# THE USE OF OVARIAN ULTRASOUND AND BIOCHEMISTRY IN THE INVESTIGATION AND MANAGEMENT OF THE FEMALE PARTNER IN COUPLES WITH UNEXPLAINED INFERTILITY

(2 VOLUMES)

VOLUME I

Mark Patrick Rogers HAMILTON ©

M.B.Ch.B., M.R.C.O.G.

Thesis submitted to
The University of Glasgow
for the degree of
Doctor of Medicine

Original research carried out in the
University Department of Obstetrics & Gynaecology,
Glasgow Royal Infirmary
&
Department of Midwifery,
Queen Mother's Hospital, Glasgow

November 1988



ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

## Declaration

The material contained in this thesis derives from work carried out by the author while employed, initially as a Medical Research Council funded research assistant in the University of Glasgow Department of Midwfery, and latterly as a registrar in obstetrics and gynaecology, based at the Queen Mother's Hospital, Yorkhill, Glasgow.

The ultrasound scans and virtually all the venesection described were performed solely by the author. Hormone assays were performed by the laboratory staff of the University Department of Obstetrics and Gynaecology, Glasgow Royal Infirmary. All data have been analysed and written up by the author.

M.P.R. Hamilton

November 1988

Glasgow

# THE USE OF OVARIAN ULTRASOUND AND BIOCHEMISTRY IN THE INVESTIGATION AND MANAGEMENT OF THE FEMALE PARTNER IN COUPLES WITH UNEXPLAINED INFERTILITY

ACKNOWLEDGEMENTS

This thesis could not have been compiled without the assistance of the following :-

The Medical Research Council kindly supplied a grant (Project Grant No. G8200415 SB) administered by the University of Glasgow, funding my salary during my research post, as well as paying for all the laboratory consumables used during this period.

Financial assistance was also provided by the Greater Glasgow Area Health Board Research Support Group for the work described in Chapter 7.

Prof. Sir M.C. Macnaughton and Prof. C.R. Whitfield were instrumental in nurturing my interest in ovarian ultrasound, and to Prof. Whitfield, in particular, I am deeply indebted, for his assistance as adviser, as well as his constant enquiries as to the progress of my work.

Dr. J.R.T. Coutts and Dr R. Fleming have been closely involved with the project, and their expertise and helpful advice has been greatly appreciated.

Dr D. Barlow also collaborated and encouraged me in this work, and this is gratefully acknowledged.

The hormone assays, on approximately 5000 blood samples, were performed by the laboratory staff of the University Dept. of Obstetrics and Gynaecology. Their invaluable assistance is

recognised.

The data thereby accumulated could only have been computed and analysed with the assistance of Mr. John Fleming, a good friend and colleague. To him and the staff of the Dept. of Ultrasonic Technology, long suffering in their accommodation of the large number of patients in my care, my thanks are extended.

The immense encouragement I have received from my family, in particular my father, has been gratefully received.

My greatest debt of gratitude is to my wife, Susan. Her unstinting support, over many years, has made all things possible. It is to her this work is dedicated.

# ABBREVIATIONS

The following are the commonly appearing abbreviations in the thesis.

| | |
|---|---|
| BBT | Basal body temperature |
| CL | Corpus luteum |
| E2 | 17-B estradiol |
| FD | Follicular diameter |
| FSH | Follicle stimulating hormone |
| GIFT | Gamete intra-fallopian tube transfer |
| GnRH | Gonadotrophin releasing hormone |
| hMG | Human menopausal gonadotrophin |
| hCG | Human chorionic gonadotrophin |
| IU/l | International units per litre |
| IVF | In-vitro fertilisation |
| LFP | Long follicular phase |
| LH | Luteinising hormone |
| LPD | Luteal phase defect |
| LUF | Luteinised unruptured follicle |
| MHz | Megahertz |
| ng/ml | Nanograms per millilitre |
| nmol/l | Nanomoles per litre |
| P | Progesterone |
| PF | Peritoneal fluid |
| PFD | Poor follicular development |
| PFM | Poor follicular maturation |
| PG | Prostaglandin |
| pg/ml | Picograms per millilitre |
| PPS | Poor progesterone surge |
| PPS-N | Poor progesterone surge to normal levels |
| PPS-S | Poor progesterone surge to subnormal levels |
| PRL | Prolactin |
| SD | Standard deviation |
| SEM | Standard error of the mean |
| SFP | Short follicular phase |
| SLP | Short luteal phase |
| UI | Unexplained infertility |
| U/S | Ultrasound |

## SUMMARY

Fertility assessment is founded firstly on the documentation of egg and sperm availability and secondly on a determination that the gametes can meet. If these criteria are met, then continued infertility is deemed to be unexplained, a situation found in 20-30% of the couples attending most infertility clinics.

Conventional tests of ovulation are, in the absence of pregnancy, indirect barometers of ovarian function, and tell us little of the dynamics of follicular growth, oocyte release and corpus luteum function. Since gonadotrophin and ovarian steroid secretion is dynamic, and the endometrium is sensitive to hormonal fluctuations during the cycle, it is clear that if reproductive function is to be assessed satisfactorily then the maximum information possible must be obtained.

The concept of luteal phase deficiency (LPD) has aroused considerable debate over the years, and disagreements over the nature, definition, diagnosis and clinical implications of the condition abound in the literature. A number of studies on patients with unexplained infertility have demonstrated subtle deviations from normal in the plasma concentrations of gonadotrophins and ovarian steroids, but none have, in substantial numbers, related these features to ultrasonically observed follicular growth patterns.

The present study was designed to explore ovarian function in women with unexplained infertility using the combined resources of ovarian ultrasound and simultaneous daily plasma biochemistry to elaborate follicular growth patterns and gonadotrophin and ovarian

steroid hormone profiles in blood. These ultrasonic and endocrine profiles were then related to those obtained from normally cycling, presumably fertile, volunteers and from spontaneous conception cycles.

Daily blood samples were taken throughout complete menstrual cycles and frequent ultrasound scans were performed during the periovulatory and luteal phases. The normal cycle data (43 cycles) were compared with that from 11 spontaneous conception cycles, and in terms of follicular growth and corpus luteum function, showed no differences, thus justifying the use of the control data as the yardstick of normality.

175 cycles from patients with unexplained infertility were studied in detail. 98 (56%) of these cycles demonstrated apparently abnormal ovarian function. The analysis of these "abnormal" cycles provides the core of the thesis.

Luteal cyst formation was seen in 41 cycles (23.4%); reference to the U/S and biochemical data discriminated two distinct subgroups - those where the dominant follicle was seen to shrink prior to luteal cyst formation, often associated with normal ovarian steroid profiles, and those cycles where no shrinkage of the follicle was seen following the LH peak, very often associated with markedly deficient luteal phase plasma P concentrations. The former, it is hypothesised, represent cystic corpora lutea and the latter, may be luteinised unruptured follicles (LUF's). Cyst size alone was not a sensitive indicator of the nature of the luteal cysts seen.

51 cycles (29.1%) were found to exhibit abnormal patterns of P

production in the early luteal phase. Many such PPS cycles exhibited mid-luteal P concentrations in excess of "normal ovulatory" criteria, indicating that infrequent sampling will miss a high proportion of abnormal cycles. 45.1% of the PPS cycles also demonstrated luteal cyst formation, the majority of which were LUF's. Thus in these cycles it is likely that impairment of oocyte release and sub-optimal endometrial receptivity render the cycle infertile. Abnormalities were seen in the gonadotrophin profiles in some cycles, suggesting that in these cases follicle recruitment might have been abnormal. The therapeutic implications of these findings are discussed.

23 cycles (13.1%) demonstrated abnormally high basal LH profiles and almost 70% of those had ultrasonically observed abnormalities of follicular function. Commonest of these was luteal cyst formation. 2/3 of the remainder elaborated subnormal luteal P production. These data are the first reported demonstrating an association between LUF cycles and disturbances of gonadotrophin secretion. The pathophysiology behind these observations and the possible therapeutic implications are discussed.

Subnormal follicular development, both biochemical (16 cycles) and ultrasonic (12 cycles), was associated with variable gonadotrophin concentrations. Reference to these profiles would suggest that in some cases the follicular deficiency is a consequence of pituitary dysfunction and in others the problem lies at the follicular level.

Abnormalities of cycle phase length constituted a small proportion of the cycles under study and the data would suggest that such disturbances are of minor importance in the genesis of

infertility in the unexplained infertile population.

Two related studies were performed, to examine further any clinical implications of cycle abnormalities such as those described in this thesis.

1) The reproducibility of cycle abnormalities was examined when 26 of the main study group, were evaluated in detail, over two cycles within a year of one another. All of the preliminary cycles had been found to be abnormal. 61% of the second cycles demonstrated abnormalities, a similar incidence to the overall incidence in the main study. Recidivism rates were similar for all the main abnormality sub-groups encountered in the preliminary cycles, though in those cases the second cycle abnormality was not always the same as that of the first cycle. Only 1 (16.7%) of 6 LUF cycles was found to recur. These results indicate that treatment prescribed in cases of unexplained infertility, on the basis of the findings in a single cycle of investigation, is probably unjustified and is unlikely to be successful.

2) The relationships between ultrasonic and biochemical abnormalities of ovarian function in unexplained infertility, in particular luteal cyst formation, and luteal phase laparoscopic findings and PF steroid concentrations were examined. 24 patients with relatively short durations of infertility, in whom a diagnosis of unexplained infertility was expected prior to the performance of laparoscopy, were shown to exhibit a lower incidence of cycle phase abnormality compared to the main study group. Neither luteal phase laparoscopic findings nor PF steroid concentrations were of diagnostic value, and it is suggested that such intensive

investigation should not be the first line approach in the management of patients with potential primary unexplained infertility.

# CHAPTER 1 INTRODUCTION

Despite many technical advances in our understanding of the processes involved in human reproduction, a core of couples still exist in whom, despite intensive investigations, over many years in some cases, infertility is unexplained. Conventional diagnostic tests will have had little therapeutic impact in such cases, yet some will conceive spontaneously as time goes by, in spite of, rather than because of, the ministrations of clinicians. Clarification of the disturbances in reproductive function in such couples is sought, not only by the patients, but also by the physicians responsible for their care.

## 1.1 Definition of unexplained infertility

Unexplained infertility (idiopathic infertility; normal infertile couples; infertility cause unknown;) should be reserved as a diagnosis only for couples who have been trying to conceive for at least two years and where investigations have shown the male to have normal semen analyses, usually greater than 20m/ml sperm, with >40% motile and >50% with normal morphology. The female should have been shown to ovulate normally and regularly and an assessment of the pelvis should have revealed normal anatomy with no evidence of tubal disease, fibroids or endometriosis. A sexual history should have failed to reveal any coital problem. Many couples will present at clinics before two years of attempting to conceive and, although distress at their inability to conceive may be considerable, they should be counselled that the chances of spontaneous conception over the succeeding year will be high (Barnea, Holford & McInnes 1985). The prognosis is undoubtedly related to the age of the female (Pepperell & McBain 1985, Hull et al 1985).

## 1.2 Incidence of unexplained infertility

Population based studies assessing the incidence of unexplained infertility are lacking and clinic based incidences will inevitably give biased figures dependent on the particular interests of the individual clinic and its resources, the population from which it receives its referrals, the protocols of investigation of the clinic and its criteria for the diagnosis of unexplained infertility. Templeton and Penney (1982) reviewed 17 papers between 1944 and 1980 and found reported incidences of between 5.8% and 58% for unexplained infertility. In their own clinic group the incidence was 23.5%, similar in both the subgroups of patients with primary and secondary infertility. This figure is slightly less than the 28% subsequently quoted by Hull et al (1985) and the 30% of Haxton et al (1987).

While it is accepted that such patients maintain a potential for spontaneous conception (Verkauf 1983, Taylor, Leader & Pattinson 1985), influenced in degree by the number of years of trying as well as the age of the female partner (Hull et al 1985), the knowledge that 36% of those with primary infertility and 21% of those with secondary infertility will remain childless after 9 years of trying (Templeton & Penney 1982) has spurred investigators to try to elaborate more clearly the nature of the deficiency in reproduction. Avenues of research have been excellently reviewed by Moghissi & Wallach (1983) and McBain & Pepperell (1987).

## 1.3 Putative "causes" of unexplained infertility

Abnormalities of the anatomical structure of the genital tract, in particular retroversion of the uterus, have been cited as being

important causative factors of infertility (McBain & Pepperell 1987) though evidence that these are of any relevance appears to be lacking except in the unusual circumstance of a congenitally abnormal uterus associated with recurrent early miscarriage.

Immunological factors are implicated in some couples' infertility (Shulman 1986), with suspicion usually aroused at the finding of a poor post-coital test. Not all authorities rely on this somewhat imprecise technique to evaluate sperm cervical mucus interaction and with newer methods now developed to define sperm antibody presence (Clarke et al 1984) insight is being gained into a previously vague impression of a relationship in the human between sperm function and fertility.

Male factors in the genesis of infertility remain difficult to evaluate and reliance is usually placed on the semen analysis in isolation to formulate an assessment. This represents a quantitative rather than qualitative method and more emphasis should be placed on the evaluation of the fertilising capacity of sperm. Available tests in this area are, in the main, limited to couples undergoing IVF, while inter-species methods of assessment, such as the zona-free hamster egg penetration test, are both costly and of debatable value. The relationship of varicoceles to male infertility is controversial and evidence seems to be accumulating that these commonly occurring phenomena are of little relevance to human reproduction (Baker et al 1985).

Occult infections of the genital tract may in some cases be linked with infertility but conclusive proof that they have an important role in unexplained infertility is lacking. The main

organisms which have been implicated are ureaplasma urealyticum and chlamydia trachomatis, the latter now being a well recognised cause of pelvic inflammatory disease. Since both organisms are found in relatively high percentages of both fertile and infertile couples, and treatment of carriers or empirical therapy in groups with unexplained infertility seems to confer no conclusive benefit to those receiving antibiotics, it seems unproven whether such organisms can be considered a cause of unexplained infertility (McBain & Pepperell 1987).

The possible association of mild endometriosis with infertility is another continuing controversy in the field and to date there have been few controlled trials objectively assessing its impact. The subject was critically reviewed by Olive & Haney (1986) who concluded that many of the assertions in relation to the disease and its treatment were based on anecdote and that prospective randomised controlled trials were urgently required in order to clarify a very confused situation. Thomas and Cooke (1987) in a placebo-control double-blind trial has suggested that eradication of mild asymptomatic disease confers no benefit in terms of cumulative chance of conception and these data cast considerable doubt on the clinical significance of commonly encountered mild endometriosis. The relationship between mild endometriosis and failure of oocyte release at ovulation (Brosens, Koninckx & Corveleyn 1978) remains unproven (see below).

## 1.4 Luteal Phase Deficiency (LPD)

The concept of the inadequate or deficient luteal phase has been espoused by numerous authorities over the years, although there has

been considerable diversity of opinion as to the nature and reproductive consequences of the abnormality.

It is common practice to regard LPD as a lack in amount and/or duration of secretion of P by the corpus luteum.

### 1.4.1 Incidence of luteal phase deficiency

The incidence of the phenomenon depends to a large extent on the group of patients under scrutiny, the methodology of diagnosis and the number of cycles in which the abnormality must be seen in a single patient to be considered significant. Jones (1976) claimed that the LPD, characterised by either a defect of P secretion by the corpus luteum or a failure on the part of the endometrium to respond to the given level of P, was the cause of infertility in only 3.5% of her clinic population. Others have cited higher rates (Israel et al 1972) though criteria of diagnosis differed in these studies. A quarter to a third of patients with a history of recurrent abortion demonstrate the abnormality (Jones & Delfs 1951, Soules et al 1977, Tho, Byrd & McDonough 1979) and it seems likely that the inadequacy of P production leads to implantation failure of the blastocyst (Jones 1976, Kusuda et al 1983) though it is possible that alterations in either tubal function, leading to abnormalities of gamete transport or secretion of fluid essential for nourishment of the conceptus, or uterine contractility secondary to the lack of P also be of importance.

Other reported clues in the history that a patient is at risk of demonstrating LPD include a history of infertility, hyperprolactinaemia, weight loss, high level exercising and athletic

training, and evidence of a long follicular phase (Balasch, Creus & Vanrell 1986) or short luteal phase. An occasional history of delayed menses (1-2 weeks) with a heavy flow when the period arrives may also suggest the possibility of LPD.

### 1.4.2 Impact of LPD

The reproductive impact of the abnormality remains controversial since perhaps with the exception of the data on patients with a history of recurrent abortion there have been few statisticaly controlled studies demonstrating a significant effect on fertility (Wentz 1982).

Few studies have addressed the question of recurrence of this phenomenon since any clinical significance will depend as much on the frequency of occurence as on the effect on fertility exerted in a single cycle.

## 1.5 Assessment of ovulation and corpus luteum function

Biophysical, biological and biochemical assays have been used, sometimes independently though often in combination, to characterise the abnormal luteal phase.

### 1.5.1 Endometrium

The classical studies of Noyes, Hertig & Rock (1950) inspired many to adopt the demonstration of features of secretory endometrium appropriate to the stage in the cycle to define normality of luteal function. In general where the endometrium was found to be two or

more days out of phase with expected histological development then the diagnosis of LPD could be made (Jones & Delfs 1951, Jones et al 1970). This bioassay of luteal function was, apart from the use of thermogenic records of shifting basal body temperature, the main method of qualitative assessment of ovulatory performance for many years. However accurate timing of the endometrial biopsy relative to ovulation is crucial for correct interpretation of the histology and this, perhaps, is a severe limitation of the technique (Koninckx et al 1977).

Gautray et al (1981) used endometrial patterns as the basis for their assessment of the luteal phase of the patients under study and found it to be best performed around day 21 ie 7 days post ovulation. The abnormalities found were sub-classified in to two main categories. Firstly those cycles where the endometrium was more than two days out of phase and secondly, those cycles where, in addition to evidence of retarded endometrium, there were stigmata of excessive estrogenic influence concurrent with, in most cases, particularly low plasma P concentrations. These data provided additional insight into LPD, and endometrial biopsy, they claimed, was an essential part of the work-up of the infertile patient. Abnormalities in the production of ovarian steroids were described in their patients as well as basal body temperature evidence of disturbed ovulation.

Some authors (e.g. Jacobsen & Marshall 1980) have cautioned that there may be a danger of reducing the potential for pregnancy in cycles in which an endometrial biopsy is taken. These data related to patients undergoing induction of ovulation with gonadotrophins and may not necessarily apply to the unstimulated situation. They found no difference in the abortion rate as a consequence of biopsy.

Gautray et al (1981) also evaluated the levels of estrogen and P receptors in patients with abnormal luteal function and found the concentrations to be lower than those in the normal cycle, accounted for in part by the observed diminished levels of steroid hormones in these women since Bayard et al (1978) had earlier demonstrated that changes in total E2 and P receptors depend on plasma levels of the hormones.

Others have hypothesised that a lack of appropriate E2 and P receptors in the endometrium may result in a situation where the endometrial stroma fails to undergo normal secretory changes despite normal plasma P levels (Keller et al 1979). This has been termed "pseudo-corpus luteum deficiency". McRae, Blasco & Lyttle (1984) found a wide range of receptor concentrations in the normal cycles they studied and consequently a considerable overlap with the values they found in patients with LPD. At present there seems to be insufficient data to draw definitive conclusions with respect to the significance of these receptor findings.

DiZerega & Hodgen (1981) suggested that the cause of the observed deficiencies in P output in patients with LPD was a lack of functional LH receptors on the surface of luteal cells, secondary to inadequate FSH stimulation in the follicular phase of the cycle. This hypothesis was supported by work carried out in primates (Stouffer & Hodgen 1980, Stouffer et al 1984) where the administration of porcine follicular fluid selectively suppressed FSH levels, resulting in a delay in folliculogenesis and ovulation and a disturbance in luteal function.

Further evidence that local endometrial factors are important in patients with SLP is the observation that some patients exhibiting short luteal phase length may menstruate prior to the fall in P concentration that normally precedes endometrial shedding (Smith, Lenton & Cooke 1983, Smith et al 1984). The SLP probably only occurs with a frequency of around 5% in ovulatory women and it is probable that not all such cycles represent a bar to conception (Lenton et al 1984)

Balasch et al (1985) in a series of patients where sequential cycles were studied through repeat endometrial sampling found that in almost 40% of the patients they studied there was inconsistency of result, fuelling speculation regarding the impact on fertility of LPD as diagnosed by endometrial studies, and the likely efficacy of corrective therapy.

### 1.5.2 Basal Body Temperature (BBT)

The use of temperature charts to time ovulation has been shown to be imprecise (Lenton, Weston & Cooke 1977, Quagliarello & Arny 1986) and it is possible that calculation of incidences of luteal abnormalities, based on a technique which can be misinterpreted in as many as a third of cases, may be inaccurate.

Perez, Plurad & Palladino (1981) also demonstrated that the temperature chart is not always a good index of ovulation and that a good plasma P level served better, with a positive predictive value in excess of 90%.

Despite this many have relied on the temperature chart as the

basis for their evaluation of the processes of ovulation (Soules et al 1977). This is not surprising since taking one's temperature is a non-invasive, inexpensive and simple technique easily applicable within the context of modern overburdened infertility services. Perhaps its best application might be as a general screening test to indicate the patients for whom the more complex and expensive tests might be applied. Definitive conclusions are best avoided with the use, in isolation, of temperature charts to assess ovulation.

### 1.5.3 Biochemical evaluation

Development of specific radioimmunoassays for E2 and P, both in urine and plasma, has led to more precise quantitative evaluation of ovarian function. The normal pattern of hormone production has been characterised and comparisons can be made with the apparently abnormal.

Considerable debate in the literature has taken place as to an acceptable plasma level of P indicative of ovulation and adequate corpus luteum function, and whether a single blood sample in the luteal phase is sufficient to comment on the whole of the post-ovulatory period, or whether more than one sample should be taken. If reliance is made on a single sample then timing of sampling is important and, as with the endometrial biopsy, careless attention to this detail may result in inaccuracies.

Israel et al (1972) reported that a serum concentration of P >3ng/ml between 11 and 4 days prior to the onset of menstruation was always accompanied by secretory endometrium and could therefore be taken as presumptive evidence of ovulation. Abraham, Maroulis &

Marshall (1974) however found that Israel's criteria failed to be met in almost 20% of their study group and suggested that the if the sum of P concentrations in 3 separate blood samples taken within the same time period as Israel's sampling was greater than 15ng/ml then this was a better determinant of ovulation.

