ASSOCIATION OF VERY HIGH HUNGARIAN RATE OF PRETERM BIRTHS WITH CERVICAL INCAPACITANCE IN PREGNANT WOMEN

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INTRODUCTION

The rate of preterm births is extremely high (about 9%) in Hungary (1) and preterm babies associated with about one-third of infant mortality in the 2000s (2) and with a major part of mental retardation (3), visual (4) and other handicaps. Thus it is an important public health task to reveal the possible causes of preterm birth and prevent them.

Some well-known causes of preterm births, e.g. multiple pregnancies cannot be prevented, while other causes such as sexually transmitted infections/diseases are preventable (5, 6). However, we have to elucidate the role of other factors in the origin of preterm births.

The first objective of our study was to determine the prevalence of cervical incompetence in pregnancy (CIP) in Hungary. The second aim of the study was to measure the association between CIP and the rate of preterm births, i.e. estimation of preterm birth risk due to CIP. Finally the third objective of the study was to check the efficacy of CIP treatment.

At present two kinds of CIP treatment compete with each other in Hungary. One group of obstetricians prefers the prophylactic surgical intervention used previously the Shirodkar suture (7), later therapeutic McDonald cerclage (8). Another group of obstetricians gives preference to the conservative treatment based on lasting bed-rest alone because some previous studies were not able to show the advantage of therapeutic cerclage (9). Thus we evaluated the rate of preterm births as an indicator of efficacy of the above two medical treatments in women with CIP.

The data of the population-based large data set of newborns without congenital abnormalities (the so-called controls) of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) (10, 6) were evaluated in the study.

MATERIALS AND METHODS

Newborn infants without congenital abnormalities were selected from the National Birth Registry of the Central Statistical Office for the HCCSCA. These newborns were controls of cases with congenital abnormality that were selected from the Hungarian Congenital Abnormality Registry (11) for the HCCSCA. Here only controls are evaluated because congenital abnormalities may have a more drastic effect for birth outcomes, e.g. preterm births than CIP and the term controls will not be mentioned later. In general, two newborns were matched individually to each case according to sex, week of birth and district of parents’ residence of cases. If selected newborns were twins, only one of them was randomly included to the data set of the HCCSCA.

SUMMARY

Background: Maternal cervical incompetence in pregnancy (CIP) showed an association with a higher rate of preterm births. The objective of this study was to determine the prevalence of CIP in Hungarian pregnant women, to determine the rate of preterm birth, and to check the preventive efficacy of preterm births due to CIP by therapeutic cerclage or bed rest alone.

Methods: Analysis of the population-based large data set of 38,151 newborns (without any defects) of the Hungarian Case-Control Surveillance System of Congenital Abnormalities (HCCSCA), born during 1980–1996, i.e. 1.8% of Hungarian newborns. Prospective cohort analysis based on medically recorded variables of CIP, birth weight and gestational age.

Results: A total of 2,795 (7.33%) newborns born to mothers with CIP. The newborns of mothers with CIP had a shorter gestational age at delivery (39.0 wk) and higher rate of preterm birth (11.1%) than the Hungarian reference sample without CIP (39.4 wk and 9.0%). Of 2,795 pregnant women with CIP 1,112 were treated by cerclage, while 1,683 with bed rest alone. The mean gestational age was shorter both after therapeutic cerclage (39.2 wk) and particularly bed rest alone (38.9 wk). The rate of preterm births was 9.1% and 12.7% after therapeutic cerclage and bed rest alone.

Conclusions: CIP is very frequent in Hungary probably due the extremely high number of previous induced abortion performed by dilatation and curettage method. CIP associates with an increased risk for preterm births; however, this increased risk was reduced by bed rest alone and mainly by therapeutic cerclage.

Key words: maternal cervical incompetence, preterm birth, therapeutic cerclage, bed rest alone

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Immediately after the selection of newborns an explanatory letter was sent to the mothers explaining the purpose of the HCCSCA, the benefit of this public health activity for them and in general for the prevention of unsuccessful birth outcomes. Mothers were asked to send us the prenatal care logbook and every other medical record regarding their pregnancy complications and diseases diagnosed during the studied pregnancy and lasting for at least three weeks. Prenatal care was mandatory 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 role of licensed obstetricians was to record all pregnancy complications (e.g. CIP), maternal diseases and related drug prescriptions in the prenatal care logbook during the studied pregnancy. If pregnant women were hospitalised (e.g. due to therapeutic cerclage), in general the discharge summary was also available.

In addition, a structured questionnaire with a list of medicines (drugs and pregnancy supplements), diseases and pregnancy complications, plus a printed informed consent form were also mailed to the mothers. The questionnaire requested information on, among other things, maternal personal (e.g. employment status) and medical (e.g. history of previous pregnancies) data, pregnancy complications, maternal diseases and medicine intakes during the studied 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 questionnaire and informed consent with their signature in our prepaid envelop.

