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Differences in the cytokine profile in cervical mucus taken between 18-23 weeks of gestation in patients with high and low risk for preterm birth

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Objective

Preterm Birth (PB) is one of the main causes of perinatal morbidity and mortality. It causes about 85% of neonatal deaths and survivors have a 20-25% risk to present some type of disability in short, medium and long term follow up. It is estimated that between 70-80% of cases of PB are spontaneous, representing a complex condition with clinical heterogeneity and biochemical mechanisms involved. Although multiple risk factors associated with PB have been identified, preterm deliveries cannot be predicted as effectively as desired. The main screening tool to identify patients at high-risk for premature deliveries is the cervical length measurement by vaginal ultrasound between 18 and 24 weeks of gestation combined with the obstetric history. Different studies have shown that this strategy only achieves a detection rate between 40-70% of patients at high risk for PB. The identification of other variables that could be included in a prediction model to identify patients at high risk for PB could increase the detection rate. Consequently, the identification of these patients would be more efficient, prevention strategies could be established and ideally the prevalence of PB could be reduced. Additionally, patients who are more susceptible to respond favorably to treatment with progesterone might be identified. The aim of this study was to examine possible differences between the cytokine profiles (pro-inflammatory and anti-inflammatory) in cervical mucus taken between 18-23. 6 weeks of gestation, in patients with high and low risk for PB, to subsequently be able to include some of these variables in a prediction model to perform a better characterization of the high and low risk groups for PB.

Methods

The study was conducted in the INPer (National Institute of Perinatology) in Mexico from June 2016 to April 2017. Patients with singleton pregnancies between 18-23. 6 weeks were included among SDG who underwent PB screening by cervical measurement using transvaginal ultrasound (TV-US). Patients who met the inclusion criteria were invited to participate, the procedure was explained and written informed consent was obtained. It is important to mention that in all these patients infectious processes were ruled out by both clinical and laboratory tools. The samples of cervical mucus were taken with the usual Papanicolau technique, transported to the immunobiochemistry laboratory where the determination of cervical cytokines was performed. The Bio-Plex kit (Bio-Rad Laboratories Inc.) was used for the measurement. The kit includes IL-1β, IL-2, IL-6, IL-8, IL-12, NTF-α, IFN-γ, IL-4, IL-10, IL-1ra.

Results

We included 60 patients in the study, 40 patients considered as "low risk for PB" considering obstetric history and cervical length measurement and 20 patients considered as "high risk for PB" (patients with a history of PB and cervical length <25 mm measured by TV-US or patients without history of PB and cervical length <20 mm measured by TV-US. The mean age was 29 years (SD 7. 1) in the low risk group and 31 years (SD 5. 8) in the high risk group, the pre-pregnancy BMI was found in the overweight range in all patients with an average of 25. 2 (DE5. 4) and 27. 5 (SD 7. 5) for the low and high risk group, respectively. The average gestational age was 21. 0 weeks of gestation (SD 7. 5) in the low risk group and 21. 2 weeks of gestation (SD 2. 0) in the high risk group. Forty percent of the patients in the high-risk group had a history of PB. The average cervical length (CL) measured by TV-US was 33. 8 mm (SD 5. 8) in the low risk group and 13. 1 mm (SD 7. 7) in the high risk group. The analysis of pro-inflammatory cytokines showed that the average concentration of IL-6 was 856. 29 pg/ml in the high-risk and 118. 32 pg/ml in the low-risk group (p 0. 001), for IL-8 the mean concentration in the low-risk group was 9695. 78 and 5882. 35 pg/ml in the high risk group (p 0. 38), the concentration of IL-2 in the high risk group was 5. 63 pg/ml vs 3. 60 pg/ml in the low risk group (p 0. 001), while for IL-12 the average concentration was 0. 34 pg/ml in the low risk group and 0. 49 pg/ml in the patients classified as high risk (p 0. 34). In the

group of cytokines with anti-inflammatory pattern the average concentration of IL-4 was 20. 98 pg/ml in the high risk group for PB vs 10. 83 pg/ml in the low risk group (p 0. 001), for IL- 10 the average concentration in the groups was 40. 44 pg/ml in the high risk group and 3. 56 pg/ml in the low risk group (p 0. 001), finally for IL-1ra the average concentration was 29768. 89 pg/ml in the high risk group and 58377. 59 pg/ml in the low-risk group (p 0. 02).

Conclusion

Our study proved differences in cytokines analyzed in cervical mucus (pro-inflammatory and anti-inflammatory). These were found in 3 cytokines with pro inflammatory pattern (IL2, IL6 and interferon gamma) which is in keeping with previously reported findings of IL-6 concentrations in patients high risk for PB. Differences were also found in 3 cytokines with anti-inflammatory pattern (IL-4, IL10, IL-1ra). Of these IL-10 had shown differences in previous studies, but no studies had been published regarding the other two interleukins. These differences explain in some degree the pathophysiological phenomenon of PB. Future research will include the following two phases: 1) High risk patients receiving vaginal progesterone for prevention of PB will have measurements 4 and 8 weeks after the initiation of progesterone treatment. Differences between baseline levels and subsequent measurements will be evaluated and related to success or failure of prevention of PB. 2) In a second phase we will try to evaluate if any of these cytokines could be markers for the prediction model of premature birth in order to increase the detection and decrease the false positive rate. This could result in more efficient economic resource distribution in countries like ours where the health system has limited economic funds.