Research Article

Birth Outcomes of Newborns after Folic Acid Supplementation in Pregnant Women with Early and Late Pre-Eclampsia: A Population-Based Study

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1. Introduction

Pre-eclampsia (PE) is frequent (2–8%) and severe complications of pregnancy, and this multisystem disorder of pregnancy is characterized by pregnancy-induced hypertension and new-onset proteinuria during the second half of pregnancy [1–3]. PE is a major contributor to maternal mortality if associates with eclampsia and HELLP syndrome [4, 5]. Furthermore, since delivery is the only cure of PE, there is a higher risk of preterm birth up to 15% [6] and intrauterine growth retardation [7] with an increase in infant mortality and morbidity.

Two important hypotheses have been generated for the pathogenesis of PE during the last decades. The first hypothesis was based on the differentiation of early and late onset PE [3] or on the two-stage model of PE [8]. The second hypothesis was based on PE associated with placental insufficiency due to hyperhomocysteinemia-related vasculopathy because 3.2–7.7-fold higher risk of PE was found in pregnant women with elevated homocysteine levels [9–16]. Folic acid supplementation lowers plasma homocysteine in general [17] and in patients with PE [18], thus folic acid containing multivitamins was tested in pregnant women with gestational hypertension [19] and in pregnant women with PE [20, 21] with significant preventive effect. However, the effect of folic acid alone was not tested though most pregnant women use only folic acid.

The first objective of our study was to evaluate the birth outcomes of pregnant women with early and late onset PE, while the second aim was to check the effect of folic
acid supplementation for the risk of preterm birth and low
birth weight in their newborn infants in the population-
based data set of the Hungarian Case-Control Surveillance
of Congenital Abnormalities (HCCSCA) [22].

2. Material and Methods

The HCCSCA is based on the comparison of exposures
studied during the pregnancy of mothers of cases with
different congenital abnormalities and the mothers of con-
trols without any defect matched to the cases. Cases with
congenital abnormalities are selected from the Hungarian
Congenital Abnormality Registry [23] for the HCCSCA.
Control newborns were selected from the National Birth
Registry of the Central Statistical Office for the HCCSCA.
In general, two newborns were matched individually to each
case according to sex, week of birth in the year when cases
were born, and district of parents’ residence of cases.

Cases were excluded from this analysis because con-
genital abnormalities may have a more robust effect for
birth outcomes than PE. Thus only 38,151 control newborns
without any defect of the HCCSCA, 1980–1996, were
evaluated in this study.

Immediately after the selection of newborns an explana-
tory letter was sent to the mothers, and they were asked to
send us the prenatal maternity logbook and all other medical
records regarding the study pregnancy; these documents
were sent back after three weeks. Prenatal care was manda-
tory for pregnant women in Hungary (if somebody did not
visit prenatal care clinic, she did not receive a maternity grant
and leave), thus nearly 100% of pregnant women visited
prenatal care clinics, an average 7 times in their pregnancies.
The first visit was between the 6th and 12th gestational
week. The task of obstetricians was to record all pregnancy
complications, including PE, maternal diseases, and related
drug prescriptions in the prenatal maternity logbook.

On the other hand, a structured questionnaire, a list of
medicines (drugs and pregnancy supplements), and a
printed informed consent form were also mailed to
the mothers. The questionnaire requested information on
maternal personal (e.g., employment status) and medical
data including pregnancy complications, maternal diseases,
and medicine intakes during the study pregnancy according
to gestational month. In order to standardize the answers,
mothers were asked to read the enclosed lists as a memory
aid before they replied and to send back the filled-in ques-
tionnaire and informed consent form with their signature in
our prepaid envelop.

The interval between the end of pregnancy and return
of the “information package” including prenatal maternity
logbook, questionnaire, and so forth, was 5.2 ± 2.9 months.

In addition, 200 nonrespondent and 600 respondent
mothers were visited at home by regional nurses as part
of two validation studies [24, 25] because the committee
on ethics considered this followup to be disturbing to the
parents of all healthy children. Regional nurses helped
mothers to fill in the questionnaire used in the HCCSCA,
evaluated the available medical documents, and obtained
data regarding the lifestyle of mothers through a cross

interview of fathers and other close relatives living together,
and finally the so-called family consensus was recorded.