Ross et al (1970) suggested that 5ng/ml was a better cut off point while Radwanska & Swyer (1974) suggested that >10ng/ml serum P level represented adequate function.

Shepard & Senturia (1977) compared the use of endometrial biopsy and serum P in confirming ovulation and evaluating luteal function and asserted that the 5ng/ml level suggested by Ross seemed to be satisfactory making the comment that histology of the endometrium seemed to correlate poorly with P levels. Of interest was the observation that in 75% of the patients studied who subsequently conceived and had normal pregnancies the endometrium showed a retarded pattern, implying that the isolated finding of such a histological feature had little bearing on future fertility.

Annos, Thompson & Taymor (1980) evaluated the consistency of parameters including BBT charts, endometrial biopsies and plasma P measurements used in diagnosing LPD in 14 patients where 2 samples of blood were taken for P levels in the luteal phase. It was found that discrepancy between the endometrial biopsy and the P level occured in over 50% of the cycles studied.

Rosenfeld & Garcia (1976) found a 93% correlation between endometrial biopsies and simultaneous P estimations in patients undergoing infertility evaluations to confirm the occurence of

ovulation. They found this combined approach to be more useful, clinically, than a more precise assessment of the day on which ovulation occured.

Hull et al (1982) suggested that a mid-luteal level in excess of 9.4ng/ml (30nmol/l) was acceptable as a satisfactory ovulatory indicator though higher levels than this might be expected in cycles where patients received drugs to stimulate follicular development. This study suggested that there was a relatively narrow range of mid-luteal values in untreated cycles and that one sample was adequate to define the ovulatory status of a patient. This finding highlighted the need to attend carefully to the detail of timing the sample. Other studies with a wider spread of values may not have been so rigorous in this detail. Hull et al found the prognostic value for future fertility of a single sample to be good.

Jones et al (1974) showed that in the mid-portion of the luteal phase there was a reliable plateau of P concentrations and, as Shangold, Berkeley & Gray (1983) subsequently concurred, favoured a single midluteal P determination, timed with the BBT, as a sufficiently precise gauge of corpus luteum function.

More recently, evidence has accrued that, in common with the pulsatile pattern of release of gonadotrophins, P itself is secreted in an episodic fashion and that an individual pulse may result in fluctuations in P concentration in excess of 1ng/ml (Healy et al 1984).

## 1.5.4 The development of ovarian ultrasound

In 1973 the first reports emerged that U/S could visualize the ovaries sufficiently clearly to permit identification of the developing Graafian follicle (Kratochwil, Jentsch & Bresina 1973).This opened up an exciting avenue of investigation of ovarian function and since 1979 the literature on the subject has expanded enormously.

Initial work was carried out using the full bladder technique (Donald 1963) with B-mode static scanners, but real-time scanning, although perhaps not giving pictures of as clear resolution, is simple to use and quicker (O´Herlihy, De Crespigny & Robinson 1980).

Follicular growth was characterised in numerous studies (Hackeloer et al 1979, Ylostalo, Ronnberg & Jouppila 1979, Renaud et al 1980, Queenan et al 1980, O´Herlihy et al 1980a, Kerin et al 1981, Bryce et al 1982, Sallam et al 1982, Funduk-Kurjak & Kurjak 1982) with in general 2 - 3 mm daily increase in FD in the unstimulated cycle. Usually the follicle was visualized with certainty from about 8 - 10 mm diameter until it reached its maximum diameter. The range of maximum FD prior to ovulation varied considerably but in most studies was found to lie between 20 and 25 mm. The particularly small values reported by Ylostalo et al (1979) may be a reflection of the velocity setting of their ultrasound machine rather than a true extreme of biological variation. FD correlates well with follicular fluid volume thus validating the use of this simpler measurement as a yardstick of Graafian follicle size (O´Herlihy et al 1980a, Kerin et al 1981). This variation in maximum follicular size exposed the problem that mere measurement of FD alone is not of predictive value

in terms of imminence of ovulation. The visualisation of the cumulus (Hackeloer et al 1979) might be thought to be a useful predictor of imminent ovulation but this is not always seen (O'Herlihy, Robinson & De Crespigny 1980, Kerin et al 1981). Picker et al (1983) have described crenellation of the follicular wall as an accurate sign of impending ovulation but this was not seen in a study on nine patients, scanned intensively following the LH surge (De Crespigny et al 1981).

There are no rigid criteria for normal corpus luteum formation; Hackeloer et al (1979) describing rapid shrinkage of the follicle followed by the appearance of low amplitude echoes within it over the succeeding few days. Queenan et al (1980) described a similar profile, but also observed variants of this, including maintenance of the cystic appearance of the follicle following luteinisation. They asserted that a single scan was unable to to distinguish between an ovulatory follicle, functional cyst and occasionally a corpus luteum, unless repeated scans were being performed, preferably by a single observer.

## 1.6 Pathophysiology of LPD

### 1.6.1 Gonadotrophins

Whatever method is used as proof of ovulation it is essential that adequacy of luteal function in maintaining a pregnancy be established (Annos et al 1980). Jones et al (1970) in an attempt to explain the poor pregnancy rates in patients with ovulatory disorders undergoing treatment with clomiphene citrate demonstrated histological abnormality in the form of defective granulosa cell

luteinization and postulated that the process of luteinization itself need not always equate with ovulation and that perhaps entrapment of the ovum might be the result of the abnormality i.e. the hormonal requirements for ovulation might not be the same as those for subsequent normal luteal function. They postulated that the underlying cause of the abnormality was a defective pattern of gonadotrophin release.

Cook, Rao & Yussman (1983) also implicated deficiencies in FSH resulting in LPD finding LH levels to be normal with a resultant low FSH : LH ratio. These patients also had normal plasma concentrations of PRL representing a potentially different sub-group of defective luteal function compared to those patients demonstrating hyperprolactinaemic associated deficiencies (Lenton et al 1979). Some authors (Seppala, Hirvonen & Ranta 1976, Bahamondes et al 1979) have hypothesised that a luteal phase abnormality associated with hyperprolactinaemia represents only a point in a spectrum of increasing ovarian disturbance, culminating in oligomenorrhoea and amenorrhoea. An alternative hypothesis might be that not all women respond in the same way to hyperprolactinaemia with some reacting with short luteal phases and others with amenorrhoea.

Sherman & Korenman (1974a&b) also found subnormal P production in association with subnormal FSH levels prior to the LH peak both in patients with irregular cycles and those with luteal phase length of less than 10 days and suggested that this might be the mechanism of the "inadequate" luteal phase they described, This theory was supported by others in more recent studies in relation to the deficient luteal phase (DiZerega & Hodgen 1981, Stouffer et al 1984). Sherman also proposed that in some cases luteinization without

rupture of a follicle might occur as Jones et al (1970) and later Jewelewicz (1975) suggested.

Decrease in the FSH : LH ratio might be explained through reduction in FSH values, but alternatively elevation in LH concentrations in the face of normal FSH levels will also reduce the ratio. It has been shown in some patients that tonically high plasma LH concentrations may be associated with LPD (Fleming et al 1981). Not all patients in this study demonstrating deficient luteal function had abnormal LH secretion. Some showed transient elevations of PRL while others had no disturbance of pituitary hormones.

Secretion by the corpus luteum modulates the pulsatile release of LH by the pituitary gland during the luteal phase in normal women (Soules et al 1984). Studies on women demonstrating LPD have shown increased follicular phase frequency of pulses, of lower amplitude than in the normal cycle, associated with abnormalities of P production by the corpus luteum (Soules et al 1984). It is not clear whether these variations in gonadotrophin secretion relate to events in the previous cycle i.e. low P secretion leading to compensatory increased pulse frequency with spillage over of abnormal pulsatility into the next cycle, or whether this represents a problem at source i.e. in the hypothalamo-pituitary axis itself, leading to decreased baseline FSH values.

### 1.6.2 Prolactin

The role PRL plays in relation to follicular development, ovulation and corpus luteum function remains unclear. A cyclical pattern of secretion has been reported with, paralleling LH and FSH

concentrations, a rise in PRL at the mid-cycle. McNeilly et al (1982) observed that high levels of PRL may be associated with deficient luteal function, though this effect was not observed in pharmacological studies where hyperprolactinaemia was induced in the luteal phase alone. It has been postulated (McNatty 1979, McNatty et al 1979) that high plasma and follicular fluid PRL concentrations interfered with granulosa cell proliferation with resultant diminution of plasma E2 levels though others (Garcea et al 1983) have found E2 levels to be normal. Inhibition of FSH production by the pituitary may also be involved (Corenblum, Pairaudeau & Schewchuck 1976). The association of raised PRL levels and the SLP (Kauppila et al 1982) is not universally accepted (Sarris et al 1978) but several workers have shown that through correction of this biochemical abnormality the luteal phase can be lengthened to normal (Del Pozo et al 1979, Seppala et al 1976).

Evidence exists that, even in women with normal menstrual rhythm and ovulatory levels of P, transient elevations in PRL may well affect fertility (Lenton et al 1979, Fleming et al 1978).

### 1.6.3 Oxytocin

It has been suggested, on the basis of *in vitro* studies, that oxytocin may be important as an agent of luteolysis (Tan, Tweedale & Biggs 1982) but this has not been demonstrated *in vivo* and no association with LPD has been found, although there is evidence that levels of this hormone are raised in the luteal phase of the cycle. It is possible that the source of the oxytocin is in the ovary (Wathes & Swann 1982).

### 1.6.4 Prostaglandins

PGF2a may also to some degree exert a luteolytic effect and be involved in disturbed luteal function, though substantive evidence for this is lacking in the literature which is based mainly on *in vitro* studies on dispersed luteal cells (Baird 1985). PG's are thought to be involved in the process of oocyte release at ovulation (Craft et al 1980) and it is possible that disturbance in PG metabolism could be involved in ovulatory disorders. Recent evidence suggests that inhibition of PG production may interfere with the processes of ovulation both in primates (Jaszczak 1983) and humans (Killick & Elstein 1987).

### 1.6.5 Endometriosis

The association between endometriosis and infertility is well known and theories abound as to the nature of the link. An increased incidence of LPD has been reported (Grant 1981). Others have confirmed this finding (Cheesman et al 1983) and it has been speculated that a link may exist between the presence of endometriosis and failure of the mature follicle to rupture, a phenomenon which has also been linked with LPD (Brosens et al 1978).

### 1.6.6 Luteinised unruptured follicle syndrome (LUF)

Assumptions that ovulation is an inevitable consequence of an LH peak (Aksel et al 1976), or definitively associated with the biochemical observation of a rise in plasma P concentrations (Laborde et al 1975), have been questioned.

Sherman & Korenblum (1974), Jewelewicz (1975) and Jones (1976) alluded to the possibility that in some cases where biochemical evidence of ovulation was found the follicle failed to rupture leading to entrapment of the oocyte within the ovary. This, it was speculated, might be the cause of failure to conceive, both in the unstimulated cycle and in the patient on clomiphene, who, despite biochemical evidence of a "satisfactory" response to therapy, remains infertile.

Koninckx, DeMoor & Brosens (1978) examined this further by performing laparoscopies in patients with unexplained infertility in the days following the mid-cycle LH peak. In addition to finding a high incidence of ovaries with no stigmata to suggest follicular rupture, many of these patients exhibited a slow rise in P concentrations similar to that seen in patients with endometriosis (Brosens et al 1978). They postulated that, perhaps due to intra-ovarian factors or external influences, such as low FSH in the follicular phase of the cycle or an elevated prolactin level, since the oocyte fails to be released after the LH peak, the onset of luteinization is delayed, linking their observation with LPD. Marik & Hulka (1978) in a population of "ovulatory" but infertile women found similar features of dysovulation in a high proportion of patients and suggested that follicular stimulation with clomiphene or gonadotrophins was likely to give a good chance of conception. Not all studies however supported the hypothesis that absence of an ovulation punctum is associated with LPD (Abdulla et al 1983).

Craft et al (1980) described the finding of oocytes within follicular structures in patients who had shown indirect evidence of ovulation suggesting that PG imbalance might account for this.

Failure to reproduce a similar picture in patients receiving aspirin was disappointing. More recently, Killick and Elstein (1987) have produced ultrasonic evidence of LUF induced by the administration of another PG synthetase inhibitor, indomethacin. Portuondo et al (1981) found an absence of stigmata of ovulation in over 57% of patients studied and suggested that it was important at which stage in the cycle a laparoscopy was performed, since re-epithelialisation of the stigma may occur disguising the fact that rupture has in fact occured.

Vanrell et al (1982) evaluated the presence of an ovulation stigma in fertile patients and found that, in almost half, no clear sign of follicular rupture could be seen. In another study a laparoscopically diagnosed LUF was seen in a cycle of conception (Portuondo et al 1983) indicating that the presence of a stigma of ovulation, as assessed, laparoscopically was subject to a great deal of observer bias. Consequently other methods of diagnosing LUF required evaluation (Mudge 1982).

De Crespigny et al (1981) described the ultrasonically observed processes of ovulation, including 3 cases in their IVF programme where an egg was retrieved from a partially collapsed follicle suggesting that oocyte release is not necessarily an immediate consequence of the rupture and release of follicular fluid but may involve a gradual extrusion of the egg following the initial release of fluid. The processes of ovulation were also described by Nitschke-Dabelstein, Hackeloer & Sturm (1981) where the authors differentiated between luteal cyst formation (a small cystic structure seen within the ovary, not exceeding 18mm in size, in patients undergoing induction of ovulation) and LUF where there appeared to be no

evidence of follicular collapse together with an increase in solid structures within an enlarging follicle in the luteal phase of the cycle. This latter was associated with an inadequate rise in the BBT and termed an ultrasound detectable LUF. Queenan et al (1980) had observed a similar appearance in some of their patients but did not ascribe the pattern to LUF. The fact that multiple follicular development in induced cycles is not associated with multiple conception in an equivalent number of cases fuelled the belief that perhaps ovulation is not an inevitable consequence of mature follicle development (Sallam, Whitehead & Collins 1983, Stanger & Yovich 1984). The use of ultrasound to define the LUF syndrome both in stimulated (Coulam, Hill & Breckle 1982, Coulam, Hill & Breckle 1983, Gibbons, Buttram & Rossavik 1984, Hamilton et al 1985, Sir et al 1987) and unstimulated cycles (Coutts, Adam & Fleming 1982, Kerin et al 1983, Liukkonen et al 1984, Daly et al 1985) became widely accepted. In these studies there was no uniformity of opinion as to what the ultrasonic criteria for defining LUF were. Delayed disappearance of the follicle (Gibbons et al 1984), a biopsy of an ultrasonically observed cyst seen in the luteal phase (Coulam et al 1983), infilling but failure to shrink of a dominant follicle (Coulam et al 1982, Liukkonen et al 1984), persistence of the cystic appearance of the follicle 36 hours after the LH peak (Kerin et al 1983, Coutts et al 1982) together with thickening of the cyst wall (Daly et al 1985), rapid expansion of follicular size following the LH peak (Hamilton et al 1985) have all been cited as the ultrasonic criteria for diagnosis of the LUF syndrome.

48% of the patients with ultrasound detected LUF in Hamilton's study were undergoing ovulation induction, most with clomiphene and thus may provide insight into the reason why, as Jones (1976)

observed, conception rates do not match biochemical response rates in many series of ovulation induction therapy. 37% also were found to have PID which is an interesting association. In total, of the patients with proven PID, over 80% demonstrated the LUF phenomenon. In this group it was postulated that subclinical oophoritis might be the cause of the disturbance in ovulation. Only 1 of 27 patients with LUF had endometriosis, not dissimilar to the findings of Holtz et al (1985) but in contrast to the findings of Konninckx & Brosens (1982) using peritoneal fluid as the diagnostic tool to define LUF. It is likely therefore that LUF is not the only pathophysiological mechanism at play in the case of LPD in association with endometriosis.

Others have also evaluated the peritoneal fluid concentrations of ovarian steroids in patients exhibiting features suggestive of LUF (Devroey et al 1983, Dhont et al 1984, Bernardus et al 1983). Where rupture of the follicle fails to occur it is held that the concentrations of the peritoneal fluid steroids and the plasma concentrations are much the same, whereas when rupture occurs with release of the steroid rich follicular fluid from the ovary then the concentrations are much higher in the peritoneal cavity. This aspect of LUF will be discussed in greater detail in Chapter 7 of the thesis.

## 1.7 Current therapeutic modalities in LPD

Many approaches have been employed to tackle the problem of LPD, with the logic behind each treatment dependent on the proponents belief as to the cause of the abnormality.

### 1.7.1 Progesterone

P supplementation is the most commonly employed approach to therapy of LPD and is given, either as a vaginal suppository or an intramuscular injection, from about 3 days after the estimated time of ovulation. Studies in the literature suffer from lack of numbers and suitable controls but good results are claimed by some (Soules et al 1977, Rosenberg, Luciano & Riddick 1980, Soules et al 1981). Others (Lenton, Adams & Cooke 1978) remain sceptical. Natural progestogens should be used since the oral synthetic formulations tend to be luteosuppressive (Andrews 1979) and most authors advocate the use of an endometrial biopsy in the luteal phase to assess adequacy of dose. Newer vehicles for administration of P are being explored (Glazener, Bailey & Hull 1985, Dalton et al 1987) and it is likely that this method of treatment will remain popular. There remains a need though for large prospective controlled trials to adequately assess the usefulness of therapy.

### 1.7.2 Clomiphene citrate

Follicular phase dysfunction with consequent disturbance in CL function has been alluded to and clomiphene citrate has been employed to redress the imbalance in FSH secretion proposed as important in the pathogenesis of LPD in some cases (DiZerega & Hodgen 1981). Clomiphene citrate might be expected to increase the gonadotrophin output in the early part of the cycle with consequent improvement in the "quality" of the follicle, higher plasma E2 levels and ultimately improved CL function. Hammond & Talbert (1982) found a significant improvement in conception rate with clomiphene citrate in patients with biochemical evidence of LPD coincidental to an elevation of the

mid-luteal P concentration to target levels in excess of 20ng/ml. Interestingly, their inclusion criteria for diagnosis as deficient luteal function was a single plasma concentration of between 4-14ng/ml which therefore may have meant that some of the study group may have been normal, if other workers' criteria are used. The study also was not controlled making conclusions difficult to derive. Downs & Gibson (1983) claimed that the response to clomiphene citrate was more likely to result in conception the greater the degree to which the endometrium was found to be out of phase. Milder degrees of abnormality responded less well in terms of ultimate conception and it was proposed that such patients might benefit more from P therapy. A troublesome paradox remains the observation that clomiphene therapy itself may not always be associated with normal follicular development (Fleming & Coutts 1982) and can result in LPD (Van Hall & Mastboom 1969, Jones et al 1976). Indeed it was these observations that provided the foundations of the assertion that the entity existed at all. Others too (Dodson, Macnaughton & Coutts 1975, Soules et al 1977, Annos et al 1980, Hattori et al 1982) have used clomiphene citrate with success but none of the studies were randomised controlled trials sufficiently large to be conclusive.

### 1.7.3 Exogenous gonadotrophins

Another approach to therapy, based on the premise that aberrant FSH production precedes LPD, is the use of exogenous gonadotrophin preparations in the follicular phase of the cycle. Initial work on primates suggested that P production could be improved (DiZerega & Hodgen 1981) and clinical studies have suggested that chances of conception may be improved. Huang, Muechler & Bonfiglio (1984) have used a purified form of menopausal gonadotrophins giving a greater

yield of FSH with some pregnancies resulting, and the use of this form of therapy is recommended by some for treatment of polycystic ovarian syndrome.

### 1.7.4 Combination therapy

Combination therapy to approach the problem has been used and Kemmann & Jones (1983) reported sequential clomiphene citrate and hMG in anovulatory and "dysovulatory" patients. However problems with poor cervical mucus and ovarian hyperstimulation were encountered indicating that this kind of treatment has to be monitored very carefully. The use of GnRH analogues to suppress the pituitary and then to supplement the patient's hormonal environment with hMG to induce ovulation has aroused considerable interest and has been used successfully in patients with LPD and normal menstrual rhythm (Fleming et al 1982) and oligomenorrhoea (Fleming et al 1985). This has resulted in a higher pregnancy rate than in patients undergoing hMG therapy alone, with a lower incidence of ovarian hyperstimulation. The chance of premature luteinization is reduced, through abolition of endogenous pituitary function, which enhances the efficacy of therapy. Similar attempts to treat patients with normal steroid production in the luteal phase have failed to achieve the same success (Fleming et al 1987).

In a small study premature luteinization has also been controlled by the combination of sulpiride (inducing a state of hyperprolactinaemia) and hMG since it was observed that patients with amenorrhoea and hyperprolactinaemia had a better response rate in terms of pregnancies to hMG/hCG treatment than those patients with luteal insufficiency undergoing similar therapy (Zimmermann et al

1984). It is possible that the high prolactin milieu damps endogenous pituitary activity in a similar way to long acting GnRH agonists.

### 1.7.5 hCG

Administration of hCG at the periovulatory period, and at intervals thereafter, has been proposed, combined in some instances with clomiphene citrate therapy, to stimulate the corpus luteum (Soules et al 1977) though this and other studies (Jones et al 1976) dealt with small numbers and conclusions are difficult to make. Jones (1976) suggested that it was likely that some corpora lutea would not be able to be rescued by hCG administration and it is probable that this therapy would be of little use in patients where the underlying abnormality was a lack of appropriate ovarian receptors or those where follicular development was suboptimal. P response in these situations would be poor (Gerhard & Runnebaum 1982). Perhaps it may have a role where the suspicion of LUF exists (Gibbons et al 1984) or where the LH surge is thought to be attenuated.

### 1.7.6 Bromocriptine

Treatment of hyperprolactinaemia associated ovulatory disorders with bromocriptine (Corenblum et al 1976, Del Pozo et al 1979) has been reported with improvement in luteal function as assessed through P estimation and pregnancy rates. It remains unclear as to whether this effect is mediated by an alteration in endocrine function at the level of the pituitary and hypothalamus, or at the ovarian level (McNatty, Sawers & McNeilly 1974, McNeilly et al 1982). P concentrations are increased and the length of the previously curtailed luteal phase is normalised. Experience of treating LPD with

bromocriptine in the presence of normal PRL is mixed (Saunders et al 1979). Padilla et al (1985) have reported the use of bromocriptine in patients with luteal defects, galactorrhoea and normoprolactinaemia. The physiology of PRL continues to be incompletely understood and the biological activity of the various isomeric forms of PRL, as elaborated through gel chromatography (Andino et al 1985), may have roles in the abnormality, as yet not understood. Many take the view that elevated PRL concentrations in the presence of normal menstrual rhythm has little influence on future fertility (Vanrell & Balasch 1983, Glazener et al 1987).

