

Research Article

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An elevated blood glucose level and increased incidence of gestational diabetes mellitus in pregnant women with latent toxoplasmosis

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Abstract: About 30–50% of the world human population are infected with the protozoan parasite *Toxoplasma gondii* (Nicolle et Manceaux, 1908). Latent toxoplasmosis has many specific behavioural and physiological effects on the human body and influences the course of pregnancy, including secondary sex ratio of children of infected mothers. It was suggested that an increased concentration of glucose could be the proximate cause of increased sex ratio. There are some indirect indications of possible association between toxoplasmosis and certain forms of diabetes. Here we searched for a possible link between latent toxoplasmosis and the level of glucose in the blood. In a cross-sectional study, we found that pregnant women with latent toxoplasmosis had significantly higher blood glucose levels during the oral glucose tolerance test ($n = 191$, $p = 0.010$; the level of fasting plasma glucose: mean = 5.04 mmol/l vs mean = 4.88 mmol/l; blood glucose level at 1 hour mean = 7.73 mmol/l vs mean = 6.89 mmol/l and blood glucose level at two hours mean = 6.43 mmol/l vs mean = 5.74 mmol/l) and higher prevalence (19.5 %) of gestational diabetes mellitus ($n = 532$, $p = 0.033$, odds ratio = 1.78) in the 24–28th gestational weeks than *T. gondii*-free women (12.0 %). Increased level of glucose and increased incidence of gestational diabetes mellitus could have considerable clinical impact as contributors to the development of the metabolic syndrome and type 2 diabetes in *T. gondii*-infected women. Our results also brought the first empirical support for the hypothesis that the glucose concentration may play a role in *T. gondii*-associated offspring sex ratio shifts.

Keywords: parasite, GDM, oral glucose tolerance test, sex ratio, risk factors, *Toxoplasma gondii*

Toxoplasmosis, an endemic zoonosis caused by a coccidian protozoan, *Toxoplasma gondii* (Nicolle et Manceaux, 1908), is probably the most widespread human parasite in developed countries. The prevalence of latent toxoplasmosis in the population ranges from 20% to 80% depending on various environmental and sociological factors, including the number of cats in the environment, latitude, moisture, hygienic standards and kitchen habits (Tenter et al. 2000). In immunocompetent humans, postnatally acquired toxoplasmosis is either inapparent, without any clinical signs, or accompanied by cervical lymphadenopathy with fever, joint pain, headache and tiredness (Beattie 1982, Jones et al. 2001). Acute disease promoted by rapidly dividing tachyzoites in cells of many tissues often progresses spontaneously to the latent phase characterised by probably permanent presence of slowly dividing bradyzoites in tissue cysts in various organs of the host.

Latent toxoplasmosis is usually considered to pose no health threat to immunocompetent individuals; however, it is accompanied by specific changes in the psychomotor

performance, behaviour and personality profile (Flegr et al. 1996, Lindová et al. 2006, Flegr 2013). A recent correlation study performed on a set of 88 countries has also shown that the prevalence of toxoplasmosis explains about 13% of the variation in the rates of congenital abnormalities between the countries (Flegr et al. 2014).

Unlike acute toxoplasmosis in pregnancy, which has been described to damage significantly the foetal development (Wolf et al. 1939, Tenter et al. 2000), latent toxoplasmosis seems to have no significant negative impact on the health of the offspring. However, pregnant women with latent toxoplasmosis have been reported to have seemingly younger (less developed) fetuses, especially at the 16th week of pregnancy (Flegr et al. 2005, Kaňková and Flegr 2007). The immunological hypothesis assumes that *T. gondii* could weaken or switch off the mechanism of spontaneous abortions, which is, under normal conditions, responsible for the elimination of embryos with developmental defects and a (statistically) slower fetal growth rate. The hypothesis was later supported by the observed increase in

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the secondary sex ratio in children of women with latent toxoplasmosis (Kaňková et al. 2007a). The probability of the birth of a boy increased up to 0.71, which means that about 250 boys were born for every 100 girls to women with moderate concentrations of anti-*Toxoplasma* antibodies (and probably with recent but already latent infection). This effect of latent toxoplasmosis was later confirmed in experimentally infected mice (Kaňková et al. 2007b). Mice with toxoplasmosis had a higher sex ratio (expressed as the proportion of males in the offspring) than controls in the early phase of latent infection. One of possible physiological mechanisms that could be responsible for *T. gondii*-associated increase of the sex ratio is an elevated concentration of glucose (Cameron 2004, Cameron et al. 2008).