Overall the necessary information was available on 83.0%
of pregnant women (81.3% from reply and 1.7% from home
visit). Here the 17 years’ data of the HCCSCA between
1980 and 1996 are evaluated because the data collection has
been changed since 1997 (all mothers are visited by regional
nurses), and the recent data had not been validated at the
time of the analysis.

Four types of hypertension in pregnant women were
classified: (i) chronic hypertension, (ii) PE, (iii) PE super-
imposed upon chronic hypertension, and (iv) gestational
hypertension [1, 2, 26]. Our plan was to evaluate the possible
association of these four types of hypertension in pregnant
women with the risk of other pregnancy complications and
adverse birth outcomes. The data of our study regarding
chronic and gestational hypertension were published [27],
while the evaluation of pregnant women with PE superim-
posed upon chronic hypertension is in process. Here the
birth outcomes of pregnant women with PE are presented.

Blood pressure and proteinuria were measured in
pregnant women at their visits in the prenatal care clinics.
If a new-onset proteinuria was found by the help of dipstick
screening test after the 20th gestational week, pregnant
women were referred to a detailed laboratory examination
(more than 300 mg in 24 h was accepted as proteinuria). PE
was diagnosed in pregnant women if they had new onset
hypertension and proteinuria. Of course, pregnant women
with secondary hypertension were also excluded from the
study.

The preliminary analysis of data showed that the diag-
nosis of PE in the questionnaire based on retrospective
maternal information was not reliable; therefore, we decided
to evaluate only medically recorded PE in the prenatal
maternity logbook. There is no consensus in the classification
of early and late onset PE, SOGC [28] and ASH [29]
recommended for late onset PE less than 34 or 35 gestational
week, respectively, while others differentiate early onset
before 24 weeks gestation [30]. Thus we decided to evaluate
the onset of PE according to gestational months.

Other pregnancy complications, PE-related drug treat-
ments and other potential confounding factors such as
maternal age, birth order, marital and employment status
as indicators of socioeconomic status [31], other maternal
diseases, and folic acid supplements were also evaluated.

Only one type of 3 mg folic acid (Alkaloida/ICN Hun-
gary) tablet was available in Hungary during the study
period.

Gestational age was calculated from the first day of the
last menstrual period. Both birth weight and gestational
age at delivery were medically documented in the discharge
summary of mothers because all deliveries took place
in inpatient obstetric clinics. The rate of low (less than
2500 gram) and large (4000 gram or more) birth weight,
in addition to the rate of preterm (less than 37 completed
gestational weeks or less than 259 days) and postterm
(42 completed weeks or 294 days or more) birth was
calculated.
2.1. Statistical Analysis of Data. We used SAS version 8.02 (SAS Institute, Cary, North Carolina, USA) for statistical analyses. The occurrence of folic acid use was compared in pregnant women with PE and the reference group including all pregnant women without PE. Contingency tables were prepared for the main study variables. First, the characteristics of pregnant women with different study groups were compared with the reference group using chi-square test for categorical variables and Student t-test for quantitative variables. Second, frequency of maternal diseases, pregnancy complications, and related drug treatments was compared between mothers with PE and the reference group by ordinary logistic regression models and odds ratios (OR) with their 95% confidence intervals (CI) being evaluated. Third, the birth outcomes of newborns were evaluated in mothers with PE compared with the reference group using adjusted Student t-test and OR with 95% CI using ordinary logistic regression model. Finally birth outcomes of newborns in pregnant women with PE were stratified according to folic acid supplementation.

3. Results

The total number of births in Hungary was 2,146,574 during the study period, thus 38,151 controls represented 1.8% of all Hungarian births. Of these 38,151 newborns, 1,017 (2.7%) had mothers with medically recorded PE in the prenatal maternity logbook. Of these 1,017 pregnant women with PE, 45 (4.4%) had later eclampsia while HELLP was not recorded.

