Risk factors for congenital hypothyroidism in Egypt: results of a population case-control study (2003-2010)

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BACKGROUND AND OBJECTIVES: Although the prevention of the neuropsychological consequences of congenital hypothyroidism (CH) through the use of replacement therapy represents an important public health success, knowledge about the modifiable risk factors could reduce the number of infants affected by this disease. This study was carried out to identify risk factors for CH at Fayoum Governorate, Egypt.

DESIGN AND SETTINGS: This was a population-based case-control study, which started in 2003 and was carried out for 8 years through Fayoum center of the Egyptian Ministry of Health and Population screening program for CH.

METHODS: This study was a population-based case-control study carried out by using national project for CH. One control was enrolled for each new CH infant; 320 cases and 320 controls were enrolled in 8 years. Maternal and neonatal influences were investigated.

RESULTS: A statistically significant association of CH was observed with birth defects, female gender, gestational age >40 weeks, and gestational diabetes. An increased risk for CH was detected in twins by a multivariate analysis.

CONCLUSION: Our results suggest a multifactorial origin of CH in which genetic (high frequency of additional malformations) and environmental factors (especially maternal diabetes) play a role in the development of the disease.
study are presented in this paper. Maternal and neonatal exposure was investigated with the aim of identifying the most important risk factors for CH at Fayoum Governorate, Egypt.

METHODS
The study enrolment started in 2003 and was carried out for 8 years. Only recently, the diagnosed cases of CH screened by the selected center were included in the study. The screening test for CH was performed on dried blood spots. Thyroid-stimulating hormone (TSH) and thyroxine (T4) were measured. The positive results of the first screening test were then confirmed by serum TSH, T4, and free T4. Infants with normalized TSH between screening and recall were not included in the sample. One control was enrolled for each new CH case. This control was the first infant recorded in the same Health office where the new CH case was recorded. Cases and controls included in the study were residents of the same region. Parents were interviewed and gave their informed consent for participation in the study. The reproductive and medical history of mothers was recorded, including gestational diabetes to assess the effect of these factors during pregnancy. Neonatal features of cases and controls were collected directly from medical records. The study protocol was approved by the institutional ethics committee (Fayoum Faculty of Medicine ethics committee).

Statistical analysis
Analyses by two-by-two contingency tables were performed to estimate the association between CH and possible risk factors. Continuous variables were categorized according to biological considerations or conventional cut-off points. Matched crude ORs were estimated by the Mantel–Haenszel method. The Mantel–Haenszel summary $\chi^2$ test was used to test the significance of the matched ORs. A conditional logistic regression was performed to evaluate the adjusted effect of the considered variables on the risk of being a CH case.

RESULTS
During the 8 years of the study, 320 cases and 320 controls were enrolled and were considered for statistical analysis. Results are summarized in Tables 1, 2, and 3.

The mother’s age at delivery was slightly higher in the CH cases than in the controls (28 [8.8%] vs. 13 [4%]; age at delivery ≥40 years). No differences in risk factors related to pregnancy (parity, previous spontaneous abortion) were observed between the 2 groups. With regard to neonatal risk factors, the frequency of females was significantly higher in the CH infants than in the controls “P=0.01.” Also, an advanced gestational age was significantly associated with CH. In fact, 113 (35.3%) of CH infants were born after 40 weeks of gestation as compared to 51 (15.9%) of the controls “P=0.01.” Overall, no statistically significant difference was found in the birth weight between the cases and controls. With regard to the other neonatal features, a higher frequency of twinning was observed among cases compared to controls (5.1% vs. 0.7%, P<0.01).

In the multivariate analysis, 4 neonatal features were significantly associated with the birth of a CH infant: female gender (OR=2.0, 95% CI: 1.2-3.3), twinning (OR=12.2, 95% CI: 2.4-62.3), additional birth defects (OR=7.5, 95% CI: 2.9-19.0), and gestational age >40 weeks (OR=3.0, 95% CI: 1.8-5.1).