Significantly lower levels of antibodies against *T. gondii* infection were detected in the autoimmune disease type 1 diabetes mellitus (T1DM) patients (Krause et al. 2009). This phenomenon in T1DM patients may be related to their younger ages, but may also point to a protective role of the infections in T1DM development in susceptible individuals. However, it has been shown that there are considerable similarities in the genetic and environmental risk factors between latent *T. gondii* infection and diabetes mellitus (Prandota 2013).

Gestational diabetes mellitus (GDM) is a form of diabetes that is diagnosed during pregnancy and increases the risk of pregnancy and fetal complications (Johns et al. 2006, Vohr and Boney 2008, Vambergue et al. 2008). Immediately after pregnancy, five to 10 percent of women with GDM are diagnosed with diabetes, usually type 2, and women with a history of GDM have 35–60% chance of developing diabetes in the next 10 to 20 years (Centers for Disease Control and Prevention, 2011). It is possible that both the toxoplasmosis-associated increase of the sex ratio and higher incidence of GDM in high-risk *T. gondii*-positive subjects may be mediated by an effect of *T. gondii* on the concentration of blood glucose.

The main purpose of the present study is to search for differences in the blood glucose levels between *T. gondii*-negative and *T. gondii*-positive pregnant women and to test the hypothesis that GDM is more often diagnosed in *T. gondii*-positive subjects.

MATERIALS AND METHODS

Patients

The experimental design was a retrospective cross-sectional study. The main data set covered 199 pregnant women screened for various clinical reasons for GDM in the 24–28th gestational weeks in the General University Hospital in Prague in 2008. The oral glucose tolerance test (OGTT) consisted of measurements of blood glucose in three blood samples from each woman collected: A) at baseline after eight hours of fasting, B) 60 min after drinking a measured dose of glucose solution, C) 120 min after drinking the measured dose of glucose solution. The second data set covered 89 women whose GDM status was known but whose tolerance test data (blood glucose concentrations) were not available. The third data set included information from a questionnaire survey of 1 381 women from the hospital databases. For

various technical reasons, the questionnaire only reached about 1 200 women. The women were asked, among other questions unrelated to the present study, whether they had gestational diabetes mellitus during pregnancy. Altogether 249 respondents not included in data sets 1 and 2 provided either a positive or negative answer.

Serum samples collected from pregnant women at the time of screening for chromosomal abnormalities, routinely performed in the 9–12th gestational weeks in this Hospital, were frozen and stored at -70 °C for later analyses. We used these samples for the retrospective detection of antibodies against *T. gondii*.

During the whole time of the study, we worked with an anonymised data set. The study was approved by the Ethical Committee of the General University Hospital and the First Faculty of Medicine of the Charles University in Prague.

Investigations on oral glucose tolerance test

Laboratory assessment was performed in a single laboratory at the Institute of Clinical Biochemistry and Laboratory Diagnostics, General University Hospital in Prague. The exclusion criterion was an acute illness like flu or other infectious disease. The women were allowed an unrestricted carbohydrate diet for 3 days prior to the oral glucose tolerance test and were requested not to eat at least eight hours before the test. They were instructed not to take their morning medication, but to wait and take it after the test is over. Blood samples were collected by venipuncture. The women were given a 75 g glucose drink to be consumed in 5 min. The first baseline blood sample was taken prior to the administration of glucose. The second and third blood samples were taken at 60 min and 120 min after glucose administration, respectively. The women remained seated and stayed in the department while undergoing the test. If some glucose was lost by vomiting, the test was terminated.

For the Czech population, the normal glucose levels in the blood range up to 5.5 mmol/l of fasting, 8.8 mmol/l at 60 min after the glucose drink and 7.6 mmol/l at 120 min after the glucose drink. A positive screening result for gestational diabetes mellitus was defined as an increase of any of these levels of more than 0.1 mmol/l above the norm (Andělová 2013).