The interval between the end of pregnancy and return of the “information package” including prenatal care logbook, questionnaire, etc. was 5.2±2.9 months. In addition, 200 non-respondent and 600 respondent mothers were visited at home as part of two validation studies (12, 13). Regional nurses helped mothers to fill in the same questionnaire, evaluated the available medical documents (prenatal logbook, discharge summary, etc.) and obtained data regarding smoking and drinking habit through a cross interview of mothers and their close relatives, in general their male partners, living together, and the results of “family consensus” was recorded.

Finally, the necessary information was obtained on 83.0% of enrolled mothers (81.3% from reply, 1.7% from visit). Prenatal care logbook was available in 94.0% of these mothers.

CIP was defined as an initial painless, progressive dilatation of the uterine cervix (15 mm in primiparous pregnant women and 20 mm or more in pregnant women with previous deliveries) during the second trimester of pregnancy under which circumstances preterm delivery seems inevitable unless intervened. The cervical length was measured rarely with transvaginal ultrasonography and/or reported during the study period.

A transvaginal cervical cerclage can be inserted prophylactically before pregnancy or during the first trimester, or therapeutically after detection of CIP. The therapeutic cervical cerclage was performed in Hungary according to the technique of McDonald (8) when dilatation of the cervix and/or bulging membranes was present during the second trimester of pregnancy. After therapeutic cerclage, according to the Hungarian practice, women needed a complete bed rest for 48 hours. On the third day they were allowed to leave the bed to use the bathroom. On the fourth day they were allowed to move three times for a quarter of an hour each time. Pregnant women were discharged from the hospital on the fifth day. At home they were allowed to be physically active 3 times for a quarter of an hour each time until the 32nd gestational week. Cerclages were removed at the beginning of labour or electively in the 37th week of gestation. Another group of women with CIP was only treated by bed rest alone until the 32nd gestational week.

Women with prophylactic transvaginal cervical cerclage before pregnancy or during the first trimester, in addition women with previous history of cold knife conisation and uterine anomalies were excluded from the study.

In Hungary practically all deliveries took place in inpatients obstetric clinics and birth attendants were obstetricians during the study period. Thus both birth weight and gestational age at delivery were medically documented in the discharge summary of mothers after delivery. Gestational age was calculated from the first day of the last menstrual period. The definition of preterm birth was less than 37 completed weeks (less than 259 days), while postterm birth was 42 completed weeks or more (i.e. 294 days or more). Thus term births occurred from 37 to less than 42 completed weeks (259 to 293 days). The definition of low and large birthweight newborns was less than 2,500 g and 4,500 g or more.

Related drug treatments were also evaluated. Other potential confounding factors included maternal age, birth order, marital and employment status as indicators of socio-economic status because they showed a good correlation with the level of education and income (14), other maternal diseases, pregnancy supplements particularly folic acid and multivitamins as indicators of the standard of preconceptional and prenatal care were considered.

Here the 17 years’ data of the HCCSCA between 1980 and 1996 are evaluated because the data collection has been changed since 1997 and this part of data set has not been validated until now.

Statistical Analysis of Data
Statistical analyses were carried-out with the statistical software SAS version 8.02 (SAS Institute Ins., Cary, North Carolina, USA). First, characteristics of newborn infants born to mothers with and without CIP as reference were compared using χ² test for categorical variables, while Student t-test for quantitative variables. Second, the characteristics of pregnant women with or without CIP were compared. Third frequencies of other pregnancy complications, acute and chronic maternal diseases, in addition maternal drug uses and vitamin supplementations were compared in mothers with or without CIP in ordinary logistic regression models and prevalence odds ratios (POR) with their 95% confidence intervals (CI) were evaluated. Finally, the birth outcomes, i.e. mean gestational age at delivery and birth weight, in addition the rate of preterm and postterm births, low and large birthweight newborns was evaluated in mothers with CIP but differentiated according to the treatment: therapeutic cerclage or bed rest alone and mothers without CIP as reference using adjusted Student t-test and POR with 95% CI.

RESULTS
The number of births was 2,146,574 during the study period between 1980 and 1996. Thus 38,151 births of our study group
represented 1.8% of all Hungarian births. The data regarding diagnosis and treatment of CIP studied were obtained prospectively through prenatal care logbooks and other medical records in 35,866 pregnant women (94.0%), and retrospectively by the questionnaire completed by 2,285 mothers (6.0%). There was no significant difference between the rate of CIP in the two subgroups, thus they were evaluated together. Of 38,151 newborns, 2,795 (7.33%) had mothers with CIP during the second trimester of the study pregnancy.

Most CIP were recorded in the 5th and 6th gestational months, however, 13.4% of women had CIP diagnosis before the 16th, but after the 12th gestational week.

