Acta Oncologica Vol. 34, No. 2, pp. 177–182, 1995

SERUM CYTOKINES IN GESTATIONAL TROPHOBLASTIC DISEASES

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Interleukin 1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were assayed by ^{125}I immunoradiometric assay in sera of 42 cases of vesicular mole (VM), 24 cases of choriocarcinoma and 23 normal pregnant women at their first trimester (controls). According to pathologic diagnosis and serial serum hCGβ assays, the cases with VM and choriocarcinoma were subdivided into remission and progressive tumor groups. The progressive tumor groups—both VM and choriocarcinoma—showed marked elevations of serum IL-1β, IL-6 and TNFα. For choriocarcinoma in remission this elevation was considerably less pronounced. The VM cases in remission had only a slight increase of the mean serum IL-6 value and none of the cases had elevated IL-1β or TNF values. These results may indicate that serum IL-1β and TNF-α assays are valuable biomarkers in the differential diagnosis of gestational trophoblastic disease (GTD). Moreover, normal values of these cytokines may rule out high-risk GTD, whereas markedly elevated values may indicate poor prognosis.

Gestational trophoblastic disease (GTD) is the general term for a spectrum of proliferative abnormalities of the trophoblast. Hydatiform mole represents usually a benign form of the disease whereas choriocarcinoma is a very malignant, frequently metastatic lesion (1). Gestational trophoblastic tumors are unique immunologically and biologically, because they express paternal antigens. The remarkable curability of gestational trophoblastic tumor has been attributed in part to the maternal host's immunological response to the trophoblastic tumor (2). Berkowitz et al. (3) studied the expression of HLA antigen on trophoblast of complete moles using monoclonal antibodies and found that class-I antigens were restricted to the cells of the villus stroma, while the villus trophoblast was not positive for the expression of HLA-A,B,C antigens. On the other hand class-II antigens are not detectable in the villus stromal cells or the villus trophoblast.

Received 3 May 1994.
Accepted 10 November 1994.
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Over the past 25 years an important group of peptide mediators has been detected, characterized and purified. These mediators, termed cytokines, function as up and down regulators of immunologic, inflammatory and reparative host responses to injury (4). Cytokines are non-antibody soluble products of activated lymphocytes (lymphokines) and macrophages (monokines). They function as intracellular growth signals that regulate local, and, at times, systemic inflammatory responses.

The presence of lymphocytes and macrophages in the female reproductive system, together with the fact that these cells may secrete soluble factors influencing embryo development and trophoblast growth, might suggest that cytokines may play a fundamental role in the mechanisms of immunological reproductive failure (5). Cytokines may have a role in regulation of maternal immune cells, corpus luteum rescue and embryonal growth and development. The close proximity of maternal immune cells to fetal trophoblast suggests a trophic cycle consisting of fetal trophoblast stimulation of maternal cytokines release, that, in turn, stimulates trophoblast function and growth (6). The placenta which contains numerous monocytes (7), is an important immunological organ that has an impact on both maternal and fetal response. A variety of cytokines have been reported to be produced by placental cells,

 ISSN 0284-186X

including interleukin 1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interferon α and γ (IFNα, γ) and tumor necrosis factor-α (TNF-α) (8).

Hill et al. (9) reported that certain lymphokines and monokines affect the development of preimplantation mouse embryo in vitro. However, TNF in addition to IFN significantly inhibited the growth of human trophoblast cell (the choriocarcinoma cell line Jeg-3) in vitro (10). These data suggest that activation of endometrial lymphocytes can produce an environment which adversely affects the preimplantation and implanting embryo. Endometrial lymphocytes and macrophages could become activated in certain women by sperm antigens, embryonic or trophoblastic antigens or by non-reproductive tissue specific antigens such as those of infectious organisms (11). Since the fetus resembles in many aspects a malignant tumor which for a limited period of time evades rejection in an immunocompetent host, some immunological dysfunction may be instrumental in the pathogenesis of certain clinical conditions such as trophoblastic diseases (12).