Only 580 (57.0%) women out of total 1,017 who were diagnosed as PE had recorded history of taking folic acid supplementation, while this figure was 54.4% (20,195/37,134) in the reference group, thus pregnant women with PE used somewhat more frequently folic acid. The indication of folic acid supplementation was the prevention of neural tube defects. The distribution of daily folic acid supplementation was the following: 22.5%, 68.6%, and 8.9% of pregnant women used one (3 mg), two (6 mg), and three (9 mg) tablets, respectively. Thus the estimated mean daily dose was 5.6 mg. The onset of folic acid supplementation was in about 10% of pregnant women before conception; however, most women started folic acid use after the first visit in the prenatal care clinic, that is, between the 6th and 12th gestational weeks, thus before the onset of PE. Practically all pregnant women continued folic acid supplementation until the end of pregnancy. Of 580 pregnant women with PE and folic acid use, 440 (75.9%) had medically recorded folic acid use in the prenatal maternity logbook while this figure was 61.3% in the reference group. Our validation study showed that maternal information regarding folic acid use was correct, but some women retrospectively forgot to mention it. Folic acid containing multivitamins was used rarely and it contained different low doses of folic acid, thus these pregnant women were excluded from the study.

Maternal characteristics are shown in Table 1. There was no difference in mean maternal age of pregnant women with or without PE, while mean birth order was lower by 0.3 in pregnant women with PE due to the higher proportion of primiparous pregnant women. In addition, the difference in the mean pregnancy order (birth + miscarriages) was 2-fold higher in women with PE (0.4) than in pregnant women without PE (0.2), and these findings indicate a higher rate of miscarriages in the previous pregnancies of women with PE. The proportion of professional women was somewhat lower in pregnant women with PE, while their proportion of managerial women and skilled workers was somewhat higher compared to pregnant women without PE. Pregnant women with PE and folic acid use were somewhat older with higher mean birth order.

Acute and chronic maternal diseases did not show significant differences between pregnant women with PE and the reference sample.

Among other pregnancy complications, threatened abortion (20.8% versus 17.0%) and placental disorders (2.2% versus 1.5%), particularly abruptio placentae occurred more frequently in pregnant women with PE than in pregnant women without PE.

Practically all pregnant women with PE were treated with antihypertensive drugs, most frequently nifedpine (15.1% versus 2.2%) and methyldopa (10.5% versus 0.9%) compared with pregnant women without PE. Dihydralazine, metoprolol, clopamide, and furosemide were also more frequently used by pregnant women with PE. However, magnesium sulphate was used only in two pregnant women with PE.

The diagnosis of PE according to gestational months is shown in Table 2. These data reflect the record of PE diagnosis in the prenatal maternity logbook, but it may be near to the onset of this pregnancy complication due to the frequent visits in prenatal care clinics. However, of 1,017 pregnant women with PE, 100 (9.8%) had not unambiguous time of diagnoses. Unexpectedly the diagnosis of PE was recorded in the fourth gestational month in 3.9% of pregnant women. In general, these pregnant women had new-onset hypertension but proteinuria was confirmed after the 20th gestational week. The maximum was found during the last two pregnancy months.

The birth outcomes of newborn infants born to pregnant women with PE and without PE as reference are shown in the lower part of Table 2. (There was no significant difference in the sex ratio of the study groups.) The mean gestational age was the same in pregnant women with or without PE but the rate of preterm birth was somewhat but not significantly higher in the group of pregnant women with PE (10.2% versus 9.1%). The mean birth weight of newborn infants born to pregnant women with PE was somewhat (41 g) larger compared to the newborns of pregnant women without PE and this small difference was significant. On the contrary, the rate of low birth weight newborns was higher in the group of pregnant women with PE (7.9% versus 5.6%), and this 40% increase is significant on both statistical and clinical aspects.

In the next step, newborns were evaluated according to gestational age and birth weight groups in pregnant women with PE and without PE as reference. A characteristic U-shaped curve was shown; the previously mentioned higher rate of preterm birth and low birth weight associated with a higher rate of postterm birth (11.2% versus 10.1%; OR
with 95% CI: 1.1, 0.7–1.7) and large birth weight (10.9% versus 7.4%; OR with 95% CI: 1.5, 1.2–2.0). However, these differences reached the level of significance only in low and large birth weight, and the mean birth weight was higher both in term and the postterm births.