Table 1 shows the data of babies born to mothers with or without CIP, the latter as reference group. There was no difference in the sex ratio between the two study groups. The rate of twins was somewhat higher in pregnant women with CIP (N: 63, 2.3%) than in pregnant women without CIP (N: 347, 1.0%) (χ² = 39.4; p = 0.0001). The rates (e.g. preterm birth) and means of birth outcomes (e.g. birth weight) in newborn infants born to mothers without CIP corresponded well to the Hungarian newborn population in the study period.

The mean gestational age at delivery was 0.4 week shorter in pregnant women with CIP than the reference 39.4 week, and it was reflected in the significantly higher rate of preterm births. The mean birth weight was lower and the rate of low birth weight newborns was also higher. However, the lower mean birth weight can partly be explained by the shorter gestational age. The proportion of postterm births and large birthweight newborns was lower. However, the lower mean birth weight was reflected in the significantly higher rate of preterm births. The use of pregnancy supplements was also evaluated and folic acid was used more frequently in pregnant women with CIP (N: 2,163, 77.4%) than by pregnant women without CIP (N: 24,611, 69.6%, OR with 95% CI: 1.5, 1.4–1.7). The use of folic acid containing multivitamins did not show difference among the study groups (N: 170 vs. 2,339; 6.1% vs. 6.6%).

Pregnant women with CIP were differentiated into two subgroups (Table 1): CIP with therapeutic cerclage and bed rest (N: 2,163, 77.4%) than by pregnant women without CIP (N: 24,611, 69.6%, POR with 95% CI: 1.5, 1.4–1.7). The use of folic acid containing multivitamins did not show difference among the study groups (N: 170 vs. 2,339; 6.1% vs. 6.6%).

Pregnant women with CIP were differentiated into two subgroups (Table 1): CIP with therapeutic cerclage and bed rest (N: 1,112, 39.8%, i.e. 2.9% of all pregnant women), however, this subgroup will be mentioned as only therapeutic cerclage later, and CIP with bed rest alone (N: 1,683, 60.2%, i.e. 4.4% of all pregnant women). Therapeutic cerclage was performed before the 27th gestational week.

### Table 1. Birth outcomes of pregnant women with CIP and without CIP as reference, and mothers with CIP by therapeutic cerclage or bed rest alone

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pregnant women with CIP (N=2,795)</th>
<th>without CIP (N=35,356)</th>
<th>Comparison</th>
<th>Pregnant women with CIP by therapeutic cerclage (N=1,112)</th>
<th>with pregnant women without CIP</th>
<th>Comparison</th>
<th>Pregnant women with CIP and bed rest alone (N=1,683)</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative</td>
<td>Mean S.D.</td>
<td>Mean S.D.</td>
<td>t=</td>
<td>Mean S.D.</td>
<td>t=</td>
<td>p=</td>
<td>Mean S.D.</td>
<td>t=</td>
</tr>
<tr>
<td>Gestational age, wk*</td>
<td>39.0 2.2</td>
<td>39.4 2.0</td>
<td>8.3</td>
<td>39.2 2.0</td>
<td>3.0</td>
<td>0.003</td>
<td>38.9 2.3</td>
<td>9.6</td>
</tr>
<tr>
<td>Birth weight, g**</td>
<td>3.200 527</td>
<td>3.282 509</td>
<td>7.9</td>
<td>3.192 501</td>
<td>7.0</td>
<td>&lt;0.0001</td>
<td>3.207 544</td>
<td>4.1</td>
</tr>
<tr>
<td>Categorical</td>
<td>No. %</td>
<td>No. %</td>
<td>POR (95% CI)</td>
<td>No. %</td>
<td>POR (95% CI)</td>
<td>No. %</td>
<td>POR (95% CI)</td>
<td>No. %</td>
</tr>
<tr>
<td>Preterm birth*</td>
<td>311 11.1</td>
<td>3,185 9.0</td>
<td>1.3 (1.1–1.4)</td>
<td>101 9.1</td>
<td>1.0 (0.8–1.3)</td>
<td>213 12.7</td>
<td>1.5 (1.3–1.7)</td>
<td>138 8.2</td>
</tr>
<tr>
<td>Low birthweight**</td>
<td>218 7.8</td>
<td>1,949 5.5</td>
<td>1.5 (1.3–1.7)</td>
<td>80 7.2</td>
<td>1.4 (1.1–1.9)</td>
<td>138 8.2</td>
<td>1.2 (1.0–1.4)</td>
<td>138 8.2</td>
</tr>
<tr>
<td>Postterm birth*</td>
<td>201 7.2</td>
<td>3,661 10.4</td>
<td>0.7 (0.6–0.8)</td>
<td>87 7.8</td>
<td>0.7 (0.6–0.9)</td>
<td>114 6.8</td>
<td>0.6 (0.5–0.8)</td>
<td>6 0.4</td>
</tr>
<tr>
<td>Large birthweight**</td>
<td>11 0.4</td>
<td>304 0.9</td>
<td>0.5 (0.2–0.8)</td>
<td>5 0.5</td>
<td>0.6 (0.2–1.4)</td>
<td>6 0.4</td>
<td>0.5 (0.2–1.1)</td>
<td>6 0.4</td>
</tr>
</tbody>
</table>

*adjusted for maternal age, birth order and maternal employment status
**adjusted for maternal age, birth order, maternal employment status and gestational age

Bold figures indicate significant associations.