## 1.8 Aim of thesis

The aim of the work presented in this thesis was to examine in detail ovarian function in the female partners of couples with unexplained infertility.

The combined resources of ovarian ultrasound and sequential biochemistry were employed to elaborate in detail the nature of follicular development and corpus luteum formation, and to relate U/S profiles to changes in ovarian steroid and pituitary gonadotrophin concentrations throughout the menstrual cycle, both in normal and infertile women.

Previous work in this area of reproductive biology has been limited and substantive data relating to large numbers of subjects with uniformity of background is lacking. Glasgow Royal Infirmary has for many years enjoyed the privilege of being a referral centre for the West of Scotland, and beyond, in matters related to

fertility, and the University Department of Obstetrics and Gynaecology's interest in unexplained infertility is well known throughout the region. For this reason it was not unduly difficult to gain access to a pool of patients with problems of unexplained infertility who could take part in the studies described in the thesis.

The work was carried out over a three year period between 1983 and 1985 and was based at the University Department of Obstetrics and Gynaecology, Glasgow Royal Infirmary and the Department of Midwifery, the Queen Mother's Hospital, Glasgow.

The thrust of the research was initially to define normal ovarian function, and generate data suitable for comparison with the infertile population. This section of work, based on 43 volunteers, is described in Chapter 2.

Since large numbers of patients were investigated it was hoped to generate information from patients who conceived during the study cycle. Few studies to date have been able to provide detailed biochemical and ultrasonic information in relation to spontaneous conception cycles and some debate exists in the literature as to the "normality" of such cycles. These data on 11 subjects are presented and discussed in Chapter 3.

The infertile subjects under study, 175 in number, were drawn from the infertility clinics of both the Royal Infirmary and the Western Infirmary in Glasgow. They are described, together with the methodology used in the study, in Chapter 4 of the thesis.

Patients with unexplained infertility were investigated using a fixed protocol to attempt to define abnormalities of ovarian function which were hitherto unsuspected from conventional techniques of investigation. Ultrasonic and biochemical disturbances of ovarian function were identified, defined and postulates made as to the possible pathophysiological processes seen and their likely role in the aetiology of the patient's infertility. These data are described in Chapter 5.

Most studies in the literature restrict investigation of infertile patients to a single cycle and doubt may be expressed as to the clinical significance of subtle abnormalities of ovarian function seen in these patients. To determine whether such phenomena were of a recurrent nature, and of consequent increased clinical importance, patients were recruited for investigation in two complete cycles. Comparisons were to be made between cycles to determine the nature of any abnormalities identified and their likely recurrence risks. 26 such patients were studied and their data is presented in Chapter 6.

The significance, if any, that the LUF syndrome plays in infertility remains uncertain. The diagnosis is difficult to make and the relationships between the different modalities of assessment which have been used in the literature are far from clear. A prospective study was therefore designed and carried out which enabled, in an unique way, the processes of ovulation and corpus luteum formation and function to be examined using plasma biochemistry, ovarian ultrasound, luteal phase laparoscopy with aspiration and biochemical analysis of peritoneal fluid. Four different avenues of investigation were thus combined to build an exceptionally detailed picture of ovarian function in 22 patients

with unexplained infertility. This aspect of study is described in Chapter 7.

General conclusions and thoughts on the implications of this work for the future are made in Chapter 8 of the thesis.

# CHAPTER 2 ESTABLISHMENT OF NORMAL RANGES

## 2.1 Introduction

Considerable debate over the years has taken place as to what should be taken as an acceptable standard of normality in relation to ovarian function. The nature of normality is fundamental to our understanding of what is, or may be, abnormal (Wentz 1982, Moghissi & Wallach 1983). Many workers have used for comparison data obtained from studies on young women, mostly volunteers, in whom normal fertility status is inferred through a history of regular menstruation, absence of menstrual disturbance and lack of use of oral contraceptives. Not all control populations are stated to be avoiding exposure to pregnancy but this would be desirable since subclinical pregnancy might adversely affect interpretation of data. Some studies in demonstrating abnormalities of ovarian function in small numbers of patients sometimes use even fewer "normal" patients for comparison.

Previous data from the Glasgow group, initially on small numbers (Dodson, Coutts & Macnaughton 1975a), and later enlarged upon (Coutts et al 1981, Fleming et al 1981), defined the control population as women with regular menstrual rhythm (27-32 days), no history of pelvic disease or contraceptive use, a biphasic basal body temperature record and a luteal phase of at least 13 days, defined as the day of maximum LH secretion to the onset of the following menstruation. Their data were in general agreement with similar other studies at the time but it was observed that if individual hormone profiles were analysed then, even within this fairly narrowly defined group, deviations from the mean values occurred. Thus it was noted

that averaging of results might mask more detailed inter-relationships between the pituitary and ovarian hormones. To establish normality daily blood sampling was felt to be required because of the rapid fluctuations observed in hormone levels from day to day.

Sobowale et al (1978) attempted to establish normality using the premise that, for a cycle to be a true expression of normal function, conception must arise. 23 cycles in 18 women, 8 of whom were trying to conceive and 10 of whom were not exposed to pregnancy were compared. The cycles in which conception occurred, those cycles which failed to result in conception and the volunteer cycles with no chance of conception were analysed. They found that, although there were slight differences in P concentrations in the non-fertile compared with the conception cycles in the mid-luteal phase, no statistically significant difference in the hormonal profiles could be found between the volunteers and the conception group. These data suggested therefore that it was valid to use such non-conception cycles to establish the hormone profiles of the normal menstrual cycle.

Dodson, Macnaughton & Coutts (1975b & c) had made the observation that in patients with ovulatory but infertile cycles, when compared to their controls, P production was sometimes found to be reduced. Lenton et al (1978) using a similar population of controls, selected on the basis of regular menstrual rhythm, unremarkable gynaecological history and in whom biochemical analysis revealed a mid-cycle LH surge, a luteal phase of more than 12 days and elevations of P in the mid-luteal phase greater than 5 ng/ml for at least 4 days (Abraham et al 1974), confirmed these findings.

Lenton and Cooke (1981) reported findings from an exhaustive study on the nature of the "normal" menstrual cycle. They compared three types of control populations namely : a) a group, similar to previous studies, of "normal" volunteers ; b) a group of patients awaiting AID due to an isolated male abnormality ; c) a number of women who were infertile because of bilateral tubal occlusion. No differences were found between the groups, particularly in relation to P production in the mid-luteal phase. This they assessed through the use of a P index, being the average of the sum of P values from days +5 to +8 relative to the day of the LH peak (day 0). Their use of the index was because P levels in the blood are subject to instability over 24 hour periods and it is unlikely that a single sample in a day would give an accurate reflection of mean circulating P. When comparison was made with women who conceived during the course of a similar investigation cycle significantly increased P indices were found in the conceiving women, both in spontaneous and induced cycles. They made the point that it is inevitable that any population of controls must contain a theoretical distribution of potentially fertile and infertile cycles. Using the P index as a guide to potential for conception then 75% of the control cycles were potentially fertile. Similar data were published in 1982 (Lenton et al), the conception cycles being a mixture of spontaneous and induced cycles. Only minor endocrine differences of limited duration were noted between the different groups of conception cycles, suggesting that P production in a conception cycle is a reproducible and quantifiable phenomenon with a narrow range of values. No differences were found with respect to E2 or gonadotrophin profiles. Another consideration raised was the possibility that a conception cycle within an infertile population might not have been representative of

a "normal" conception cycle. Since the other hormones apart from P were similar to the controls Lenton et al concluded that their data probably represented normal conception. It is possible that the differences between their groups might be explained through their controls having a higher than expected incidence of infertile cycles with low P production. Even after exclusion of cycles with clearly abnormal P production from the control group median P levels did not approach the conception levels.

Although some workers have also found higher P levels in conception cycles compared to controls (Kato et al 1982) this has not been universally the case (Laufer, Navot & Schenker 1982, Hull et al 1982, Abdulla et al 1983). Much of the published data deals with patients undergoing induction of ovulation or IVF, or is limited through sampling deficiencies (Dlugi et al 1984, Yovich et al 1985a, Yovich et al 1985b).

Healy et al (1984) have shown, in studies on monkeys, that P is released in a pulsatile fashion mediated through GnRH and that fluctuations of more than 1 ng/ml can be seen over periods of 2 hours. This lends further weight to the argument that it is better to take into account more than a single estimation of P to achieve a more accurate reflection of the adequacy of luteal function.

It would seem logical, therefore, in defining the normal biochemical profile of the menstrual cycle to restrict one's admission criteria to data in women who are unlikely to have abnormal ovarian function, on the basis of careful gynaecological history, and who are not exposed to the possibility of pregnancy.

Similar constraints should apply in defining the normal population when assessing follicular growth profiles using ultrasound, and most studies in the literature have adopted that attitude. The range of maximum FD varies considerably with most values lying in the 20-25 mm range. (Hackeloer et al 1978, Renaud et al 1980, O´Herlihy et al 1980a, Queenan et al 1980, O´Herlihy et al 1980b, Kerin et al 1981 and Bryce et al 1982). FD seems to correlate well with follicular fluid volume thus validating the use of this simpler method of assessing follicular size. Conception cycle data in some studies have shown differences from non-conception data, and so one should be cautious in the use of such cycles as controls (Zegers-Hochschild et al 1984). Polan et al (1982) described a population of women with tubal disease, using 9 of these patients as controls. Such criteria are inadequate since patients with pelvic abnormalities can hardly be representative of the normal population and there is a suggestion in the literature that pelvic inflammatory disease may predispose patients to abnormal follicular growth profiles (Hamilton et al 1985). Uncontrolled studies, while anecdotally interesting are not valuable scientifically in determining the significance of observed follicular profiles (Eissa et al 1986).

The construction of normal biochemical and ultrasonic profiles for the studies to be described hereafter therefore took into account the considerations discussed above.

## 2.2 Materials and Methods

The control population was obtained through recruitment of volunteers, mainly hospital personnel such as nursing staff, doctors and medical students, though some members of the general public were

included.

Criteria for inclusion as "normal" controls were :-

1. A history of having normal menstrual rhythm (cycle length 24-42 days over the preceeding 6 months.

2. No past history of gynaecological disease.

3. No history of oral contraceptive use over the previous 6 months.

4. At the time of study not engaging in sexual intercourse.

Over the period of study, 43 volunteers with similar characteristics were recruited. The protocol for investigation followed the same lines as that used for the main study (Chapter 4).

1. Blood samples

These were taken daily at approximately the same time each day, (0900-1000hrs) from the first day of menstruation throughout the cycle until the onset of the next period. The samples were centrifuged within 2 hours of collection and the supernatants removed and stored at -20 degrees celsius for subsequent analysis. Thus all samples for a cycle were analysed in the same batch (Coutts et al 1981)

2. Ultrasound scans

Ovarian ultrasound was performed using the full bladder

technique (Donald 1963). A B-mode static scanner (Nuclear Enterprises 4201, Fischer (Edinburgh)) with a 3.5 MHz probe, calibrated to 1540 metres per second, was employed to image the developing Graafian follicle. The follicles were measured in 3 dimensions. The maximum diameter in the longitudinal axis was defined and noted. The diameter at right angles to this was next ascertained. In this manner one had record of the longitudinal and antero-posterior diameters of the follicle. In transverse scanning the final dimension was taken by measuring the maximum transverse diameter. Follicular diameter (FD) was expressed as a mean of these three measurements. Scans were performed from the eighth day of the cycle onwards. Once the developing follicle was identified scans were performed daily, as far as possible, until the characteristic infilling of the follicle as it became a corpus luteum was observed. Thereafter scans were performed every 48 hours until the end of the cycle. Not all volunteers could attend as frequently as this ideal schedule demanded, but in practice no fewer than four scans in the peri-ovulatory period and three in the luteal phase (after the day of the LH peak) were performed.

### 3. Hormone assays

The levels of E2, P, FSH and LH were assayed in all plasma samples at the end of each cycle using sensitive, specific and precise radioimmunoassays (Coutts et al 1981). The details of the assays for each hormone are shown in table 2.1.

### 4. Interpretation of results

Analysis of the results was orientated around the day of the LH peak (day 0) and days prior to this (follicular phase) were denoted negative and days after this (luteal phase) were denoted positive. In this way cycles of differing lengths could be compared and data

combined.

5. Volunteers

These fell, on the basis of the data obtained in to 3 broad groups :-

1. In the early part of the study, before patients were being actively recruited for investigation, different biochemical methods were used, and though the day of the LH peak could be identified for cycle orientation, absolute values of hormone levels could not be combined with the data from the new methods. Regrettably sufficient plasma was not retained from these volunteers for re-assay of the hormone levels. Thus only the ultrasound data is included from these 15 cycles.

2. 16 cycles in which complete ultrasonic and biochemical data using the new methods were obtained.

3. Certain volunteers, for a variety of logistical reasons, were unable to attend for sufficient ultrasonic examinations to meet the criteria for inclusion of their follicular diameter data in the control figures. Blood samples however were obtained on almost all days, and the ultrasound scans which were performed failed to demonstrate any abnormalities worthy of remark. This subgroup comprised 12 cycles and only their biochemical data is included.

The data from these sub-groups were compared using both non-parametric (Wilcoxon rank sum test) and parametric methods (Student's

t-test, unpaired samples) to ensure that there was no difference between them, permitting combination of the data.

Thus the control data consisted, in total, of observations from 43 cycles in 43 volunteers :

31 cycles - U/S data

28 cycles - hormone data.

## 2.3 Results

The age of the volunteers ranged from 18 to 36 years (median 26 years). Follicular phase length was defined as the number of days from the first day of menstrual bleeding up to, and including, the day of the LH peak (day 0). Luteal length was the number of days following, but not including, the day of maximum LH concentrations until the day prior to to the start of the next menstrual period. Cycle length was the sum of these figures. The median length of the follicular phase was 14 days with a range of 10 to 21 days. Luteal phase length ranged from 13 to 17 days (median 15 days). Total cycle length lay between 24 and 35 days (median 29 days) (Table 2.2). These data are similar to those of previous studies (Smith et al 1983, Lenton et al 1984).

The different sub-groups within the control population were compared to evaluate and confirm their similarity, validating their amalgamation into a larger data pool. Using the student's t-test for unpaired samples and the non-parametric Wilcoxon rank sum test the following comparisons were made :-

A. Group 1 vs Group 2 (U/S vs Bioch + U/S)

1. Follicular Diameters Days -5 to Day 0

B. Group 2 vs Group 3 (Bioch + U/S vs Bioch)

1. E2 levels - Days -8,-4 to +2, and +8
2. E2 Index - Calculated for each patient on the basis of total E2 production over the peri-ovulatory period (days -2 to +1) and expressed as the mean of the sum of the 4 values on these days in pg/ml.
3. P levels - Days 0 to +6.
4. P Index - This was calculated for each patient on the basis of total P production in the early luteal phase and expressed as the total of all P values for each patient between days +2 and +6 in ng/ml. (Coutts et al 1982)
5. FSH levels - Days -5, -2 to +2, and +8.
6. LH levels - Days -5, -2 to +2, and +8.

As table 2.3 shows, no significant difference was found between groups 1 and 2 in FD values. Between groups 2 and 3 minor differences were found in the values of E2 on days -4 and +2, but these were found not to be significant when subjected to non-parametric analysis(table 2.4). P levels were found to be comparable in the groups except on day +2 but as table 2.5 shows this minor difference was not reinforced by a significant overall reduction in P production in the early luteal phase as assessed by the P index. Gonadotrophin values in the mid-follicular, periovulatory and mid-luteal phases were similar for both groups (tables 2.6 & 2.7).

On this basis the 3 sub-groups were combined to achieve an ultimate data pool from 43 cycles.

## DESCRIPTION OF CONTROLS

### Biochemical data

1. 17B-estradiol (E2)

Table 2.8 shows the median values for plasma E2 levels in pg/ml from day -10 to day +14 together with the mean values, standard deviations, standard errors of the means and the 95% confidence limits of the mean. The 95% confidence limits are graphically represented in figure 2.1.

From a median basal value of 75.0 pg/ml the level of E2 rose, gradually at first, but more steeply from day -5 onwards to reach a peak median of 220.0 pg/ml on day -1. The level dropped to 210.0 pg/ml on day 0, the day of the LH peak, and continued to fall until day +3 when the characteristic secondary rise of E2 in the luteal phase was observed, reaching a peak of 168.0 pg/ml on day +9. E2 levels fell thereafter to basal levels and menstruation ensued.

An estradiol index was calculated for E2 over the peri-ovulatory period (days -2, -1, 0 and +1). The mean total value was 186.9 (SD 29.4) and the 95% confidence intervals limits are shown in table 2.9. These values were standardised such that the mean value was translated to be 100. Thus a periovulatory E2 profile equivalent to the mean of the normal cycle data had an E2 index of

100. The 95% confidence limits lay between 93.9 and 106.1.

2. Progesterone (P)

Table 2.10 shows the median and mean plasma P levels in ng/ml, standard deviation, standard error of the mean and 95% confidence limits of the control population from day 0 to day +14. In all cases P levels prior to this were steady below 0.9 ng/ml, their being no evidence of luteinisation prior to the LH surge. The P levels rose steadily until a peak was reached on days +6 and +7 of about 19.0 ng/ml. The graph (figure 2.2) shows that between days +5 and +9 the levels were consistently over 14.8 ng/ml. In all cases a mid-luteal P level of greater than 10 ng/ml was found between days +5 and +9.

In order to obtain a P index of luteal function, the sum of P values between days +2 and +6 inclusive were calculated for each cycle. This total gave an impression of overall P production during the early luteal phase. The mean P index was 63.7 ng/ml (standard deviation 17.2 ng/ml) and the 95% confidence limits lay between 56.9 ng/ml and 70.5 ng/ml. Expanding the confidence limits to the 99% level gave a range of 54.8 ng/ml to 72.6 ng/ml. For future comparisons these values were converted to percentage points. In other words, a luteal phase profile equivalent to the mean of the normal cycle data would therefore have a progesterone index of 100 and the 95% confidence limits of the normal data would be converted to 89.5 and 110.5 ng/ml. The 99% confidence limits were 85.9 and 114.1 ng/ml (table 2.11).

3. FSH levels.

Table 2.12 shows the median, mean, standard deviation, standard error of the mean and the 95% confidence limits of the plasma FSH levels from days -10 to +14 inclusive. Figure 2.3 portrays the 95% confidence limits graphically. In the early part of the follicular phase the levels were rather higher than in the later part, in keeping with current theory regarding the role of FSH in follicle recruitment. Peak levels (11.5 IU/l) were reached on day 0, coincidental to the LH peak, with a gradual fall in the luteal phase to a basal value of 1.8 IU/l on day +9. In the few days prior to menses FSH levels started to rise again, preparatory to follicle recruitment in the next cycle.

4. LH levels.

All cycles showed a classical mid-cycle peak of LH. Table 2.13 and figure 2.4 reveal the data. The median level in the early and mid-follicular phase remained fairly stable, 8.1 IU/l on day -5. The level increased on day -2 and the maximum level on day 0 was 73.5 IU/l. Occasionally some cycles showed a broad peak, where LH levels were high on more than one day. The higher value was therefore taken as depicting day 0 or, if the two values were similar, then the day on which the E2 level was found to be lower was taken as the reference day. In only two of the 28 cycles with biochemical data was reference to the E2 levels necessary in order to define day 0. Levels of LH fell sharply following the LH peak to 11.6 IU/l by day +2 and in the mid/late luteal phase were fairly stable at between 5 and 7 IU/l.In the 15 cycles where old standards were used the day of the LH peak was unequivocally clear

in all.

The LH:FSH ratio was calculated for each day and, as table 2.14 shows, the median ratio was equal to or less than 2:1 until day -3, when it rose to 2.8, reflecting the proportionately greater increase in LH in the peri-ovulatory period. On day 0 the mean ratio was 6.1:1, falling to 3.9 on day +1 and 2.9 on day +2. The ratio fluctuated thereafter, never being greater than 3.1:1, save on day +9 (3.7:1). By day +14 the ratio had fallen to below 2:1, similar to the early follicular phase level (figure 2.5)

Ultrasound data

In all cases a single Graaffian follicle was seen to develop and, following the LH peak, disappear. Table 2.15 shows the median, mean, standard deviation, standard error of the mean and 95% confidence limits of FD's in mm, in the 31 volunteers who underwent ultrasound examinations. These are graphically represented in figure 2.6. The smallest diameter at which a follicle could confidently be seen was 8mm. The follicle enlarged in a linear fashion from day -5 until the day of maximum FD, usually day 0. In 7 cases maximum FD was reached on either day -1 (2 cycles), day +1 (4 cycles) or day +2 (1 cycle). In all cases shrinkage of the follicle was observed following the LH surge and in 29 of the 31 cycles the corpus luteum had become indistinguishable from the surrounding ovarian tissue by day +5. Median maximum FD on day 0 was 21.0 mm.

Mean values of FD were correlated with mean levels of plasma E2 between day -5 and day 0. These were found to be highly significantly correlated ($r = 0.97$, $p < 0.01$). The regression line is shown in

figure 2.7 ( y = 4.49 + 0.07x). This correlation was even more pronounced when the values were compared between day -5 and day -1 (r = 0.998, p <0.001). The regression line is shown in figure 2.8 (y = 5.9 + 0.06x).

There was no correlation between FD and plasma P levels.

Of the 5 patients where follicular shrinkage was delayed until day +2 and +3, in only 1 case was this found to be associated with a broad LH peak. In this case the profiles were as follows :-

| Day | LH (IU/l) | FD (mm) |
|---|---|---|
| -1 | 14.0 | no measurement |
| 0 | 72.0 | 18.0 |
| +1 | 61.0 | 21.0 |
| +2 | 27.0 | 23.5 |

The other 4 cycles, and the 2 cycles where maximum FD was reached prior to the LH peak, showed no unusual gonadotrophin patterns.

In conclusion, the temporal relationship between the circulating levels of gonadotrophins and ovarian steroids was confirmed in the volunteer group. The circulating levels of the hormones seemed to be similar to those reported previously in the literature (Dodson et al 1975, Kletzky et al 1975, Sobowale et al 1978, Coutts et al 1981, Lenton et al 1982), though not quite as high as those reported by

Pauerstein et al (1978). Results from differing studies are of course not directly comparable since it is unlikely that uniform radio-immunoassays will be used in all centres.

