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STUDY OF ROLE OF COLOR FLOW PULSED DOPPLER AND ENDOMETRIAL BIOPSY FOR DETECTION OF LUTEAL PHASE DEFECT IN INFERTILITY AND RECURRENT SPONTANEOUS ABORTION

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ABSTRACT

BACKGROUND: Infertility is defined as Inability of a couple to achieve conception following one year or more of regular, unprotected intercourse. WHO estimates that approximately 8-10% of couples experience some form of infertility. Luteal phase defect (LPD) is one of the causes of unexplained infertility and recurrent pregnancy loss. It is defined as inadequate production of progesterone by the corpus luteum resulting in insufficient maturation of endometrium. Endometrial biopsy is the gold standard for diagnosis of luteal phase defect which is based on the characteristic histologic changes resulting from the action of progesterone. Introduction of Color Doppler imaging and pulsed Doppler analysis has provided a non-invasive method of assessing the vascular and morphological changes in the ovary and the endometrium.**METHODS:** This prospective study included 50 women with history of infertility or history of recurrent abortions attending the Obstetrics & Gynecology OPD at PMCH. Another group of 50 women were taken as control. All the women had normal Complete Blood Count, Mantoux Test, Chest X-Ray, Hysterosalpingography, and their husbands had normal seminogram. There was no Rh incompatibility, normal TORCH titre, normal Blood sugar studies, and HIV & VDRL were negative for both partners. The patients had normal menstrual cycles and the date of their last menstrual period was known. They were not taking any medication and had not undergone any prior ovarian or adnexal surgery.**RESULTS:** The incidence of luteal phase defect was 32.8% in infertile population and 12% in the fertile women. When the LPD group of patients were compared with the fertile group of women, a significantly higher pulsatility index in ovarian artery was found in mid luteal and late luteal phases with $p \leq 0.001$.The resistance index of ovarian artery was also significantly higher in the luteal phase defect group in late follicular, mid luteal and late luteal phases with $p \leq 0.001$. In our study, endometrial biopsy was 60% sensitive with 56.2% positive predictive value for the diagnosis of luteal phase defect in patients with history of infertility or recurrent pregnancy losses.**CONCLUSION**: Although timed endometrial biopsy has been the gold standard for diagnosing luteal phase defect, introduction of color Doppler imaging and pulsed Doppler analysis, has provided a new non-invasive method for assessing the vascular and morphological changes in the ovary and endometrium implicated in luteal phase defect.

KEYWORDS

Luteal phase defect, Endometrial biopsy, Color flow pulse doppler

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INTRODUCTION

Infertility, whether male or female is defined as Inability of a couple to achieve conception following one year or more of regular, unprotected intercourse. WHO estimates that approximately 8-10% of couples experience some form of infertility. On a worldwide scale, this means that 50-80 million people suffer from infertility.

Luteal phase defect is one of the causes of unexplained infertility and recurrent pregnancy loss[1,2,3]. It is defined as inadequate production of progesterone by the corpus luteum resulting in insufficient maturation of endometrium. It is a cause of a non-receptive endometrial environment, and occurs due to poor follicle production, premature demise of the corpus luteum, failure of the uterine lining to respond to normal level of progesterone, polycystic ovarian disease, hyperprolactinemia etc.

Endometrial biopsy is a gold standard tool for the diagnosis of LPD. Currently, the diagnosis of the LPD requires that histological maturational retardation of more than 2 days be demonstrated in at least 2 cycles[4].

Introduction of color Doppler imaging and pulsed Doppler analysis has provided a non-invasive method of assessing the vascular and morphological changes in the ovary and the endometrium[5]. LDL cholesterol serves as a substrate to the corpus luteum for progesterone production and is made available to the corpus luteum through adequate neovascularisation. We hypothesise that LPD occurs due to decreased vascularisation of corpus luteum causing reduced delivery of steroid precursors to the ovary, thereby resulting in inadequate progesterone production. Thus, the color Doppler assessment of the blood flow pattern through newly laid vessels of the corpus luteum may be considered as one of the non-invasive modalities to detect luteal phase defect.

METHODOLOGY

The present study was carried out from September 2009 to September 2011 in the Department of Obstetrics and Gynecology in collaboration with Department of Radiology in Patna Medical College and Hospital, Patna, Bihar. It was a prospective study of 50 women with history of infertility or history of recurrent abortions attending the female OPD of P.M.C.H. was done. Another group of 50 women were taken as control. This population consisted of a normal fertile group of female volunteers.

The patient population had history of either primary or secondary infertility or had history of recurrent abortions. The following preliminary investigations were normal

- Husband's seminogram
- Hb, TLC, DLC and ESR
- Mantoux test
- Chest X-ray
- Hysterosalpingography
- ABO Rh of husband and wife
- Fasting & Post Prandial Blood Sugars
- TORCH titres
- HIV of husband and wife
- VDRL of husband and wife

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The patients had normal menstrual cycles and the date of their last menstrual period was known. There was no history of any medication or prior ovarian/adnexal surgery.

