Preterm Birth and Licorice Consumption during Pregnancy

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Heavy licorice (glycyrrhizin) consumption has been associated with shorter gestation. The aim of the present study was to test whether this association also applies to preterm (<37 weeks) births. In 2000–2001, a sample of 95 Finnish women who delivered preterm singletons was compared with controls (n = 107) who delivered babies of normal gestational age in the same hospital. Glycyrrhizin intake was calculated from questionnaires containing detailed items on licorice consumption. Glycyrrhizin exposure was grouped into three levels: low (<250 mg/week), moderate (250–499 mg/week), and heavy (≥500 mg/week). Heavy consumption versus a lower level of consumption was associated with a more than twofold increased risk of preterm (<37 weeks) delivery. The association was stronger when only the 40 births classified as early preterm delivery (<34 weeks) were included (odds ratio = 3.07, 95% confidence interval: 1.17, 8.05 for the fully adjusted model). In conclusion, heavy glycyrrhizin exposure was associated with preterm delivery and may be a novel marker of this condition.

gestational age; glycyrrhizic acid; pregnancy

Abbreviation: SD, standard deviation.

Licorice consumption is very popular among women of childbearing age in Finland as well as some other western countries (Denmark, the Netherlands, parts of northern Germany, Greenland, and New Zealand). The specific reason is a mystery. In Finland, consumption of licorice candies is a socially acceptable habit not linked to social class or any known psychological characteristics.

In a previous cross-sectional study on licorice and birth outcome (1), we noticed a statistically significant inverse association of heavy licorice and consequently glycyrrhizic acid (3β-D-diglucuronyl-18β-glycyrrhetinic acid) consumption with length of gestation. This finding was interesting, because the etiology of preterm birth is still poorly understood (2–4), and both glycyrrhizic acid and the mechanism of delivery are associated with glucocorticoid and prostaglandin metabolism (1). However, our previous study, based in a city hospital (secondary level) in which few preterm births occurred, was not designed to detect an association with preterm births. Because the association, if real, might shed light on the mechanism of preterm birth, we decided to reexamine this finding in the university clinic (tertiary level) that, while also handling normal births, treats more preterm deliveries.

MATERIALS AND METHODS

The original aim of the present study (2000–2001) was to collect data on 100 preterm births (<37 weeks of gestation) and compare them with 100 full-term births (≥37 weeks) designated as controls. Midwives in three maternity wards of the Department of Obstetrics and Gynecology of the University of Helsinki, Finland, were asked to distribute our questionnaire, during the postnatal period, to all mothers who had given birth to full-term and preterm (<37 weeks) babies. Gestational age is routinely determined for all mothers with an ultrasound examination at 12–13 weeks of pregnancy and is also marked in the mothers’ hospital records. Preterm births associated with twins, elective cesarean section, or induced delivery were a priori excluded because the goal was to study a metabolic, “spontaneous” cause of singleton
preterm delivery. For the same reason, we also a priori excluded chorioamnionitis diagnosed on the basis of clinical signs in combination with either leucocytosis (white blood cell count > 15 x 10^9/liter) and/or plasma C-reactive protein levels of more than 50 mg/liter. The prevalence of cesarean section in our tertiary hospital is 22 percent.

The questionnaire contained demographic items including gestational age (in months and days, for cross-checking purposes), a question about smoking, and detailed questions about licorice consumption during pregnancy. These questions were identical to those in the previous study (1). In that larger study (1, 5), glycyrrhizin intake was not connected with various lifestyle parameters (alcohol, coffee, or tea consumption; maternal stress during pregnancy), body mass index, or blood pressure; therefore, to reduce the size of the questionnaire and to improve compliance, these items were not included in the present questionnaire. Glycyrrhizin intake was calculated from answers to detailed questions on licorice consumption, and glycyrrhizin exposure was grouped into three levels: low (<250 mg/week), moderate (250–499 mg/week), and heavy (≥500 mg/week), as described earlier (1). Because of a threshold effect, in the analyses, heavy consumption was compared with moderate and low levels combined.

NCSS software (Kaysville, Utah; Internet Web site: www.ncss.com) was used for statistical analyses. Continuous variables were compared by using the Mann-Whitney U test, and logistic regression was used for multivariate analyses. In our series, mother’s age and length of gestation were correlated positively (r = 0.25, p = 0.0004), with no evidence of a shortening at older ages; consequently, we used mother’s age as a continuous variable in the analyses. Parity was used as a dichotomous variable (>1 = 1).

RESULTS

The response rates were 67.6 percent and 64.2 percent among mothers delivering full-term and preterm babies, respectively (no significant difference). Data on nine twin births were discarded from the analyses of the preterm group; thus, our sample included 107 controls (mean gestational age, 39.8 weeks; standard deviation (SD), 1.3) and 95 cases (mean gestational age, 33.3 weeks; SD, 3.3; p < 0.0001). Of all mothers, 51.5 percent were primiparous and 11.4 percent were smokers, with no statistically significant differences between the groups. In addition, the mothers’ ages were fairly similar, although the mothers associated with preterm births were statistically significantly younger (30.2 years; SD, 5.1 vs. 32.3 years; SD, 5.3; p = 0.007).