The ultrasonic data are in keeping with other reports, in particular those already published from the same department (Hackeloer et al 1978) using identical ultrasound equipment. None of the control group revealed any of the ultrasonic abnormalities which are to be discussed in later chapters.

These 43 cycles provide the data for normal ranges for the biochemical and U/S parameters. These "normal" ranges are used for comparison with the hormone and U/S profiles observed in individual women with unexplained infertility.

# CHAPTER 3 CONCEPTION CYCLES

## 3.1 Introduction

The detection of ovulation remains something of an enigma in the investigation of infertility. Reliance is placed on the use of tests which reflect, on the whole, only indirectly the events which transpire following luteinisation of the granulosa cells of the presumed mature Graaffian follicle. However, ovulation need not necessarily follow an LH rise (Laborde et al 1976), the use of the temperature chart has been criticised (Lenton et al 1977, Quagliarello & Arny 1986), controversy exists as to what should be considered an acceptable level of plasma P consistent with ovulation (Israel et al 1972, Abraham et al 1974, Hull et al 1982) and even the observation that follicular rupture has occurred has not been shown to be conclusive evidence that ovum release has occurred (Craft et al 1980, Stanger & Yovich 1984).

Unequivocal evidence that ovulation has taken place exists when conception occurs and, as referred to in Chapter 2, some authorities claim that only conception cycles can reflect true adequacy of ovarian function. This view is not universally held, though there can be no doubt that such a cycle's declaration of normality is powerful, since the reproductive goal of ovulation resulting in pregnancy has been achieved.

Claims have been made that, both endocrinologically (Sobowale et al 1978, Lenton et al 1981, Lenton et al 1982, Kato et al 1982) and ultrasonically (Zegers-Hochschild et al 1984), differences exist

between the spontaneous conception cycle and the non-fertile "ovulatory" cycle, though others (Laufer et al 1982, Hull et al 1982, Abdulla et al 1983, Eissa et al 1986) dispute this. Unfortunately many of the studies are limited in the amount of data presented through sampling and timing deficiences. In attempting comparison with control cycles where menstruation ensues, great care must be taken that blood samples are taken from patients at the identical phase of the cycle, a difficult task when the anticipated next period fails to occur.

During the main study on unexplained infertility presented in this thesis patients were referred for detailed cycle analysis. Some of these did not meet the strict criteria for inclusion in the main analysis largely because the duration of their "infertility" was less than 3 years. During such investigations 11 patients spontaneously conceived thus providing a data pool permitting detailed and accurate analysis ultrasonically and biochemically of ovarian function in cycles of conception. These conception cycle "controls" could therefore be compared and contrasted with the "normal control cycle data".

## 3.2 Materials and Methods

11 patients were investigated using an identical protocol, involving daily blood sampling and detailed ultrasonic monitoring of follicular development, to that described for the main study (Chapters 2 & 4). 10 of the 11 patients had essentially unexplained subfertility, with normal biochemistry, a normal pelvis, as assessed through laparoscopy within the previous 18 months, and whose male partner had demonstrated a normal semen analysis on at least two

occasions. The duration of their involuntary infertility was less than 3 years. One patient had previously been found to have a modestly elevated serum prolactin concentration of 1200 IU/l and was being treated with bromocriptine, 2.5mg per day. Three months after initiating therapy her prolactin level was 280 IU/l, well within the lower limit of normal for the laboratory of 500 IU/l. Six months after starting therapy conception had still not occurred and she was referred for detailed cycle investigation. Her overall duration of involuntary infertility was 5 years.

These patients all conceived during their investigation cycles, as evidenced by delay in menses associated with elevations in B-hCG (>50 IU/l).

The resulting biochemical (daily estimations of E2, P, LH & FSH) and ultrasonic data (frequent scans in the peri-ovulatory and early luteal period) were compared to the control data obtained from the 43 volunteers described in chapter 2, none of whom were exposed to the possibility of pregnancy.

Statistical analysis was performed using both parametric (Student's t-test for unpaired samples) and non-parametric (Wilcoxon rank sum test) methods.

## 3.3 Results

Table 3.1 shows the E2 data of the conception cycles from day -9 to day +14 inclusive. The median values are plotted graphically in figure 3.1 with the median concentrations of the normal cycle data (Chapter 2). The pattern in the conception cycles was very similar to

that of the controls with an exponential rise of E2 being observed until day -1. Following the LH peak E2 levels dropped, as for the control cycles, followed by a secondary rise again characteristically seen in the normal cycle volunteers. Divergence from the conventional pattern was seen only from day +10 with this becoming statistically significant from day +11 ($p < 0.001$).

The P profile of the conception cycle group is shown in table 3.2 together with the P index. Graphically portrayed in figure 3.2 it is seen that this profile is comparable to the control cycle data. The influence of conception on the profile is again not strikingly obvious until day +10 when the levels are seen to rise ($p < 0.02$ on day +10). The mean P index was 105.0, similar to the control mean of 100. ($t = 0.486$, $p > 0.2$). However there was a wide range of values in the conception group (50 to 170), incorporating 1 cycle with markedly deficient luteal function (P index 50) and 2 other cycles with borderline P indices, 72 and 76 respectively. Two cycles exhibited very high levels of P (P indices 140 and 170) and in both of these multiple follicular development was observed on ultrasound.

FSH concentrations parallelled the non-conception cycle data and although minor differences were observed, particularly in the luteal phase where levels were slightly lower, these did not reach statistical significance (table 3.3, Figure 3.3).

LH profiles are documented in table 3.4 and figure 3.4. Deviation from the normal was likewise not seen until beyond the time of embryonic implantation with statistical significance being achieved on day +12 ($p < 0.001$). These elevations would be due to cross reaction of B-hCG of the pregnancy in the LH assay.

Despite small numbers, ultrasonic data was obtained on more than half the group during the periovulatory period. With the exception of the two patients with elevated P levels described above, a single dominant follicle was seen to develop and, following the LH peak, shrink and disappear. In no case was the cystic nature of the follicle retained beyond day +2. A scan was performed on day 0 in 8 of the patients, with a median diameter of the dominant follicle of 20.8mm being observed on that day (table 3.5). This was statistically similar to the control cycle data (figure 3.5). In the two patients where secondary follicles were observed the maximum diameters of the smaller follicles were 17.0mm and 12.0mm respectively.

## 3.4 Discussion

The data presented above relates to patients where diagnosis of pregnancy was based on the clinical observation of delay in menses associated with elevations in B-hCG. It has been estimated that in a fertile population the expectation of conception in a cycle is almost 60% (Edmonds et al 1982). In over half of these cases the woman may be unaware of the pregnancy, which results in a sub-clinical abortion, manifest, perhaps, as a heavy period, delayed by a few days. Embryonic loss, except in a research context, is currently difficult to quantify but Whittaker, Taylor & Lind (1983) suggested that Edmond's figure might be rather high. They found that in monitoring 226 ovulatory cycles, 85 clinical pregnancies occurred. In addition, 7 women, despite experiencing menstruation when expected, were found to have elevated B-hCG in the luteal phase. These sub-clinical pregnancies amounted to 7.6% of all conceptions. It is unlikely that other patients, in the series described in this thesis,

conceived, since, although B-hCG was not assayed as a routine in the protocol of investigation, cross reactivity of LH with B-hCG would have been expected to detect these conceptions, as in the cycles described here.

Some previous reports suggested that P concentrations in the mid-luteal phase of the conception cycle are higher than in the ovulatory non-fertile cycle. Lenton et al (1981 & 1982) found this to be the case in both unstimulated and stimulated cycles. They speculated that the early pre-implantation embryo might, through elaboration of an as yet unknown factor, influence the steroidogenic potential of the corpus luteum. It has been suggested through studies on rats that the non-gravid part of the uterus may have some influence on corpus luteum function leading to increased P production (Kato et al 1982). Few studies' protocols have dictated blood sampling of patients as frequently as the Sheffield group's but since it is established in the non-human primate that P levels are subject to fluctuation (Healy et al 1984) it is desirable that as detailed information as possible be obtained (Dodson et al 1975b). Comparison with studies opposing the view that the conception cycle exhibits greater P production is hindered by paucity of sampling during the luteal phase. Thus the contention that no difference exists between cycles of conception and the non-conception cycle (Laufer et al 1982, Hull et al 1982) requires confirmation through more detailed analysis. The literature also contains reference to cycles of conception in IVF programmes and, although the evidence seems persuasive that P concentrations are higher in successful treatment cycles (Garcia et al 1984, Dlugi et al 1984, Yovich et al 1985a, 1985b) these data are unlikely to be relevant to the physiological processes of the normal fertile cycle and spontaneous conception.

The data of the present study meet the requirements of frequency of sampling. No difference was found between the conception cycles and the controls. Wide variations in CL function were observed and deficient P indices were obviously not a bar to conception. The higher P indices were accounted for by multiple follicular growth and presumably luteinisation.

Three of the group (27.3%) aborted prior to ultrasonic confirmation of a viable intra-uterine pregnancy. These patients had P indices of 50, 87 and 140 respectively; thus only one of them exhibited a markedly deficient luteal phase, using the P index as the criteria of efficiency. This patient, and indeed all the other patients, met the criteria of ovulation set by various authorities on the basis of P levels in the mid-luteal phase i.e. Israel et al (1972) - >3ng/ml; Abraham et al (1974) - >15ng/ml sum of P values on 3 days in the mid-luteal phase; Hull et al (1982) - >9.4ng/ml. Abnormal ovarian function was thus not a barrier to conception but the observed abnormality might have prejudiced the outcome of the pregnancy. The patient aborted on day +35 and diagnostic curettage confirmed the presence of chorionic villi. Kusuda et al (1983) have suggested that corpus luteum insufficiency may cause infertility mediated through a defect in nidation. This is in agreement with the observations that the luteal phase defect has an association with recurrent abortion (Jones 1976, Tho et al 1979). The patient with the markedly reduced P index had regular periods prior to her cycle of conception but it is possible that she might have had prior sub-clinical pregnancies, perhaps related to a recurrent defective luteal phase. Soules et al (1981) has observed that corpus luteum function in cases of luteal deficiency may be enhanced through treatment with

clomiphene citrate compared with P supplementation, although pregnancy rates seem to be better with the latter. This patient was undergoing treatment for modest hyperprolactinaemia with bromocriptine but did not receive P supplementation. Her PRL levels in the conception cycle were checked retrospectively and found tobe within the normal range. PRL levels in conception cyles have been reported as no different from the non-conception cycle (Lenton et al 1979, Adejuwon et al 1984).

The other cases of spontaneous abortion were not found in association with deficient P production. They occurred at day +37 and +47 respectively. Embryonic abnormalities may have been the cause of pregnancy loss but the products of conception were not subjected to genetic analysis to confirm this.

Papiernik et al (1979) suggested that delayed ovulation through prolongation of the follicular phase in cycles of conception might predispose to embryonic mortality and fetal growth retardation. The length of the follicular phase was 13, 14 and 14 days in the patients described above.

Two other patients with lowish P indices, 72 and 76 respectively, had unremarkable normal pregnancies.

The finding of normal E2 profiles is in agreement with the previously published data of Smith et al (1980) and Lenton et al (1982) though the former study had limited data.

Follicular growth patterns in the patients studied followed the normal pattern with secondary follicles observed in two of the

patients. In all cases, except one of the aborters, follicular collapse was observed within 48 hours of the LH peak. The "stabilisation" of follicular development described by Zegers-Hochschild et al (1984) in the 24 hours prior to rupture was not a feature in these patients and the pattern of events was no different between the controls and the study group. The present study agrees with the data of Eissa et al (1986) but in addition provides a needed comparison with normal non-conception data. In no case was there evidence of ultrasonically defined luteal cyst formation (Chapter 5). Although follicular rupture need not necessarily lead to release of an ovum (Craft et al 1980, Stanger & Yovich 1984), this obviously occurred in the present series. De Crespigny et al (1981) described several variants of follicular collapse, as observed ultrasonically, including initial rapid reduction in size with subsequent shrinkage lasting from five to thirty-five minutes. Ovum release need not coincide with the initial rapid release of fluid and the egg may be extruded with the subsequent slow follicular collapse.

Secondary follicular growth is not an unusual phenomenon (Breitenecker, Friedrich & Kemeter 1978, O´Herlihy et al 1980a, Queenan et al 1981, Kerin et al 1981, Sallam et al 1983). In the patients described, although multiple ovulation was possible in the patient with the 17mm secondary follicle and improbable in the patient with the 12mm follicle, both cycles were associated with high P indices and ensuing singleton pregnancies. The role of secondary follicles remains unclear.

In conclusion these data would suggest that the human conception cycle does not differ in terms of follicular growth and corpus luteum function from the normal non-fertile cycle thus justifying the use of

non-conception data as a physiological yardstick of normality. Deficient luteal function, as measured by plasma P concentrations, is not a bar to conception but may be associated with embryonic loss, the precise cause of which is unclear.

# CHAPTER 4 INVESTIGATION OF UNEXPLAINED INFERTILITY

## 4.1 Materials

The patients under study attended the infertility clinics of Glasgow Royal Infirmary and the Western Infirmary, Glasgow. For all patients, no explanation had been found for their failure to conceive. Their unexplained infertility was defined as follows :

1. All patients had a history of regular menstrual rhythm with cycle length, in the 6 months prior to investigation, of between 24 and 42 days duration.
2. All had had a pelvic assessment with laparoscopy in the previous two years. In all cases this had revealed normal pelvic organs with no evidence of endometriosis or pelvic inflammatory disease.
3. All male partners had provided at least two semen samples which fulfilled the laboratory's criteria of normality - volume 2-6ml, sperm density >20M/ml, motility >40%, normal morphology >60%.
4. All patients had undertaken a post-coital test which had revealed active sperm in the cervical mucus.
5. All couples denied any sexual problems, and had been having regular unprotected intercourse for a minimum of 3 years.

The bulk of the patients were recruited from the infertility clinic of the Royal Infirmary which for some years has enjoyed a reputation as a centre with a particular interest and expertise in the investigation and management of patients with unexplained infertility. Referrals from all over the West of Scotland and beyond

are received by the clinic and largely as a result of this, during the period of study (October 1982 to September 1985), it was possible to recruit 175 patients who fulfilled the above criteria.

## 4.2 Methods

All patients gave their informed consent to the investigations which were standardised for all.

### 1. Blood Samples

Commencing on the first day of the cycle, all patients provided a blood sample (10ml) which was collected in to a lithium heparin tube. Samples were obtained each day at about the same time (0900-1000hrs), wherever possible, and spun down in a centrifuge to separate the plasmas, which were then labelled and stored at -20 degrees celsius until assayed. Patients provided blood samples every day throughout their entire menstrual cycle. Most attended the relevant hospital for this to be carried out, but where long distances were involved the patients' general practitioners were asked to assist in the collection of specimens. These were then posted in except when the patient was attending the hospital for ultrasound scans.

### 2. Ultrasound Scans

These were performed by a single operator (the author) in the ultrasound department of the Queen Mother's Hospital, Glasgow. The methodology was exactly the same as that employed in the establishment of the normal ranges (Chapter 2). The same ultrasound

machine was used (Nuclear Enterprises 4201, Fischer (Edinburgh), B-mode static scanner with a 3.5MHz probe, calibration 1540m/s) and the timing of scans was similar.

Patients were asked to phone the author with the onset of menses in the cycle under investigation. The first ultrasound scan was then arranged for the eighth day of the cycle. The full bladder technique (Donald 1963) provided excellent imaging of the ovaries. Scans were performed every 48 hours from day 8 until the developing Graafian follicle could be visualised, whereupon scans were carried out daily, until the characteristic infilling of the follicle as it became a corpus luteum was observed. Thereafter, scans were performed every 48-72 hours throughout the luteal phase, until the beginning of the next menses.

Follicular diameter was calculated as in section 2.2.

Logistically (due to travel problems etc.) not all patients were able to attend as frequently as this ideal protocol dictated, but in practice no fewer than four scans in the follicular phase and three in the luteal phase (after the day of the LH peak) were performed on each patient.

## 3. Hormone Assays

The plasma concentrations of E2, P, FSH and LH for all samples from the cycle under study were assayed retrospectively, using sensitive, specific and precise radioimmunoassays. These were processed in a single batch to eliminate between assay variations. The details of these assays are described in table 2.1.

## 4. Interpretation of Results

This followed the schedule laid out in section 2.2 with orientation of each cycle around the day of the LH peak (day 0) in order to permit comparison of cycles of differing length.

No assumptions were made regarding the distribution of the data in respect of these cycles and, except where indicated, non-parametric methods of statistical analysis (Wilcoxon Rank Sum Test) were employed to determine differences between groups. Differences in frequencies were assessed using the Chi-square test or Fisher's exact test where appropriate.

## 4.3 Safety of U/S monitoring of follicular development

Concern has been expressed in the literature regarding the safety of diagnostic ultrasound, principally in the context of fetal exposure during antenatal scanning. A report by Testart et al (1982) suggested that ovulation might occur prematurely in patients undergoing follicular monitoring with frequent ultrasound scans during the peri-ovulatory period but others (Fleischer et al 1984) have been unable to reproduce this observation.

Most studies on the biological effect of ultrasound have been conducted at cellular levels under laboratory conditions, and it is difficult to extrapolate data obtained in such an environment to the clinical realities of an in-vivo situation. Bomsel-Helmreich (1985) observed that fertilization rates and the characteristics of blastocyst formation in IVF programmes based on ultrasound seem

similar to those in the few programmes where ultrasound is not used. Post-implantation effects are possible but difficult to evaluate, and with so many variables surrounding success or failure in IVF programmes, it is doubtful if an effect, exclusive to ultrasound could be demonstrated conclusively.

Statements from ultrasound related societies such as the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) (1984) and the Bioeffects Committee of the American Institute of Ultrasound in Medicine (AIUM) (1984) have emphasised the lack of convincing evidence that ultrasound causes any ill effects on the developing fetus at the intensities used in diagnostic imaging. McNay and Fleming (1984) concurred that there appeared to be no evidence suggest that the benefits of diagnostic ultrasound should be witheld from patients undergoing fertility investigations, ovulation induction or in-vitro fertilization.

The average rate at which tissue receives ultrasonic energy is usually expressed as the temporal average of the most intense region in the beam (McNay and Fleming 1984). This intensity (I) is referred to as the spatial peak, temporal average (spta). The statement from the AIUM affirmed that, in the low MHz frequency range, there have been no, independently confirmed, significant biological effects in mammalian tissues exposed to I(spta) below 100mW/cm2.

For the ultrasonic equipment used in this study (NE4201, 3.5MHz), I(spta) has been calculated as 61mW/cm2 (Duck et al 1985). The output of the equipment was attenuated by 20db i.e. by a factor of 100, and consequently the actual I(spta) in this study was 0.61mW/cm2, over 160 times lower than the maximum recommended by

AIUM. The statement also affirmed that ultrasound exposure times up to 500 seconds were not associated with significant biological effects, even at intensities higher than 100mW/cm2. Average scanning time per patient in the present study was in the region of 300 seconds, thus it would seem to be highly unlikely that the investigation posed any risks to the patients or their putative conceptuses.

# CHAPTER 5 RESULTS

98 of the 175 cycles investigated (56.0%) demonstrated disturbed ovarian function, in the form of either biochemical or ultrasonic deviations from the normal patterns described above.

These abnormal cycles are defined and described in relation to their frequency of occurrence, in the following sections of the thesis :

| | | |
|---|---|---|
| 5.1 | Luteal cyst formation | (41 cycles) |
| 5.2 | Poor progesterone surge | (51 cycles) |
| 5.3 | High LH concentrations | (23 cycles) |
| 5.4 | Poor follicular maturation | (16 cycles) |
| | Poor follicular development | (12 cycles) |
| 5.5 | Short luteal phase | (6 cycles) |
| | Long follicular phase | (9 cycles) |
| | Short follicular phase | (6 cycles) |

The abnormalities to be described were not mutually exclusive. 77 cycles (44.0%) fulfilled the criteria of normality set out in Chapter 2.

# SECTION 5.1 LUTEAL CYST FORMATION

## 5.1.1 Definition

Normal follicular development and corpus luteum formation have been discussed in chapter 2. In a high proportion of the cycles under study the normal ultrasonically observed process of collapse, infilling and eventual disappearance of the dominant follicle following the LH peak did not occur. Instead the follicle retained its cystic appearance, in some cases continuing to enlarge throughout the luteal phase.

Luteal cyst formation was diagnosed on the basis of ultrasonic examinations, between days +5 and +8 relative to the LH peak, of the ovary ipselateral to that which contained the dominant follicle. If the cystic nature of the follicle was found to have persisted between these days then the structures were termed luteal cysts. The diameters of the cysts were calculated on the basis of the mean of all diameters measured between days +5 and +8.

## 5.1.2 Introduction

Previous studies have described similar structures in the luteal phase and much discussion has taken place as to whether they represent the LUF syndrome. As alluded to in chapter 1, data in this area has suffered from lack of numbers (Coutts et al 1982, Coulam et al 1982, Coulam et al 1983), failure to evaluate the relationship of observed abnormalities to biochemical indices of luteal function (Nitschke-Dabelstein et al 1981, Gibbons et al 1984, Daly et al 1985), and failure to discriminate between cycles where induction of

ovulation was being carried out and unstimulated cycles (Nitschke-Dabelstein et al 1981, Gibbons et al 1984, Hamilton et al 1985). The ultrasonic criteria for defining the LUF syndrome have varied considerably in the studies cited.

Kerin et al (1983) used sequential ultrasound to determine the incidence of LUF, defined as failure of the dominant follicle to lose its cystic appearance within 36 hours of the peak LH concentration in blood, in a mixture of patients, some with tubal disease, some awaiting artificial insemination with donor sperm (AID), a small number with endometriosis and only a small number with unexplained infertility. The incidence of "LUF" was 4.9%. One of the six patients with unexplained infertility demonstrated the LUF phenomenon. The biochemical data in this study were limited to steroid assays only at three to five day intervals in the luteal phase, and thus the conclusion that P concentrations in the LUF cycles were normal must be viewed with caution. In some cases the diagnosis of LUF was made on the basis of scans performed only two days after the LH peak and it is possible that these data represent a variant of normal : one of the conception cycles described in chapter 3 demonstrated this periovulatory pattern of follicular growth. No data were supplied of the dynamics of these phenomena beyond day +4, nor was any discrimination made between the cycles where the follicle was seen to shrink and the cycles where the follicle retained its periovulatory dimensions or expanded. No data were provided regarding the follicular phase biochemical profiles of the gonadotrophins, nor of E2 prior to day 11 of the cycle, and thus it is difficult to speculate on the likely pathogenetic mechanisms at play in these cycles. In addition the cycles are drawn from such a heterogeneous population that one cannot draw a firm conclusion with respect to

incidence of the phenomenon in unexplained infertility. The fact that it was seen in the AID patients suggests that, on occasion, LUF may occur in potentially fertile women since, as a group, when treated, these women exhibit only slightly reduced fecundity compared to normal (Mathews and Peek 1987).

