ACCEPTANCE OF THE OFFER OF INTRA-ARTICULAR CORTICOSTEROID INJECTION AT THE KNEE JOINT

To the Editor:

Intra-articular corticosteroid injection (IACI) at the knee joint is a common procedure in orthopedic and rheumatology clinics [1]. It is usually helpful for pain relief in both degenerative and inflammatory changes in the knee [2]. The procedure is considered safe, with only a few contraindications such as skin infection overlying the joint and allergy to corticosteroids [3]. Sometimes patients are reluctant to receive an IACI. This reluctance could be due to several factors, the most common being the fear of "corticosteroids" and their adverse systemic effects. Other fears or concerns include the "pain" associated with the procedure. There were no studies in the English medical literature addressing patients' acceptance of the offer of an IACI at the knee joint.

Non-selected patients attending the orthopedic and rheumatology clinics in the Nazareth area complaining mainly of knee pain were asked to participate in our study. The diagnosis in those patients whose knee pain seemed to be related to an intra-articular problem (inflammatory or degenerative) was based on history, physical examination and imaging. Since treatment with non-steroidal anti-inflammatory medications did not lead to a satisfactory response these patients were offered an IACI of 80 mg methylprednisolone acetate at the knee joint. Epidemiological, clinical and laboratory characteristics of the patients were documented, including, age, gender, ethnicity, immigrant status (yes or no), education (total years of study including academic), income, previous IACI at the knee joint, previous IACI anywhere on the body, duration of knee pain, grade of pain, diabetes (yes or no), first or previous visit to the clinic, being alone at the clinic or accompanied by another person/s, effusion at the knee joint (yes or no), erythrocyte sedimentation rate level, C-reactive protein level, and radiographic changes. A total of 143 patients were offered an IACI at the knee joint, of whom 126 (~88%) accepted and 17 (~12%) rejected the offer. There was no correlation between the chance of IACI offer-acceptance and any of the demographic, clinical or laboratory parameters evaluated. Significantly more Jewish patients refused the offer than Arab patients. On the other hand, a subgroup analysis showed that immigrant Jews (mainly from Russia and Ukraine) had a high acceptance rate (96%), which was higher even than that of Arab patients. So even within ethnicity itself, especially among Jews in Israel, there are subgroups that are "culturally" different from each other, including immigrant Jews. Seventy-five percent of non-immigrant Jews refused the offer. This high percentage of refusal, despite the relatively small number of patients, resulted in a significant difference of acceptance of the offer between Arab and all Jewish patients. Perhaps it would be more appropriate to say that acceptance of the offer of IACI at the knee joint is "culturally" related rather than "ethnically" related. However, it is not easy to define and categorize culture in such studies.

As expected, the most common expressed reason for refusal was fear of "steroids" (~30% of those who refused). Other reasons included: a) the desire to use other conservative measures before IACI, b) patients' belief that IACI would not be helpful based on previous experience, c) patients' belief that the source of pain was outside the knee cavity, and d) patients' fear of "leg paralysis." Interestingly, anticipated pain from the IACI procedure itself was not the reason for refusal in any of the patients. It seems that ongoing knee pain surpasses the anticipated transient local pain associated with the procedure.

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DOES ESTROGEN STIMULATE THE PATHOGENIC SORT OF ANTICARDIOLIPIN ANTIBODIES?

To the Editor:

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects several organ systems in the body. SLE is characterized by the production of pathogenic autoantibodies resulting in part from abnormal interactions between T and B cell signaling [1]. Some autoantibodies, genetic susceptibility and environmental triggers contribute to SLE disease onset [1]. However, the greatest risk factor for developing SLE is female gender [2]. Sex hormones contribute to this gender bias in SLE but the mechanisms involved have not been fully elucidated. Although estrogens have been proposed as the obvious candidate to explain this sexual dimorphism, measurement of plasma estradiol levels did not reveal significant differences between normal women and women with SLE; nevertheless, abnormal levels of estrogenic metabolites have been identified in the latter [2].

The antiphospholipid syndrome (APS) is characterized by the association of recurrent arterial and venous thrombosis and/or fetal loss and usually mild to moderate thrombocytopenia, in the presence of elevated antiphospholipid antibodies (aPL) [3]. Examination of aPL in SLE patients of the older or reproductive age groups is essential for evaluating the risk of thrombosis and for developing strategies to improve the pregnancy outcome and prevent thromboembolic accidents. Therefore, the investigation of possible risk factors for APS is clinically extremely relevant.

We wished to explore the possible influence of hyper-estrogenic levels in SLE female patients on the production of anticardiolipin antibodies (aCL) and the potential contribution of estrogens and thrombotic events in SLE with APS.