The prognosis of patients with gestational choriocarcinoma has been correlated with the intensity of lymphocytic infiltration at the tumor-host interface and homologically active cells may promote the regression of choriocarcinoma through the release of lymphokines and monokines. Furthermore, lymphokines and monokines individually or in combination, may be useful in the treatment of gestational choriocarcinoma (13).

The present study was undertaken to investigate the clinical value of cytokine measurements in GTD by determination of the circulating levels of the monokines (ILI β, IL-6 TNFα) in the first trimester of normal pregnant women as well as in patients with GTD.

Material and Methods

Eighty-nine women attending Cairo University Hospital during the period from October 1991 till September 1993 participated in the study. They were divided into two groups with comparable age and parity. The first group comprised 23 normal, pregnant, healthy women at their first trimester of pregnancy who served as a control group. All controls had a single viable fetus at a gestational age ranging from 6 to 12 weeks with a mean value of 9.2 weeks as estimated by ultrasonography. The second group comprised 66 patients suffering from gestational trophoblastic disease. Their ages ranged from 18 to 43 years with a mean value of 23.6 years. Parity ranged from 0 to para 4 with a mean of 1.5. Diagnosis of trophoblastic disease was based on histopathologic examination of biopsy specimens obtained from endometrial curettage in cases of choriocarcinoma and molar tissue in patients with vesicular mole. Molar pregnancy cases included 24 cases who presented with vaginal bleeding and passage of vesicles and 18 cases with undue uterine enlargement with intact vesicular mole that was confirmed by ultrasonography. Cases of choriocarcinoma were treated by hysterectomy and chemotherapy (methotrexate), while molar pregnancy cases were managed by either oxytocin infusion followed by suction evacuation or by hysterectomy in multiparous women above 40 years of age.

A blood sample from each case was withdrawn at the first visit by a sterile plastic syringe. Serum was collected in a sterile, clean, dry tube where it was rapidly separated after coagulation. A portion of serum was assayed for hCGβ by a solid phase ^{125}I radioimmunoassay. Reagent kit was purchased from Diagnostic Product Corporation (DPC), CA, USA. Another portion of serum was kept frozen at $-70°C$ till time of assays for IL-1β, IL-6 and TNFα levels. Follow-up serum hCGβ was determined at weekly intervals following management for 3 months and then monthly for one year. According to the pathologic diagnosis and serial serum hCGβ values 24 cases of choriocarcinoma were subdivided into 10 progressive tumor cases (Chorio P) with ascending serum hCGβ values and 14 remission cases (Chorio R) with descending serum hCGβ values. Similarly the 42 cases with vesicular mole were subdivided into 12 progressive tumor cases (VMP) and 30 remission cases (VMR).

Serum IL-β, IL-6 and TNFα concentrations were determined by the corresponding solid phase ^{125}I immunoradiometric assay. Reagent kits were purchased from Medgenix Diagnostics SA, Belgium. The intra- and interassays CV as well as the sensitivity of assays were as follows:

	IL-β	IL-6	TNFα
Intraassay CV%	3.2	5.3	3.2
Interassays CV%	6.5	4.6	5.8
Sensitivity (pg/ml)	5	6	5

The results were statistically analyzed using Student's t-test of significance.

Results

Serum hCGβ concentration in the first trimester of normal pregnancy varied from 24 to 194 IU/ml. In cases of vesicular mole, remission group (VMR) serum hCGβ level varied between 20 and 900 IU/ml. The mean value of serum hCGβ in VMR (435 ± 89 IU/ml, mean $\pm$ SE) was significantly higher than in the normal first trimester pregnant women (100 ± 7.76 IU/ml; $p < 0.005$). The mean fold rise was found to be 4 times the mean control value. Values of serum hCGβ above 194 IU/ml were encountered in 21 out of 30 VMR cases. Serum hCGβ concentration in the VMP group was markedly and significantly elevated (mean 400 ± 53 IU/ml) when compared to that of normal first trimester pregnant women ($p < 0.0005$). The mean fold rise of serum hCGβ was found to be 3.7 times that of the