Liukkonen et al (1984) restricted analysis to patients with presumed unexplained infertility. However, when laparoscopy was performed, in close temporal proximity to the cycles of investigation, significant pelvic pathology was discovered in 36.0% of the series, suggesting that the patients studied did not represent an homogeneous group. The definition of LUF was based on the observation of intrafollicular echoes in the absence of shrinkage within the dominant follicle. No comment was made with respect to the follicular dynamics prior to presumed ovulation in the study group and the data were not compared to suitable controls. In addition, biochemical data were not provided in the study. It is difficult, therefore, to draw conclusions on the nature of the structures observed in the absence of these important points of information.

Hamilton et al (1985) provided more substantial data in respect of ultrasound diagnosed LUF syndrome in that follicular profiles were analysed and biochemical data were provided, albeit on a limited basis, since blood samples were taken only on the days of ultrasound scans, and infrequently in the luteal phase. Comparison was made with suitable controls but the strength of the analysis was somewhat diluted by the heterogeneity of patients under study. 11 of the 27 patients demonstrating LUF, defined as failure of the follicle to rupture despite signs of luteinisation (elevation in basal body temperature and a rise in plasma P), were undergoing ovulation

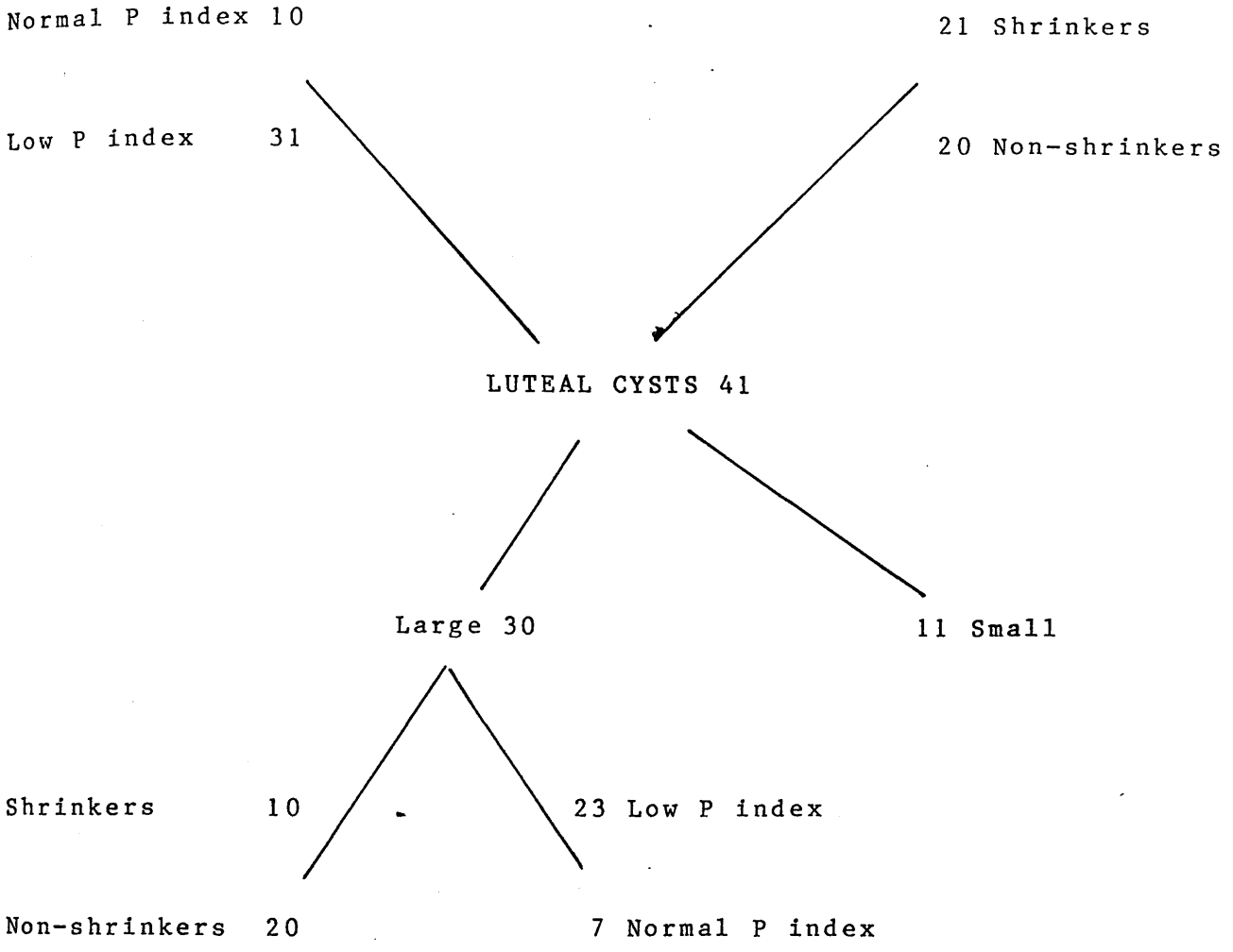
induction. 11 of the patients had been demonstrated to have significant pelvic pathology (pelvic inflammatory disease or endometriosis) and only 10 had unexplained infertility. In the study mention was made of patients with "cystic corpora lutea" where decrease in the mean follicular diameter of the pre-existing follicle was seen several days prior to the luteal cyst. No data was supplied on the number, the follicular profiles or the biochemical patterns of these cycles. The higher concentrations of E2 observed in the follicular phase of the "LUF" cycles could be explained by the relatively high number of patients undergoing ovulation induction.

### 5.1.3 Analysis

#### Description of analysis

41 (23.4%) of the 175 cycles under study were found to demonstrate luteal cyst formation.

Analysis of the biochemical and ultrasonic profiles of these cycles is structured as follows :


Normal P index 10
21 Shrinkers
Low P index 31
20 Non-shrinkers
LUTEAL CYSTS 41
Large 30
11 Small
Shrinkers 10
23 Low P index
Non-shrinkers 20
7 Normal P index

A. Size

An arbitrary distinction was made between large and small cysts on the basis of the mean diameter of the dominant follicle in the control cycles on day 0, i.e. 20mm. Large luteal cysts (>20mm) were found in 30 of the 41 cycles (73.2%) while small cysts were seen in 11 (26.8%).

B. Shrinkage

Frequent scanning over the peri-ovulatory period permitted discrimination to be made between those cycles where the dominant follicle was seen to reduce in size following the LH peak (21 cycles (51.2%)), and those where the dominant follicle did not show evidence of shrinkage after day 0 (20 cycles (48.8%)).

C. P index

Comparison was made between those cycles where luteal cyst formation was associated with deficient P production in the early luteal phase (P index <89.5, i.e. <95% confidence limit of the mean of the normal range) and those cycles associated with normal P production. There were 31 cycles with a low P index (73.2%) and 11 (26.8%) with a normal value.

D. Large cysts & shrinkage

The 30 cycles exhibiting large luteal cyst formation were analysed with respect to the ultrasonic profiles in the immediate period following the LH peak. 10 (33.3%) showed shrinkage, as defined

above, while the remaining 20 (66.6%) did not.

E. Large cysts & P index

23 of the 30 cycles with large cyst formation (76.7%) were found to have a low P index (<89.5) and these were compared with the remaining 7 cycles (23.3%) with normal P indices.

Table 5.1.1 shows the patient and cycle characteristics (as defined in chapter 2) of the various sub-groups within the luteal cyst formation population. There was no significant difference between any of the groups, and when comparison was made with control data, apart from the age of the infertile group being greater, there was again no difference (Wilcoxon rank sum test).

A. Large (>20mm) & small (<20mm) cysts

Tables 5.1.2 to 5.1.11 detail the biochemical and ultrasonic data relating to these sub-groups of cyst formers. The median, mean, SD, SEM and 95% confidence limits are shown for E2, P, LH, FSH and FD measurements together with statistical significance, where found, in comparison between the groups and also with the control data (Wilcoxon rank sum test). These values are graphically illustrated in figures 5.1.1 to 5.1.5 where the median values for the hormones and the follicular diameters are plotted against the background control cycle medians.

E2 (Tables 5.1.2 & 3, Figure 5.1.1)

There was no significant difference in E2 concentrations between

large and small cyst formers, except for a slightly higher day 0 level in the small cyst formers (235pg/ml compared with 196pg/ml ($p < 0.05$)). Although small cyst formers tended to have higher mid-luteal E2 concentrations, these differences did not achieve statistical significance when compared with the >20mm group. Neither sub-group exhibited any significant difference compared to the control data.

P (Tables 5.1.4 & 5, Figure 5.1.2)

Both large and small cyst formers demonstrated significantly reduced P production in the early luteal phase compared with the controls. More profound reduction occurred in the group with cysts >20mm diameter, reflected in their markedly reduced P index (median 66.0, control 100.0, $p < 0.001$). Small cyst formers' P index was 84.0, reduced compared to the controls' ($p < 0.05$), though the difference between the cyst sub-groups did not achieve statistical significance. P production in the late luteal phase was similar in both groups though differences were observed between both groups of cyst formers and the controls on days +11 and +12 (and +13 in the case of the large cyst group).

LH (Tables 5.1.6 & 7, Figure 5.1.3)

Apart from a slightly reduced peak value (median 42.5IU/l) in the small cyst formers as compared to the large cyst formers (66.0IU/l, $p < 0.05$), there were no differences seen between the groups. Day 0 levels were comparable in the control population and the small cyst group.

FSH (Tables 5.1.8 & 9, Figure 5.1.4)

Both large and small cyst formers exhibited minor differences in FSH concentrations compared with controls, with FSH secretion significantly higher in the mid/late-luteal phase (days +6 to +10) in the >20mm group. Over a similar period, in comparison with the small cyst formers, there was no difference. In the latter's case the profile was not significantly different from the control profile. Minor differences were seen in both the cyst groups, compared to controls, in the early follicular phase, with slightly elevated FSH concentrations and, although the levels were higher in the large cyst group, both populations of cyst formers were statistically similar.

FD (Tables 5.1.10 & 11, Figure 5.1.5)

Although FD measurements tended to be slightly lower in the group ultimately forming luteal cysts >20mm diameter, the differences between this group and the small cyst formers, as well as the controls, did not achieve statistical significance. Median cyst size in the large cyst former group was 29.5mm and 16.0mm in the small cyst formers ($p < 0.001$).

Comment

Follicular function as assessed by plasma E2 measurements and FD's would appear to be similar in these two populations of cycles. The slightly lower day 0 E2 levels seen in the large cyst formers was accompanied by a slightly reduced FD on day 0, but the significance of this finding is debatable since peak E2 (day -1) concentrations were virtually the same in both groups.

The gonadotrophin differences are interesting in that FSH levels tended to be higher in the early follicular phase in both the groups. This might indicate a follicular defect since FSH at this stage in the cycle might have some bearing on the eventual selection of the dominant follicle. High levels of FSH may be a compensatory phenomenon for a functional defect of the follicle, perhaps as a result of receptor deficiency and/or dysfunction, or might be consequent upon a lack at this stage in the cycle of a gonadotrophin suppressant compound e.g. inhibin, perhaps produced in normal circumstances by the developing follicle, or as recent evidence suggests, the corpus luteum of the previous cycle. Impairment of inhibin synthesis and or secretion in the luteal phase of the cyst formers may also account for the observed elevation in FSH at this time. Luteal cyst formation could thus be interpreted as a sequel to abnormal follicular development, as suggested by DiZerega and Hodgen (1981), though U/S FD profiles were, in the present study, unable to discriminate between the normal and abnormal cycle prior to the LH peak.

P production was reduced in both cyst former groups. The lack was more profound in the large cyst formers, though the difference between the sub-groups was only significant on day +5. P indices were not significantly different. Some of the cycles with large cyst formation were associated with normal P production and it would therefore seem that such a group does not represent a homogeneous population.

Current thinking with respect to the mechanism of steroidogenesis in the corpus luteum (Carr et al 1981) suggests that

granulosa lutein cells require intimate contact with blood to take up the necessary LDL precursors for luteal phase steroidogenesis. If reduction in size of the dominant follicle represents a breach in the "blood follicle barrier" then study of cycles where differences are seen in follicular dynamics as assessed by ovarian ultrasound at the periovulatory period might provide valuable insight into the pathogenesis of luteal phase defects.

## B. Shrinkers & non-shrinkers (all cysts)

Tables 5.1.12 to 5.1.21 detail the biochemical and ultrasonic data relating to these sub-groups of cyst formers. The median, mean, SD, SEM and 95% confidence limits are shown for E2, P, LH, FSH and FD measurements together with statistical significance, where found, in comparison between the groups and also with the control data (Wilcoxon rank sum test). These values are graphically illustrated in figures 5.1.6 to 5.1.10 where the median values for the hormones and the follicular diameters are plotted against the background control cycle medians.

### E2 (Tables 5.1.12 & 13, Figure 5.1.6)

E2 profiles were virtually identical in both groups and no differences were found in comparison with the controls.

### P (Tables 5.1.14 & 15, Figure 5.1.7)

P concentrations in the cycles where no shrinkage of the dominant follicle was seen following the LH peak, were profoundly reduced (median P index 53.5) compared to the control cycles (P

<0.001) and to the cycles where shrinkage of the follicle was observed (median P index 84.0, p <0.001). Although P concentrations were reduced in the cycles with shrinkage this difference did not achieve statistical significance when comparison was made with the controls. P concentrations in the late luteal phase were greater in the study cycles compared to the controls between days +11 and +13, but by day +14 basal levels were reached.

LH (Tables 5.1.16 & 17, Figure 5.1.8)

LH production was similar in the study groups and no differences were found in comparison with the control cycle data.

FSH (Tables 5.1.18 & 19, Figure 5.1.9)

In those cycles where shrinkage of the follicle was observed, FSH levels were found to be significantly higher in the early follicular phase (days -9 to -6) compared to the control data, and, in comparison to the non-shrinkage cycles, also tended to be higher, though this achieved statistical significance only on day -7. Mid-cycle levels were similar in both groups and the controls. In the luteal phase there were minor differences in both groups compared to the controls and this was more pronounced in the cycles where no shrinkage was seen, with concentrations being significantly elevated on days +6 to +10.

FD (Tables 5.1.20 & 21, Figure 5.1.10)

There was no difference between the two study groups in FD profiles up to, and including, day 0. Divergence occurred from day +1

onwards. The follicular phase profiles were similar in both groups to the control cycles. Median cyst size was significantly greater in the non-shrinkage (33.0mm) compared to the shrinkage cycles (18.5mm, $p < 0.001$).

Comment

Cycles in which the FD profiles were destined to differ could not be predicted on the basis of follicular maturation as assessed by circulating E2 concentrations or follicular growth profiles.

Circumstantial evidence that the different U/S profiles observed do represent abnormal phenomena derives from the associated subnormal P concentrations in the luteal phase. The nature of the differences lends support to the concept that follicular rupture is a necessity for efficient P production in the luteal phase, and that the discrimination seen could perhaps represent two distinct pathophysiological events.

The follicles where no shrinkage occurs and where P production is seriously impaired may represent the LUF syndrome. The other sub-group, where some shrinkage (?rupture) was observed and with less impairment of steroid production, could be described as cycles with cystic corpus luteum formation. Neither of these phenomena were seen in the control cycles (chapter 2) nor in the cycles studied where conception occurred (chapter 3). The occurrence of a luteal phase cyst indicated a sub-fertile cycle, the nature of which could only be clarified by detailed study of peri-ovulatory events and subsequent ovarian steroid biochemistry.

Although LH concentrations in the cyst formers did not differ overall from the control data some cycles were found to be associated with tonically high LH levels and may represent a manifestation of the PCO syndrome. This will be discussed further in section 5.3.

The FSH data are interesting with the higher values in the early follicular phase in the shrinkage cycles seeming to discriminate this population from the normal cycles. It is not apparent whether the differences in FSH production are a cause, or a consequence, of abnormal follicular development in these cycles. Higher FSH values in the luteal phase in the luteal cyst cycles were more pronounced in the non-shrinker sub-group than in the shrinkers and may represent an increased resistance on the part of these CL's to the gonadotrophin output by the pituitary, or a reduction in the synthesis and/or secretion of inhibin by the luteinised follicle, as a consequence of cyst formation. Gonadotrophin output in both sub-groups during the peri-ovulatory period gave no clue to the cause of the striking differences seen, ultrasonically, subsequent to the LH peak.

Luteal cyst formation was analysed further to determine if the cycles where P concentrations were found to be normal demonstrated any differences, as a group, compared to the cycles where P profiles (P index) were deficient (<95% confidence limits of the normal range).

C. Normal P index & low P index (All cysts)

Tables 5.1.22 to 5.1.31 detail the biochemical and ultrasonic data relating to these sub-groups of cyst formers. The median, mean, SD, SEM and 95% confidence limits are shown for E2, P, LH, FSH and FD

measurements together with statistical significance, where found, in comparison between the groups and also with the control data (Wilcoxon rank sum test). These values are graphically illustrated in figures 5.1.11 to 5.1.15 where the median values for the hormones and the follicular diameters are plotted against the background control cycle medians.

E2 (Tables 5.1.22 & 23, Figure 5.1.11)

Minor differences in E2 concentrations were identified between the two sub-groups with slightly higher levels found, in the cycles associated with deficient P levels in the early luteal phase, on days +1 and +2 compared with controls, and on days +2 and +3 compared with normal P index cycles. In the remainder of the luteal phase, although E2 production was higher in the low P index cycles, the differences observed were not significant, and profiles were similar to the control data, except on day +13.

P (Tables 5.1.24 & 25, Figure 5.1.12)

Striking differences were observed between the two sub-groups from day +2 onwards. Low P index cycles' diminished P production, compared with the normal P index cycles, was apparent throughout the greater part of the luteal phase, but levels were similar from +11 onwards.

Normal P index cycles were found to have significantly greater levels of P production compared to the control cycles from days +6 until +12. In the late luteal phase (days +11 to +13) the low P index cycles were found to have slightly higher P levels compared with

controls.

The median P index in the low P index group was 62.0 (control 100.0, $p < 0.001$) and 101.0 in the normal P index group (no difference from controls).

LH (Tables 5.1.26 & 27, Figure 5.1.13)

There was no difference observed in LH secretion between the sub-groups, and both profiles were similar to the control data.

FSH (Tables 5.1.28 & 29, Figure 5.1.14)

Compared with the controls, the normal P index cycles' FSH concentrations were significantly higher in the early part of the follicular phase (days -10, -9, -7 and -6). Thereafter, control and normal P index profiles were similar.

Low P index cycles were associated with reduced FSH secretion in the early follicular phase (days -9 and -7), compared to the normal P index cycles, but thereafter the two sub-groups had similar profiles.

Low P index cycles, in comparison with controls, were found to have slightly higher mid-luteal levels of FSH (days +6 to +10).

FD (Tables 5.1.30 & 31, Figure 5.1.15)

The normal P index cycles had slightly higher FD's on days -1 and 0 compared with the low P index cycles, but in comparison with the controls there was no difference.

Large and small cyst formation was observed in both sub-groups. In the low P index cycles the diameter of the cysts was greater (median 27.0mm) than in the normal P index cycles (median 20.5mm). This difference was not statistically significant.

Comment

Luteal cyst formation of all previously mentioned types i.e. large, small, shrinkers and non-shrinkers were seen in both the sub-groups under scrutiny, though the commonest pattern in the low P index group was that of a large cyst showing no evidence of shrinkage. Follicular dynamics were similar in both groups prior to the LH peak and together with the similarities observed in E2 profiles would suggest that discrimination between the two types of cycle cannot be made with these parameters alone.

The steroid output in the luteal phase, in the low P index cycles in particular, is interesting. The role of LDL as a precursor of P synthesis in the luteal phase has been alluded to. Disruption of a barrier between blood and the granulosa lutein cells seems necessary for the initiation and maintenance of corpus luteum function. The lag in P production observed in the low P index cycles could be explained by the failure, in many cases, of the granulosa cell layer to undergo neo-vascularisation as a consequence of follicular rupture, or impairment of basement membrane disruption of the granulosa and theca cell layers. Availability of steroid precursors would thus be diminished. In cycles with a normal P index availability of precursors in the early luteal phase cannot have been affected, despite luteal cyst formation and provides evidence, as in

the previous section, that limited ultrasound data of periovulatory follicular dynamics cannot discriminate absolutely between normal and abnormal potential for steroid production.

In the mid to late part of the luteal phase P production in the normal P index cycles was found to be greater than in the control cycles. In the case of E2 the concentrations were similar to the controls, though insignificantly lower than in the normal P index cycles. Study of gonadotrophin secretion at this time revealed that the output of FSH, in the cycles with lower P production, was greater than in the control cycles. The principle luteotrophin is thought to be LH but it is possible that FSH may play a subordinate role (Hillier & Wickings 1985). The finding of high FSH secretion in the low P index cycles could represent an attempt at compensation for defective luteal function but the mediator between the ovary and the pituitary in this situation is unclear, since E2 levels were no different from normal cycle patterns and broadly similar to the cycles with normal P indices. The integrity of a barrier between blood and the granulosa lutein cells would require to be maintained throughout the luteal phase if P production was to be kept at a low level. Higher P concentrations observed in the low P index cycles towards the end of the luteal phase may represent an eventual breach in this barrier. It is possible that cystic CL's have increased concentrations of steroid precursors stored and available for P biosynthesis once the cellular conditions are optimised, late in the luteal phase. It is also likely that ageing granulosa and theca cells behave differently from younger cells and may in part account for the differences in circulating P concentrations.

Higher than normal P production in the normal P index cycles is

more difficult to explain. Higher FSH concentrations were observed in these cycles and perhaps, as a consequence, may have led to an alteration in the number of gonadotrophin receptors in the follicle. Responses to the LH surge and the subsequent gonadotrophin output by the pituitary might be modified as a result. In these cycles it is possible that the blood-follicle barrier is overcome in a way that is not detectable through ultrasound, and that steroid precursors can be metabolised at increased rates given the right pre-, peri- and post-ovulatory conditions. The subtle aberrations from normal in gonadotrophin secretion seen in these cycles are similar to the patterns observed in the analysis of cycles where cyst formation was associated with shrinkage of the dominant follicle following the LH peak.

