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Correlation of Basal Menses CA-125 Levels and 6 Month Pregnancy Rates in Women Undergoing Treatments for Infertility Without Assisted Reproductive Methods

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PROBLEM: The objective of this study was to evaluate the correlation of menstrual CA-125 levels with pregnancy rates (PRs) after 6 months of treatment for infertility.
METHOD: The sample consisted of a heterogenous group of 160 women who sought treatment for infertility. Treatments include progesterone supplementation, donor insemination, intrauterine insemination, and ovulation induction therapy. No laparoscopies were done during the study period. A baseline CA-125 level was drawn during menses before the initiation of therapy. Patients were followed for 6 months of treatment or until a pregnancy was achieved.
RESULTS: There was no difference in the 6 month PR or viable PR by CA-125 level.
CONCLUSIONS: Elevated CA-125 levels are not predictive of poor fertility potential at least during the first 6 months of infertility therapy. Even though these higher levels sometimes suggest that endometriosis is present, the data suggest that correction of male factor, cervical factor or ovulation factor provides effective PRs without the need for laparoscopic intervention.

Key words:
Embryo toxic factors, endometriosis, fecundity, unexplained infertility

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INTRODUCTION

Endometriosis has been, for many years, associated with infertility. When it causes pelvic adhesions and mechanical impairment of tube-ovum pick-up, the mechanism of how it can decrease fertility potential is quite clear. However, there are many clinicians and researchers who believe that even in the absence of mechanical factors, endometriosis may reduce fecundity. Accumulating evidence indicates that immunologic factors are involved not only in the pathogenesis of endometriosis, but in the impairment of the fertility process.

However it is well known that many women have extensive endometriosis and yet have no problem in conceiving or carrying the pregnancy full term. If a woman has a normal post-coital test, makes a mature follicle, demonstrates subsequent oocyte release by sonography and the endometrial biopsy is not retarded (or if one or more of these factors had been present, but corrected for several cycles without conception) the next diagnostic step is usually the laparoscopy. The cause of infertility

would be considered endometriosis if any implants are found and the tubes look normal and there is no adhesive disease but would be called unexplained infertility if endometriosis was not seen. Since sometimes the implants are clear or white, they can be lost in the light source of the laparoscope[1–3] and thus occult endometriosis could still be the etiologic factor in some cases of unexplained infertility.

The possibility also exists that endometriosis may be a cause of pelvic pain and infertility when causing impairment to tube-ovum pick-up or when it leads to luteal phase defects[4,5] or luteinized unruptured follicle syndrome,[6] but it is just an incidental bystander when no pathological process can be found. It should be noted that there are studies that dispute the association between endometriosis and luteal phase deficiency[7] or the luteinized unruptured follicle syndrome.[8]

There is increasing interest in exploring the possibility that the etiology of infertility in women whose only diagnosis is endometriosis may be through immunologic or inflammatory mechanisms. The possibility exists that these same factors may also be instrumental in causing infertility in cases of unexplained infertility. Thus, it is not clear as to whether endometriosis may lead to infertility related to immunologic/inflammatory mechanisms or whether long standing infertility related to these factors can lead to the development of endometriosis.

The true prevalence of endometriosis in the "fertile" population is not known since laparoscopies would rarely be performed in this group. Similarly, some difficulty would occur in determining the actual frequency of endometriosis in an infertile population with remedial causes since pregnancies are usually attained before laparoscopies are performed.

Serum CA-125 levels have been found to be increased in women with endometriosis.[9–14] We considered that there was a greater chance of women with higher CA-125 levels to have endometriosis. The study presented herein assessed the correlation between CA-125 levels obtained during menses and the pregnancy rate following 6 months of treatment in an infertile population.

MATERIALS AND METHODS

The women chosen for the study were consecutive patients with a minimum of 1 year of infertility. If hysterosalpingography demonstrated one or two blocked fallopian tubes the patients were excluded from the study. All patients had serum CA-125 levels obtained during menses. Also required for inclusion was completion of 6 months of therapy unless a pregnancy occurred before that time.

