

## Usefulness of the Determination of Interleukin-6 (IL-6) in Amniotic Fluid in Women at Risk of Preterm Birth

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### Abstract

**Objective:** We compare the levels of IL-6 in the AF of pregnant women with cervical shortening versus women with normal cervical length subjected to amniocentesis for other prenatal reasons (fetal malformations or high risk in prenatal screening), with the aim of establishing a cut-off point to facilitate prediction of the outcome of pregnancy.

**Material and Methods:** A descriptive case-control study design was applied to subjects (n=40) with available information on the results of amniotic fluid IL-6 levels. We examined perinatal outcomes.

The study comprised 40 women: 6 cases with cervical shortening (15%) and 34 controls with normal cervical length throughout pregnancy (85%). The mean IL-6 concentration among the cases was 758.83 pg/ml versus 1291.53 pg/ml in the control group, which moreover registered the highest concentration (16,383 pg/ml). The mean gestational age at delivery was 33 ± 6 weeks among the cases and 40 ± 3 weeks in the control group.

**Results:** Our results do not indicate that the determination of IL-6 in AF is useful for the diagnosis of subclinical chorioamnionitis as a possible cause of cervical shortening and consequent PB, since the controls with normal cervical length and full-term delivery showed higher concentrations than the women with cervical shortening.

**Conclusion:** Our findings do not suggest the determination of IL-6 in AF to be useful for the early diagnosis of such disorders and thus for the prevention of PB.

**Keywords:** Preterm Birth; Interleukin-6; Amniotic Fluid; Chorioamnionitis; Cervical Length; Amniocentesis

### Introduction

Preterm birth (PB), defined as birth taking place between week 20 and the end of week 37 of pregnancy, is a frequent obstetric complication and constitutes the leading cause of perinatal death and short- and long-term morbidity among the survivors. The PB rates have doubled in Europe since the 1970s, reaching 7-8% of all deliveries. In Spain, the perinatal surveys of the Spanish Society

of Gynecology and Obstetrics found the prevalence of PB to be 7.4% in the year 2010, with even higher figures in some regions of the country (9.8% in the Canary Islands and 9% in the Valencian Community) [1].

Preterm birth is of multifactorial origin. Approximately 75% of all PBs are spontaneous and are preceded by threatened preterm labor (TPL), while the rest are deliveries indicated due to medical, maternal or fetal complications [2].

There are four clearly recognized causes of TPL: systemic and intrauterine infection, premature activation of the maternal and fetal hypothalamic-pituitary-adrenal axis, choriodecidual hemorrhage, and pathological uterine distension: multiple pregnancies and polyhydramnios [3].

According to the literature, amniotic cavity or chorioamniotic space are normally sterile, and intrauterine infection as the main cause of PB [4]. The amniotic fluid (AF) concentrations of proinflammatory cytokines (and particularly of IL-6) are significantly higher in women with TPL than in those with full-term delivery. This situation is observed even in the absence of symptoms or signs of infection, in the context of subclinical chorioamnionitis, which represents 80% of all cases of chorioamnionitis [4-6].

The present study was carried out to establish an IL-6 concentration cut-off point capable of predicting TPL and pregnancy outcome. This would facilitate the adoption of measures to reduce perinatal and infant mortality, with improved patient quality of life.

## Material and Methods

A descriptive case-control study was made between March 2018 and February 2019, with the inclusion of 40 pregnant women in the Department of Gynecology and Obstetrics of Dr. Peset University Hospital (Valencia, Spain).

The institutional review board approved the protocol, and written informed consent was obtained from all patients in compliance with the Declaration of Helsinki.

Six of the total patients (15%) presented cervix shortening (cases), while 34 (85%) exhibited normal cervical length throughout pregnancy (controls). The amniotic fluid IL-6 levels were compared between the cases with amniocentesis performed to discard possible subclinical chorioamnionitis and the controls in which amniocentesis was carried out for other reasons (fetal polymalformation, suspected heart disease, high chromosomopathy risk, etc.). Searches were subsequently made in PubMed, SciELO and the Cochrane Library to compare our data with those found in the current literature.

## Results

The study comprised 40 pregnant women: 6 cases with cervical shortening (15%) and 34 controls with normal cervical length

throughout pregnancy (85%). The mean IL-6 concentration among the cases was 758.83 pg/ml versus 1291.53 pg/ml in the control group, which moreover registered the highest concentration (16,383 pg/ml).

The mean gestational age at the time of amniocentesis was  $25 \pm 3$  weeks among the cases and  $19 \pm 5$  weeks in the control group. The mean gestational age at delivery was  $33 \pm 6$  weeks among the cases and  $40 \pm 3$  weeks in the control group.

Vaginal infection due to *Ureaplasma parvum* was evidenced in three of the cases, with vulvovaginal candidiasis in one case, and infection due to *Ureaplasma urealyticum* in two cases. In contrast, only one of the controls presented vaginal infection, attributable to *Trichomonas*.

## Comment

- **Main findings:** The results obtained in our center do not indicate that the determination of IL-6 in AF is useful for the diagnosis of subclinical chorioamnionitis as a possible cause of cervical shortening and consequent PB, since the controls with normal cervical length and full-term delivery showed higher concentrations than the women with cervical shortening.
- **Comparison with existing literature:** Our results differ from those reported in the literature, where interaction between the bacterial products and the host monocyte-macrophage system results in the release of proinflammatory cytokines (interleukin-1 beta [IL-1], interleukin-6 [IL-6] and tumor necrosis factor-alpha [TNF $\alpha$ ]) by the immune cells, and these cytokines play an important role in the labor cascade. They directly and indirectly stimulate the production of prostaglandins, leukotrienes and oxytocin in the fetal membranes and decidua, and improve interstitial collagenase synthesis – this resulting in a decrease in extracellular matrix of the fetal membranes and cervix. Amniotic cell death is also induced, with activation of the complement and coagulation cascade, and this gives rise to endothelial damage and myometrial contractions that can result in PB [5,6].

Proinflammatory cytokines are described as being responsible for both term and preterm birth - though their concentrations are reportedly higher in the latter case, since PB is almost always

associated to subclinical infection. In this respect, IL-6 in AF is described as the best intra-amniotic infection marker.

Accordingly, the determination of proinflammatory cytokines in AF is described as useful for the early diagnosis of subclinical chorioamnionitis and for the prevention of PB [7].

Furthermore, recent studies point to the possibility not only of using interleukins as early diagnostic tools but also as prognostic markers or even as potential therapeutic targets [4].

### Strengths and limitations

The discrepancy between our findings and those of the literature can probably be explained by biases found in our study that may have altered the results, such as the performing of amniocentesis at different gestational ages, the potential influence of different prescribed treatments, or the small sample size involved. We thus intend to more precisely analyze the two study groups and suppress the different sources of confounding bias.

### Conclusions and Implications

Based on our experience, and in concordance with the literature, it can be affirmed that subclinical chorioamnionitis is more common than clinical chorioamnionitis. In contrast to the literature, however, our findings do not suggest the determination of IL-6 in AF to be useful for the early diagnosis of such disorders and thus for the prevention of PB.

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