Low FSH secretion in the early follicular phase was not a feature in the profiles of the cyst formers and is in contrast to the data implicating this mechanism in the pathogenesis of the deficient luteal phase (Jones et al 1970, Sherman & Korenman 1974a, DiZerega & Hodgen 1981, Cook et al 1983, Stouffer et al 1984).

Large cysts were almost three times as common as small cysts and the latter as a matter of course exhibited shrinkage. To determine whether the exclusion of the small cyst formers in the analyses might provide further insight in to the pathogenesis of disordered luteal function in these cycles similar comparisons to the above were made in the 30 cycles with large cyst formation alone.

## D. Large Cysts (>20mm) - shrinkers & non-shrinkers

Tables 5.1.32 to 5.1.41 detail the biochemical and ultrasonic

data relating to these sub-groups of cyst formers. The median, mean, SD, SEM and 95% confidence limits are shown for E2, P, LH, FSH and FD measurements together with statistical significance, where found, in comparison between the groups and also with the control data (Wilcoxon rank sum test). These values are graphically illustrated in figures 5.1.16 to 5.1.20 where the median values for the hormones and the follicular diameters are plotted against the background control cycle medians.

E2 (Tables 5.1.32 & 33, Figure 5.1.16)

Profiles were similar in the sub-groups and exhibited no significant differences when compared with the control data, although the large cyst-formers which exhibited shrinkage did demonstrate a tendency to reduced luteal phase E2 production.

P (Tables 5.1.34 & 35, Figure 5.1.17)

Comparison of the P profiles revealed profound differences between the sub-groups. As described in analysis B, those cycles lacking evidence of follicular shrinkage after the LH peak were associated with marked reduction in P concentrations from days +1 to +8. As a consequence the P index was significantly reduced (median 53.5) compared to controls ($p < 0.001$) and to cycles where shrinkage was observed (median 90.0, $p < 0.001$). The reduction in P production in the cycles with shrinkage did not achieve statistical significance in comparison with controls. In both sub-groups, late luteal P production was higher than the control data, significantly so on days +11 to +13.

LH (Tables 5.1.36 & 37, Figure 5.1.18)

No significant difference was found between the sub-groups, and, in comparison with the control data, profiles were again similar.

FSH (Tables 5.1.38 & 39, Figure 5.1.19)

As before, in the cycles where shrinkage of the follicle was evident and ultimately P levels achieved virtually normal proportions, the concentrations of FSH in the early follicular phase were slightly higher than normal; this was only statistically significant on days -9 and -7. The concentrations were significantly higher than those in patients with no shrinkage on day -7.

In the mid to late luteal phase, although shrinkage cycles had higher median concentrations than the non-shrinkage group, the differences observed did not achieve statistical significance. Interestingly, although the levels were lower in the non-shrinkage cycles, when comparison was made with controls it was in these cycles only that the elevation in concentrations with respect to the control data achieved a degree of significance, a reflection of the small numbers and wide range of values in the shrinkage sub-group. These data present similar findings to section B.

FD (Tables 5.1.40 & 41, Figure 5.1.20)

Prior to the LH peak, FD profiles were similar in each sub-group, and when compared to controls no difference was observed. Median cyst size in the shrinkage sub-group was 18.5mm, significantly smaller than that of the non-shrinkers (33.0mm, $p < 0.001$).

Comment

These data present similar trends to those revealed in section B.

As before the E2 profiles and FD curves gave no clue as to the impending abnormality in the ultrasonically observed ovulation dynamics. P production by the corpus luteum was profoundly impaired in the non-shrinkage cycles suggesting that follicular shrinkage was a prerequisite for efficient steroid biosynthesis and release by the granulosa lutein cells.

6 of the 10 cycles (60%) showing shrinkage of the dominant follicle prior to cyst formation were associated with normal P production as opposed to only 2 of the 20 cycles (20%) where no shrinkage was observed ($p = 0.007$, Fisher's exact test).

It is interesting that luteal phase E2 release was normal in these cycles, the main site of this steroid's biosynthesis probably being through aromatisation of androgens, produced in the theca lutein cells, by the adjacent granulosa lutein cells. Since the source of androgen may be within the theca lutein cell itself (Macnaughton et al 1981) breakdown of the blood-follicle barrier may not be a necessity for E2 production, in contrast to the biosynthetic pathway of P.

There is no doubt that in the human the luteotrophic complex requires LH, but whether this is required alone or in concert with other factors is open to doubt. In both the sub-groups, FSH levels

were found to be slightly higher than in the controls in the mid-luteal phase. It is possible that FSH is involved in the luteotrophic influence at this point in the cycle, acting on its receptor in the granulosa cell membrane. Inhibin concentrations, in blood, have recently been found to rise in the luteal phase of the cycle (Baird 1988) and, as before it is hypothesised that luteal cyst formation is associated with reduced concentrations of inhibin and elevated FSH concentrations as a consequence.

Differences in FSH secretion in the early follicular phase were not as marked as in section B, but the concentrations in the shrinkers did tend to be slightly higher than in the cycles where no shrinkage was seen.

## E. Large Cysts (>20mm) - Normal P index & Low P index

The cycles where large cyst formation was seen were subdivided in to those where normal P production was seen and those where the P index was low. These sub-groups were compared.

Tables 5.1.42 to 5.1.51 detail the biochemical and ultrasonic data relating to the 30 cycles in these sub-groups of cyst formers. The median, mean, SD, SEM and 95% confidence limits are shown for E2, P, LH, FSH and FD measurements together with statistical significance, where found, in comparison between the groups and also with the control data (Wilcoxon rank sum test). These values are graphically illustrated in figures 5.1.21 to 5.1.25 where the median values for the hormones and the follicular diameters are plotted against the background control cycle medians.

E2 (Tables 5.1.42 & 43, Figure 5.1.21)

Concentrations of E2 were similar in both sub-groups in the follicular phase. Concentrations were slightly higher in the luteal phase of the low P index cycles, but the differences did not achieve statistical significance. Compared with the control data, apart from a minor elevation on day +1 in the low P index group and a reduction on day +6 in the normal P index group, the sub-groups were broadly similar.

P (Tables 5.1.44 & 45, Figure 5.1.22)

The median P index in the normal P index group was 101.0, similar to the control cycles' data.

The low P index cycles' value (median 63.0) (by definition) represented a profound reduction ($p < 0.001$), and P concentrations in this sub-group were significantly reduced from days +1 to +8 compared to controls, and days +1 to +9 compared with the normal P index sub-group.

As in the previous analyses, P concentrations were found in these cyst formers to be higher than the control data in the later part of the luteal phase (days +11 to +13 in the case of the low P index group, and days +7 and +9 to +12 in the case of the normal P index group).

LH (Tables 5.1.46 & 47, Figure 5.1.23)

Cycles with normal P indices exhibited no differences when compared with the control data, and with the low P index data.

The low P index cycles, when compared with controls, showed minor elevations on days +3, +5 and +9.

The concentrations, in both sub-groups, were similar to those of the control data at the mid-cycle peak.

FSH (Tables 5.1.48 & 49, Figure 5.1.24)

In the follicular phase the normal P index cycles tended to have higher concentrations of FSH than the low P index cycles, but the differences observed were not statistically significant. In comparison with the controls the elevation was significant only on day -10.

Peak values on day 0 did not vary from normal.

In the luteal phase the low P index cycles had higher concentrations on days +6 to +10 when compared to controls, but when comparison with the normal P index cycles was made no differences could be found. The normal P index sub-group did not differ from the control cycle data.

FD (Tables 5.1.50 & 51, Figure 5.1.25)

In the low P index group the median FD's on days-1 and 0 were

slightly smaller than in the normal P index group. Overall cyst size was greater in the low P index group (median 32.0mm), though this did not achieve significance (median cyst size normal P index 24.5mm).

Compared to the controls, the pre-ovulatory profiles were similar in both groups except for a minor reduction in size on day -1 in the low P index group.

18 of the 23 cycles demonstrating no evidence of shrinkage (78.3%) were associated with deficient P production, while only 2 of the 7 cycles where P production was normal (28.6%) demonstrated this ultrasonic pattern ($p = 0.025$, Fisher's exact test).

Comment

The high proportion of cycles in the low P index group which were associated with lack of evidence of follicular shrinkage is reflected in the deficient P profiles observed. This difference is similar to that shown in section C where the 11 small cyst formers, all of whom exhibited follicular shrinkage, were included in the analyses. Inclusion of their data in the previous section would not appear to have biased the results.

## 5.1.4 General Discussion

Luteal cyst formation was found to be the commonest ultrasound abnormality detected in this population of patients with unexplained infertility, all of whom were investigated in spontaneous cycles. 41 such cycles, 23.4% of the total investigated, have been described,

providing substantial biochemical and ultrasonic data on such abnormalities, in a uniform patient population, which have, until now, been lacking.

The data presented in this section of the study demonstrate that, while there is a close relationship between ultrasonographic and hormonal assessment of luteal function, definition of luteal phase abnormalities requires consideration of biochemical and ultrasonic indices together, rather than independently. Luteal cyst formation cycles do not represent a homogeneous population. The ultimate size of the cyst is not a sensitive indicator of the nature of the structure, or its effect on luteal function, and, while shrinkage of the dominant follicle prior to cyst formation is a major determining factor of the steroidogenic potential of the luteinized follicle, it is not the only one.

At least two distinct populations of luteal phase cystic structures have been described. The first, where luteal function in terms of steroid production was maintained, and the second where markedly deficient progesterone in the peripheral plasma was evident.

In the study by Hamilton et al (1985), peak LH values were found to be reduced significantly in the LUF patients, compared to the controls, and the suggestion was made that this might have played a role in the pathogenesis of the LUF syndrome. Insufficient data on spontaneously cycling patients with unexplained infertility were provided in that study to permit comparison with the data in this section of the thesis. It would have been useful, as the present study has done, to assess gonadotrophin and steroid production serially in the early follicular phase, a time when normal ovulatory

processes might be determined, and to assess in detail the hormonal dynamics following the LH peak. In this way discrimination between the potential sub-groups of luteal cyst formation, some representing the LUF syndrome, and some merely cystic corpus luteum formation, might be possible.

In a recent publication, Eissa et al (1987) used sequential ovarian ultrasound and serial biochemistry to study follicular function in 113 cycles in a heterogenous group of 45 patients, 22 of whom had unexplained infertility, the remainder having endometriosis or tubal disease. They described four dysfunctional ultrasonic and biochemical patterns, including one group termed "LUF" cycles. This occurred in 22.1% of the series, and was characterised by shrinkage of the dominant follicle following the LH peak but maintenance of its cystic appearance during the luteal phase. This pattern was associated with normal endocrine profiles, between days -8 and +8, and would seem to be comparable to the 11 cycles described in the present study where cyst size was found to be less than 20mm diameter (section A), seen in 6.3% of the 175 cycles studied. The small cyst formers in this study did, however, exhibit slight differences in FSH concentrations in the early follicular phase and P concentrations in the luteal phase in comparison with the controls.

Eissa's paper also described in 16 cycles (14.2%) a second type of cyst formation where a normal pattern of follicular growth was observed, though E2 concentrations were low in the mid-cycle. Following the LH peak no ultrasonic features of luteinisation were seen and the follicle continued to grow. This pattern was termed a "dysfunctional ovulation cyst" and was associated with low P concentrations up to the final day of sampling (+8). Gonadotrophins

were normal. The ultrasonic pattern described would appear to be similar to that of the 20 cycles (11.4%) in the present series where no shrinkage of the dominant follicle was seen following the LH peak (sections B & D). No difference in E2 concentrations was seen in these cycles but P production was markedly reduced for the reasons hypothesised above. FSH concentrations in contrast were found to be higher in the mid to late luteal phase. Eissa did not observe any of the sub-group with large cyst formation, seen in 1/3 of the cycles described here, where expansion of the follicular structure occurred following signs of shrinkage at the time of the LH peak.

A strong association has been shown between the observation of shrinkage of the follicle and efficient P production, while the failure to observe follicular shrinkage was associated with markedly deficient luteal function. It might be postulated, therefore, that the ultrasonic patterns represent, in the case of the luteal cyst formers without shrinkage, the LUF syndrome, and in the remaining cyst formers with some evidence of shrinkage, cystic corpus luteum formation. These hypotheses are in contrast to those of Eissa et al, as it is tempting to equate ultrasonically observed follicular shrinkage with follicle rupture.

It is possible that the two groups presented here may not be as distinct as their ultrasonic and biochemical patterns might suggest. The process of ovum release may not always be consequent upon ultrasound observed follicular shrinkage (Craft et al 1980, Stanger & Yovich 1984) and ovum entrapment may have occurred in some of the cycles where shrinkage of the dominant follicle was observed. Conversely, in some of the non-shrinking cyst formers, it is possible that a diminution in size of the follicle might have been missed in

the periods between ultrasonic observations. This type of error was kept to a minimum by the endeavour to scan patients evey day over the periovulatory period, but it is possible, since the processes of follicular rupture, as observed ultrasonically, take place over a relatively short period of time (de Crespigny et al 1981), that some overlap of the two groups of cycles occurred.

These patterns were seen neither in the control cycles (chapter 2) nor the conception cycles (chapter 3), and it could be argued that such discrimination may only be of academic importance since both variants may represent infertile cycles.

Deficiency of FSH secretion was not, as others have suggested (Sherman & Korenman 1974a & b, Jones et al 1970, di Zerega & Hodgen 1981, Cook et al 1983, Stouffer et al 1984) found in these cycles. Indeed it was found that cycles more often associated with normal P production were found to have slightly increased FSH output in the early follicular phase. Those with deficient P production could not be distinguished from the controls. Some have suggested that an approach to treatment of the LUF syndrome could be to stimulate gonadotrophin secretion in the early part of the cycle through use of anti-estrogens, or to administer exogenous gonadotrophins. These data would not appear to support this concept.

In summary, luteal cyst formation has been shown not to be uniform in its presentation. Study of ultrasonic and plasma P profiles can distinguish several distinct groups of abnormalities, some of which may represent the LUF syndrome and others merely cystic corpus luteum formation.

## SECTION 5.2 POOR PROGESTERONE SURGE (PPS)

### 5.2.1 Definition

The normal luteal phase profile of P concentration in plasma has been outlined in chapter 2.1. From very low levels prior to the LH peak, there is a steady increase in concentrations until a plateau is reached between days +5 and +8, with concentrations at this time being between 17.0ng/ml and 19.1ng/ml. Thereafter concentrations fall steadily until the onset of menstruation.

In a high proportion of the cycles under study the rise in plasma P concentrations was observed to be slower than in the normal cycles. Where the concentrations in the study cycle between days +1 and +5 were found to be more than one standard deviation below the normal mean on two or more days, the cycle was described as demonstrating a "poor progesterone surge (PPS)".

### 5.2.2 Analysis

51 (29.1%) of the 175 cycles under study were found to demonstrate PPS profiles.

The median age of the PPS patients was 30 years (range 22 to 40 years) which was greater than that of the control population ($p < 0.001$). Follicular phase length ranged from 8 to 27 days (median 15 days), while median luteal phase length was 15 days (range 11 to 18 days). (See Table 5.2.1). These cycle characteristics, as defined in chapter 2, did not differ significantly from the control data.

Tables 5.2.2 to 5.2.6 detail the biochemical and ultrasonic data relating to the PPS cycles. The median, mean, SD, SEM and 95% confidence limits are shown for E2, P, LH, FSH and FD measurements, together with statistical significance, where found, in comparison with the control data (Wilcoxon rank sum test). These profiles are graphically illustrated in figures 5.2.1 to 5.2.5 where the median values for the hormone concentrations and the follicular diameters are plotted against the background control cycle medians.

E2 (Table 5.2.2, Figure 5.2.1)

In the early follicular phase plasma E2 concentrations tended to the lower end of the normal range, and were significantly reduced, compared to the control data, between days -5 and -1. The median peak E2 level (day -1) was 205.0 pg/ml.

The E2 concentration coincident to the day of the LH peak (day 0) was within the normal range.

The profile in the luteal phase was similar to that of the control cycles' and, although median concentrations were high on days +11 to +13, the differences observed did not achieve statistical significance.

P (Table 5.2.3, Figure 5.2.2)

P concentrations were dramatically reduced for the greater part of the early to mid-luteal phase. The differences observed achieved statistical significance on days +1 to +8. The impairment of steroid production by the corpus luteum, which justified the PPS definition,

was reflected in the significant reduction in the P index (median 61.0, control 100.0, p <0.001).

On days +11 to +13, P concentrations were slightly higher than the normal range, but were comparable by day +14.

LH (Table 5.2.4, Figure 5.2.3)

Median plasma LH concentrations tended to be at the upper end of the normal range throughout the cycle. This tendency was more noticeable in the luteal phase and a significant difference was seen on days +5 and +7. Peak LH concentration did not differ from normal. As the high SD's indicate, a fairly wide range of concentrations was observed.

FSH (Table 5.2.5, Figure 5.2.4)

Concentrations of FSH were significantly elevated on days -10, -6 and -3. In the remainder of the follicular phase, values tended to the upper limit of the normal range.

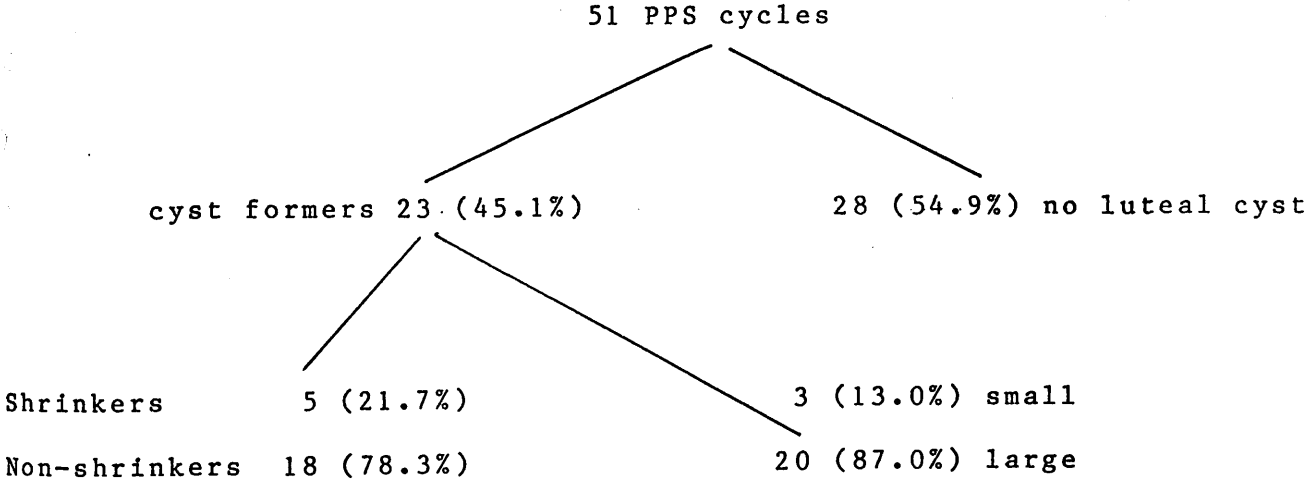
Median peak concentration (day 0) did not differ from normal but, in the luteal phase, the observed tendency to high concentrations was significant from days +4 to +10.

FD (Table 5.2.6, Figure 5.2.5)

Until the LH peak (day 0), FD profiles were found to follow a linear growth pattern, at the lower end of the normal range. This bore a resemblance to the lowish E2 profile already described.

Although the observed difference in diameter on day -1 was statistically significant (median 18.0mm, control median 20.0mm, $p < 0.01$), the maximum follicular size seen on day 0 (19.0mm) was similar to that of the control population.

Following the LH peak, 23 (45.1%) of the PPS cycles demonstrated luteal cyst formation (viz. section 5.1). The majority of these (18 (78.3%)) followed the pattern, previously described, of cyst formation without shrinkage of the dominant follicle. The remaining 5 (21.7%) elaborated a periovulatory pattern of follicular reduction in size followed by luteal cyst formation. 20 of the cysts (87.0%) were greater than 20mm. Median cyst size was 30.0mm (mean 31.5mm, SD 10.9mm, SEM 2.3mm).



## 5.2.3 Discussion

The incidence of PPS in the population of unexplained infertility patients under examination is similar to that described in preliminary work carried out in the same laboratory (Fleming et al 1981). Virtually all the cycles exhibited a mid-luteal plasma concentration of P in excess of the "normal" ovulatory criteria demanded by previous studies using single (Israel et al 1972, Shepard et al 1977, Hull et al 1982, Abdulla et al 1983) and limited multiple (Abraham et al 1974) sampling techniques. The data presented would suggest that such methods are likely to miss, in a similar population, a considerable number of abnormal cycles.

Lenton et al (1978) in a small study found similar early luteal P profiles in infertile women but did not examine the follicular dynamics of such patients using ultrasound.

The implications for the fertility of the cycle demonstrating PPS would appear to be considerable. Koninckx et al (1978) observed, in a population of women with unexplained infertility, a high incidence of delay in the onset of luteinisation determined by elevation in BBT, as compared to infertile patients with tubal occlusion. It was postulated that this was a manifestation of the LUF syndrome, since a high proportion of the patients demonstrating delayed luteinisation lacked a punctum on the corpus luteum when subjected to laparoscopy. The pattern of a slow rise in P concentrations seen in the present study would support the concept of defective luteinisation in the period immediately following the LH peak and the observation of such a high incidence of luteal cyst formation, most of which were of the type suggestive of unruptured

follicles, would lend credence to the hypothesis that the process of LUF, in addition to impedence of oocyte release (Aksel 1987), may also affect endometrial receptiveness to the implanting blastocyst (Wentz 1982, Kusuda et al 1983). A disturbance such as this might have profound implications for the successful continuation of pregnancy beyond the first few weeks of gestation (Soules et al 1977, Tho et al 1979, Annos et al 1980) (viz. chapter 2).

Follicular phase determinants of abnormal luteal function, in particular diminished gonadotrophic stimulation, have been alluded to previously (Sherman & Korenman 1974a, Stouffer & Hodgen 1980, Aksel 1980, DiZerega & Hodgen 1981, Gautray et al 1981, Cook et al 1983). McNatty et al (1975) observed that an absence of an intercycle increase in FSH was often associated with luteal inadequacy. This was not the case in the cycles under study where the FSH concentrations tended to the upper limit of the normal range. It is possible that this reflected an attempt by the hypothalamo-pituitary axis to compensate for a deficiency within the follicle since E2 production in the cycle was slightly low, significantly so in the late follicular phase. Previous work suggesting that this abnormality might be of central origin (Gautray et al 1981) must now be re-evaluated carefully.

