SUMMARY

Introduction: Syphilis is a systemic infection caused by the spirochete (Treponema pallidum). There are 12 million new cases diagnosed worldwide each year, of which 2 million affect pregnant women. Pregnancy has little influence on the clinical presentation of syphilis, but syphilis infection can have major impact on the course of pregnancy: infection during pregnancy is associated with risk of transplacental transmission, and if undiagnosed, untreated or inadequately treated, causes a wide range of complications in the child. The risk of intrauterine transmission exists at every stage of pregnancy. To date, the immunological processes and relationships that occur in pregnant women with syphilis have not been described in detail. Single monographs describing animal models are available in the literature, but they mainly concern congenital syphilis. It has been observed that in pregnant women treated for syphilis compared to non-pregnant patients, serological response to treatment is slow, which is of great concern to the patient and the treating physician. In studies of non-pregnant patients, it has been shown that more rapid serological response to early syphilis treatment is associated with an increased pro-inflammatory response during the first period of infection, and that the trend towards seroresistance appears to be related to the predominance of regulatory mechanisms in the response to Trepanema pallidum infection. Considering that, immunologically, pregnancy being semi-transplantation with a significantly impaired cytotoxic response and a predominance of regulatory mechanisms, it seems interesting whether changes in immune system function during pregnancy are associated with the response to treatment of early syphilis in pregnancy.

Methods: 24 patients with early syphilis, including 14 pregnant women, recruited at the Dermatology Outpatient Clinic of the Jagiellonian University CM or the Obstetrics and Gynecology Outpatient Clinic of the Jagiellonian University CM were included in the study. In all patients, venous blood was secured for: (1) serological tests (RPR and TPHA), (2) basic analytical tests, (3) tests for other sexually transmitted diseases (HIV, HBV, HCV) and (4) immunological tests. All patients received a single intramuscular injection of 2.4 million IU of benzathine penicillin. Follow-up serological blood tests (RPR) were performed at monthly intervals. At 6 months after the end of treatment, venous blood was again secured for immunological testing. Serological and clinical follow-up was carried out until a normal serological response to treatment was achieved.

Results: Twenty-four cases of women with early syphilis aged 20-33 years were analysed, including 14 pregnant patients (median gestational age 20.5 weeks; min-max: 16-22 weeks). Pregnant patients statistically less frequently presented with skin with lesions typical of early syphilis compared to non-pregnant patients. The analysed 2 groups of patients did not differ significantly in the results of basic blood analytical parameters and age. The differences in the frequency of individual titres of RPR reaction in blood serum before the treatment between the groups were not statistically significant. All patients included in the study had achieved remission of early lesions one month after penicillin administration. Six months after completion of syphilis treatment, 42.9% (n=6) of pregnant patients at the time of infection, had an abnormal serological response to treatment, defined as the absence of at least a 4-fold decrease in the RPR reaction titer compared to pre-treatment values. Importantly, normal serological response to treatment was noted in all nonpregnant patients during this time period. Non-pregnant patients achieved normal serological response to treatment significantly faster ($p<0.0002$). Pregnant patients with syphilis had significantly higher concentrations of cytokines typical for regulatory response (IL-10 and TGF-β) both before and 6 months after penicillin treatment. There were no significant differences in the mean concentrations of IFN-γ, TNF-α, IL-4 and IL-1β. After penicillin treatment, concentrations of cytokines typical for regulatory response were significantly reduced in both pregnant and non-pregnant syphilis patients. There was no significant change in the concentrations of other cytokines (IFN-γ, TNF-α, IL-4 and IL-1β) as a result of treatment. There were significantly higher concentrations of cytokines typical for regulatory response (i.e. IL-10 and TGF-β) in pregnant patients group with abnormal serological response to treatment, in comparison to pregnant patients with normal decrease of RPR reaction titer; significant differences were noted both before and 6 months after treatment. The analysis found that the older the pregnancy at the time of syphilis diagnosis, the significantly longer the time required to achieve a normal serological response to penicillin treatment. Higher baseline RPR reaction titres were associated with shorter time to normal serological response to syphilis treatment and lower baseline TGF-β levels.

Time to normal serological response positively correlated with TGF-β concentration (pre-treatment value) and negatively with serum IFN-γ concentration (pre-treatment value). Higher concentrations of cytokines typical for regulatory response sustained 6 months after penicillin treatment were associated with longer time to normal serological response to treatment.

6 months after syphilis treatment, a reciprocal significant correlation was noted between concentrations of cytokines typical of the regulatory response. Baseline RPR titre (RPR 0) was an independent predictor of time to normal serological response to syphilis treatment in pregnant patients (R2=-0.63; p=0.027): the higher the baseline RPR titre, the faster the normal serological response to syphilis treatment occured.
No adverse effects of benzathine penicillin treatment were reported in any of the included patients. All pregnancies ended on time, none of the children showed clinical and laboratory features typical for congenital syphilis, and none of them showed specific IgM antibodies directed against the antigens of the pale spirochete 1) at birth and 2) at 6 months of age.

Conclusions: Pregnant patients treated for syphilis during pregnancy, compared to not pregnant, have a slower serological response to penicillin treatment of early syphilis. The predominance of regulatory mechanisms over inflammatory mechanisms in the response to spirochetal infection and that associated with pregnancy itself (baseline, by design) may be an important element explaining this observation. The clinical significance of the slower serological response to syphilis treatment in pregnant patients remains unclear. Treatment of syphilis in pregnancy with penicillin is safe for both mother and child.