

# INFERTILITY ASSOCIATED WITH INADEQUATE LUTEAL PHASE WITH SEPCIAL REFERENCE TO MANAGEMENT BY TESTOSTERONE

by

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## Introduction

The term inadequate luteal phase means a condition in which endometrium is incapable of proper development necessary to support nidation. In such cases, either corpus luteum fails to develop normally or regress too quickly. Such condition may exist inspite of normal ovulatory mechanism or may follow infrequent and induced ovulation.

## Objective of the Present Study

The underlying cause of inadequate luteal phase leading to infertility is not very clear. This is because in the biology of human conception, the mechanism involved for the maintenance of corpus luteum from the time of ovulation till the time when HCG becomes available in adequate quantities is ill understood. For this purpose, substances like pituitary LH and prolactin have been involved without general agreement.

Mukherjee (1972) and Mukherjee and Chakravarty (1974), while working on the probable role of testosterone and the

related androgenic steroids on the female reproductive organs of rats briefly reported a potent positive luteotropic effect of testosterone and dehydroepiandrosterone (DHEA) in this species, as well as in the human female. Based on the result of this experimental observation, a brief clinical trial with testosterone in infertility associated with inadequate luteal phase has already been reported in a previous communication (Chakravarty and Mukherjee, 1977).

The objective of this presentation is to corroborate further this experimental observation by clinical trial with testosterone in a larger group of infertile women in whom the infertility was believed to be due to inadequacy of corpus luteum function.

## Materials

Out of 1588 cases of infertility investigated from January, 1975 to April, 1980, the diagnosis of inadequate luteal phase was established in 278 cases (19.5%). These cases did not reveal any other obvious accountable factor for their infertility. Criteria for diagnosis of inadequate luteal phase were based on basal body temperature record and endometrial histology. In 37 selected cases endometrial histology was correlated with endometrial histochemistry, vaginal cyto hormonal pattern

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(CHP) and basal body temperature chart. Seven fertile women were also studied in a similar manner who served as controls.

#### Methods of Diagnosis of Hypoluteal Phase

The patterns of B.B.T. in hypoluteal phase are shown in Figs. 1 and 2. Endometrial biopsy was obtained in two consecutive menstrual cycles—one in the midpostovulatory phase and the other in the immediate premenstrual phase.

The findings of 'Out of Phase' or 'Underripening' (discrepancy of secretory picture by 2 days or more) and 'Discordant' (disparity in the growth pattern between gland and stroma or amongst adjacent glands) pattern of endometrium suggested the possible existence of hypoluteal phase.

In vaginal cytology, inadequate midzone shift (less than 25%) in the maturation index suggested corpus luteum deficiency.

For histochemical studies, endometrium was stained for glycogen (PAS method—Little, 1965), Acid mucopolysaccharide (Mowry's Alcian blue method, Lillie, 1965), Alkaline phosphatase activity (modified Gomori's method, Pearse, 1968) and for reticulin (Gomori's method—Lillie, 1965). With adequate progesterone activity, there should be minimum glycogen and AMP in the gland epithelium with relative increase of concentration in the stromal cells and in addition there should be dense reticulin network around glands and spiral arterioles. Alkaline phosphatase activity which is high in late proliferative phase should diminish in the secretory stage.

Histological diagnosis of hypoluteal phase was almost always corroborated by histochemical findings. But, often histologically normal endometrium was found to be histochemically discordant (Figs. 3, 4, 5 and 6).

#### Observation

**Diagnosis:** The parameters by which the diagnosis of hypoluteal phase was based in 241 random, 37 selected and 7 control cases are shown in Tables I and II.

TABLE I  
Types of Endometrium: (241 random cases)

Endometrium	No. of cases	Per cent
Discordant	80	33.2
'Out of Phase' or 'Underripening'	123	51.04
Mixed (Proliferative and Secretory)	15	6.2
Late Secretory—but B.B.T. discordant	23	9.5

#### Treatment with Result

Four groups of drugs have been used. Trial was given with each drug for at least 3 cycles and in case of failure another drug was tried.

The results tabulated in Table III indicate the ultimate success achieved by a particular drug. Testosterone in this respect was found superior to the other varieties of luteal phase supporting drugs. However, the number of abortion following successful therapy with testosterone was higher than following successful therapy with allyloestrinol.

#### Treatment with Low Dose Testosterone

Testosterone in the form of Perandran tablets (5 mgm. CIBA)—one tablet daily was administered in the early luteal phase for 5 consecutive days. The precise date of ovulation must be determined by B.B.T. chart—because if testosterone is administered prior to ovulation—it might



TABLE II  
Comparative Observation of Other Parameters in 7 Control and 37 Selected Cases

		Control Group	Study Group
B.B.T.	Biphasic	7 (100%)	—
	Biphasic but discordant OR short luteal elevation	—	29 (78%)
	Uniphasic	—	6 (16%)
	Irregular	—	2 (6%)
Vaginal CHP	25 and >25 (%) of midzone shift	6 (86%)	11 (30%)
	<25 (%) „	1 (14%)	26 (70%)
Endometrial findings	Normal	7 (100%)	10 (27%)
Histological	Luteal phase defect	—	27 (73%)
Endometrial findings	Normal	7 (100%)	2 (6%)
Histochemical	Luteal phase defect	—	35 (94+)

TABLE III  
Comparative Evaluation of Results of Treatment With Different Drugs

Drugs used	No. of cases treated	Number conceived	Term delivery	Abortion	Not yet delivered
Testosterone	278	112 (40.4%)	78	30	4
Gestanin	216	62 (28.7%)	52	9	1
Duphaston	67	3 (4.5%)	—	—	—
Profasi (HCG)	10	—	—	—	—

inhibit ovulation. On the other hand, if it is continued upto late luteal phase the drug may virilise a female embryo.