The gestational age at delivery and birth weight were moderately modified by folic acid supplementation from the early pregnancy (Table 2). The mean gestational age was 0.3 week longer in pregnant with PE after folic acid supplementation compared to pregnant women with PE, but without folic acid use. These data were in agreement with their lower rate of preterm births (8.8% versus 12.1%). However, folic acid supplement associated with only 46 g larger mean birth weight and with moderate reduction of low birth weight (7.2% versus 8.7%) and these differences were not significant. If only medically recorded folic acid uses were

Table 1: Characteristics of pregnant women without pre-eclampsia (PE) as a reference and with PE, in addition pregnant women with PE supplemented with folic acid.

| Variables | Without PE (N = 37,134) | With PE (N = 1,017) | Pregnant women with PE + folic acid (N = 580) |
|-----------|--------------------------|---------------------|----------------------------------------------|
| Maternal age (yr) | | | |
| 19 or less | 3,191 (8.6) | 86 (8.5) | 43 (7.4) |
| 20–29 | 26,877 (72.4) | 725 (71.3) | 410 (70.7) |
| 30 or more | 7,066 (19.0) | 206 (20.3) | 127 (21.9) |
| Mean ± S.D. | 25.5 ± 4.9 | 25.5 ± 5.0 | 25.7 ± 4.9 |
| Birth order | | | |
| 1 | 17,603 (47.4) | 706 (69.4) | 340 (58.6) |
| 2 or more | 19,529 (52.6) | 311 (30.6) | 240 (41.4) |
| Mean ± S.D. | 1.7 ± 0.9 | 1.4 ± 0.9 | 1.6 ± 1.1 |
| Pregnancy order | | | |
| 1 | 15,780 (42.5) | 540 (53.1) | 301 (51.9) |
| 2 or more | 21,354 (57.5) | 477 (46.9) | 279 (48.1) |
| Mean ± S.D. | 1.9 ± 1.2 | 1.8 ± 1.2 | 1.8 ± 1.1 |
| Unmarried | 1,443 (3.9) | 29 (2.9) | 14 (2.4) |
| Employment status | | | |
| Professional | 4,330 (11.7) | 93 (9.1) | 56 (9.7) |
| Managerial | 9,960 (26.8) | 305 (30.0) | 181 (31.2) |
| Skilled worker | 1,551 (31.1) | 357 (35.1) | 202 (34.8) |
| Semiskilled worker | 5,998 (16.2) | 163 (16.0) | 89 (15.3) |
| Unskilled worker | 2,140 (5.8) | 47 (4.6) | 24 (4.1) |
| Housewife | 2,310 (6.2) | 40 (3.9) | 22 (3.8) |
| Others | 841 (2.3) | 12 (1.2) | 6 (1.0) |

Table 2: Onset (diagnosis) of pregnant women with pre-eclampsia according to gestational month and their birth outcomes.

| Gestational months | No. | % | Gestational age (wk) | Birth weight (g) | Preterm birth | Low birth weight |
|--------------------|-----|---|----------------------|-----------------|--------------|-----------------|
| IV                 | 36  | 3.9 | 39.2 ± 2.7 | 3,365 ± 540 | 7 | 19.4 | 2 | 5.6 |
| V                  | 109 | 11.9 | 39.5 ± 1.9 | 3,414 ± 523 | 6 | 5.5 | 3 | 2.8 |
| VI                 | 115 | 12.5 | 39.3 ± 2.4 | 3,339 ± 660 | 14 | 12.2 | 12 | 10.4 |
| VII                | 185 | 20.2 | 39.1 ± 2.3 | 3,234 ± 622 | 25 | 13.5 | 22 | 11.9 |
| VIII               | 246 | 26.8 | 39.1 ± 2.2 | 3,263 ± 603 | 29 | 11.8 | 24 | 9.8 |
| IX                 | 226 | 24.7 | 39.9 ± 1.7 | 3,383 ± 503 | 9 | 4.0 | 9 | 4.0 |
| Subtotal           | 917 | 100.0 | 39.4 ± 2.1 | 3,318 ± 583 | 90 | 9.8 | 72 | 7.9 |
| Unknown            | 100 | 9.8 | 39.1 ± 2.2 | 3,296 ± 615 | 14 | 14.0 | 8 | 8.0 |
| Total              | 1,017 | 100.0 | 39.4 ± 2.1 | 3,316 ± 586 | 104 | 10.2 | 80 | 7.9 |
| Reference          | 37,134 | — | 39.4 ± 2.0 | 3,275 ± 509 | 3,392 | 9.1 | 2,087 | 5.6 |
| Comparison         | | | | | | | | |
| With folic acid    | 580 | 57.0 | 39.5 ± 2.0 | 3,334 ± 577 | 51 | 8.8 | 42 | 7.2 |
| Without folic acid | 437 | 43.0 | 39.2 ± 2.2 | 3,291 ± 597 | 53 | 12.1 | 38 | 8.7 |