Male factor was treated by therapeutic donor insemination if semen parameters were very severely impaired or azoospermia was present, or with intrauterine insemination (IUI), as previously described,[15] or with clomiphene citrate (CC) if serum follicle stimulating hormone was below mid-normal,[16,17] or with chymotrypsin-galactose if there were antisperm antibodies attached to the sperm.[18] Cervical factor was treated with guaifenesin, 1,200 mg twice daily, from day 3 to ovulation[19] or IUI.[15] Anovulation was treated with either CC or low dose human menopausal gonadotropin[20] and progesterone support in the luteal phase.[21] Luteal phase defects, which were diagnosed by one endometrial biopsy being 2 or more days retarded, were treated according to follicular maturation studies with either progesterone exclusively or CC or gonadotropins or bromocriptine, as previously described.[22,23] Unexplained infertility was treated as a possible luteal phase defect so that progesterone was supplemented in the luteal phase. Superovulation and IUI, a method previously reported to improve pregnancy rates in patients with endometriosis,[24] was not used in this study. No laparoscopies or surgical procedures were performed during the study period.

CA-125 levels were determined by an immunoradiometric assay (Centocor, Malvern, PA) and are expressed in arbitrary units based on a primary reference standard. The inter-assay and intra-assay coefficients of variation were 11.5% and 9.5%, respectively. Levels <35 U/mL were considered normal, levels >35 U/mL were considered elevated.

Chi-square analysis was used to compare the pregnancy rates by CA-125 levels. Mean and median ages were calculated for the group with elevated (>35 U/mL) CA-125 levels and the group with normal levels and differences in mean ages was analyzed by analysis of variance.

RESULTS

There were 160 women who fulfilled the inclusion criteria. A total of 136 patients had serum CA-125 levels <35 U/mL and 24 had levels >35 U/mL.

The 6 month pregnancy rate in those patients with normal CA-125 levels was 70.5% (96/136) as compared to 79.2% (19/24) for those with elevated CA-125 levels (P=0.89, NS). The spontaneous abortion rates were 19.8% (19/96) and 26.3% (5/24), respectively. The viable pregnancy rate was therefore 56.6% and 58.3%, respectively (P=NS).

The data was further analyzed by subdividing them into small groups based on several threshold values of CA-125. The results are seen in Table I. No significant differences or even trends were noted.

The age of the patients ranged from 23–51 years old. There were no significant differences in age by serum CA-125 levels. The 136 patients with normal CA-125 levels ranged in age from 23–51 years with a median age of 33.5 and a mean ±SD of 33.8 ± 5.3 years. The 24 patients with elevated CA-125 levels ranged in age from 27–41 years with a median age of 32.5 and a mean ±SD of 33.6 ± 4.1 years. Similarly, there were no differences in age according to the other threshold values for CA-125 as seen in Table II.

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TABLE I. Comparison of Pregnancy Rates by Basal CA-125 Levels

CA-125 group	Pregnancies	Viable (past first trimester)	Failed (non-viable, ectopic, chemical)[a]
<8 U/mL (n = 15)	12 (80%)	11 (73.3%)	1 (8.3%)
8–15 U/mL (n = 48)	35 (72.9%)	26 (54.2%)	9 (25.7%)
16–30 U/mL (n = 65)	44 (67.7%)	36 (55.4%)	8 (18.2%)
31–35 U/mL (n = 17)	12 (70.6%)	10 (58.8%)	2 (16.7%)
45–60 U/mL (n = 9)	7 (77.8%)	5 (55.5%)	2 (28.6%)
>60 U/mL (n = 6)	5 (83.3%)	5 (83.3%)	0 (0.0%)
Total	115 (71.9%)	93 (58.1%)	22 (19.1%)

[a]Data is number of failure, percent. P, NS, comparing pregnancy rate by CA-125 level.

DISCUSSION

There is considerable suspicion that immune factors play a role in infertility in patients with endometriosis. There are many studies demonstrating that the total number of macrophages is elevated in infertile women with endometriosis. Though some studies show increased levels of total macrophages in patients with endometriosis compared to unexplained infertility,[25–28] others have reported no differences in these groups.[29–32] The total number of peritoneal macrophages is not correlated[33] or is negatively correlated[34] with the extent of endometriosis further supporting the concept that infertility, rather than endometriosis per se, is related to increased macrophage number.

