Turk J Med Sci
31 (2001) 439-444

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Serum Triglyceride and Lipoprotein-Cholesterol Levels in Patients with and Without Luteal Phase Defect

Received: August 24, 2000

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Abstract: **Objective:** To evaluate the serum triglyceride and lipoprotein-cholesterol levels in subjects with and without luteal phase defect.

Method: Early follicular and midluteal phase serum triglycerides, lipoprotein-cholesterol and progesterone levels were assessed in 19 subjects with and in 73 subjects without luteal phase defect. The criterion for diagnosis of luteal phase defect was histological development of endometrium delayed for more than 2 days according to the chronological day. The data were analyzed by paired and unpaired t tests, Chi-square test and correlation analysis.

Results: The early follicular serum triglyceride and lipoprotein-cholesterol levels of the two groups were similar ($p>0.05$). The midluteal serum progesterone levels of the subjects without luteal phase defect was significantly higher than those of the patients with luteal phase defect ($p<0.01$), and the midluteal triglyceride and lipoprotein-cholesterol levels of the two groups were also similar ($p>0.05$). The midluteal serum progesterone levels had no significant correlation with the serum triglyceride or lipoprotein-cholesterol levels ($p>0.05$).

Conclusion: Serum triglyceride or lipoprotein-cholesterol levels, which were similar in subjects with and without luteal phase defect, does not play a significant role in the ethiopathogenesis of this disease.

Key Words: Lipoprotein-cholesterol, Luteal Phase Defect, Progesterone, Triglyceride

Introduction

Luteal phase defect, defined as a clinical situation in which the development of endometrium is deficient due to insufficient secretion and/or effect of progesterone during the luteal phase of repetitive ovulatory cycles, is encountered in 3.7-44.0% of cases of infertility or recurrent early pregnancy loss (1,2). Although abnormal response of endometrium to progesterone is thought to play a role in the pathogenesis of luteal phase defect, it is emphasized that the main problem in the majority of the cases is the insufficient production and/or secretion of progesterone by the corpus luteum (1-4).

Insufficient synthesis and/or secretion of progesterone in the luteal phase has been shown to be the result of granulosa or luteal cell defects, abnormal follicle stimulating hormone (FSH) secretion in follicular phase or luteinizing hormone (LH) secretion in the luteal phase or inappropriate preovulatory peaks of these hormones (1-4). However, it is also suggested that abnormalities of the serum level of the precursors of progesterone could affect the synthesis of progesterone and lead to luteal phase defect (5-9). Cholesterol is the main precursor of progesterone produced by the corpus luteum. Although the main source of cholesterol is known to be the low density lipoprotein (LDL) in circulation, it was demonstrated that high density lipoprotein (HDL) and very low density lipoprotein (VLDL) could also be used effectively as sources (10-11). It is also well known that the steroid hormones synthesized in the ovary or administered as medication can affect lipoprotein production in the liver (12,13). According to these findings, it is speculated that insufficient lipoprotein-cholesterol levels in the circulation can also affect the steroid hormone production and might cause luteal phase defect due to the results of interaction between the metabolisms of progesterone and lipoprotein-cholesterols (5,9).

This prospective study was designed to evaluate the correlation between the serum levels of progesterone and triglyceride or lipoprotein-cholesterol in subjects with and without luteal phase defect.

Materials and Methods

A total of 120 subjects who had had spontaneous ovulation and unexplained infertility diagnosed by clinical, hormonal and laparoscopic evaluation for whom intrauterine insemination was planned were included in the study. While spontaneous follicle development and ovulation were observed in only 38 of the subjects (SO group), follicular development was induced by clomiphene citrate (CC group), by human menopausal gonadotropin (Gntr group) and by human menopausal gonadotropin after desensitization with gonadotropin releasing hormone analog (GnRH group) in 38, 18 and 26 of the subjects, respectively. Following adequate follicle development, intramuscular 5000 IU human chorionic gonadotropin (hCG) was used to stimulate ovulation all patient whose follicle growth was induced by medical methods.

Transvaginal folliculometric evaluations of all subjects were performed by using a Toshiba SS-A-250 instrument with a 5 MHz probe beginning from the second or third day of every cycle. The disappearance of the dominant follicle with a dimension of 18 to 24 mm prior to the occurrence of a hyperechogenic structure in the same ovary, and the presence of fluid in the posterior cul-de-sac were considered evidence of ovulation (14). The day on which these findings were obtained was considered the ovulation day, and chronological dating of endometrium was calculated prospectively according to the ovulation day (14).