Patients not fulfilling the above criteria were excluded from the study.

A group of 50 healthy fertile female volunteers with the following criteria was taken as control:

- 18-35 years of age
- History of regular menstrual cycles.
- Normal reproductive history.
- Not taking any medication on a regular basis
- Weight within ±10% of ideal body weight.

TECHINIQUES EMPLOYED

1. Endometrial Biopsy

The specimen was taken from the fundus

- Endometrial biopsy was taken on D_{25} of the cycle.
- Dating was done in a 48-hour span POD8-9, POD_{9-10} according to Noyes criteria (1950)[4].
- Biopsies were considered out for phase, if they were dyssynchronous by > 2 days in relation to the day of ovulation as determined by transvaginal sonography[6].

2. Transvaginal Sonography

- Day of ovulation was determined by potential signs of impending ovulation.
- Ovulation was confirmed by the disappearance of the follicle or a decrease in the follicle size with development of intrafollicular echoes, accompanied by fluid in the Pouch of Douglas.
- Cyclic change of the endometrium was imaged using TVS during different phases of menstrual cycle. The characteristic sonographic pattern and endometrial thickness were measured during Early Follicular, Late follicular. Early, Mid and Late Luteal phases of the menstrual cycle.

3. Transvaginal Pulsed Doppler Study

Color Doppler study was performed using LOGIQ 500. Scanning was performed transvaginally with 7.20 MHz transducer. Peak Systolic Velocity and End Diastolic Velocity were measured for both ovarian as well as the uterine arteries. The frequency peaks were traced manually. The onboard computer calculated the mean velocities.

Pulsatility index was calculated as $\frac{Vmax - Vmin}{Vmean}$

Resistance index was calculated as $\frac{Vmax - Vmin}{Vmax}$

Where, Vmax – Peak systolic velocity
Vmin – End diastolic velocity
Vmean – Mean velocity for the entire cardiac cycle

The above indices were measured for the ovarian and uterine arteries in Late Follicular (cycle days 9-12); Mid Luteal (day of ovulation plus 5-6 days); and Late Luteal (day of ovulation plus 9-11 days) phases of the menstrual cycle.

RESULT

Out of 50 cases, 4 patients did not show any sonographically visible dominant follicle and corpus luteum and remained anovulatory. This was evident by very low progesterone concentration (<3.0ng/ml) and a proliferative endometrium at biopsy in the late luteal phase. These patients were excluded from the study. Out of 46 ovulatory women, 15 (32.6%) were diagnosed as LPD and 31 (67.39%) had no LPD. All 15 patients with LPD had progesterone level <10ng/ml as determined from D4-D9 of ovulation by ultrasonography. Out of 50 controls, 6 women (12%) had LPD.

The age of patients in this study ranged from 21-35 years with mean age 30.67 years for study group and 30.98yrs for control group. P Value >0.05(not significant).

Table 1 Comparison Of Pulsatility Index Of Ovarian Artery In Lpd And Fertile Group

TIME OF SCAN	STUDY GROUP LPD PATIENTS (Mean ± SE)	CONTROL GROUP FERTILE PATIENTS (Mean ± SE)	P Value
LF	(n-12) 0.916 ± 0.010	(n-41) 0.918 ±0.0013	>0.05 (NS)
ML	(n-11) 0.662 ±0.009	(n-44) 0.428 ±0.002	<0.001
LL	(n-9) 0.893 ±0.004	(n-44) 0.642 ±0.002	<0.001

Table 2 Comparison Of Resistance Index Of Ovarian Artery In Lpd And Fertile Group

TIME OF SCAN	STUDY GROUP LPD Pt. (Mean ± SE)	CONTROL GROUP FERTILE Pt. (Mean ± SE)	P Value
LF	(n-12) 0.613 ± 0.006	(n-41) 0.563 ± 0.010	<0.001
ML	(n-11) 0.559 ± 0.004	(n-44) 0.386 ± 0.003	<0.001
LL	(n-9) 0.664 ± 0.010	(n-44) 0.429 ± 0.001	<0.001

Table 3 Comparison Of Pulsatility Index Of Uterine Artery In Lpd And Fertile Women

TIME OF SCAN	STUDY GROUP LPD Pt. (Mean ± SE)	CONTROL GROUP FERTILE Pt. (Mean ± SE)	P Value
LF	(n-15) 2.522 ± 0.006	(n-44) 2.362 ± 0.005	<0.001
ML	(n-15) 2.840 ± 0.006	(n-44) 2.088 ± 0.007	<0.001
LL	(n-15) 2.898 ± 0.008	(n-44) 2.020 ± 0.003	<0.001

Table 4 Comparison Of Resistance Index Of Uterine Artery In Lpd And Fertile Women