Median glycyrrhizin intakes (interquartile range) among the mothers of cases and controls were 150.0 mg/week (75.0–409.0) and 104.0 mg/week (50.0–310.0), respectively. The heavy glycyrrhizin intake group included 19/95 (20.0 percent) mothers of cases and 11/107 (10.3 percent) mothers of controls (p = 0.06). The association of heavy intake with preterm (<37 weeks) and early preterm (<34 weeks) delivery was further investigated in multivariate analyses, and the results are shown in table 1. The point estimates for preterm delivery remained over 2 and changed very little when covariates were added to the model. The effect tended to be even larger for early preterm delivery (odds ratio = 3.07, 95 percent confidence interval: 1.17, 8.05 for the fully adjusted model).

### DISCUSSION

Results confirm the association of heavy glycyrrhizin (licorice) intake with shorter gestation that we found in a previous cross-sectional study (1) that included only a few preterm births. In the present study, we demonstrated that heavy consumption is also associated with a twofold-to-threefold increase in the risk of preterm (<37 weeks) birth. Although the 95 percent confidence interval overlapped 1 when parity and smoking were added to the model, the odds ratio for preterm delivery associated with heavy glycyrrhizin intake changed hardly at all after adjustment for covariates. A true association was further supported by our finding that early preterm delivery (<34 weeks) was significantly associated with heavy glycyrrhizin intake.

A possible limitation of this study is that information on licorice consumption during pregnancy was collected retrospectively. However, a pilot study conducted in the antenatal clinics found similar patterns of consumption among pregnant women (unpublished observations). Another limitation is the possibility of confounding. Licorice consumption simply might be associated with some other factor(s) causally related to preterm birth. We have no such evidence, however. A recent social history (6) on a special type of licorice popular in Finland, the Netherlands, and Denmark (salty licorice, “salmiak”) was a Christmas bestseller in Finland.

**TABLE 1. Odds ratios of preterm (<37 weeks) and early preterm (<34 weeks) delivery associated with heavy glycyrrhizin consumption during pregnancy.** Finland, 2000–2001

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>&lt;37 weeks (n = 95)</th>
<th>95% confidence interval</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2.18</td>
<td>0.98, 4.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Mother’s age (continuous)</td>
<td>2.28</td>
<td>1.01, 5.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above + sex (female = 0, male = 1)</td>
<td>2.25</td>
<td>0.99, 5.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above + parity (&gt;1 = 1)</td>
<td>2.28</td>
<td>1.00, 5.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above + smoking (no = 0, yes = 1)</td>
<td>2.15</td>
<td>0.93, 4.95</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Heavy (≥500 mg/week) consumption was compared with a lower level of consumption.
That book cited consumer surveys by the industry showing that licorice consumption in Finland is especially popular among those under 35 years of age and among women, that is, females of childbearing age. Licorice consumption is a socially neutral phenomenon; it is not considered to confer either a negative or positive stigma on users. Common knowledge and previous, partly unpublished results from our earlier, larger study (1) suggest that licorice consumption among Finnish women is not related to type of work, socio-economic status, or various lifestyle factors. A specific association with licorice consumption, rather than a general association with consumption of confectionery, is supported by the finding that chocolate consumption was not related to birth outcome in our earlier study (1). In that study, we also found a significant association between perceived stress during pregnancy and chocolate, but not licorice, consumption (5).

Our finding is also biologically plausible because of the effects of glycyrrhizin on cortisol and prostaglandin metabolism. Glycyrrhizin inhibits the local breakdown of cortisol in placenta, leading to increased cortisol levels that may affect prostaglandins. Carbenoxolone, a synthetic analogue of glycyrrhizin, inhibits prostaglandin-metabolizing enzymes (7) and, in the stomach, causes a local increase in prostaglandin levels. If glycyrrhizin has similar effects, it is possible that intake during pregnancy could cause a local increase in prostaglandins in the uterus and lead to contractions (4). Interestingly, in traditional medicine, licorice has been used as an abortifacient (8), but there is no experimental evidence to support this use. Further elucidation of the pathogenetic mechanisms could contribute to the research on preterm delivery. Measurement of the activities of placental enzymes or maternal plasma concentrations of glucocorticoids, corticotrophin-releasing hormone (CRH) (9, 10), and prostaglandins in heavy licorice consumers might be important.

Preterm birth is a multifactorial state (4), and heavy licorice consumption is only one of the possible factors affecting preterm delivery. In our study, the effect of licorice was clearly stronger than that of smoking, a factor conventionally associated with preterm birth. This finding implies a clinically significant effect of licorice, and the possible connection should be determined. In the present and the earlier (1) studies, approximately 10 percent of the women were considered heavy licorice consumers during pregnancy, and 500 mg of glycyrrhizin (heavy intake) corresponds to approximately 250 g of licorice per week. In Finland, packages of licorice confectionery now commonly contain 200 g or even 400 g, a quantity easily consumed by aficionados. Confectionery is the major source of glycyrrhizin in Finland and probably other western societies as well, but other forms of consumption (for example, herbal products) also may be common in some parts of the world. Their possible role in preterm births might warrant further exploration.

REFERENCES