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# Interleukin-2 receptor serum concentrations in normal pregnancy and pre-eclampsia.

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**Key words:** Cytokines, interleukin-2, interleukin-2 soluble receptor, pre-eclampsia, pregnancy.

**Abstract.** The purpose of this research was to assess interleukin-2 receptor serum levels in normal pregnancy and pre-eclampsia. Sera from 90 healthy pregnant women (30 for each trimester), 30 with pre-eclampsia and a group of 30 healthy non-pregnant were analyzed. Soluble interleukin-2 receptor was measured by specific double antibody enzymatic immunoassay (ELISA). Results were: 267.5 ± 12.3 (mean ± s.e.m) pg/mL in the uncomplicated first trimestre sample, 300.9 ± 14.5 pg/mL in the second trimester and 248.8 ± 12.5 pg/mL in the third. The non-pregnant control group had 443.7 ± 39.6 pg/mL, significantly different from normal pregnancy in all trimesters ($p < 0.001$). The concentration in pre-eclamptic patients was 382.2 ± 24.2 pg/mL, with $p < 0.01$ with regard to the normal third trimester group. The conclusion is that interleukin-2 receptor serum levels diminish in normal pregnancy and rise in preeclampsia. The first finding seems to be a protective mechanism to the fetal allograft. The latter, point to increased cellular activity.

## Concentraciones séricas del receptor soluble de la Interleucina–2 en embarazo normal y en preclampsia.

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**Palabras clave:** Citocinas, embarazo, interleucina-2, receptor soluble de Interleucina-2, preeclampsia.

**Resumen.** El propósito de este trabajo fue estudiar las concentraciones séricas del receptor soluble de la Interleucina-2 (IL-2) en embarazo normal y en pre-eclampsia. Se analizó suero de 30 mujeres sanas no embarazadas, 90 embarazadas normales: 30 de cada trimestre y 30 pacientes con pre-e-

clampsia. Las concentraciones del receptor se midieron siguiendo una técnica de inmunoanálisis enzimático de doble anticuerpo (ELISA). En las embarazadas no complicadas fueron: 267,5 ± 12,3 pg/mL (media ± error estándar) en el primer trimestre; 300,9 ± 14,5 pg/mL en el segundo; y 248,8 ± 12,5 pg/mL en el tercero. En el grupo de no embarazadas los niveles fueron de 443,7 ± 39,6 pg/mL, significativamente diferentes de los tres grupos de embarazo normal ($p < 0,001$). En pre-eclámpticas fueron de 382,2 ± 24,2 pg/mL, con $p < 0,01$ en comparación con el tercer trimestre de embarazo normal. Se concluye que las concentraciones séricas del receptor soluble de IL-2 disminuyen en los tres trimestres del embarazo normal y se elevan en pre-eclampsia. Lo primero parece ser una respuesta protectora del aloinjerto fetal; lo último representa un incremento en la actividad celular.

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## INTRODUCTION

The maternal-fetal interface has a very peculiar immunological activity. It has been stated that healthy pregnancy is a Th2 phenomenon (1), characterized by the predominant secretion of cytokines involved in humoral immunity, and considered pregnancy protectors, over those related to cellular immunity, whose effects could be harmful to the fetus. Pre-eclampsia is a disease characterized by defective trophoblast invasion and decidual vascular pathology (2-5), which promote subnormal blood flow and hypoxia of the placenta. Immunological disturbance and impaired cytokine balance seem to play an important role on its pathogenesis (6).

Interleukin-2 (IL-2), is a Th1 cytokine whose overexpression inhibits pregnancy viability in mice (1, 7), women whose conceptions end in abortion have significantly high IL-2 serum levels (8). Elevated IL-2 serum concentrations have been found during the first trimester in women who later developed pre-eclampsia (9).

Soluble interleukin-2 receptor (sIL-2R) is a characteristic marker of T lymphocytes activity. Its binding to circulating IL-2 counteracts the union of the cytokine with the cell surface receptor, affecting the interleukin specific cellular response (10, 11). High sIL-2R values have been encountered in several pathological conditions, including pre-eclampsia (12).

The purpose of this paper is to establish the serum sIL-2R levels in uncomplicated pregnancy and pre-eclampsia.

## MATERIAL AND METHODS

Five groups were studied: 90 women with non complicated pregnancy (30 for each trimester), 30 with pre-eclampsia and 30 healthy non pregnant as controls. All of them were recruited in obstetrical care centers from Maracaibo, Zulia State, Venezuela.

Diagnostic criteria for pre-eclampsia were: patients with diastolic blood pressure of 90 mmHg or more, in at least two examinations separated by six or more hours and, who were normotensive before the $20^{th}$ week of pregnancy, with edema and proteinuria (higher than 300 mg in 24-hour urine).

The age of the women corresponding to the uncomplicated pregnancy groups ranged between 18 and 34 years, with 27.8 ± 0.4 (mean ± s.e.m.) for the first trimester, 25.8 ± 0.7 for the second one and 27.5 ± 0.05 for the third. The age of the pre-eclampsia group ranged from 15 to 35

year-old (22.1 ± 1.2.). The control group included women from 20 to 34 year-old (27.7 ± 0.7).

Gestational age in the first trimester normal pregnancy group ranged from 5 to 10 weeks, with a mean equal to 8 ± 0.3 weeks, 14 to 26 and 18.7 ± 0.7 in the second, and 27 to 39, 30.8  0.6. in the third. Patients with pre-eclampsia had from 30 to 40 weeks, 37.0 ± 0.5. No woman in labor was included in the investigation.