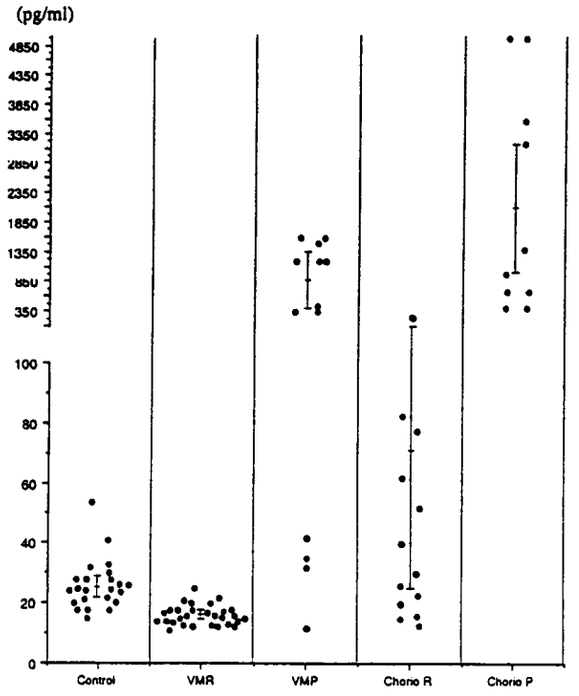

Fig. 1. Individual data of serum IL-1β (pg/ml).

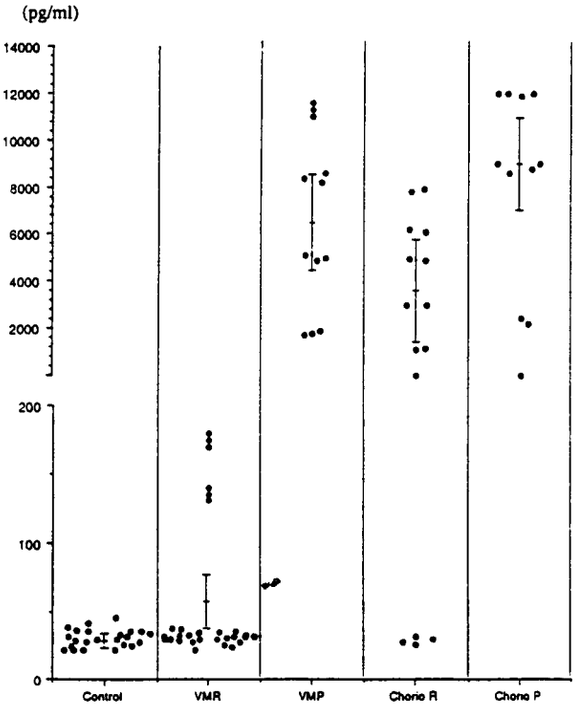

Fig. 2. Individual data of serum IL-6 (pg/ml).

control value. All patients in this group showed abnormal elevated serum hCGβ values. The Chorio R group showed a significantly elevated serum hCGβ level (584 ± 166 IU/ml) when compared to that of control ($p < 0.01$), with a

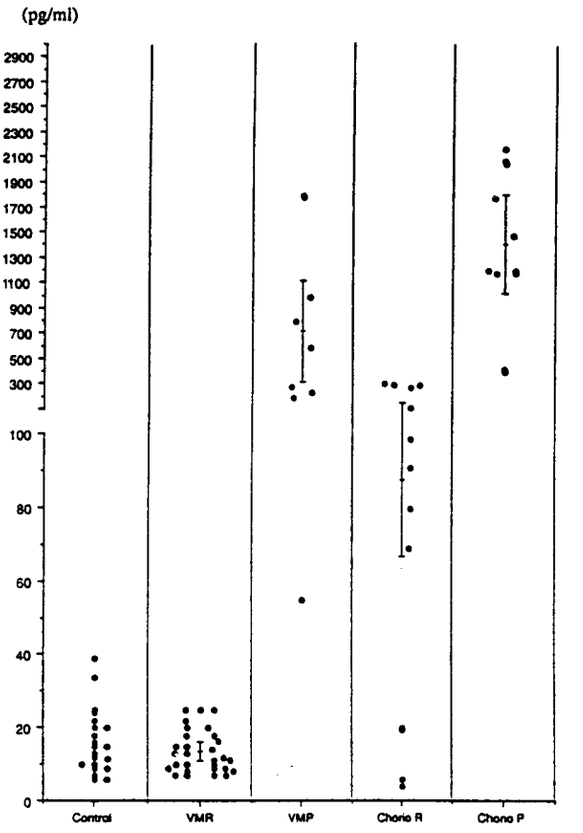

Fig. 3. Individual data of serum TNFα.