The endometrial biopsies of all cases were taken seven, eight or nine days after ovulation as determined by ultrasonography. All of the biopsies were evaluated histologically according to Noyes' criteria by a consultant of pathology (15). All subjects whose endometrial histological development was found to be delayed 2 or more days according to the chronological day calculated by the ovulation day, were diagnosed with luteal phase defect (1-4).

Serum levels of progesterone, triglyceride, total cholesterol and HDL-cholesterol in all cases were assessed from the fasting morning venous blood samples taken on the second day of the menstrual cycle and on the seventh day of ovulation. Serum levels of progesterone were determined by the two-sided chemoluminometric immunoassay method, in which an automated Ciba Corning chemoluminosense system was used. Enzymatic cholesterol lipase-glycerol kinase, enzymatic cholesterol ester hydrolyze-cholesterol oxidase and magnesium-dextran sulfate HDL precipitation methods were used for the assessment of serum triglyceride, serum total cholesterol and HDL-cholesterol levels respectively, all of which were calculated as mg/dl. The serum LDL-cholesterol level was calculated by dividing the serum triglyceride value by five and the VLDL cholesterol level was calculated subtracting the HDL-cholesterol and LDL-cholesterol values from the total cholesterol value. The serum hCG level was assessed 11 to14 days after ovulation and those subjects who were found to be pregnant were excluded from the study. Ages, weights, heights, tobacco or alcohol consumption, exercise habits, medical and obstetric histories and infertility periods were obtained by interviewing the patients. The body mass index was calculated by dividing the weight (kg) of the patient by the square of her height (m).

A total of 28 paients who had an endocrine disease or a medication intake that could affect the serum progesterone or lipoprotein-cholesterol levels, whose cycle was canceled, whose ovulation did not occur or who became pregnant during the study period were excluded from the study. Thus, the data of a total of 92 cases including 28 cases in the SO group, 30 cases in the CC group, 14 cases in the Gntr group and 20 cases in the GnRH group, were included in the study. Paired t-test, unpaired t-test, Chi-square test or correlation analysis were used for statistical analysis.

Results

Ultrasonographic folliculometric follow-up, assessment of serum midluteal progesterone levels and histopathological evaluation of endometrial biopsies revealed that ovulation occurred in all of the 92 cases included in the study. While 73 (79.3%) of the 92 cases had normal endometrial development, luteal phase defect was found in 19 (20.7%) of them, including 5 (17.9%) of the 28 cases in the SO group, 5 (16.6%) of the 30 cases in the CC group, 3 (21.4%) of the 14 cases in the Gntr group and 6 (30.0%) of the 20 cases in the GnRH group.

Characteristics of the 19 cases with luteal phase defect and 73 cases without luteal phase defect are shown in Table 1. None of the patient in either group was found to do exercise or use alcohol regularly, and the two

Table 1. Population characteristics of the 19 cases with luteal phase defect and 73 cases without luteal phase defect*.

	Cases with Luteal Phase Defect (n:19)	Cases without Luteal Phase Defect (n:73)
Age (year)	27.7 ± 1.3	29.3 ± 1.5
Gravidity (n)	0.84 ± 0.16	0.63 ± 0.18
Parity (n)	0.26 ± 0.14	0.18 ± 0.16
Abortion (n)	0.58 ± 0.21	0.45 ± 0.25
Infertility Period (year)	6.4 ± 1.2	7.1 ± 1.4
Body Weight (kg)	60.7 ± 2.7	62.3 ± 2.9
Body Mass Index (kg/m^2)	22.5 ± 0.9	23.8 ± 1.7
Tobacco use (n)	2 (10.5%)	13 (17.8%)

*p>0.05

Table 2. The mean serum progesterone, triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol and VLDL-cholesterol levels of the 19 cases with luteal phase defect and 73 cases without luteal phase defect obtained in early follicular and midluteal phases of the menstrual cycle.