Immunological tests for toxoplasmosis

The complement-fixation test (CFT) which determines the overall levels of IgM and IgG antibodies of particular specificity, and Enzyme-Linked Immunosorbent Assays (ELISA) (IgG ELISA: SEVAC, Prague, IgM ELISA: TestLine, Brno) were used to detect toxoplasmosis status of the women. Using ELISA, specific classes of antibodies (IgG, IgM) enabled to discriminate between the acute and latent phases of the infection. Positivity for toxoplasmosis was defined as a CFT titre of 1 : 4 and more, together with an index of positivity (IP) of > 1.2 for IgG ELISA antibodies against *T. gondii*.

Statistics

The statistical program Statistica 9.0 was used for all testing. The influence of latent toxoplasmosis on the blood glucose level was first evaluated using the General Linear Model (GLM) repeated measure analysis, with three dependent variables, namely the blood glucose levels after 8 h of fasting and 60 min and 120 min after the glucose drink as repeated measures. Subsequently, these

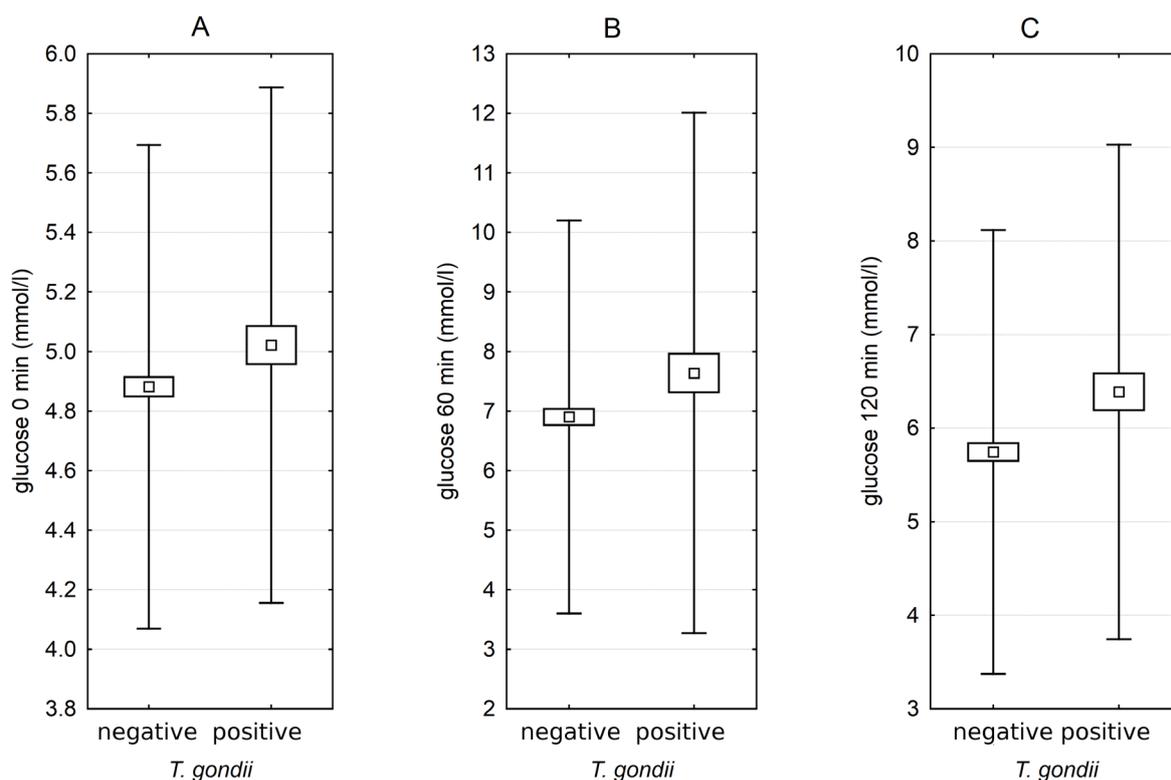


Fig. 1. Differences in the blood glucose levels between *T. gondii*-positive and *T. gondii*-negative pregnant women screened for gestational diabetes (24–28th gestational weeks). The boxes and spreads show standard error and standard deviation ranges, respectively. **A** – baseline glucose levels after 8 hours of fasting (0 min); **B** – glucose levels 60 min after the glucose drink; **C** – glucose levels 120 min after the glucose drink.