mean fold rise of 5.3 times the mean control value. Twelve out of 14 cases in the Chorio R group revealed abnormal elevated serum hCGβ values. The Chorio P group had significantly higher serum hCGβ level (1040 ± 180 IU/ml) than the controls ($p < 0.0005$), with a mean fold rise of 9.54 times the mean control value and all patients in this group showed abnormal elevated values exceeding the upper 95% confidence limit of controls.

The serum interleukin 1-β (IL-1β) level in the first trimester of normal pregnancy varied between 9.8 and 42.6 pg/ml. The serum IL-1β level in the VMR cases (16.45 ± 0.57 pg/ml) was significantly lower than that of the controls (26.2 ± 1.71). However, no single case of VMR had an abnormally low value (i.e., below the lower limit of the 95% confidence range of controls, 9.8 pg/ml). In the VMP group the serum IL-1β level varied between 42 and 1600 pg/ml. The VMP group was characterized by having serum hCGβ above 20 000 mIU/ml, 4 weeks after evacuation and/or progressive rise of serum hCGβ after evacuation. In the VMP group, the mean value of serum IL-1β (798 ± 177 pg/ml) was significantly elevated when compared to that of the controls. The mean fold rise was 30.5 times the mean control value and abnormally elevated serum IL-1β values were encountered in 9 out of 12 cases. The serum IL-1β level in the Chorio R group varied

between 13 and 270 pg/ml. This level (71.2 ± 22.4 pg/ml) was significantly higher than that of the controls ($p < 0.05$). However, the mean value in the Chorio R group was 2.7 times that in the controls, and abnormally elevated values were encountered in 6 out of 14 cases. In the Chorio P group the IL-β value varied between 420 and 5000 pg/ml. The mean value in this group (2144 ± 561 pg/ml) was significantly elevated when compared to that of the controls. The mean fold rise of serum IL-1β in the Chorio P group was 82 times the mean control value and all patients revealed abnormally elevated serum IL-1β values.

The serum interleukin-6 (IL-6) levels in the controls varied between 17.9 and 43.1 pg/ml. In the VMR group there was a significant rise of serum IL-6 (55.9 ± 9.38 pg/ml) when compared with the control group (30.5 ± 1.31 pg/ml). The values in the VMR group varied between 29 and 175 pg/ml. The mean value of serum IL-6 in this group was 1.83 times the mean control value and 6 out of the 30 cases showed abnormal values. In the VMP group the mean value of serum IL-6 was 217 times that of control, and all cases had markedly elevated values, varying from 5000 to 11 300 pg/ml with a mean of 6625 pg/ml ± 1031 (SE). In the Chorio R group, the mean fold rise of serum IL-6 was 108 times the mean control value, and varied from 26 to 7800 pg/ml with a mean value of 3301 pg/ml ± 767. Ten out of 14 Chorio R cases revealed abnormally high serum IL-6 values. In the Chorio P group, the mean value of serum IL-6 amounted to 288 times the mean control value, and varied between 2200 and 12 000 pg/ml with a mean of 8790 pg/ml ± 1118. All cases in this group had markedly elevated serum IL-6 values.

The 95% confidence upper limit of serum TNF-α in normal first trimester pregnancy (controls) was 32.6 pg/ml. In VMR cases the serum TNF-α level (13.55 ± 1.05 pg/ml) was not significantly different from that of control (16 ± 1.73 pg/ml). No single VMR case had an abnormally high serum TNF-α. On the contrary, all VMP cases had abnormally high serum TNF-α ranging from 55 to 1800 pg/ml. The mean value of serum TNF-α in VMP (724 ± 197 pg/ml) was 45 times the mean control value. In the Chorio R group, the serum TNFα varied between 4 and 320 pg/ml. The mean level (129 ± 30.5 pg/ml) was significantly higher than in the controls ($p < 0.025$), and the mean fold rise was 8 times the mean control value. Only 10 out of the 14 cases showed values above 32.6 pg/ml. In the Chorio P group, serum TNFα varied between 430 and 2200 pg/ml with a mean value of 1430 ± 198 pg/ml. The mean fold rise of serum TNFα in this group was 89 times the mean control value, and all cases had abnormally high serum TNFα values.