It is well recognised that FSH is the stimulus to the antral follicle's proliferation of granulosa cells (McNatty et al 1975, Breitenecker et al 1978, Marut, Huang & Hodgen 1983) leading to the eventual dominance of a single follicle from which the majority of the circulating E2 is produced (Baird & Fraser 1974). Although the follicular growth profiles in the PPS cycles did not differ markedly from normal, save on day -1, the E2 and FSH data suggest that the

dominant follicles recruited in these cycles could have been abnormal, accounting for subsequent endocrine dysfunction, in many cases associated with luteal cyst formation.

Soules et al (1984) reported abnormalities of pulsatile LH secretion in patients demonstrating LPD, associated with slightly diminished secretion of FSH in the early follicular phase. The pulsatility patterns of LH release were not evaluated in the present study, but the fact that FSH concentrations were higher in the PPS group would suggest that these potentially represent a different population of cycles from those in the cited studies with low FSH output. The LH profiles in the PPS cycles showed a wide variation with median concentrations lying in the upper range of normal. In some cases the concentrations were quite high and these cycles are included in the analysis in the next section.

Marut et al (1983) observed in primate studies that removal of the granulosa cells from pre-ovulatory follicles produced diminished corpora lutea characterised by decreased P secretion. The granulosa lutein cells would therefore seem to be the predominant source of P production. However, they observed that luteal E2 production, despite the lack of granulosa cells, seemed adequate, and concluded that E2 in these cycles emanated principally from luteinised theca cells. This would be in accordance with the observations of Macnaughton et al (1981) who alluded to the likely differing cellular pathways of E2 and P production in the luteal phase. In respect of the data presented here, it would seem to offer an explanation for the normality of luteal E2 concentrations in cycles with markedly deficient P production. Taking into account the data presented in the previous section, there could be two variants of PPS. The first where

luteal P production is diminished through lack of functional granulosa cells as reflected in the above data where follicular phase E2 concentrations are low with compensatory high FSH secretion. The second form of deficient early luteal P production could be where, through failure of the blood follicle barrier to be broken down, as in the non-shrinking luteal cyst formers, the necessary precursors are not made available to granulosa lutein cells, present in normal amounts as reflected in normal follicular phase E2 concentrations.

These data may have important implications for theraputic strategies in these patients. In the cycles where LPD might be due to a follicular abnormality then stimulating these abnormal follicles with endogenous or exogenous gonadotrophins is unlikely to meet with success. On the other hand if therapy could achieve breakdown of the blood-follicle barrier in the second type of cycle, perhaps with exogenous gonadotrophins, as in the Glasgow approach (Fleming et al 1982, Fleming et al 1987), then the chances of success might be fairly good.

It was interesting to note that, of the 51 PPS cycles, only 2 (3.9%) were associated with a short luteal phase, 11 days in length in both cases (SLP = luteal phase length of 11 days or less (Smith et al 1984)).

## SECTION 5.3 HIGH LH

### 5.3.1 Definition

The normal cyclical pattern of LH secretion by the pituitary has been outlined in Chapter 2.

Cycles designated "high LH" were defined on the basis of the proportion of samples in the follicular phase of the cycle with LH concentrations greater than normal. Where more than 50% of the values in either the follicular phase were more than 2 SD above the normal mean, then the cycle was regarded as demonstrating a "high LH" profile.

### 5.3.2 Analysis

23 (13.1%) of the 175 cycles demonstrated high LH profiles.

3 of the total demonstrated biochemical features of anovulation, with cycle lengths of 22, 22 and 30 days respectively. Plasma E2 concentrations remained below 145 pg/ml throughout the period of sampling and P concentrations did not rise above basal levels at any stage. LH concentrations were consistently high throughout, with virtually all values being in excess of 20mIU/ml. No surge in concentration, sufficient to constitute an LH peak, was observed. FSH concentrations were in the normal range in these cycles, save that no peak was observed. Ultrasound examination revealed follicular structures in all 3 cycles, from the 8th day of sampling through until the onset of menstruation. These, once visualised, usually

remained static in terms of size and echogenicity, ranging from 15.0 to 25.0mm diameter.

The remaining 20 high LH cycles constitute the basis for the biochemical and ultrasonic data presented.

Table 5.3.1 shows the age and cycle characteristics, as defined in chapter2, of these 20 patients. The age of the patients was similar to that of the control cycles, but the duration of the cycle was rather greater in the high LH group, largely due to lengthening of the follicular phase of these cycles. The range of follicular phase length was considerable (11-29 days), with 4 patients having a follicular length in excess of 20 days.

Tables 5.3.2 to 5.3.6 detail the biochemical and ultrasonic data relating to the high LH cycles. The median, mean, SD, SEM and 95% confidence limits are shown for E2, P, LH, FSH and FD measurements together with the statistical significance, where found, in comparison with the control data (Wilcoxon rank sum test). These values are graphically illustrated in figures 5.3.1 to 5.3.5 where the median values for the hormones and the follicular diameters are plotted against the background control cycle medians.

E2 (Table 5.3.2, Figure 5.3.1)

In the follicular phase E2 concentrations were reduced, significantly so between days -4 and -1. Median day 0 concentration did not differ significantly from the control data although the value (192.5 pg/ml) lay at the lower end of the normal range.

No significant deviations from normal were seen in the luteal phase, except on days +11 and +13 when the E2 concentrations were slightly higher in the high LH cycles.

P (Table 5.3.3, Figure 5.3.2)

The rise in P concentration in this group of cycles was found to be slow, with concentrations significantly lower on day +4. This pattern was reflected in the significant reduction in median P index (71.5) compared with the controls (100.0, $p < 0.01$).

Late luteal P concentrations were higher than in the control data on days +10 to +13.

Evidence of premature luteinisation (P concentrations >1.5 ng/ml on day 0) was found in 4 cycles (20%). 3 of these cycles had very high early luteal P concentrations (P indices of 121, 157 and 158). None showed ultrasonic evidence of multiple follicular development or luteinisation prior to the LH peak, though one of these cycles was associated with a luteal cyst, 25.0 mm diameter. The cyst showed evidence of shrinkage (see section 7.3.1). The other cycle showed premature luteinisation, with a reduced P index (50), and developed a 54mm luteal cyst, with no shrinkage.

LH (Table 5.3.4, Figure 5.3.3)

18 of the 23 high LH cycles (78.3%) were found to have elevated concentrations in both the follicular and the luteal phase of the cycle. The remaining 5 cycles (21.7%) exhibited high LH only in the follicular phase of the cycle.

Having excluded the anovulatory cycles, all of whom had high LH concentrations throughout the period of blood sampling, it was noted that, despite high basal LH concentrations, the characteristic LH peak was still identifiable in the remaining 20 cycles. The peak, as evidenced by the median LH concentration on day 0 (75.0 IU/l), was not attenuated.

The cycles with premature luteinisation included 1 cycle with elevation only in the follicular phase (P index 157), while the others demonstrated high LH throughout.

By the end of the luteal phase (+12 to +14), LH concentrations were indistinguishable from the control cycles.

FSH (Table 5.3.5, Figure 5.3.4)

Apart from a minor elevation on day +9, the concentration of FSH throughout the cycle, including the day of the FSH peak (day 0), was indistinguishable in the high LH group from the control cycle data.

FD (Table 5.3.6, Figure 5.3.5)

As a group, the high LH cycles demonstrated reduced FD's on days -2 and -1 but the median diameter on day 0 was 21.0mm, no different from the controls.

Looking in more detail at the individual cycles, a high percentage demonstrated ultrasonically abnormal ovarian function (16/23 (69.6% of all high LH cycles), 13/20 (65% of the "ovulatory"

cycles)). These are listed below :

a) Anovulation, as already alluded to, was observed in 3 cycles.

b) Luteal cyst formation was seen in 8 cycles. Cyst size ranged from 22-54mm diameter (median 31.0mm).

5 of the cysts failed to show evidence of shrinkage and all of these had P indices below the 95% confidence limits (89.5) of the normal data (range 29-72, median 50). The remaining 3 cyst formers demonstrated shrinkage, and had P indices of 86, 120 and 157.

8 of the 12 cycles where no luteal cyst formation was evident had low P indices (median 66, range 36-85) while the remaining 4 cycles without cyst formation had P indices of 94, 96, 121 and 158.

c) Poor follicular development (see section 7.3.4) was observed in 3 cycles. 1 of these cycles also demonstrated luteal cyst formation (30mm, non-shrinker, P index 60).

d) 1 cycle demonstrated an unusual follicular diameter profile with an FD of 20.5mm on day -4. This represented a measurement in excess of 3 SD above the normal mean. The FD was found to be 24.0mm on day -1 and 25.0mm on day 0. Thereafter normal corpus luteum formation was seen with a high P index of 158. P concentration on day 0 was 1.8 ng/ml, indicating that premature luteinisation had

occurred.

e) 1 cycle was found to develop a dominant follicle which achieved maximum follicular diameter 2 days prior to the LH peak. This dissociation was associated with a slightly reduced P index (86), but not cyst formation.

### 5.3.3 Discussion

Fleming et al (1981) first drew attention to the finding, in a small number of women with unexplained infertility, in addition to a pattern of early luteal P deficiency, an associated elevation in the concentration of LH, particularly in the follicular phase. The data presented here provide an insight in to the frequency of the phenomenon, in a large population of patients with unexplained infertility, and provide original information on the follicular dynamics in these abnormal cycles.

That the pathogenesis of LPD may be linked to abnormalities of pituitary secretion of gonadotrophins has been suggested for some time, with the emphasis on deficiencies in production of FSH. Jones et al (1970) speculated that the cause of reproductive failure in some ovulatory patients was defective patterns of release of gonadotrophins, in particular FSH, but observed that in some cases (Jones 1976) the adequacy of the LH surge was an important factor in determining luteal function. Sherman and Korenman (1974) did not find, in the small number of cycles they studied, any evidence of abnormal LH secretion but, as others were to confirm later in primate studies (Stouffer and Hodgen 1980, Dizerega and Hodgen 1981, Stouffer et al 1984) and in infertile women (Aksel 1980, Cook et al 1983),

reduction in FSH secretion with a resultant high LH : FSH ratio, can often lead to subsequent luteal dysfunction, reversible with administration of exogenous gonadotrophins in the follicular phase (DiZerega and Hodgen 1981). These data suggested that reduction in follicular phase FSH lead to an impairment of the expression of LH receptors during folliculogenesis, irreversibly altering ovarian LH responsitivity, resulting in defective luteal function. In these and other studies (Lenton et al, 1978, Lenton et al 1982), including women with unexplained infertility, abnormally high LH secretion has not been described.

In the high LH group described here, low E2 production was seen in the late follicular phase, with an associated slight reduction in FD prior to the LH peak, though day 0 E2 and FD were within the normal range. FSH concentrations were normal. Luteal function in the group as a whole was impaired and, since LH concentrations were abnormally high in the follicular phase of these cycles, it might be speculated that the imbalance in gonadotrophin secretion may have modified the expression of FSH and LH receptors on the granulosa cells of the follicle. The response to the LH surge could thus have been modified with the induction, as a result, of luteal phase deficiency.

As the ultrasonic data reveal, the nature of LPD in these cycles was not uniform. Luteal cyst formation was seen in 40% of the cycles, most of which were of the type demonstrating no shrinkage of the follicle. 66.6% of the cycles with no evidence of cyst formation, however, also demonstrated LPD. Gonadotrophin concentrations in cycles demonstrating the LUF syndrome have not been found, in the past, to be abnormal (Konninckx et al 1978, Konninckx and Brosens

1982). Recent studies, describing ultrasonically observed luteal phase cysts in patients with unexplained infertility (Hamilton et al 1985, Eissa et al 1987), possibly analagous to the LUF syndrome, have not alluded to abnormalities of LH secretion in the, relative to the present study, small numbers of patients under examination.

It has been demonstrated (McNatty et al 1975, McNatty & Sawers 1975) that FSH is a necessary component in the preparation of the antral follicle for production of E2 and the pre-ovulatory production of P under the influence of LH. They suggested that abnormalities of luteal function might arise through the interference by LH during the growth of these follicles under the influence of FSH. Later work (McNatty et al 1979) established a relationship between FD and the number of granulosa cells, and that antral follicular E2 and FSH levels were directly related to the resumption of oocyte meiosis in vitro. If, as is possible, tonically high LH concentrations alter the endocrine microenvironment of the follicle, then it is possible that this could affect the potential fertility of the cycle, irrespective of the quality of luteal function subsequent to the LH peak. There is some evidence from IVF studies that patients with raised basal LH levels during the follicular phase of treatment achieve reduced fertilization rates and it is possible therefore that this may be a reflection of the disturbances alluded to here (Stanger and Yovich 1985).

The mechanism whereby high LH concentrations obtain in these cycles remains obscure. In cycles demonstrating LPD, significantly greater LH pulse frequency has been observed in the early follicular phase (Soules et al 1984) but,in the small number of cycles studied, the absolute plasma concentrations of LH did not differ from normal.

Interestingly, FSH concentrations in these cycles were found to lie within the normal range, albeit at the lower end. This is in contrast to a study on patients with polycystic ovarian disease where no specific abnormality in the pulsatile release of LH was found (Molloy et al 1984). Most of these patients however presented with oligomenorrhoea rather than normal menstrual rhythm.

That polycystic ovarian disease may be associated with high LH levels is well known (Duignan 1976). Some patients with the condition may, in addition to features of disturbed gonadotrophin secretion, manifest ultrasonically demonstrable structural ovarian abnormalities - multiple small cysts with an increase in ovarian stroma (Adams et al 1985). These were not a feature in the patients in this study.

Patients with polycystic ovarian disease may also have disturbed menstrual patterns, often with prolongation of the follicular phase of the cycle. 4 of the high LH series (20%) described here had follicular phase lengths in excess of 20 days. In the 175 patients studied in total only 9 cycles (5.1%) were found to demonstrate a prolonged follicular phase ($p = 0.03$, Fisher's exact test). These cycles will be described in section 7.5. The low incidence of long follicular phase length in this population of unexplained infertility is similar to the expected distribution of phase length in the normal population (Lenton et al 1984) but the disturbed endocrine and ultrasonic profiles demonstrated in this group of cycles illustrate, as others have, the high potential for infertility these circumstances create (Sherman and Korenman 1974a, Balasch et al 1986).

The 3 anovulatory cycles, all in patients with normal menstrual

rhythm, comprising only 1.7% of the total population of unexplained infertility, may, as has been suggested (Aksel et al 1976), represent a severe form of LPD. Aksel's series included a description of 5 such cycles, 3 of which were found to be associated with high LH concentrations. Laborde et al (1976) observed that a significant mid-cycle rise in LH does not guarantee that ovulation or luteinisation will definitely occur. In this series, none of the "aluteal" cycles demonstrated a rise in plasma LH, at any stage in the cycle, above the tonically elevated basal concentrations.

Therapeutic choices in these patients revolve around the need to improve the quality of ovulation and luteal function, avoiding the potentially deleterious effects of premature luteinisation and hyperstimulation. One approach might be to utilise a GnRH analogue to suppress the endogenous levels of LH and thereafter to stimulate the ovary with exogenous gonadotrophins. This approach has already been used in Glasgow in the treatment of patients with unexplained infertility and normal menstrual rhythm, who have demonstrated an early luteal pattern of PPS in the presence of normal LH concentrations. Experience has also been gained in the use of this combination to treat oligomenorrheic women with high LH concentrations and polycystic ovarian disease and, compared to the use of exogenous gonadotrophins in isolation, a good response has been achieved, with a reduced incidence of premature luteinisation (Fleming et al 1985, Fleming et al 1987). It would be interesting to see what the responses to such an approach would be in the patients described above, with normal menstrual rhythm but tonically high LH concentrations. Since FSH concentrations were normal in these cycles it would seem unlikely that clomiphene citrate would achieve much, but perhaps the use of P (Rosenberg et al 1980), particularly in the

cycles where no luteal cyst formation is found, would be an option for consideration. However, as alluded to above, it is possible that, even if oocyte release occurs, the fertilizability of the egg may have been jeopardised early in the follicular phase, irrevocably impeding fertility.

## SECTION 5.4 POOR FOLLICULAR MATURATION

### 5.4.1 Definitions

In keeping with previous biochemical observations in patients with unexplained infertility (Dodson et al 1975, Fleming et al 1981), a small proportion of cycles were found to manifest deficient ovarian function in the follicular phase of the cycle. This took the form of reduced follicular phase E2 concentrations or, in some cases, FD profiles culminating in maximum diameters below the normal range.

Poor follicular maturation refers to those cycles where more than 50% of the plasma E2 concentrations, between days -5 and -1, were below the 99.9% confidence limit of the mean of the control cycles, for the same period.

Poor follicular development refers to those cycles where follicular diameter on day 0 was found to be less than the 99.9% confidence limit of the mean of the control cycles on that day i.e. <17.1 mm diameter.

### 5.4.2 Analysis

16 patients demonstrated poor follicular maturation (PFM) and the patient details and cycle characteristics are listed in Table 5.4.1. Median follicular phase length was 15.5 days, while median luteal length was 16.0 days, both slightly greater than the control data. The patients, as in the other infertile groups were slightly older than the controls.

In 12 cycles, the FD on day 0 fulfilled the diagnostic criteria of poor follicular development (PFD) and the cycle characteristics for this group of patients are presented in Table 5.4.2. An age difference was observed, but the phase lengths were similar to the controls.

Tables 5.4.3, 5.4.5, 5.4.7, 5.4.9, & 5.4.11 detail the biochemical and ultrasonic data relating to the PFM data, while those data relating to the PFD subgroup are shown in Tables 5.4.4, 5.4.6, 5.4.8, 5.4.10, 5.4.12. The median, mean, SD, SEM and 95% confidence limits are shown for E2, P, FSH, LH and FD measurements, together with statistical significance, where found, in comparison with control data (Wilcoxon rank sum test). These profiles are graphically illustrated in figures 5.4.1, 5.4.3, 5.4.5, 5.4.7 & 5.4.9 for the PFM cycles, and figures 5.4.2, 5.4.4, 5.4.6, 5.4.8 & 5.4.10 for the PFD cycles. Median values for the hormone concentrations and the follicular diameters are plotted against the background control cycle medians.

E2 (Tables 5.4.3 & 4, Figures 5.4.1 & 2)

In the PFM sub-group, E2 concentrations were observed to be significantly lower than the controls throughout the follicular phase, and for the greater part of the luteal phase. Peak concentrations were achieved on Day 0 (165.0 pg/ml), the day of the LH peak, followed by a precipitous fall, rising again, in a similar fashion to the mid-cycle rise in normal cycles, and eventually achieving levels within the normal range from day +10 onwards.

The PFD cycles also exhibited a lower than normal E2 profile but

the observed differences achieved statistical significance only on days -6, +2, and +5 to +9 inclusive. The median concentration of E2 on day 0 (195.0 pg/ml) was within the normal range.

P (Tables 5.4.5 & 6, Figures 5.4.3 & 4)

P concentrations in the early luteal phase in both groups were sub-normal but only in the PFM cycles did this achieve significance in terms of the P index (67.0, controls 100.0, $p < 0.001$)

Both the PFD and the PFM cycles demonstrated supranormal P concentrations in the late luteal phase.

FSH (Tables 5.4.7 & 8, Figures 5.4.5 & 6)

The PFM cycles were associated with normal FSH profiles in the follicular phase, with a mid-cycle surge similar to that of the controls. In the mid-luteal phase, concentrations were slightly higher (days +5 to +7, +9), but were normal thereafter.

The PFD cycles exhibited slightly higher FSH concentrations on days -6, -5 and -3. Peak concentrations on day 0 were also higher than the norm and this elevation was sustained until day +8. In the late luteal phase concentrations were normal.

LH (Tables 5.4.9 & 10, Figures 5.4.7 & 8)

Apart from minor deviations in the case of the PFM cycles on days -4 and +1, LH concentrations were normal throughout in both groups.

FD (Tables 5.4.11 & 12, Figures 5.4.9 & 10)

The small numbers of cycles in each sub-group is reflected in the wide confidence limits seen. On the whole the FD measurements tended to lie below the normal range in the peri-ovulatory period. Day 0 median FD in the PFM group was 16.0 mm, and 15.0 mm in the PFD group.

Luteal cyst fomation was seen in 1 cycle in the PFD group (size 30mm, non-shrinker, P index 64) (this cycle also demonstrated high LH described in section 7.3.3), and 3 cycles in the PFM group (size 20, 22 & 54mm, shrinker, non-shrinker & non-shrinker, P indices 94, 33 & 50 respectively).

## 5.4.3 Discussion

5 of the PFD sub-group had scans on day +1 which demonstrated FD's lying within the normal range. It could be argued that inclusion of these cycles in the analysis would bias the E2 concentrations upwards in the group, but when these cycles were removed the E2 profiles remained similar :

| | Nos | Median | Mean | SD | SEM | Range |
|---|---|---|---|---|---|---|
| Day -3 | 7 | 135 | 155.6 | 70.7 | 26.7 | 100-308 |
| Day -2 | 7 | 150 | 176.6 | 69.2 | 26.1 | 120-325 |
| Day -1 | 7 | 190 | 220.9 | 63.5 | 24.0 | 150-313 |
| Day 0 | 7 | 200 | 190.1 | 37.1 | 14.0 | 120-225 |
| Day +1 | 7 | 105 | 104.3 | 34.0 | 12.8 | 45-140 |

E2 production, in the follicular phase of the cycle, is dependent on granulosa cell aromatase activity, which has been shown, in in-vitro studies on human cells, to be greatest in the period immediately prior to ovulation (Hillier 1981). Since follicular diameters in the PFM group described here were found to be significantly reduced in the days prior to the LH peak, it is probable that the observed reduction in aromatase activity, associated with low plasma E2 concentrations in these cycles, is consequent upon a reduction in the total population of granulosa cells in the dominant follicle.