TIME OF SCAN	STUDY GROUP LPD Pt. (Mean ± SE)	CONTROL GROUP FERTILE Pt. (Mean ± SE)	P Value
LF	(n-15) 0.845 ± 0.003	(n-44) 0.837 ± 0.002	>0.05 (NS)
ML	(n-15) 0.942 ± 0.010	(n-44) 0.735 ± 0.003	<0.001
LL	(n-15) 1.012 ± 0.007	(n-44) 0.751 ± 0.017	<0.001

Table 5 Timed Endometrial Biopsy In Study Population

Endometrial biopsy	LPD Pt.	Non LPD Pt.	Total
Biopsy out of phase	9 (TP)	8 (FP)	17
Biopsy in-phase	6 (FN)	23 (TN)	29
Total	15	31	46

DISCUSSION

Luteal phase defect, first described by Georgeanna Jones in 1949, is characterised by the failure of development of a fully mature secretory endometrium. Despite the relative infrequency of this entity, luteal phase defect was identified in about 32.8% of infertile and 12% of fertile women in our population. Brumsted and Glock (1995), based on an endometrial lag >3 days and low progesterone values and Jordan et al (1994), based on low progesterone level, reported an incidence of LPD in 33.3% and 21% women respectively among infertile patients.

Color flow pulsed Doppler is a unique non-invasive technology to investigate the circulatory changes in organs like uterus and ovaries. While monitoring follicular growth in our patients, follicular flow appeared when the dominant follicle reached 12-15mm in diameter in late follicular phase as a ring of angiogenesis around it. Our findings were similar to the findings of Kujrak et al (1991) who demonstrated appearance of perifollicular blood at a size of 10-12mm[5]. Increased vascularity results in preferential delivery of gonadotropic hormones or other growth factors and substrates required for steroidogenesis to the individual follicles which are destined to be recruited and mature. This hypothesis is supported by histomorphometric studies in the rhesus monkey that have shown a distinctly higher vascularisation in the theca layer of the dominant follicles as compared with that of the smaller follicles (Zeleznik et al., 1981)[7].

In our study, transvaginal pulsed Doppler study was done in late follicular (cycle days 9-12); mid-luteal (day of ovulation plus 5-6 days) and late luteal (day of ovulation plus 9-11 days) phases of the menstrual cycle.

Our fertile patients showed a decrease in the PI in ovarian artery from late follicular phase to mid-luteal phase and increase in late luteal

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phase but still lower than follicular phase. Weiner et al (1993) demonstrated similar findings[8]. On the contrary, Campbell et al (1993) reported a fairly constant PI during periovulatory period[9]. When the fertile group of women were compared with the luteal phase defect group of women, a significantly higher PI in mid-luteal and late luteal phases ($p<0.001$) was found in the LPD patients but not in late follicular phase.

The RI in ovarian artery in fertile patients was 0.563±0.001 in late follicular phase; reached its nadir in mid luteal phase (0.386±0.003), then again rose to a level of 0.429±0.001 in the late luteal phase, still lower than that seen in the follicular phase. When fertile group of patients were compared with the LPD patients, a significantly lower RI ($p<0.001$) was found. These observations lead to a conclusion that vascular changes occurring in the corpus luteum is of great significance in infertility caused by luteal phase defect.

In fertile patients, PI of uterine artery decreased in the different phases of menstrual cycle progressively from late follicular to late luteal phase. When LPD patients were compared with fertile patients, PI was significantly high ($p <0.001$) in all phases. As blood supply to the uterus should be high in the luteal phase (Kurjak et al., 1991; Goswamy et al., 1988; Battaglia et al., 1991), the decrease in the uterine artery flow in the luteal phase in LPD patients may cause poor endometrial receptivity and hence infertility or repeated abortions[5,11]. Scholtes et al. (1989), Goswamy et al. (1988), Steer et al. (1990) and Kurjak et al. (1991) obtained similar reports on the PI of uterine artery in a normal menstrual cycle[5,10,11,12].

When fertile group of patients were compared with LPD group of patients, RI of uterine artery was significantly high ($p <0.001$) in mid-luteal and late luteal phases of LPD patients, but not significant ($p >0.05$) in late follicular phase and was consistent with Nargund G (1995) study[13].

In our study, sensitivity of endometrial biopsy in diagnosing luteal phase defect was 60% and specificity was 74.2%. Jordan et al (1994) also demonstrated the similar sensitivity (57%) of endometrial biopsy in late luteal phase for diagnosis of LPD, but specificity was 44%[14].

CONCLUSION

Although timed endometrial biopsy has been the gold standard for diagnosing luteal phase defect, introduction of color Doppler imaging and pulsed Doppler analysis, has provided a non-invasive method for assessing the vascular and morphological changes in the ovary and endometrium implicated in luteal phase defect. It demonstrates a functional relationship between utero-ovarian hemodyanamics and follicular development and can assess corpus luteal function, implantation success rate and can reveal unexplained infertility problems.

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