	Cases with Luteal Phase Defect (n:19)		Cases without Luteal Phase Defect (n:73)	
	Early Follicular Phase	Midluteal Phase	Early Follicular Phase	Midluteal Phase
Triglyceride (mg/dl)	132.4 ± 16.3	139.7 ± 22.1	130.5 ± 12.9	142.3 ± 15.2
Total Cholesterol (mg/dl)	162.4 ± 21.8	173.6 ± 18.1	154.6 ± 15.9	178.1 ± 17.4
VLDL-Cholesterol (mg/dl)	26.5 ± 2.3	28.1 ± 3.2	26.2 ± 1.9	28.5 ± 2.5
LDL-Cholesterol (mg/dl)	104.4 ± 10.3	106.9 ± 13.4	101.1 ± 8.3	107.1 ± 9.7
HDL- Cholesterol (mg/dl)	44.2 ± 5.8	45.6 ± 6.0	48.2 ± 3.4	48.8 ± 3.8
Progesterone (ng/ml)	0.56 ± 0.03	11.4 ± 1.1*	0.61 ± 0.04	27.8 ± 3.2*

*p<0.01

groups were similar with respect to mean age, gravidity, parity, abortion, period of infertility, body weight, body mass index and rate of tobacco use, which might affect serum lipoprotein levels (p>0.05).

The mean serum progesterone, triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol and VLDL-cholesterol values obtained in the early follicular phase (the second day of the menstrual cycle) or midluteal phase (the seventh day of the luteal phase) of the patients with or without luteal phase defect are presented in Table 2. Although the early follicular mean serum progesterone levels of the two groups were similar (p>0.05), the midluteal mean serum progesterone level of the patients with luteal phase defect was significantly lower than that of the patients without luteal phase defect (p<0.01). However, neither the early follicular phase nor the midluteal phase serum triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol and VLDL-cholesterol levels of the patients with luteal phase defect were significantly different from those of the patients without luteal phase defect (p>0.05). Moreover, there was no significant difference between the early follicular and midluteal phase serum triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol and VLDL-cholesterol levels in the two groups (p>0.05). There was no significant correlation between the midluteal serum progesterone level and serum triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol or VLDL-cholesterol level of the patients with luteal phase defect or those without luteal phase defect with correlation coefficients ranging from 0.014 to 0.923 and from 0.017 to 0.026, respectively (p>0.05).

Discussion

Luteal phase defect is defined as a clinical situation characterized by deficient endometrial development due to insufficient effect and/or production of progesterone during the luteal phase in recurrent ovulatory cycles (1,2). Luteal phase defect can be seen in 3.7-20.0% of all infertile patients, in 12.0-44.0% of patients with unexplained infertility and in 20.0-40.0% of those with recurrent early pregnancy loss (1-4). It is thought that blastocyst implantation of cannot occur or the maintenance of pregnancy in the early period cannot be achieved as a result of insufficient endometrial development. The occurrence of low pregnancy rates in spite of high ovulation rates in induced cycles is also thought to support this idea (1-4).

The observation of insufficient endometrial development in patients with normal ovarian function with sufficient luteal serum progesterone levels is believed to show that endometrial cell defects or abnormality of progesterone receptors may play a role in the pathophysiology of luteal phase defect (1,3). However, corpus luteum dysfunction with abnormal synthesis of progesterone has been observed to be the main problem in the majority of patients with luteal phase defect (1-4). Significant correlations have been found between the serum level of progesterone and endometrial development, which was observed to be delayed in patients with low serum progesterone levels (1-4). It is known that insufficient secretion of FSH or LH in the follicular or luteal phase or defects of granulosa or corpus luteum cells can cause corpus luteum dysfunction and decreased progesterone production (1,3). However, insufficiency of circulatory cholesterol, which is the main precursor of progesterone, has also been claimed to affect progesterone production and to result in luteal phase defect in some cases (5,9).