Discussion

The malignant potential of GTD is best evaluated by the hCGβ regression curve together with clinical evaluation of the patient. However, also in cases with similar clinical outcome the regression curve can vary considerably (14, 15). Moreover, in the absence of obvious clinical manifestations, there is no conclusive evidence of the malignant potential in about 20% of the patients with vesicular mole and the diagnosis must be deferred until observing the postevacuation hCGβ regression curve. In the present study the mean value of serum hCGβ in molar pregnancy approximated 500 000 mIU/ml. Nevertheless, in 21% of cases (9 out of 42 cases), the levels were comparable to those in normal pregnancy controls. This may be explained by the predominant production of α subunits of hCG by some trophoblastic tumors and seems to increase the risk of malignant disease and cereberal metastasis (16). The mean values of serum hCGβ in the remission groups of vesicular mole and choriocarcinoma were not significantly different. These results are consistent with those reported by Lee et al. (17) and Shaarawy & Nagui (18) who could not differentiate molar pregnancy and choriocarcinoma on the basis of the serum hCGβ level.

Cytokines constitute a class of soluble small regulatory peptides or glycoproteins with a molecular weight ranging from 6000 to 60 000 which are synthesized and secreted by activated immune and mesenchymal cells (19). They represent the intracellular signaling from hematopoiesis and immune reactions. During the last 10 years, 20 or more cytokine genes have been cloned. The common characteristic feature of cytokines is that they are pleiotropic, that different cytokines may have redundant activities and that they form a complex, poorly understood network in vivo. Cytokines may have both deleterious and beneficial consequences for tumor growth. The dysregulation of cytokine genes may contribute to the malignant transformation as proposed by the autocrine growth hypothesis (20). On the other hand cytokines may have value in cancer treatment due to their capability to induce or augment immune response. Moreover, early preimplantation embryos are accessible targets of cytokines that might affect their growth and differentiation, similar to their pleiotropic effects on the immune system and other tissues (21).

A variety of cytokines have been reported to be produced by placental cells including IL-1, IL-2, IL-6, IFNα and γ and TNFα (8). Human IL-1 is a key mediator of the host response to various infections, inflammatory and immunological challenges. Two distinct polypeptides IL-1α and IL-1β mediate IL-1 biological activities and bind to the same cell surface receptor. Both are initially synthesized as 31-kDa intracellular precursors that are subsequently found as mature proteins of 17 kDa in monocyte supernates (22). ILβ is the major form secreted by monocytes and macrophages. The cytokine has an essential role in T cell activation providing one of the necessary signals for IL-2 (T cell growth factor) production (23).

In the present study the mean values of serum IL-1β in progressive tumor cases of vesicular mole and choriocar-

cinoma were 30.5 and 82 times higher than the mean control values respectively. On the other hand, the remission subgroup of choriocarcinoma showed only a 2.7-fold rise of serum IL-1β, whereas in the remission subgroup of vesicular mole there was no single case with elevated serum IL-1β but a significant decrease of the mean value by 37% when compared to the controls. A normal or low value of serum IL-1β in GTD might thus indicate a good prognosis. To our knowledge, there are no previously published data on the level of serum IL-1β in GTD. The marked elevation of serum IL-1β in more aggressive forms of GTD may be explained by the associated endometrial and myometrial involvement, since Ramzy (24) reported that normal invasion of the trophoblast provokes an inflammatory maternal response resulting in syncytial endometritis and myometritis.