three dependent variables were also evaluated separately using a simple GLM technique. An independent continuous variable, maternal body weight in the 9–12th gestational weeks, was included in all models. The influence of the binary variable latent toxoplasmosis on the probability of a positive GDM screening result was evaluated using the contingency table method. Four women with twin pregnancies were excluded from the analysis. For a particular category of analysis, some data were not available and the numbers of women varied between analyses.

RESULTS

The final data set covered 195 pregnant women. However, all three measurement data were available only for 191 of them. GLM with the blood glucose levels after 8 h of fasting and 60 min and 120 min after the glucose drink as repeated measures and independent binary variables toxoplasmosis and maternal body mass showed that *Toxoplasma gondii*-positive women had higher glucose levels in the blood ($n = 191$, $p = 0.010$, $\eta^2 = 0.024$) than *T. gondii*-negative women. The effect of the continuous predictor maternal body mass was positive and also significant ($p = 0.003$, $\eta^2 = 0.030$).

The univariate GLM analysis with the glucose level as the dependent variable and binary variable toxoplasmosis and continuous variable maternal weight in the 9–12th gestational weeks as independent variables showed that 45 *T. gondii*-positive women had higher levels of fasting plasma glucose (OGTT 0 min) (mean = 5.04 mmol/l; $CI_{95} = 4.92, 5.17$) than 149 *T. gondii*-negative wom-

en (mean = 4.88 mmol/l; $CI_{95} = 4.82, 4.95$) ($p = 0.026$, $\eta^2 = 0.026$) (Fig. 1A). A positive correlation also existed between maternal weight in the 9–12th gestational weeks ($p < 0.001$, $\eta^2 = 0.145$). The same model was used for evaluating the effect of toxoplasmosis on the blood glucose level at 1 hour (OGTT 60 min) or two hours (OGTT 120 min) after the glucose drink (Fig. 1B,C).

Sixty min after the glucose drink, 45 *T. gondii*-positive mothers had higher blood glucose levels (mean = 7.73 mmol/l; $CI_{95} = 7.09, 8.37$) than 147 *T. gondii*-negative mothers (mean = 6.89 mmol/l; $CI_{95} = 6.61, 7.16$), ($p = 0.007$, $\eta^2 = 0.038$) and the effect of the continuous predictor maternal weight was again significant ($p = 0.002$, $\eta^2 = 0.051$).

Two hours (120 min) after the glucose drink, 44 *T. gondii*-positive mothers had higher blood glucose levels (mean = 6.43 mmol/l; $CI_{95} = 6.03, 6.83$) than 148 *T. gondii*-negative mothers (mean = 5.74 mmol/l; $CI_{95} = 5.55, 5.93$), ($p = 0.001$, $\eta^2 = 0.053$), but the effect of the continuous predictor maternal body mass was not significant ($p = 0.22$, $\eta^2 = 0.008$).

The GLM analysis showed a positive correlation of anti-*T. gondii* IgG antibodies and blood glucose level at 120 min after the glucose drink for 45 *T. gondii*-positive women (partial Kendall test with maternal age as a covariate: $p = 0.049$; Fig. 2). This correlation was not significant either at 0 min ($p = 0.456$) or 60 min ($p = 0.206$), neither was the correlation between the concentration of IgG antibodies and blood glucose level and the concentration of an-

