Proteinuria (g/L)[b] | – | 1.0 [0.5, 1.8] |
| Gestation age at delivery (weeks) | 39.8 ± 1.0 | 38.1 ± 2.0[#] |
| Folate supplementation, *n* (%) | 4 (16.7) | 2 (12.5) |
| Maternal homocysteine (μmol/L)[b] | 8.7 [6.8, 11.0] | 8.2 [7.0, 10.6] |
| Fetal homocysteine (μmol/L)[b] | 10.5 [9.0, 12.4][*] | 9.5 [7.4, 11.9] |
| Maternal folate (nmol/L)[b] | 10.7 [6.2, 19.4] | 6.8 [5.3, 14.1] |
| Fetal folate (nmol/L)[b] | 22.2 [17.8, 32.7][*] | 16.4 [11.3, 23.4][*] |

[a] Values represented as means ± SD.
[b] Values represented as median [IQR]. Further demographic and pregnancy outcome details have been previously published [31].
[#] $P < 0.05$ between normotensive and pre-eclamptic pregnancies.
[*] $P < 0.05$ between maternal and fetal samples.

is responsible for approximately 60,000 deaths each year [2]. Pre-eclampsia is now commonly regarded as being a state of oxidative stress [3]. It is thought that primarily inadequate placental perfusion results in excessive production of reactive oxygen species giving rise to endothelial cell dysfunction and thus clinical manifestations of pre-eclampsia [4].

Homocysteine is a metabolic product of methyl-group donation by the amino acid methionine; remethylation is catalysed by folate. Small increases in plasma homocysteine concentrations are associated with increased risk of vascular disease [5], Alzheimer's disease [6] and neural tube defects [7] in the general population. Elevated homocysteine concentrations contribute to oxidative stress and endothelial dysfunction [8] and are thus also potentially implicated in the pathogenesis of pre-eclampsia. Some studies report raised homocysteine concentrations in pre-eclampsia (e.g. [9,10]) while others have shown no significant differences [11,12]. Maternal and fetal plasma homocysteine concentrations have been reported to be directly correlated in healthy nulliparae [13] and do not appear to change significantly during the course of pregnancy [14]. If plasma homocysteine concentrations are indeed raised in pre-eclampsia, and there is similar parallelism, then the fetus will be exposed to potentially damaging levels of homocysteine even before birth, which might have long-term consequences. Important factors influencing homocysteine concentrations are folate and vitamin $B_{12}$ status and the methylenetetrahydrofolate reductase (MTHFR) polymorphisms [15]; once again the data on these in pre-eclampsia is conflicting [16,17].

There is considerably less, but similarly conflicting, evidence linking folate concentrations and pre-eclampsia [18,19]. The fetus must receive an adequate supply of folate for growth and development; inadequate concentrations will also, *inter alia*, impede the remethylation of homocysteine. Both metabolites have active transport systems in the placenta [20] and impaired placentation is believed to be central to the pathogenesis of pre-eclampsia. Folate has recently been shown to possibly play a direct role in extravillous trophoblast invasion [21], thus highlighting the need for adequate folate concentrations pre-pregnancy and during the early stages of pregnancy. Studies linking homocysteine and folate in the mother and fetus are very limited [17]. We therefore felt it to be important to measure fetal, as well as maternal, concentrations of homocysteine and folate at delivery.

Folate intake among women of reproductive age in the UK is reported to be low [22]. There is an increased demand for folate during pregnancy, which can result in suboptimal folate status [23], although there is some evidence to suggest that folate turnover during pregnancy does not appear to change if folate intake is adequate [24]. Increasing parity has been associated with decreasing plasma folate concentrations [25,26], presumably because lactation is a further drain on folate reserves [27]. If dietary intake is suboptimal, these stores may not be replenished before a subsequent pregnancy, especially in cases of short inter-pregnancy intervals [25,28]. We are unaware of any studies relating these low folate levels to increased plasma homocysteine concentrations in either parous women as a group, or parous women who develop pre-eclampsia. However, there is indirect evidence for an interaction between parity and raised plasma homocysteine concentrations which has been related to increased risk of pre-eclampsia [29,30]. We hypothesised that plasma folate concentrations would be lower, and homocysteine higher, in pre-eclamptic women and their babies than in normotensive pregnant controls. We also opportunistically examined the effect of parity on maternal plasma folate concentrations in normal and pre-eclamptic pregnancy.

## 2. Methods

### 2.1. Subjects

These investigations formed part of a detailed study of selenium and glutathione peroxidases in pregnancy, requiring recruitment of 25 pregnant women to each arm (see [31]). The current study had a power of 80% to detect a difference of 1SD in maternal plasma folate concentration between the 24 normotensive and 16 pre-eclamptic

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