The prevalences of other pregnancy complications are shown in Table 3. Threatened preterm delivery is not evaluated because CIP was equivalent with the diagnosis of threatened preterm delivery. The prevalence of threatened abortion, placental disorders particularly premature separation of placenta (abruption of placentae), poly/oligohydramnios and anemia was higher in pregnant women with CIP, while the occurrence of preeclampsia-eclampsia was somewhat lower.

All but one acute and chronic maternal disease showed a similar occurrence in pregnant women with CIP and without CIP. The exception was hemorrhoids which was recorded more frequently in pregnant women with CIP (N: 131, 4.7%) than in pregnant women without CIP (N: 1,137, 3.2%).

Table 4 shows the frequently used drugs. The tocolytic treatment based on terbutaline and fenoterol completed with verapamil and spasmodic aminophylline and drotaverine, in addition the sedative diazepam and promethazine was more frequent in pregnant women with CIP. Allylestrenol and magnesium treatments are common in pregnant women at high risk in Hungary. Other drugs were used due to other diseases of pregnant women.

The use of pregnancy supplements was also evaluated and folic acid was used more frequently by pregnant women with CIP (N: 2,163, 77.4%) than by pregnant women without CIP (N: 24,611, 69.6%, POR with 95% CI: 1.5, 1.4–1.7). The use of folic acid containing multivitamins did not show difference among the study groups (N: 170 vs. 2,339; 6.1% vs. 6.6%).

Pregnant women with CIP were differentiated into two subgroups (Table 1): CIP with therapeutic cerclage and bed rest (N: 1,112, 39.8%, i.e. 2.9% of all pregnant women), however, this subgroup will be mentioned as only therapeutic cerclage later, and CIP with bed rest alone (N: 1,683, 60.2%, i.e. 4.4% of all pregnant women). Therapeutic cerclage was performed before the 27th gestational week.
### Table 2. Characteristics of pregnant women with cervical incompetence in pregnancy (CIP) and without CIP as reference, and mothers with CIP treated by therapeutic cerclage or bed rest alone

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pregnant women with CIP (N=2,795)</th>
<th>Pregnant women without CIP (N=35,356)</th>
<th>Comparison</th>
<th>Pregnant women with CIP by therapeutic cerclage (N=1,112)</th>
<th>Pregnant women with CIP and bed rest alone (N=1,683)</th>
<th>Comparison with pregnant women without CIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;19 or less</td>
<td>226 8.1</td>
<td>3,051 8.6</td>
<td>X^2=1.8, p=0.40</td>
<td>820 73.7</td>
<td>1,200 71.3</td>
<td>X^2=3.9, p=0.14</td>
</tr>
<tr>
<td>&gt;20–29</td>
<td>2,015 72.1</td>
<td>25,587 72.4</td>
<td>X^2=1.0, p=0.59</td>
<td>674 40.0</td>
<td>1,009 60.0</td>
<td>X^2=2.2, p=0.03</td>
</tr>
<tr>
<td>30 or more</td>
<td>554 19.8</td>
<td>6,718 19.0</td>
<td>X^2=3.9, p=0.14</td>
<td>486 27.5</td>
<td>820 49.5</td>
<td>X^2=1.0, p=0.59</td>
</tr>
<tr>
<td>Mean, S.D.</td>
<td>25.6±4.7</td>
<td>25.4±4.9</td>
<td>X^2=1.8, p=0.40</td>
<td>25.4±4.9</td>
<td>25.4±4.9</td>
<td>X^2=1.8, p=0.40</td>
</tr>
<tr>
<td>Birth order</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1,132 40.5</td>
<td>17,077 48.3</td>
<td>X^2=63.1, p&lt;0.0001</td>
<td>462 41.5</td>
<td>674 40.0</td>
<td>X^2=46.1, p&lt;0.0001</td>
</tr>
<tr>
<td>2 or more</td>
<td>1,663 59.5</td>
<td>18,279 51.7</td>
<td>X^2=19.7, p&lt;0.0001</td>
<td>650 58.5</td>
<td>1,009 60.0</td>
<td>X^2=19.7, p&lt;0.0001</td>
</tr>
<tr>
<td>Mean, S.D.</td>
<td>1.8±0.8</td>
<td>1.7±0.9</td>
<td>X^2=76.6, p&lt;0.0001</td>
<td>1.8±0.9</td>
<td>1.8±0.9</td>
<td>X^2=76.6, p&lt;0.0001</td>
</tr>
<tr>
<td>Employment status</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional</td>
<td>370 13.2</td>
<td>3,983 11.3</td>
<td>X^2=1.4, p=0.23</td>
<td>49 4.4</td>
<td>49 4.4</td>
<td>X^2=1.4, p=0.23</td>
</tr>
<tr>
<td>Managerial</td>
<td>876 31.3</td>
<td>9,258 26.2</td>
<td>X^2=76.6, p&lt;0.0001</td>
<td>180 16.2</td>
<td>252 15.0</td>
<td>X^2=76.6, p&lt;0.0001</td>
</tr>
<tr>
<td>Skilled worker</td>
<td>786 28.1</td>
<td>10,904 30.8</td>
<td>X^2=76.6, p&lt;0.0001</td>
<td>292 26.3</td>
<td>495 29.4</td>
<td>X^2=76.6, p&lt;0.0001</td>
</tr>
<tr>
<td>Semiskilled worker</td>
<td>430 15.4</td>
<td>5,353 15.1</td>
<td>X^2=76.6, p&lt;0.0001</td>
<td>352 30.5</td>
<td>502 29.0</td>
<td>X^2=76.6, p&lt;0.0001</td>
</tr>
<tr>
<td>Unskilled worker</td>
<td>99 3.5</td>
<td>1,760 5.0</td>
<td>X^2=76.6, p&lt;0.0001</td>
<td>49 4.4</td>
<td>50 3.0</td>
<td>X^2=76.6, p&lt;0.0001</td>
</tr>
<tr>
<td>Housewife</td>
<td>102 3.7</td>
<td>1,936 5.5</td>
<td>X^2=76.6, p&lt;0.0001</td>
<td>49 4.4</td>
<td>53 3.2</td>
<td>X^2=76.6, p&lt;0.0001</td>
</tr>
<tr>
<td>Others</td>
<td>132 4.7</td>
<td>2,162 6.1</td>
<td>X^2=76.6, p&lt;0.0001</td>
<td>49 4.4</td>
<td>107 6.4</td>
<td>X^2=76.6, p&lt;0.0001</td>
</tr>
</tbody>
</table>