Corpus luteum cells are able to synthesize cholesterol de novo. However, as the capacity of this function is limited, most of the cholesterol used in these cells is supplied by lipoprotein particles in the circulation (10,11). Although LDL is the most important source of cholesterol for corpus luteum cells, HDL and VLDL particles can also be effectively used as cholesterol sources (10,11). However, lipoproteins have to bind to their receptors located on the cell membrane for releasing their cholesterol content into the luteal cells (10). Therefore, it is suggested that a sufficient amount of cholesterol cannot be supplied and synthesis of progesterone decreases not only in cases with insufficient serum lipoprotein level but also in those with low density of lipoprotein receptors, and these abnormalities may result in luteal phase defect (5-9). While some clinical studies showed that the LDL receptor density of the luteal cells increased to the highest level during the midluteal period concomitantly with the significant increase in the production of progesterone. Other experimental studies have found that progesterone synthesis increased significantly in vitro with the addition of LDL particles into the medium of luteal cell cultures (7-9). Significantly lower serum progesterone levels in the luteal phase were reported in patients with abetalipoproteinemia, a rare hereditary disease characterized by complete absence of all apoprotein-B containing lipoproteins including LDL and VLDL, which were believed to be necessary for the transport of cholesterol and the production of progesterone (5,6). However, although the rate of spontaneous abortion was very high, successful pregnancy outcomes have been observed in these patients (16). This condition may be explained by increased de-novo cholesterol synthesis by luteal cells or by using HDL as a main source of cholesterol (9). Achieving successful pregnancies in other patients with low luteal phase serum progesterone levels suggested that serum progesterone level might be sufficient in local uteroplacental circulation, although it was found to be low in peripheral circulation (3).

Insler et al. reported in a clinical study in which the relation between the serum level of lipoproteins and luteal phase defect was evaluated, that serum lipoprotein levels of patients with luteal phase defect were similar to those of the patients without luteal phase defect and the incidence of luteal phase defect was not increased in patients with lower serum lipoprotein levels (17). In a similar study, Hansen et al. also observed that serum VLDL-cholesterol, LDL-cholesterol, HDL-cholesterol, total cholesterol and triglyceride levels of patients with luteal phase defect were not different from those of patients without luteal phase defect and reported that no significant correlation was found between the histological development of endometrium and the serum levels of lipoprotein-cholesterol or triglyceride (18).

In this study, although the midluteal mean serum progesterone levels of 19 patients with luteal phase defect were found to be significantly lower than those of

the 73 patients without luteal phase defect, early follicular phase or midluteal phase mean serum triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol and VLDL-cholesterol levels of the two groups were found to be similar ($p>0.05$). Moreover, neither the patients with luteal phase defect nor those without luteal phase defect had any significant correlation between the midluteal serum progesterone levels and serum lipoprotein-cholesterol or triglyceride levels, with very low correlation coefficients ranging from 0.014 to 0.026 ($p>0.05$). These results, which are in concordance with those in the literature, suggest that serum triglyceride or lipoprotein-cholesterol levels did not affect the production of progesterone by the corpus luteum. Thus, variation of the serum levels of these substances, which did not have any correlation with the serum level of progesterone, could not be responsible for the abnormal development of the endometrium and could not play a role in the pathophysiology of luteal phase defect.

It is known that steroid hormones produced de novo by the ovary or administered as a medication can affect lipoprotein production in the liver (10,11). Decreased serum HDL-cholesterol and increased serum LDL-cholesterol levels, which occur due to hypoestrogenemia during the postmenopausal period and increase the risk of cardiovascular disease, can be reversed by estrogen replacement therapy 11. Adding exogenous progesterone to the replacement therapy decreases HDL-cholesterol and increased serum LDL-cholesterol levels (11). However, Carr et al. reported that serum LDL-cholesterol levels significantly decreased simultaneously with increased serum progesterone levels in the luteal phase and there was a significant negative correlation between these substances during the reproductive period (19). In this study, although it was determined that midluteal phase mean serum progesterone levels of cases with luteal phase defect were significantly lower than those of patients without luteal phase defect and both groups had significantly higher midluteal phase mean serum progesterone levels compared to those obtained in the early follicular phase, the midluteal phase mean serum triglyceride and lipoprotein-cholesterol levels of both groups were similar to those obtained in the early follicular phase. These results suggested that, in contrast to the exogenous progesterone intake, increased endogenous progesterone synthesis within the physiologic limits did not affect the lipoprotein production in liver or change the levels of these substances in the circulation.

The data of this study suggested that the early follicular and midluteal serum triglyceride or lipoprotein-cholesterol levels were similar in patients with and without luteal phase defect and there was no significant correlation between them and the serum progesterone levels. Therefore, serum lipoprotein-cholesterol levels could not be responsible for the insufficient progesterone synthesis in cases with luteal phase defect and could not play an important role in the pathophysiology of luteal phase defect.

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