* OR (95% CI).
Table 3: Distribution of gestational age (preterm, term, postterm) and birth weight (low, average, large) groups in pregnant women without PE (as reference) and with PE, in addition in pregnant women with PE with folic acid supplementation.

| Gestational age groups | Pregnant women without PE | Pregnant women with PE | Pregnant women with PE + FAS |
|------------------------|---------------------------|------------------------|-----------------------------|
|                        | Birth weight (g)          | Birth weight (g)        | Birth weight (g)             |
|                        | No.  | %     | Mean ± S.D. | No.  | %     | Mean ± S.D. | No.  | %     | Mean ± S.D. |
| −37                    | 3,392 | 9.1   | 2,486 ± 435 | 104  | 10.2  | 2,401 ± 460 | 51   | 8.8    | 2,440 ± 401 |
| 38–41                  | 29,994 | 80.8  | 3,322 ± 428 | 799  | 78.6  | 3,376 ± 491 | 460  | 79.3   | 3,384 ± 506 |
| 42–                    | 3,748  | 10.1  | 3,612 ± 485 | 114  | 11.2  | 3,729 ± 473 | 69   | 11.9   | 3,663 ± 468 |
| Total                  | 37,134 | 100.0 | 3,275 ± 509 | 1,017 | 100.0 | 3,316 ± 580 | 580  | 100.0  | 3,334 ± 57  |

Table 4: The effect of folic acid for birth outcomes of pregnant women with early and late onset PE.

| Gestational months | No. | %   | Gestational age (wk) Mean ± S.D. | Birth weight (g) Mean ± S.D. | Preterm birth No. | %   | Low birth weight No. | %   |
|--------------------|-----|-----|---------------------------------|------------------------------|-------------------|-----|----------------------|-----|
| All                | 917 | 100.0 | 39.4 ± 2.2                    | 3,374 ± 589                  | 27                | 10.4 | 17                  | 6.5 |
| IV–VI              | 260 | 28.4 | 39.4 ± 2.2                    | 3,374 ± 589                  | 27                | 10.4 | 17                  | 6.5 |
| VII–IX             | 657 | 71.6 | 39.4 ± 2.1                    | 3,296 ± 579                  | 63                | 9.6  | 55                  | 8.4 |
| Total              | 917 | 100.0 | 39.4 ± 2.1                    | 3,318 ± 583                  | 90                | 9.8  | 72                  | 7.9 |
| With folic acid supplementation |     |      |                               |                             |                   |      |                      |     |
| IV–VI              | 147 | 27.2 | 39.6 ± 2.1                    | 3,419 ± 560                  | 10                | 6.8  | 7                   | 4.8 |
| VII–IX             | 394 | 72.8 | 39.4 ± 2.0                    | 3,302 ± 575                  | 38                | 9.6  | 32                  | 8.1 |
| Total              | 541 | 100.0 | 39.5 ± 2.0                    | 3,334 ± 573                  | 48                | 8.9  | 39                  | 7.2 |