Bold figures indicate significant associations.

### Table 3. Pregnancy complications

<table>
<thead>
<tr>
<th>Pregnancy complications</th>
<th>Pregnant women with CIP (N=2,795)</th>
<th>Pregnant women without CIP (N=35,356)</th>
<th>Comparison</th>
<th>Pregnant women with CIP by therapeutic cerclage (N=1,112)</th>
<th>Pregnant women with CIP and bed rest alone (N=1,683)</th>
<th>Comparison with pregnant women without CIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea–vomiting</td>
<td>1,491 53.4</td>
<td>18,477 52.3</td>
<td>X^2=1.0, p=0.9-1.1</td>
<td>602 45.1</td>
<td>888 52.8</td>
<td>X^2=1.0, p=0.9-1.1</td>
</tr>
<tr>
<td>Intending abortion</td>
<td>654 23.4</td>
<td>5,858 16.6</td>
<td>X^2=1.0, p=0.9-1.1</td>
<td>203 7.3</td>
<td>144 8.6</td>
<td>X^2=1.0, p=0.9-1.1</td>
</tr>
<tr>
<td>Preeclampsia– eclampsia</td>
<td>203 7.3</td>
<td>3,018 8.5</td>
<td>X^2=1.0, p=0.9-1.1</td>
<td>88 3.0</td>
<td>114 6.8</td>
<td>X^2=1.0, p=0.9-1.1</td>
</tr>
<tr>
<td>Placental disorders*</td>
<td>74 2.7</td>
<td>518 1.5</td>
<td>X^2=1.0, p=0.9-1.1</td>
<td>39 3.5</td>
<td>25 1.5</td>
<td>X^2=1.0, p=0.9-1.1</td>
</tr>
<tr>
<td>Polyoligohydramnios</td>
<td>23 0.8</td>
<td>182 0.5</td>
<td>X^2=1.0, p=0.9-1.1</td>
<td>7 0.5</td>
<td>12 0.7</td>
<td>X^2=1.0, p=0.9-1.1</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>25 0.9</td>
<td>245 0.7</td>
<td>X^2=1.0, p=0.9-1.1</td>
<td>9 0.6</td>
<td>12 0.7</td>
<td>X^2=1.0, p=0.9-1.1</td>
</tr>
<tr>
<td>Anemia</td>
<td>592 21.2</td>
<td>5,764 16.3</td>
<td>X^2=1.0, p=0.9-1.1</td>
<td>141 12.7</td>
<td>451 26.8</td>
<td>X^2=1.0, p=0.9-1.1</td>
</tr>
</tbody>
</table>

*placenta previa, premature separation of placenta, antepartum hemorrhage

Bold numbers show significant associations.
The second objective of the study was the analysis of birth outcomes according to the treatments of CIP (Table 1). There was no significant difference in sex ratio (i.e. in the proportion of boys) of newborns and rate of twins between the groups of therapeutic cerclage and bed rest alone. The mean gestational age at delivery was shorter by 0.3 week in babies born to mothers with CIP treated by bed rest alone than to mothers with CIP treated by therapeutic cerclage and bed rest alone. The mean birth weight was significantly higher in babies born to mothers with CIP treated by bed rest alone than to mothers with CIP treated by cerclage. This difference was reflected in the rate of large birth weight newborns did not show significant difference explained partly by the limited number of subjects.