Following conception, each patient was treated with allyloestrinol for variable period of pregnancy because there was an apprehension that inadequate luteal phase, which was the cause of infertility could also lead to abortion when these cases subsequently conceived.

#### Interval between treatment with testosterone and conception

Out of 112 conceptions, success was achieved following first course of treatment extending for 3 months in 62, while in the remaining 50, pregnancy followed ultimately with further courses of testosterone when other drugs failed.

TABLE IV  
Success With Testosterone in Relation to Age Group

Age in years	No. of cases	No. conceived	Per cent
Below 20	48	7	14.6
21-30	167	82	49.1
31-35	39	20	51.2
36 and above	24	3	12.5

Success was maximum in the age group 21 to 35 years. The oldest woman who conceived with testosterone was 38 years.

There was no significant difference in the incidence of pregnancy in relation with duration of infertility upto 10 years. Maximum duration of infertility at which

TABLE V  
*Success With Testosterone in Relation to Duration of Infertility*

Duration of infertility in years	No. of cases	No. conceived	Per cent
1-2	83	34	40.9
2-5	125	57	45.6
5-10	42	16	38.09
10-and above	28	5	17.8

success was achieved with testosterone in the present series was 13 years.

#### Comments

Many cases of unexplained infertility can be explained on the basis of inadequacy of corpus luteum phase. Balin (1967) reported an incidence of 20 per cent and the incidence in the present series is 17.5%. Several parameters have been used for studying luteal phase insufficiency.

Though estimation of serum progesterone and urinary pregnanediol has been supposed to be very dependable in evaluating corpus luteum function by some investigators (Bell *et al* 1964; McArthur *et al* 1964), according to others it is not so. Jones (1973) states that pathophysiology of luteal phase insufficiency is multifactorial and its diagnosis is best made by endometrial biopsy in the late luteal phase which serves as a bio-assay, assessing the complete corpus luteum function. Novak and Woodruff (1967) however believe that proper functional evaluation of endometrium can be done more thoroughly by consideration of its various histochemical properties.

The usual treatment of such corpus luteum inadequacy is substitutional therapy with progesterone or progestogens. Palmer (1959) however, believes that administration of progestogens may improve the quality of secretory endo-

metrium but the drugs suppress progesterone production by the ovaries.

On the other hand, our experiments suggest that androgens help to maintain the structural and functional integrity of the corpus luteum.

It has been demonstrated that there is a significant rise of plasma androgens in the periovulatory period (Vermeulen and Verdonck, 1976) in normally menstruating women. The physiological purpose of this periovulatory surge has not been explained but it appears that acceleration of luteotropic activity of the existing corpus luteum might be one of the reasons of increased androgen level during this period.

It appears that androgens preserve and stimulate the corpus luteum to produce more progesterone necessary to build up an adequate secretory endometrium and thus prepare the bed for the fertilised ovum to be implanted. Further it seems (Mukherjee and Chakravarty, 1974) that androgens not only exert a luteotropic effect in the postovulatory phase but also antagonise the possible luteolytic activity of progesterone-prostaglandin complex.

In some cases, even if the endometrium is normal secretory, exogenous stimulation is indicated because in these cases endometrium needs more than the customary quantity of endogenous progesterone to develop properly (Balin 1967). Twenty-three similar cases have been recorded in the present series.



While other treatments failed to induce pregnancy in these "apparently" normal infertile women, success with testosterone was achieved in 40.3% of cases in the present series which was higher than the success achieved by other drugs. The dosage of androgen used was very much within the safe pharmacological limits and uptill now, in 78 babies already delivered, there was no evidence of any abnormality.

#### Summary

1. Two hundred and seventy-eight infertile women have been recorded where infertility was believed to be due to only inadequacy of corpus luteum phase.

2. The diagnosis was mainly based on the record of basal body temperature chart and report of premenstrual endometrial biopsy obtained during two consecutive menstrual cycles. In 37 selected cases, vaginal cytohormonal pattern and endometrial histochemistry were performed to corroborate the histological diagnosis.

3. While other drugs were tried, the results of treatment appeared encouraging following testosterone therapy.

4. It has been suggested that testosterone not only helps to maintain the structural and functional integrity of corpus luteum but also antagonises the luteolytic activity of progesterone-prostaglandin complex.

5. The dose of testosterone used was within safe pharmacological limits and no untoward effect was noticed in 78 new born babies delivered so far.

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See Figs. on Art Paper I-II