4. Discussion

The primary aim of the study was to evaluate birth outcomes of pregnant women with early ("placental") and late ("maternal") PE. The risk of adverse birth outcomes cannot be differentiated according to early and late onset PE defined in our study, because the onset between sixth and eighth gestational months associated with a higher risk of preterm birth and low birth weight. The secondary aim of the study was to estimate the possible effect of folic acid for the risk of preterm birth and low birth weight of their newborns. On one hand, the high dose of folic acid used in early pregnancy reduced the rate of preterm birth but not modified significantly the higher rate of low birth weight, that is, intrauterine growth retardation in pregnant women with early PE. On the other hand, this preventive effect of folic acid was not observed in pregnant women with late PE; in fact, there was somewhat but not significantly higher rate of preterm birth and low birth weight in pregnant women with late PE after folic acid supplementation.

The prevalence of PE was 2.7% in pregnant women without PE superimposed upon chronic hypertension. Eclampsia is defined as the occurrence of tonic-clonic seizures in pregnant women with PE, and recently eclampsia has manifested only in 1-2% of women with severe PE [3]. However, this figure was 4.4% in the study explained by the
possible overdiagnoses and mainly by the lack of magnesium sulphate treatment in Hungary during the study period.

The primary goal is to prevent the manifestation of PE with maternal complications; however, a reasonable secondary goal is to reduce the adverse birth outcomes of pregnant women with PE. The rate of preterm births (10.2% versus 9.1%) and mainly of low birth weight (7.9% versus 5.6%) was higher in the newborns of pregnant women with PE than in the newborns of pregnant women without PE, though these figures were lower than rates found in previous studies [32, 33]. These differences may reflect the improvement of medical care of pregnant women with PE. However, the unexpected findings of the study were the higher rate of postterm birth (11.2% versus 10.1%) and mainly of large birth weight (10.9% versus 7.4%) in the newborns of pregnant women with PE. The latter explains the larger mean birth weight of newborn infants born to pregnant women with PE compared to the newborns of pregnant women without PE. The mild U-shaped distribution of gestational weeks is in agreement with the same mean gestational age at delivery in the groups of pregnant women with or without PE.

The use of folic acid modified these findings; the mean gestational age was somewhat longer with a lower rate of preterm birth. Similar beneficial effect was not found in the rate of low birth weight newborns. However, an important observation of our study is that the beneficial effect of high dose of folic acid use from early pregnancy occurred only in pregnant women with early (placental) onset PE.

Our previous study showed that the high dose of folic acid during pregnancy associated with a minor increase of birth weight but a longer gestational age at delivery and significant reduction in the rate of preterm birth [34]. In this study, we found similar findings, but these effects were moderate, thus the maternal pathological conditions are important in the effect of folic acid.

The major expected benefit of antihypertensive therapy is the reduction of hypertension of pregnant women with PE [27] to reduce maternal complications and adverse birth outcomes. However, it was not successful in many women in our material. Magnesium sulphate is recommended for the treatment of severe PE [35, 36]; unfortunately, it was used rarely in Hungary.

Our study confirmed the role of nulliparity [3] and the higher rate of previous miscarriages [37] in the origin of PE.

The strengths of the HCCSCA are that it is a population-based large data set including 1,017 pregnant women with prospectively and medically recorded PE in an ethnically homogeneous European (Caucasian) population. We were able to differentiate PE from the other types of hypertension in pregnant women. Additional strengths are medically recorded other pregnancy complications and birth outcomes, in addition to the available data of potential confounders.

However, this data set also has limitations. (i) Other pregnancy outcomes, for example, miscarriages were not known in the study pregnancy. (ii) Lifestyle factors could not be evaluated in the total data set due to the unreliability of maternal self-reported data [38], though smoking seems to be protective for PE [39–41].

In conclusion, a higher risk of preterm births and mainly low birth weight was found in the newborns of pregnant women with PE. The use of high dose of folic acid from early pregnancy resulted in a reduction of preterm birth in pregnant women with early onset PE; however, similar beneficial effect was not found in the rate of low birth weight and in pregnant women with late onset PE. The clinical importance of these statistically significant changes is necessary to be validated in well-controlled prospective studies.

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