The total number of T cells, CD4+ T-helper cells and CD56+ natural killer (NK) cells was found to be increased in the peritoneal fluid from infertile women with endometriosis and in women with unexplained infertility as compared to fertile women with a normal pelvis.[32] The fact that the induction of endometriosis in rabbits did not result in an increased total number of peritoneal fluid macrophages[35] also supports the concept that although patients with endometriosis may have increased peritoneal fluid macrophages, lymphocytes, T cells, T-helper, CD4+, and NK cells compared to fertile controls, this may be more related to their infertility than the presence of endometriosis. The total number of macrophages, lymphocytes, and lymphocyte subsets are comparable in the peripheral blood from infertile women with and without endometriosis.[32,36,37]

Though other benign pelvic conditions could have caused the elevation of the serum CA-125 level,[38–40] probably the majority of cases had endometriosis. Though the CA-125 assay is not very sensitive for detection of endometriosis it does have good specificity.[13,14] Thus, the conclusions from the data presented herein is that once one corrects for male factor, cervical factor, anovulation, luteal phase deficiency, and luteinized unruptured follicle syndromè, the possible presence of endometriosis as indicated by elevated CA-125 levels does not significantly reduce fecundity.

Pittaway found that 123 of 342 (36%) women reaching the laparoscopy stage of investigation had endometriosis.[41] There were 56 (45.5%) of these patients who had CA-125 levels >16 U/mL.[41] Interestingly, he found no difference in mean serum CA-125 concentrations pre-operatively in those conceiving vs. those who did not become pregnant. However, they did find that the CA-125 levels were significantly lower post-operatively in those who conceived versus those who did not.[41] This finding using a second generation CA-125 assay confirmed previous data using a first generation assay.[42] These data suggest that at least in some cases endometriosis may have a direct effect in reducing fertility potential. The persistence of elevated CA-125 levels post-operatively probably indicates inadequate surgical treatment probably related to disease that is either not visible or extends deeper in the subperitoneal tissue that can be appreciated.[43,44]

There are other data supporting the concept that endometriosis without causing apparent mechanical problems may reduce fertility potential and that surgery may improve fecundity. Nowroozi et al. found in a randomized study, that 42 of 69 (60.8%) women with mild endometriosis achieved a pregnancy within 8 months following laparoscopic fulguration of endometriotic implants compared to only 10 of 54 (18.5%) patients whose endometriosis was left intact.[45] These findings were subsequently confirmed by Murphy et al.[46] The important thing to note is that in the study of Nowroozi et al.[45] a laparoscopy was only performed after

TABLE II. Mean and Median Age (Years) According to Serum CA-125 Levels

CA-125 group	Mean ± SD age	(Range) median age
<8 U/mL (n = 15)	30.8 ± 4.8	(23–42) 31
8–15 U/mL (n = 48)	34.8 ± 5.2	(27–51) 34
16–30 U/mL (n = 65)	33.9 ± 5.2	(24–49) 34
31–45 U/mL (n = 17)	33.2 ± 4.8	(36–44) 33
45–60 U/mL (n = 9)	33.7 ± 4.9	(28–40) 31
>60 U/mL (n = 6)	33.7 ± 4.1	(31–41) 31.5

8 cycles of treatment in which all other infertility factors have been corrected.

The results of the study presented herein do not allow the conclusion that mild endometriosis does not lead to a significant reduction in fertility potential since other infertility factors that may be associated with endometriosis, e.g., luteal phase defects and luteinized unruptured follicle syndrome, were corrected. However, it should be noted that the association of endometriosis with these infertility factors is purely anecdotal.

The results do not exclude the possibility that endometriosis without tubal occlusion does reduce fertility potential in a certain minority of cases. However, the main conclusion from these data is that patients should be apprised that if they have an increased serum CA-125 level during menses, that they can attempt more conservative correction of other infertility factors and circumvent immediate laparoscopic treatment for probable endometriosis without significantly reducing their 6 month pregnancy rate. Therefore, measurement of serum CA-125 during the initial investigation for infertility should be restricted to those individuals who would still opt to have a laparoscopy even for the small benefit it would provide.

Thus, if endometriosis can cause infertility through an immunologic mechanism, e.g., increasing toxic TH1 cytokines,[47] then this would seem to be an operative mechanism in only a minority of cases. Alternatively, perhaps these embryo toxic factors were inadvertently treated by an aggressive use of progesterone in this study.

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