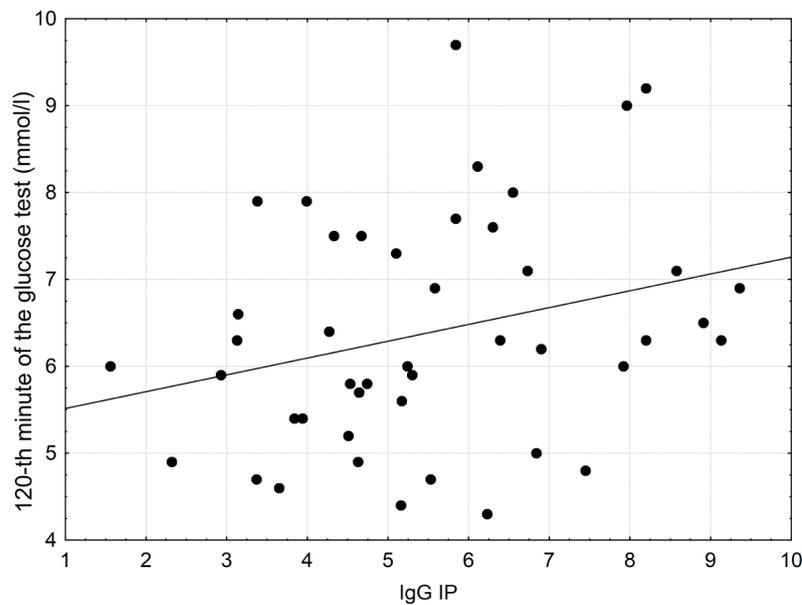


Fig. 2. Correlation of anti-*Toxoplasma gondii* IgG antibody levels (index of positivity) and blood glucose at 120 minutes after the glucose drink in *T. gondii*-positive pregnant women screened for gestational diabetes (24–28th gestational weeks).

ti-*T. gondii* IgG antibodies at any minute after the glucose drink for *T. gondii*-negative women (partial Kendall test with maternal age as a covariate 0 min: $n = 151$, $p = 0.618$; 60 min: $n = 149$, $p = 0.676$; 120 min: $n = 150$, $p = 0.979$).

The difference in the prevalence of gestational diabetes mellitus between *T. gondii*-positive and *T. gondii*-negative women was searched for in a combined set of 532 women whose OGTT data were available. Of 409 *T. gondii*-negative women, 49 (12.0 %) were screened positive for GDM while the GDM prevalence rate in 123 *T. gondii*-positive women was 19.5% (24 cases). This difference was significant ($n = 532$, $\chi^2 = 4.53$, $p = 0.033$, odds ratio = 1.78).

DISCUSSION

Pregnant women with latent toxoplasmosis had significantly higher blood glucose levels in the oral glucose tolerance test at baseline after 8 hours of fasting and at 60 and 120 minutes after the 75 g glucose drink. The glucose level positively covaried with the concentration of anti-*Toxoplasma gondii* antibodies, suggesting that the effects of toxoplasmosis decreased with the time from infection. *Toxoplasma gondii*-infected women showed higher prevalence of gestational diabetes than *T. gondii*-free women.

Our results, namely the increased blood glucose level and higher incidence of GDM in *T. gondii*-infected women could also have considerable clinical impact. For example, these associations may provide new clues to the understanding of the complex pathogenesis of GDM. This disorder has important short-term as well as long-term consequences for women and their offspring. The major of them is a predisposition to the development of metabolic syndrome and type 2 diabetes. Even in developed countries, women with GDM may remain undiagnosed despite the fact that a proper lifestyle intervention has been documented to prevent or at least reduce the development of these severe conditions. It would be therefore useful to examine

T. gondii-positive mothers for GDM during the first trimester. This is probably especially true in the countries with high prevalence of toxoplasmosis or in countries where the screening for GDM in pregnancy is mandatory (e.g in the Czech Republic).

The extensive genetic heterogeneity of *T. gondii* strains also needs to be taken into account. Recent studies have shown that the strains of this parasite may differ dramatically in their impact on the physiology, health and also behaviour of the infected host (Morisset et al. 2008, Kannan 2010, McLeod 2012). In the future studies, it would be desirable to perform serological or even genetic typing of *T. gondii* isolates. Two-tailed statistical tests demonstrated a significant correlation between the concentrations of specific antibodies and glucose 120 minutes, but not at the 60 minutes after the glucose drink and at baseline (0 minute) before the glucose drink. It suggests that this effect might be probably linked to an increase in insulin resistance.