DISCUSSION
Our study confirmed the already known higher prevalence of CH among females than males. In fact, in this case-control study, a 2-fold higher risk of permanent CH was estimated in females than in males. However, it is still unclear why females were more susceptible to developing CH.

In our study, a significant association was observed between prolonged gestational age (>241 weeks) and CH. Some authors had suggested that infants with CH had a tendency to a prolonged gestation.13,14

With regard to the other neonatal risk factors, our
results showed that twins had a high risk for CH. However, further investigations were needed to understand the causal association between twinning and CH.

As expected, a high frequency of malformations had been observed among cases with CH 45 (14.3%) while a frequency similar to that expected in the general population was found in the control group 7 (2.1%). Although the association of congenital birth defects and CH had already been well documented, the inclusion of that variable in the multivariate model allowed an adjusted estimate of the relative risk for other factors, such as twins pregnancy, related to both CH and malformations.

Our results reported an increased risk of CH with gestational diabetes. These results were also consistent with those obtained by other authors in an experimental model; it was reported in this report that maternal diabetes in pregnancy negatively affects the fetal thyroid hormone status in pregnant rats with streptozotocin-induced diabetes mellitus. The causal relationship between diabetes in pregnancy and CH is not clear. However, it is well known that maternal diabetes affects embryonic development, leading to increased morbidity in the offspring.

In addition to the inherent limitations of this type of study, we used a sample of convenience from Fayoum Governorate, a technique that may have limited the generalizability of our findings. To help overcome this limitation, we selected our participants via a population-based case-control study to reduce the selection bias from the sample. Fortunately, the demographics of our sample were similar to the overall population of Egyptian mothers.

In conclusion, our results suggest that genetic (high frequency of malformations) and environmental factors (especially maternal diabetes) play a role in the development of CH at Fayoum Governorate, Egypt.

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| Table 2. The neonatal characteristics of CH cases compared to their matched controls. |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Neonatal characteristics | Cases (n=320) | Controls (n=320) | p-value |
|-----------------|-----------------|-----------------|-----------------|
| Female gender | 201 | 62.8 | 154 | 48.12 | <.01 |
| Gestational age (weeks) | 23 | 7.18 | 15 | 4.68 | .15 |
| ≤37 | | | | |
| 37-40 | 184 | 57.50 | 254 | 79.37 | <.01 |
| ≥41 | 113 | 35.31 | 51 | 15.93 | <.01 |
| Birth weight (grams) | 21 | 6.56 | 17 | 5.31 | .20 |
| ≤2500 | | | | |
| 2500-3500 | 196 | 61.25 | 196 | 61.12 | |
| 3500-4500 | 98 | 30.62 | 104 | 32.50 | |
| ≥4500 | 5 | 1.56 | 3 | 0.93 | .09 |
| Twins | 16 | 5 | 2 | 0.62 | <.01 |
| Additional birth defects | 45 | 14.06 | 7 | 2.18 | <.01 |

Overall χ² test

| Table 3. The OR for CH estimated by the conditional logistic regression. |
|-----------------|-----------------|-----------------|-----------------|
| Risk factors | Cases (n=320) | Controls (n=320) | 95% CIs |
|-----------------|-----------------|-----------------|-----------------|
| Female gender | 2.0 | 1.2-3.3 |
| Mother’s age (years) | 1.7 | 0.96-3.4 |
| ≤25 | | |
| ≥40 | 1.6 | 0.8-4.6 |
| Gestational age (weeks) | 1.4 | 0.5-3.9 |
| ≤37 | | |
| ≥40 | 3.0 | 1.8-5.1 |
| Twins pregnancy | 12.2 | 2.4-62.3 |
| Additional birth defects | 7.5 | 2.9-19.0 |

OR: Odds Ratio; CI: Confidence Interval. CH: Congenital hypothyroidism.
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