However, it is worth analyzing the possible confounders at the comparison of two subgroups with CIP. Table 2 summarizes the basic characteristics of pregnant women with CIP treated by cerclage and bed rest alone as well. The mean maternal age was somewhat higher in the subgroup of pregnant women with CIP treated by bed rest alone. Mean birth order was similar in these two subgroups, while the proportion of unmarried pregnant women was lower in women with CIP treated by bed rest alone. Maternal employment status showed some differences between the two subgroups of cerclage and bed rest alone, but no characteristic pattern was observed.

At the evaluation of other pregnancy complications (Table 3), intending abortion and placental disorders were more frequent in both subgroups of pregnant women with CIP treated by therapeutic cerclage and bed rest alone. However, the occurrence of anemia showed a controversial pattern, less frequent in pregnant women with CIP treated by cerclage and more frequent in pregnant women with CIP treated by bed rest alone compared to the proportion of unmarried pregnant women without CIP.

Table 4 shows the frequently used drugs in both subgroups of pregnant women with CIP. Allylestrenol (1.6, 1.4–1.9) was used more frequently, while aminophylline (0.6, 0.5–0.8), drotaverine (0.8, 0.6–0.9), penamecillin (0.7, 0.5–0.9) and pholedrin (0.6, 0.5–0.7) were used less frequently in the subgroup of pregnant women with CIP treated by cerclage.
0.4–0.9) were used less frequently by mothers with CIP and bed rest alone. (In brackets POR with 95% CI are shown.) CIP with therapeutic cerclage may associate with intrauterine infections, and it explains the higher use of penicillin (and some other rarely used antibiotics, not shown in this table) only in this subgroup of pregnant women.

The use of folic acid was more frequent by pregnant women with CIP treated by cerclage (N: 714, 64.2%; POR with 95% CI: 1.5, 1.4–1.7) than by pregnant women with CIP and bed rest alone (N: 1,024, 60.8%; POR with 95% CI: 1.3, 1.2–1.4) though both figures exceeded the reference value of women without CIP.

**DISCUSSION**

Our study resulted in three main findings. First, the prevalence of CIP was 7.33% in Hungary during the study period, and it is unexpectedly high compared with about 1% prevalence of CIP in other countries (15, 16). Second, the previously known association of CIP with a higher risk for preterm birth (17, 18) was confirmed in our study. Third, the therapeutic cerclage in pregnant mothers with CIP was a more effective method for the reduction of preterm births than the bed rest alone. However, the preterm birth preventive effect of cerclage was associated with a mild intrauterine growth retardation of the fetus.

The strengths of HCCSCA can be explained by the population-based large data set including 2,795 pregnant women with CIP in the ethnically homogeneous Hungarian (Caucasian) people. The nature of our study design was a cohort based on medically and prospectively documented CIP, in addition medically recorded gestational age at delivery and birth weight. Furthermore potential confounding factors were available for analysis. Of course, limitations of the data set need to be mentioned as well. 1. Our analysis was based on the medically recorded CIP, however, in 6% of pregnant women this diagnosis was based on maternal information. 2. We were not able to check the validity of medically recorded CIP diagnoses, i.e. whether clinicians followed the recommended diagnostic criteria of CIP or not. In addition, the length of cervical canal was not measured and/or reported during the study period. Thus the diagnosis of CIP was based on a clinical assessment of obstetricians and the severity of CIP was not known. However, these weaknesses were similar in the two subgroups treated by cerclage or bed rest alone. 3. We had no information regarding the origin of CIP. Our questionnaire requested information on the outcomes of previous pregnancies, but induced abortions due to social reasons were omitted from this list. 4. We did not know exactly the occurrence of preterm births in previous pregnancies because gestational age at delivery was not mentioned in the previous pregnancies of several women. However, about 40% of our pregnant women with CIP were primiparae and the evaluation of primiparous women with or without CIP resulted in similar findings as in the total data set. 5. We did not know how well obstetricians accomplished the Hungarian protocol of CIP treatment by cerclage after the surgical intervention and bed rest alone, in addition we cannot estimate the compliance of patients. However, we suppose a similar bias in the two subgroups of pregnant women with CIP treated by cerclage or bed rest alone. 6. Our data were not appropriate to evaluate the causes for the choice of cerclage or bed rest alone treatment, therefore we did not know whether more severe CIP were selected for therapeutic cerclage or it depended only on the attitude of obstetricians in the given medical institutions. 7. The occurrence of maternal smoking as confounder was not known in the total data set. Our previous study showed the low validity of retrospective maternal self-reported information regarding smoking and alcohol drinking during pregnancy (19), therefore these data were collected only from 800 pregnant women based on the cross interview of women and their family members at the home visit in the data set of the HCCSCA. Of these 800 pregnant women, 152 (19.0%) smoked during pregnancy which corresponded well to the figure of smoking among Hungarian pregnant women (20). Of these 800 pregnant women, 64 had CIP, and among them 11 (17.2%) smoked during the study pregnancy. 8. The medically recorded birth weight is a reliable variable of newborns, however, the medically recorded gestational age was measured on the basis of the first day of the last menstrual period without confirmation with ultrasound during the study period and this variable is incorrect in approximately 10% of pregnancies (6). However, we may suppose that this bias was similar in all study groups. 9. The response rate of mothers was 83% and only 200 non-respondent women were visited at home. However, there was no difference in the distribution and occurrence of frequently used drugs and diseases between respondent and non-respondent mothers in our validation studies (13).