This study was approved by the University Hospital Split Institutional Review

Figure 1. [A] Positive correlation between the level of estradiol and IgM aCL antibodies. **[B]** Positive correlation was also determined between the level of estradiol and IgG aCL antibodies

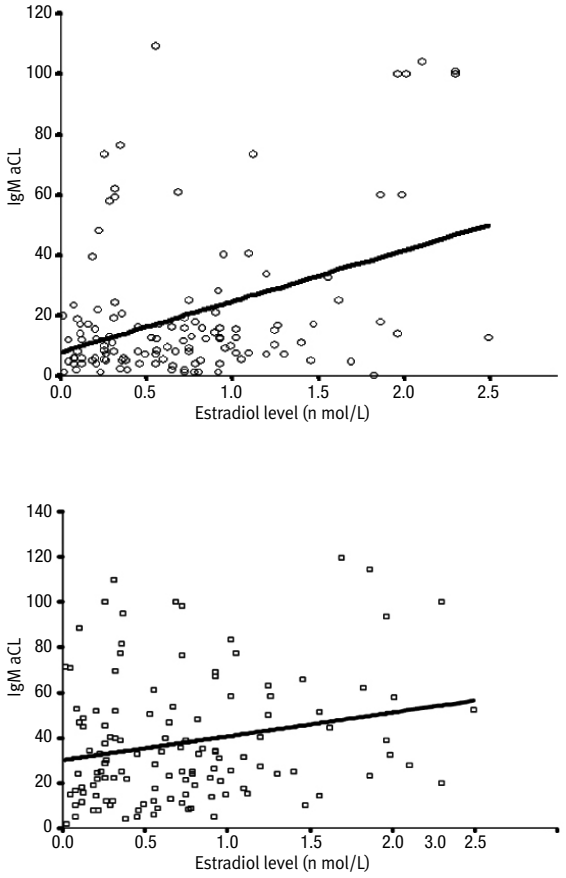

Table 1. Laboratory characteristics (aCL antibodies, estradiol) in SLE premenopausal females with APS and without APS

	No APS	APS	*P*
IgG aCL (GPL units)	30.60 ± 22.67	53.81 ± 30.25	‹ 0.001*
IgM aCL (MPL units)	15.63 ± 18.10	30.47 ± 33.86	0.002*
Estradiol (ng/ml)	0.65 ± 0.53	0.93 ± 0.64	0.009*

Values are mean ± standard deviation $P < 0.05$

Board and all subjects provided written informed consent prior to participation. The study group comprised 124 female premenopausal patients (mean age ± SD 33.9 ± 9.8 years) who fulfilled the American College of Rheumatology classification criteria [3]. The patients were excluded if their disease duration was less than 6 months. We reviewed all SLE patient charts for clinical manifestations of APS, including venous/arterial thrombosis and pregnancy loss. Venous thrombosis was confirmed by venography or ultrasonography and arterial thrombosis by computed tomography, magnetic resonance imaging, or arteriography. SLE activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). The disease was considered active when SLEDAI was ≥ 4, and inactive when SLEDAI was < 4. Participants in this study had regular menstrual cycles and none was taking hormone replacement therapy, oral contraceptives, or had a history of other collagen vascular diseases. Blood collection for such measurements was performed simultaneously with those for the tests used for determining SLEDAI.

Of the 124 SLE premenopausal female patients, 39 (31.4%) presented with at least one of the diagnostic criteria for APS. Most patients had SLE in remission or with mild activity, as shown by the SLEDAI scores (data not shown).There was a positive correlation between the estradiol serum concentration and IgG aCL, IgM aCL levels ($P = 0.007$, $r = 0.222$; $P < 0.001$, $r = 0.392$, respectively) [Figure]. General values of aCL antibodies and estradiol in patients with and without APS are shown in Table 1. We confirmed hyper-estrogenic levels in the group of patients with APS as compared to patients without APS ($P = 0.009$). Comparing the frequency of APS clinical features in patients with normal and with high levels of estradiol showed that all of the studied manifestations with the exception of thrombocytopenia were more frequent in patients with high estradiol levels (data did not shown). Patients with high estradiol levels exhibited transient ischemic attack ($P < 0.05$ Fisher's exact test) as well as stroke ($P < 0.01$ Fisher's exact test) significantly more frequently than patients with normal estradiol levels.

Our results provide evidence that hyper-estrogenic levels in premenopausal SLE women are associated with increased risk of APS and cardiovascular manifestation. An increased risk of hyper-estrogenic levels was expected based on the results of other research, particularly the extensive experimental studies of estrogen and androgen exposure in relation to disease progression in mice. Gonadoctomized or intact male and female non-autoimmune C57BL/6 mice treated with exogenous estrogen express aCL. These antibodies persisted for months after estrogen has been terminated, but there was no proof that these antibodies had a pathologic role [3].

Some antibodies in humans may persist for years without evidence of autoimmune tissue accident, raising the question: what will induce aCL to become pathologic? It is already proven that estrogens enhance thrombotic events in SLE patients, and we assume that the estrogens especially stimulate the pathological type of aCL [4].

This observation, if confirmed by other studies, raises interesting questions about the interrelation between estrogens and autoimmunity, with a potential impact on the risk of thrombosis and cardiovascular disease.

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"I have learnt silence from the talkative, toleration from the intolerant, and kindness from the unkind; yet strange, I am ungrateful to these teachers"

Kahlil Gibran (1883-1931), Lebanese poet and artist, chiefly known in the English-speaking world for his 1923 book *The Prophet*