Human IL-6 is a 184 amino acids polypeptide with potential O- and N-glycosylation sites and a significant homology with granulocyte colony stimulating factor (G-CSF). It is produced by various cells including T and B cells, monocytes, endothelial cells and several tumor cells. IL-6 regulates the growth and differentiation of various cell types with major activities on the immune system, hematopoiesis and inflammation. It co-stimulates T cell growth and cytotoxic T cell differentiation. It is a potent growth factor for myeloma/plasmacytoma cells (25). In the present study, serum IL-6 level in the vesicular mole remission group was significantly higher than in the controls.

In the progressive groups of vesicular mole and choriocarcinoma the mean values of serum IL-6 were 217 and 288 times the mean control value respectively. In cases of progressive choriocarcinoma, all cases showed markedly elevated serum IL-6 values ranging from 2200 to 12 000 pg/ml, i.e. 72- to 393-fold rise. In the remission group of choriocarcinoma the mean fold rise of serum IL-6 was 108 and the maximum value encountered represented a 256-fold rise. These results indicate that serum IL-6 below 175 pg/ml may favor good prognosis in cases of vesicular mole, whereas values above 7800 pg/ml may be highly suggestive of metastatic spread in choriocarcinoma. The elevation of serum IL-6 in more aggressive forms of GTD may partially be attributed to the associated syncytial endometritis and myometritis. Nishimoto (26) reported that IL-6 is a major inducer of the acute phase reactions in response to inflammation or injury and that the elevation of serum IL-6 proceeds that of acute phase proteins. Berek et al. (27) reported that IL-6 is a useful marker in epithelial ovarian cancer where it correlates with tumor burden and survival. According to the present investigation, serum IL-6 may be a useful prognostic marker in GTD.

IL-6 has been shown to be produced by human tumor cells including cardiac myxoma cells (28) and myeloma cells (29). There is evidence that IL-6 is produced by both human epidermal and epidermoid carcinoma cells lines (30) as well as epithelial tumors including bladder carcinoma (31) and renal cell carcinoma (32). Tabibzadeh et al. (33) found that the majority of human tumors of epithelial or mesenchymal origin stain positive for IL-6. It has been proposed by Tamm et al. (34) that IL-6 may promote tumor metastasis and invasion because exogenous IL-6 has been shown to increase motility and decrease adherens junctions in breast carcinoma cell lines. Also, IL-6 could play an important role in the establishment of autonomous tumor by acting as an angiogenesis inducing factor (35).

Human TNFα, also named cachectin, is a 157 amino acids unglycosylated polypeptide mainly produced by activated macrophages (36). Abnormally high levels of serum TNF-α have been described in septic shock, graft rejection, parasitic infections and cancers (37). In the present investigation, serum TNT-α level in the vesicular mole remission group was not significantly different from that of the controls. There was no single case showing an abnormally high serum TNF-α value. On the other hand, the mean values of serum TNF-α in the progressive cases of vesicular mole and choriocarcinoma were 45 and 89 times higher than the mean control values respectively. These results may indicate that a normal value of serum TNF-α rules out high risk GTD. All cases initially categorized as progressive vesicular mole had abnormally high values of TNF-α. These patients had also abnormal hCGβ regression curves. On the basis of the elevated serum TNF-α level, such cases could be categorized as high-risk cases without awaiting the hCGβ regression curve. This may allow us to identify the about 20% of the cases with clinically diagnosed vesicular mole who will eventually develop malignant disease without awaiting the hCGβ regression curve. It may also justify prophylactic chemotherapy for cases showing abnormal TNFα at the initial evaluation. A marked elevation of serum TNFα to a value of above 430 pg/ml may be indicative of poor prognosis with possible metastatic spread. It is noteworthy to mention that Shaarawy & Abdel-Aziz (38) reported that serum TNFα is a valuable marker for the differential diagnosis of benign and malignant lesions of the endometrium in women with postmenopausal bleeding.

In conclusion, our results indicate that serum IL-1β, IL-6 and TNF-α assays may be valuable biomarkers in the differential diagnosis of GTD. Moreover, normal values of these cytokines may rule out high-risk GTD whereas markedly elevated values may indicate poor prognosis as evidenced by malignant transformation in benign GTD and metastatic spread in malignant GTD.

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