The high prevalence of CIP in Hungary needs some comments. The main explanation is the extremely high number of induced abortions performed by the old-fashioned method of mechanical dilatation of cervix by Hegar devices + curettage (D+C) after the free Abortion Law in 1956 (21). The ratio of livebirths and induced abortions due to mainly social reasons was 1.00:1.19 (2,499,248 vs. 2,971,250) between 1957 and 1973. The Abortion Law was restricted in 1973, after this but before the period of this study, this ratio was 1.00:0.51 (1,072,031 vs. 546,362) between 1974 and 1979. The ratio of livebirths and induced abortion was 1.00:0.65 (2,146,574 vs. 1,397,188) during the study period (i.e. 1980–1996). The late adverse effect of induced abortions (as a main method of birth control in Hungary) causes a 1.1–2.9 higher risk for preterm births due to CIP in the next pregnancies (22, 23), and this risk is increasing with the number of previous induced abortions (24, 25). These associations were found by Hungarian experts as well, and the dose-effect relation (number of previous abortion associated with a higher risk for preterm birth) was also confirmed (26, 27). Unfortunately the use of abortion pills was not introduced in Hungary in order to prevent CIP until now, though this method does not associate with CIP (25).

Our study confirmed the association of CIP with the higher risk for preterm births, this risk means about a 30% excess risk thus may explain about one-quarter of preterm births in Hungary. Thus CIP can be considered one of the most frequent causes of preterm births in Hungary. The higher rate of twins may have some association with CIP.

As far as we know, previously three observational studies evaluated the effect of cerclage versus no cerclage treatment after detection of short cervical length. Two studies indicated the benefit of cerclage on the basis of longer gestational age and lower rate of preterm delivery (28, 29) while there was no significant difference in these variables between cerclage and bed rest alone groups in the third study (9). The results of two randomised controlled
trials showed controversial findings. Rust et al. (15) randomly allocated 61 pregnant women with a cervical length of <25 mm or prolapse of the fetal membranes into the endocervical canal for more than 25% of the original cervical length, measured between 16 and 24 weeks of gestation to receive a therapeutic McDonald cerclage with bed rest or bed rest alone. There was no statistically significant difference in mean gestational age at delivery (33.5 ± 6.3 vs. 34.7 ± 4.7 weeks) and in the prevalence of preterm births. However, Althuisius et al. (30) reported that therapeutic McDonald cerclage resulted in a longer cervical length (measured by transvaginal ultrasonography) in women with CIP. The final results of the Cervical Incompetence Prevention Randomized Cereclage Trial (CIPRACT) (16) based on 35 women showed that therapeutic cerclage with bed rest reduced preterm delivery (before 34 weeks of gestation) in women with risk factors and/or symptoms of CIP and cervical length of <25 mm before 27 weeks of gestation. In addition the comparison of McDonald cerclage and bed rest versus bed rest alone indicated that preterm delivery was more frequent with a higher admission to the neonatal intensive care unit (as indicator of neonatal morbidity) or neonatal death in the group of women with CIP and bed rest alone.

Our findings showed the higher efficacy of therapeutic McDonald cerclage in the reduction of preterm births in women with CIP than bed rest alone in Hungary. However, it is necessary to consider the very high prevalence of CIP in Hungarian pregnant women due to the extreme frequency of previous induced abortions for social reason and circumstances of clinical diagnosis of CIP. The possible intrauterine growth retardation of fetus after the surgical intervention of CIP by cerclage would need further studies because a lower birth weight was found in the CIPRACT (16) as well. However, the CIPRACT included antimicrobial (amoxicillin, clavulanic acid, metronidazole) treatment in women with CIP and indomethacin suppository to inhibit possible contractions caused by cerclage. The Hungarian protocol of therapeutic cerclage did not contain these complementary treatments, though several pregnant women were also treated by antimicrobial drugs. On the other hand the rate of low birthweight newborns was not higher and the proportion of large birthweight newborns was not smaller in babies born to mothers with CIP treated by cerclage than in women with CIP and bed rest alone and these findings are against intrauterine fetal growth retardation.