Twenty mL of venous blood were withdrawn from the antecubital vein, without anticoagulant, separating the serum by centrifugation at 1000 g for 10 minutes. The samples were divided in aliquots and stored in plastic test tubes at –70°C until the procedure. A technique of double antibody enzymatic immunoanalysis (Elisa) was used to measure the sIL-2R ("Quantikine immunoassays", "R and D systems", kit 9714083). The method sensitivity is 24 pg/mL. Results were expressed in absolute values, and mean ± s.e.m. The one-way ANOVA test with Tukey post test was used for groups comparison. The statistical confidence index was 95%.

## RESULTS

Soluble IL-2R concentrations were 443.7 ± 39.6 pg/mL for the control healthy non-pregnant women. In the first trimester values fell to 267.5 ± 12.3. Mean and s.e.m. for the second trimester group were 300.9 ± 14.5 pg/mL, and 248.8 ± 12.5 for the third. The three normal pregnancy groups had significantly lower sIL-2R levels than the non-pregnant group ($p < 0.001$). sIL-2R concentration was 382.2 ± 24 pg/mL in the pre-eclampsia group, significantly higher than the third trimester group ($p < 0.01$). A graphical representation of the results is shown in Figure 1.

## DISCUSSION

The sIL-2R release is considered to be a characteristic T and B lymphocyte activation marker, which might be useful to immunoregulation during cellular proliferation and differentiation. High sIL-2R serum concentrations are encountered in patients with several kinds of diseases (13-22), as well as in kidney and liver transplant rejec-

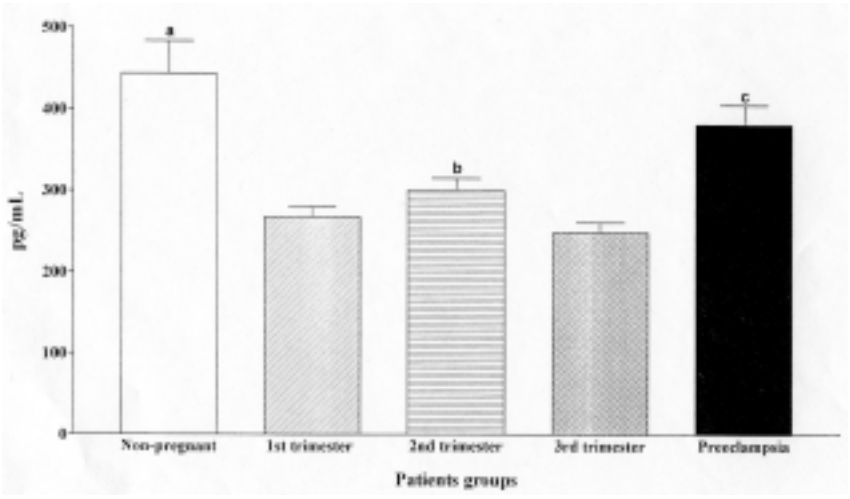


Fig. 1. Serum concentrations of sIL-2R in normal pregnant and preeclampsia (means ± SE). [a]Different significantly from first, second and third trimester ($p < 0.001$). [b]Different significantly from third trimester ($p < 0.01$). [c]Different significantly from third trimester ($p < 0.01$).

tion (23, 24), and occlussive venous disease in bone marrow transplant recipients (25).

Normal pregnancy sIL-2R levels, lower than those of the non-pregnant group, reveal a down-regulated cellular activation, compatible with better conditions for the fetal allograft. Regarding the second trimester rise encountered in normal pregnancy in comparison with first and third trimester, it might be theoretically interpreted as a competitive inhibitory mechanism of IL-2 binding to the membrane receptor of cells such as natural killers, capable of inducing fetal resorption. Third trimester sIL-2R decrease is coincident with a previously described IL-2 rise (26), which could be related to the role of proinflammatory cytokines in the uterine events previous to labor.

The significantly higher sIL-2R concentrations demonstrated in the pre-eclampsia samples, although below the non-pregnancy values, may be explained on the basis of cellular activation, which is in agreement with the fetal immune maladaptation hypothesis in the physiopathology of the disease (6, 27). The immunological disorder of pre-eclampsia occurs at the early stages of pregnancy, disappearing, in the extravillous trophoblast, one of the non-classical MHC Ib molecules: the HLA-G protein, whose expression is necessary for pregnancy establishment and progress. It is likely that direct contact of HLA-G expressing trophoblast with maternal mononuclear cells is a healthy pregnancy "sine qua non". HLA-G non-expression could also cause non-immunological effects, such as defective angiogenesis (28). A consequence of the immune dysfunction is the enhancement of the Th-1 phenotype cytokines, impeding the physiological Th2 condition (1), and determining reduced trophoblastic invasion to decidua and vessels. In a longitudinal investigation, Eneroth and col. (12) have reported augmented sIL-2R serum concentration during the first trimester in women who later became pre-eclamptic, suggesting a possible diagnostic predictive value of the receptor titers in this pathological condition. TNF-$\alpha$ and IFN-$\gamma$, other Th1 cytokines, have also been studied in regard to their potential role in the pre-eclampsia mechanism of disease (6, 26).

Further research on this subject is needed, but current knowledge support the importance of the immunological maladaptation mechanism in the genesis of pre-eclampsia, and points out to serum sIL-2R as a possible diagnostic and prognostic marker in this devastating pregnancy complication, such as has been observed for other clinical conditions like: systemic sclerosis (13), reumathoid arthritis (14), systemic lupus erythematosus (15), acquired immunodeficiency syndrome (16), lymphoma (17), T-cells leukemia (18), chronic myelogenic leukemia (19), hairy cells leukemia (20, 21) and other hematological disorders (22).

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