The present study also showed higher prevalence of GDM in *T. gondii*-infected women. *Toxoplasma gondii*-positive women had higher body mass before pregnancy than *T. gondii*-negative women (Flegr et al. 2005, Kaňková et al. 2010). It is known that high maternal weight is associated with a substantially higher risk of GDM (Chu et al. 2007). The effect of *T. gondii* positivity on higher prevalence of GDM could just be a side-effect of the influence of toxoplasmosis on body weight. Our data, however, did not support this hypothesis as the effect of latent toxoplasmosis on the higher blood glucose level was significant in the model with body mass as a covariate.

The original aim of the present study was to find the mechanisms underlying the observed associations of the sex ratio and GDM with *T. gondii* infection (Cameron 2004, Cameron et al. 2008). Latent toxoplasmosis increases the secondary sex ratio in humans and laboratory mice

(Kaňková et al. 2007a,b). The physiological mechanism of this effect is unknown; however, we hypothesise that a manipulation of the blood glucose concentration could play a role in it (Larson et al. 2001).

Research on the role of glucose in the reproductive functions has shown that excess glucose favours the development of male blastocysts, providing a potential mechanism for sex-ratio variation in relation to maternal condition around conception (Cameron 2004). Also, the change in glucose levels resulted in a change in sex ratios, with more daughters being born to females with experimentally lowered glucose (Cameron et al. 2008). A study using mice as an animal model for human diabetes has found that an increase in circulating glucose resulted in a male-biased sex ratio (Machado et al. 2001).

Our present study suggests that *T. gondii*-infected women have increased blood glucose levels, which is in accordance with our hypothesis suggesting that the glucose concentration plays a role in *T. gondii*-associated sex ratio shifts. This hypothesis is also supported by the existence of a positive correlation between the concentration of anti-*T. gondii* IgG antibodies and the blood glucose concentration. The concentration of anti-*T. gondii* IgG antibodies is known to decrease with the time passed since infection (Kodym et al. 2007). In the early phase of latent toxoplasmosis, i.e. in mice that delivered in the fourth month of infection, the sex ratio was higher than in controls, whereas the mice in a later phase of infection, i.e. those that delivered in the fifth to eighth month of infection, had a lower sex ratio than controls (Kaňková et al. 2007b).

In a large cross-sectional study in a sample of 1 803 clients, the probability of the birth of a boy was also increased in women with the highest concentrations of anti-*T. gondii* antibodies while decreased in those with a low concentration of anti-*Toxoplasma* antibodies (Kaňková et al. 2007a). The reduction of the positive effect of *T. gondii* on the concentration of glucose with decrease of anti-*T. gondii* IgG antibody level, which was observed in the present study, supports the hypothesis that the glucose could be the proximate cause of the toxoplasmosis-associated changes in the offspring sex ratio.

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Recently, it was suggested that maternal T and potentially also B cells transferred during pregnancy and/or the breast milk feeding and their encounter with the antigen in mesenteric lymph nodes might play a role in development of T1DM (Roy et al. 2011). Maternal microchimerism in peripheral blood was demonstrated to be significantly higher in patients with T1DM compared to unaffected siblings and healthy subjects (Nelson et al. 2007). It was suggested that *Toxoplasma*-containing cells of fetal origin could disseminate the parasite in the maternal organism (Prandota 2012). It has been reported recently that *Toxoplasma* increases migration activity of infected leukocytes, which could help spread infection in various tissues of the host's body (Fuks et al. 2012).

Toxoplasma gondii infection during gestation and/or after birth may be responsible for development of both T1DM and type 2 diabetes mellitus (T2DM) in children, adolescents and adults (Prandota 2013). Moreover, a significantly lower occurrence of antibodies against *T. gondii* found in the sera of patients with T1DM compared with their first-degree family members or healthy controls may be due to their T and/or B cell exhaustion perspective caused by chronic infection with the parasite (Krause et al. 2009). In contrast, patients with T2DM had increased anti-*T. gondii* antibodies significantly more frequently than respective controls (Gokce et al. 2008). Impaired vascular endothelial function characteristic for the patients with diabetes mellitus may be at least in part due to the preferential *T. gondii* infection of endothelial cells (Prandota 2013).

However, it must be reminded that all previous studies have focused on the effect of the glucose concentration on the sex ratio at the time of conception, while we addressed the concentration of glucose during pregnancy. Further work would be necessary to confirm our results in a population of non-pregnant women in child-bearing age.

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