Our study showed the higher rate of placental disorders particularly abortion placentae in women with CIP which was found in other studies as well (15), in addition the higher use of folic acid may indicate a better preparation for pregnancy or prenatal care. The possible association between CIP and hemorrhoids, in addition the controversial prevalence of anemia in women with CIP treated by cerclage or bed rest alone also need further studies.

In conclusion, our study showed that CIP is very frequent in Hungary probably due to the extremely high number of previous induced abortion with D + C method. Our findings confirmed the higher risk for preterm birth in pregnant women with CIP though their CIP was treated. The higher risk for preterm births due to CIP can be reduced more effectively by the therapeutic cerclage than by the bed rest alone.

Acknowledgement
This study was partly sponsored by a generous grant from Richter Gedeon Pharmaceuticals Ltd., Budapest, Hungary.

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Received February 24, 2009
Accepted in revised form July 15, 2009

BOOK REVIEW

Christos S. Mantzoros, editor
Nutrition and Metabolism:
Underlying Mechanisms and Clinical Consequences

The editor of the book is Christos Mantzoros, an Associated Professor of Medicine at Harvard Medical School and an Associate Professor in Environmental Health at the Harvard School of Public Health. He serves as the Clinical Research Overseer of the division of Endocrinology, Diabetes and Metabolism at Beth Israel Deaconess Medical Centre and the Joslin Diabetes Centre. He conducts research on obesity and diabetes/metabolic diseases, as reflected in the presented book, Nutrition and Metabolism.

This book, written by 29 co-authors, with 423 pages, consists of five basic segments, i) defining the scope of obesity and the metabolic syndrome problem, ii) their genetics and pathophysiology, iii) public health perspective related to obesity, iv) nutritional recommendations, and v) clinical assessment and management of obesity. The appendix of the book recapitulates methods for classifying, diagnosing, and monitoring of obesity and diabetes mellitus type 2.

In the first section “Nutrition and Metabolism Syndrome: A Twenty –First Century Epidemic of Obesity and Eating Disorders” Prof. Mantzoros explains that excessive caloric intake leading to obesity and to metabolic syndrome in adults and especially children and adolescents is becoming more and more prevalent in affluent western societies. This phenomenon has resulted in increased prevalence of type 2 diabetes among adolescents and is expected to shift the age for diagnosis of obesity and associated co-morbidities, including cardiovascular diseases and cancers to a younger age-group. The author warns that the potential financial, psychological, and public health implications of these changes are enormous and have not yet been fully appreciated. If the current trends continue it is expected that by the year 2020 more than 50% of Americans will be obese, possibly making obesity the norm and leanness the exception.

In the second section attention is paid to the genetics and pathophysiology of obesity.

The discussion is focused on how genes, alone and in combination with the environment, can give rise to obesity and metabolic syndrome. Monogenic, syndrome ( mendelian) and polygenic obesity as well as metabolic syndrome and type 2 diabetes phenotypes according to their genetic traits are described, together recent knowledge obtained from candidate gene analyses in particular and from genome wide linkage scan approach methodology.

The pathophysiology of obesity is explained in chapters describing environmental inputs, intake of nutrients and endogenous molecules contributing to the regulation of energy homeostasis, as central integration of environmental and endogenous signals and regulation of food intake and energy expenditure.

New research findings in the area of energy regulation are summarised, starting from the original classical hypotheses proposing metabolite sensing, through peripheral tissue-brain interactions, and coming full circle to the recently discovered pathways regulating energy homeostasis. Inputs important for the regulation of energy homeostasis such as i) metabolic, ii) endocrine, iii) neural, and iv) exogenous, environmental signals and environmental inputs represented by orosensory properties of food and emotional eating are described in detail. The fact that obesity rates have been gradually increasing is related to a rapidly changing so-called obesitogenic environment and associated lifestyle changes, especially characterised by a sedentary lifestyle and diet.

Explanation of the role of particular nutrients in the diet such as dietary fats, fatty acids, carbohydrates in regulation of energy homeostasis as well as the role of hormones from adipose tissue, the gastrointestinal tract, and the pancreas for the regulation of food intake and energy balance comprise the core of this chapter. Information is presented on factors and molecules involved in the pathophysiology of metabolic syndrome and particularly the role of adipokines, free fatty acids and inflammatory markers; dysfunctional adipose tissue is considered by the authors as the “condition sine qua non” for the development of metabolic syndrome.

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