E2 concentrations in the PFD group, although a little lower, were not significantly different from the control data. Median FD in this group on day 0 was profoundly reduced (15mm, $p < 0.001$). These data would therefore suggest that FD and granulosa cell numbers cannot be the only determinant of aromatase activity at this stage in the cycle. Follicular phase FSH concentrations in this group were higher than in the controls, in contrast to the cycles with a PFM profile. This may indicate in some cases, an attempt, at the level of the hypothalamus and pituitary, perhaps mediated through feedback mechanisms, to compensate for sub-optimal follicular development. Since the regulation of granulosa cell aromatase activity has been shown to be FSH dependent, those cycles with dominant follicles which, although small, are associated with normal plasma E2 concentrations and elevated FSH concentrations, may well be demonstrating a form of granulosa cell "rescue", with normal or even enhanced aromatase activity. It could be hypothesised that the elevation in FSH might be a consequence of a reduction in the amount, or bioactivity, of an inhibin-like peptide produced by these follicles. Conversely, the normal FSH concentrations, observed in

some cycles with small dominant follicles, may be consequent upon normal production of an inhibin-like peptide by these follicles, and the low E2 concentrations seen may be the end result of failure, on the part of the hypothalamo-pituitary-ovarian axis, to compensate for abnormal follicular development. Higher luteal phase FSH concentrations, seen particularly in the PFD cycles, may also be consequent upon impaired inhibin production or secretion by the granulosa lutein cells of the corpus luteum in these cycles. As specific assays for this peptide become available, further insight may be gained into the pathophysiology of these abnormalities of ovarian function.

E2 concentrations in the luteal phase were similarly depressed in both groups, as were P concentrations, though in both cases this was more marked in the PFM group. In some cases this was associated with luteal cyst formation (seen in 3 of the PFM and 1 of the PFD cycles). The possible mechanisms for reduced steroidogenesis in these circumstances have already been discussed (section 5.1). In the absence of cyst formation, it is possible that the diminished steroid production was a result of reduced populations of granulosa cells, and decreased expression of LH receptors on the surface of the cells. Defective luteinisation would be an inevitable consequence of these pre-ovulatory conditions. In contrast to the data of DiZerega and Hodgen (1981), low FSH concentrations in the follicular phase were unusual.

Tonically elevated LH concentrations were seen in 3 of the PFD cycles (section 5.3) and the observed increase in the length of the follicular phase of the group as a whole may be a consequence of this. Despite this, plasma LH concentrations, in both the follicular

and the luteal phase, were normal in both groups.

Defective follicular development has previously been diagnosed on the basis of reduced plasma concentrations of E2. As has been shown, poor follicular development can be associated with E2 concentrations not significantly different from normal, and consideration of the follicular phase gonadotrophin patterns, together with the ultrasonic profiles before and after the LH peak, are essential to clarify the pathological processes involved if optimal therapeutic strategies are to be devised. Four circumstances bear consideration :

i. Small follicle, E2 low, FSH normal

The use of clomiphene citrate to enhance endogenous production of gonadotrophins might prove efficacious in these cases. As has been hypothesised, inhibin-like activity in these cycles may be normal, and the failure of the pituitary to respond to the low E2 concentrations in plasma requires to be overcome.

ii. Small follicle, E2 normal, FSH high

Since E2 production by these follicles is normal, probably as a consequence of the elevated FSH secretion by the pituitary, it could be argued, that since physiological compensation has taken place, no treatment is necessary. However,the fact that FD is well below the normal range, and luteal function is depressed in these cycles indicates that, despite these adjustments, ovarian function is not normal. Further enhancement of gonadotrophin secretion with clomiphene citrate might increase follicular phase E2 production but whether the dominant follicle would respond in terms of FD, granulosa cell proliferation, and

subsequent improved luteal phase steroid production is less certain, since the poor follicular development in these cases may signify an inherent defect within the follicle itself, beyond rescue by external influences.

iii. Small follicle, high LH

As alluded to earlier (section 5.3), high LH concentrations may interfere with oocyte quality and possibly be associated with premature luteinisation. Combined treatment involving down-regulation of the pituitary and subsequent ovarian stimulation with exogenous gonadotrophins may lead to improved follicular development, reduced chance of premature luteinisation and improved luteal function. P supplementation, in isolation, might not be expected to achieve success since, even if ovulation occurs in these cycles, the potential fertilizability of the oocyte is in doubt.

iv. Small follicle, luteal cyst formation

Three of the 4 cysts observed were of the category which showed no evidence of shrinkage, possibly therefore representing the LUF syndrome (see section 5.1). In these circumstances, in a similar fashion to the approach described above, abolition of endogenous control of follicular development with long acting GnRH analogues and subsequent HMG therapy may well be the best approach. The observations that follicular development was sub-optimal and, in addition, the LH surge was not attenuated would suggest that expression of granulosa LH receptors in these cycles would be low and, consequently, one could not expect administration of hCG to achieve an improvement in the ovulatory mechanism. P therapy would confer no therapeutic benefit in

these cycles.

## SECTION 5.5 ABNORMALITIES OF CYCLE PHASE LENGTH

### 5.5.1 Definitions

The cycle characteristics of the control population under study have been discussed earlier (chapter 2), and were found to lie within fairly narrow limits. The 175 patients with unexplained infertility had similar follicular and luteal phase lengths :
follicular - mean 14.4 days, SD 3.5 days, SEM 1.1 days
luteal - mean 14.6 days, SD 1.6 days, SEM 0.1 days.

The short luteal phase (SLP) has been defined by most authorities as a luteal phase (the number of days following, but not including, the day of peak LH concentrations until the day of onset of subsequent menses) of less than 12 days. Lenton et al (1984) in an exhaustive analysis of over 300 cycles in apparently ovulating women found the lower 95% probability limit of luteal length in their study population to be 11.3 days. In the infertile population under study here the lower 95% probability limit (1.96 x SD) of luteal length was 11.4 days and so it would appear that the populations are comparable. In this analysis, a cycle was taken as exhibiting a SLP if luteal length, as defined above, was 11 days or less.

Lenton et al (1984) in their studies also examined the variation in the length of the follicular phase of the cycle. They defined the follicular phase length as the number of days up to, but not including the day of peak LH concentrations. The lower 95% probabilty limit of this substantial population was 10.3 days. In the present study the definition of follicular length included the day of the LH peak, and the lower 95% probability limit of the infertile population

was 7.6 days. Only 2 cycles in the entire study exhibited a follicular phase length less than this (6 days in both cases). In keeping therefore with the data of Lenton et al (1984) a short follicular phase (SFP) was designated if the duration of follicular length was 10 days or less.

The upper 95% probability limit in Lenton et al's data for follicular phase length was 20.5 days, while the figure in the present study was 21.2 days. Few cycles in this study exhibited a follicular length greater than 21 days and in order to provide a substantial enough group for analysis, an arbitrary distinction between normal and abnormal was made at 20 days follicular phase length. Thus a long follicular phase (LFP) cycle was defined as one with a follicular length of 20 days or more.

Of the 175 cycles under study, 6 (3.4%) were found to demonstrate a short luteal phase. There were 9 cycles with a long follicular phase (5.1%), and 6 (3.4%) demonstrating a short follicular phase.

## 5.5.2 Analysis (short luteal phase)

The patient and cycle characteristics of the SLP cycles are shown in Table 5.5.1 with the biochemical (plasma E2, P, LH & FSH) and ultrasonic data in Tables 5.5.2 to 5.5.7. Since small numbers were involved the mean, SD, SEM, median and ranges are shown rather than the 95% confidence limits. These data are graphically represented, in a similar fashion to that of previous analyses, in figures 5.5.1 to 5.5.5, with the median values plotted against the medians of the normal cycles. Significant differences, in comparison

with the controls (Wilcoxon rank sum test), are shown on the relevant tables.

The median age of the SLP patients was 33 years, significantly older than the control cycles (median 26 years, $p < 0.001$). Luteal phase length varied between 9 and 11 days (median 10.5 days, controls 15.0 days, $p < 0.001$) with an associated reduced median overall length of the cycle (25.0 days, controls 29.5 days, $p < 0.01$).

E2 (Table 5.5.2, Figure 5.5.1)

There were no significant differences in E2 concentrations throughout the cycle in comparison with the controls, with peak concentrations seen on day -1 (median 283.0 pg/ml). Luteal levels peaked on +7, similar to the control cycles, but fell sharply thereafter. In one cycle the E2 concentration on the day of menses was 200 pg/ml (P concentration on this day was 1.5 ng/ml).

P (Table 5.5.3, Figure 5.5.2)

The early part of the luteal phase in these cycles was similar to that of the control cycles with a steady rise in plasma P concentrations up until day +5. The P index, although slightly decreased (median 77.5), was not significantly different from the normal range. From day +6 onwards, P concentrations fell, with the onset of menstruation, in all cases, coincident to P concentrations of 1.5 ng/ml or less.

LH (Table 5.5.4, Figure 5.5.3)

No significant differences were seen with respect to LH concentrations. Although the median day 0 peak concentration was slightly reduced, the observed difference did not achieve statistical significance.

FSH (Table 5.5.5, Figure 5.5.4)

FSH concentrations in the SLP cycles were indistinguishable from the normal cycle data.

FD (Table 5.5.6, Figure 5.5.5)

Median FD followed a linear course similar to the control cycles. Maximum FD was seen on day 0 when the median FD was 22.0 mm. Only one of the cycles demonstrated luteal cyst formation and this was a small cyst (16mm diameter, P index 89).

### 5.5.3 Comment

The low incidence of SLP (3.4%) would suggest that this phenomenon is an extremely uncommon occurence in women with unexplained infertility. The incidence of cycles with luteal phase length of less than 11 days in fertile women has been shown to lie between 5 and 9% (Lenton et al 1984, Smith et al 1984) and consequently it would appear that this phenomenon is unlikely to be a major contributing factor to the continuing infertility of the couples in whom it is identified. The rigid methodology in the present study, incorporating daily blood sampling in all cycles,

would suggest that the observed incidence of SLP is accurate, since cervical mucus assessments and measurement of BBT, used in some studies, are relatively inaccurate methods of pinpointing the onset of the luteal phase (Templeton et al 1982, Lenton et al 1977).

Sherman et al (1974) defined the short luteal phase in the 4 cycles they studied as having a duration of <10 days. In contrast to the data presented above, they found reduced plasma levels of E2 in the follicular phase with a subnormal peak E2 concentration, together with reduced concentrations of FSH. P concentrations, in their series, were reduced throughout the luteal phase in contrast to the above data where the pattern in the first five days following the LH peak was similar to normal profile. E2 concentrations, in contrast to the present series were found to be sub-normal in the luteal phase.

Smith et al (1983) in a study of 20 cycles with luteal lengths of <12 days found similar E2 concentrations to the present study but, in contrast to the present data, found a number of cycles of apparent short luteal length where P concentrations were high at the time of menstruation. All patients described above menstruated when P concentrations were 1.5 ng/ml or less, so it would appear that none complied with the hypothesis that, in some cases of SLP, the abnormality of luteal length represents endometrial dysfunction manifest as premature menstruation in the presence of normal plasma P concentrations, rather than early demise of the corpus luteum.

Fleming et al (1981) observed subtle abnormalities of PRL secretion, in the periovulatory period, in 4 out of 5 cycles with luteal phases of less than 11 days. PRL was not assayed in the present study and it may be that some of the cycles described may

have had similar profiles. The role of PRL in LPD remains unclear (see chapter 1) and further work is required in this area.

Whether these cycles, although abnormal, were truly infertile is debatable, since pre-ovulatory follicular dynamics, and luteal function in the immediate post-ovulatory period, were normal. It is not clear what the cause of premature luteolysis is in these cycles. Central (hypothalamic or pituitary), ovarian or uterine factors could be involved leading to a disturbance in the balance of luteotrophic and luteolytic factors (Baird 1985). Conception and consequent interaction between the embryo and the corpus luteum might be an important, though as yet ill understood, mechanism whereby infertile cycles might be "rescued" and rendered potentially "fertile". The fact that SLP cycles are seen with similar frequency in fertile and infertile populations (Smith et al 1984) is evidence that the reproductive implications of this phenomenon are not perhaps as serious as have previously been thought.

### 5.5.4 Analysis (Long follicular phase)

The patient and cycle characteristics of the 9 LFP cycles are shown in Table 5.5.7 with the biochemical (plasma E2, P, LH & FSH) and ultrasonic data in Tables 5.5.8 to 5.5.12. The mean, SD, SEM, median and 95% confidence limits are shown and these data are graphically represented, in a similar fashion to that of previous analyses, in figures 5.5.6 to 5.5.10, with the median values plotted against the medians of the normal cycles. Significant differences, in comparison with the controls (Wilcoxon rank sum test), are shown on the relevant tables.

The median age of the LFP patients was 27 years, similar to that of the control cycles (median 26 years). Median follicular phase length (25 days) was, by definition, greater than the controls (14 days, $p < 0.001$) but luteal phase length was similar.

E2 (Table 5.5.8, Figure 5.5.6)

Plasma E2 concentrations were similar, in both the follicular (days -10 to 0) and luteal phases, to the control data. Median peak concentration on day 0 was 220.0 pg/ml. There was a minor deviation from the norm on day +12 but concentrations thereafter were indistinguishable from the controls.

P (Table 5.5.9, Figure 5.5.7)

P concentrations in the early luteal phase, although reduced, did not differ significantly from the control cycles. The median P index was 83.9.

In the late luteal phase (days +11 to +13) the LFP cycles had slightly higher P concentrations than the controls.

LH (Table 5.5.10, Figure 5.5.8)

LH concentrations in the follicular phase were found to be significantly elevated on days -9 to -4, -2 and -1. Peak concentrations (day 0) were normal, and in the luteal phase no deviations from the norm were encountered.

FSH (Table 5.5.11, Figure 5.5.9)

Although tending to the lower end of the normal range, plasma FSH concentrations were not different from the controls throughout these cycles.

FD (Table 5.5.12, Figure 5.5.10)

The follicular phase FD profile was indistinguishable from the controls with median day 0 FD 21.0mm. In 1 of the 9 cycles (11.1%) luteal cyst formation was observed. In this instance the cyst was 32mm diameter, showed no evidence of shrinkage following the LH peak, and was associated with marked reduction in P concentrations in the early luteal phase (P index 29).

## 5.5.5 Comment

The length of the follicular phase has been alluded to in the context of the cycles with high LH concentrations (section 5.3). Of the 9 cycles with LFP patterns, 4 demonstrated high LH profiles, accounting for observed increase in LH concentrations in the group as a whole. FSH concentrations in the group were at the lower end of the normal range and the mechanism for delay in initiation of follicular growth and rise in plasma E2 concentrations in cycles with normal gonadotrophin concentrations remains obscure. Central problems, such as abnormalities in the GnRH pulse regulatory mechanism in the hypothalamus, or ovarian disturbances, such as delay in the expression of appropriate receptors on the granulosa cell surface could be involved. It is possible that circumstances in the luteal phase of the preceding cycle, such as a diminution in gonadotrophin

concentrations, perhaps secondary to high E2 production by the corpus luteum of that cycle, might cause a depletion in the pool of developing follicles reaching the final stages of growth preparatory to the last days of expansion leading to ovulation (Baird et al 1975). As a result follicular recruitment to ovulation might take longer than the normal cycle. Study in successive cycles might have shed some light in this regard.

Balasch et al (1986) observed that deficient luteal function, as assessed through endometrial biopsy, was found in almost 40% of cycles with follicular length in excess of 20 days, four-fifths of whom had normal plasma P concentrations. The authors used the BBT in order to determine the time of ovulation, and it is possible that this may have led to an imprecise assessment of the endometrial specimens obtained. Luteal phase length in their study was not affected by the polongation in the follicular phase, and is in agreement with the observations in the present study. 3 of the 9 (33.3%) cycles were found to demonstrate poor progesterone surge, and one of these cycles demonstrated luteal cyst formation. Thus, although some authors have suggested that fertility bears little relation to follicular phase length (Broom et al 1981, Aksel 1981), the observed reduction in P concentrations would appear to be a manifestation of abnormal luteal function, with impaired fertility, perhaps secondary to a disturbed endometrial environment, a probable consequence of this. However, the fact that the majority of LFP cycles demonstrated normal luteal function, and the group as a whole accounted for only 5.1% of the total unexplained infertile population, would suggest that this form of disturbed ovarian function is of minor importance in the genesis of infertility.

The observation that FD profiles, in all but one case, and follicular phase E2 concentrations were normal in these cycles would suggest that, to a significant degree, these patients' continued infertility is a function of the reduced frequency with which ovulation occurs, as much as the likelihood of any associated disturbance in the hormonal environment.

## 5.5.6 Analysis (short follicular phase)

The patient and cycle characteristics of the SFP cycles are shown in Table 5.5.13 with the biochemical (plasma E2, P, LH & FSH) and ultrasonic data in Tables 5.5.14 to 5.5.18. Since small numbers were involved the mean, SD, SEM, median and ranges are shown rather than the 95% confidence limits. These data are graphically represented, in a similar fashion to that of previous analyses, in figures 7.3.5.11.to 7.3.5.15, with the median values plotted against the medians of the normal cycles. Significant differences, in comparison with the controls (Wilcoxon rank sum test), are shown in the relevant tables.

As with most of the other sub-fertile groups, the age of the SFP patients was greater than the controls (median 32 years, controls 26 years, $p < 0.01$). Follicular phase length, by definition, (median 8 days) and cycle length (median 23.5 days) were significantly reduced (controls 14 days ($p < 0.001$), 29 days ($p < 0.001$)).

E2 (Table 5.5.14, Figure 5.5.11)

Although E2 concentrations were reduced in the luteal phase and peak follicular phase concentrations were seen on day -2, the

differences from the controls did not achieve statistical significance.

P (Table 5.5.15, Figure 5.5.12)

P concentrations in the early luteal phase were lower than the control cycles, but the difference only achieved statistical significance on day +4. The P index was also lower than normal (median 79.0) but this difference was not statistically significant. On days +11 and +13 the concentrations were higher than the controls. 2 of the 6 cycles exhibited a PPS profile.

LH (Table 5.5.16, Figure 5.5.13)

In the follicular phase, LH concentrations tended to be slightly lower than the control cycles with the differences observed achieving significance on days -7, -4 and -3. The LH peak was significantly reduced in the group as a whole (median 37.8 IU/l, controls 73.5 IU/l, $p < 0.001$). In the luteal phase concentrations were normal throughout.

FSH (Table 5.5.17, Figure 5.5.14)

Concentrations of FSH were significantly higher in the luteal phase (+2 to +11) in the SFP cycles. Peak concentrations (day 0), although higher, did not differ significantly from the controls. Follicular phase concentrations were normal.

FD (Table 5.5.18, Figure 5.5.15)

FD's in this small group of patients did not show any differences from normal with median maximum FD, on day 0, 19.0mm. Luteal cyst formation was observed in one cycle (23.5mm, non-shrinker, P index 25).

## 5.5.7 Comment

As with the SLP cycles it is difficult to make definitive conclusions about the nature of the pathophysiological processes, if any, occurring in these cycles. Events in the preceding cycle may have had an important influence on the subsequent biochemical and ultrasonic profiles observed, namely the striking elevation of FSH in the days after the LH peak, in association with reduced E2 concentrations, and relatively normal P concentrations. The principle source of E2 in the luteal phase of the cycle is the theca lutein cells of the corpus luteum (Baird et al 1975, Macnaughton et al 1981) while P derives from the granulosa lutein cells (Carr et al 1981). The elevated FSH concentrations might reflect an attempt at compensation for a pre-determined follicular abnormality resultant in quantitative and/or qualitative alteration in the balance of these two types of cell. No evidence for this exists in the literature. Alternatively, high FSH concentrations may reflect reduced luteal phase inhibin concentrations, consequent upon follicular abnormality.

Despite the brevity of the follicular phase, E2, FSH and FD profiles were normal. LH concentrations, however, were lower and it may be that expression of receptors in the theca layer of these follicles was impaired. Granulosa cell receptor expression, however,

may have been normal and, as a result, responsive to the mid-cycle LH surge, which in the group as a whole was sub-normal. The abnormality in LH secretion could reflect a central disturbance in the pulsatile release of GnRH. Further work in this area would be a fruitful avenue of research into the understanding of the pathophysiology of these subtle abnormalities of ovarian function.

In summary, cycle phase length abnormalities are rare in patients with unexplained infertility, only accounting for between 5 and 10% of the patients in this study. Disturbances in ovarian function may be encountered in these sub-groups but the majority of cycles are found to elaborate almost normal biochemical and ultrasonic profiles. Whether such "abnormalities" invoke a reduction in fertility potential is uncertain, though undoubtedly in individual cycles profound deviations from the normal can be seen, which are likely, in these cases, to be a major influence on the chances for successful conception in that particular cycle. Since only a small prportion of patients with unexplained infertility demonstrate such phase length abnormalities, it is probably unnecessary, unless the phenomena recur, to treat these patients on the information gained in a single cycle of investigation.

# CHAPTER 6 CYCLE TO CYCLE VARIATION IN OVARIAN FUNCTION

## 6.1 Introduction

A wealth of data now exists in the literature describing abnormalities of ovarian function in patients with infertility and claims are made that such variations from normal are causal factors of the patients' infertility. Genuine though these observations may be, few studies address the crucially important question as to whether any deviation, usually observed in only one cycle of study, is a recurrent, or an isolated phenomenon.

With respect to the diagnosis of the LPD in infertile populations, Jones (1976) demonstrated that to be of clinical significance histologic evidence for luteal insufficiency must be found consistently and repetitively. Employing such constraints she found an incidence of 3.5% in her infertile population, contrasting with the data of Israel (1972) who found, through employing endometrial biopsy in a single cycle, a much higher incidence of 19%. That such abnormalities do in certain patients recur with high frequency is supported by data from patients presenting with a history of recurrent abortion (Jones & Delfs 1951, Tho et al 1979) where therapeutic success has been obtained through administration of exogenous progestogens to supplement endogenous P production. Others (Soules et al 1977, Andrews 1979) have also emphasised the need for more than one endometrial biopsy to define the deficient luteal phase, while Shepard et al (1977) showed that the finding of a luteal abnormality in a single cycle had little prognostic importance for their study population's future fertility. Others (Aksel 1980, Wentz 1982) would agree with this observation. Balasch et al (1985), having

noted a highly significant tendency in their patients for change in endometrial assessment from cycle to cycle, have proposed that three samples of endometrium are required to confirm the diagnosis of luteal phase insufficiency.

Conversely, there is a need in the subfertile population to confirm the regularity of normality, as much as abnormality (Moghissi & Wallach 1983), since normal ovarian function may be an isolated occurence in some patients rather than the norm.

Sherman and Korenman (1974a) in a study on obese patients with prolonged cycles found abnormalities of both FSH and P production and, in finding the deficient luteal phase to recur in two of the ten patients studied, observed that these cycles might not be characteristic of the patients' entire menstrual history. In a parallel study the authors (1974b) found the short luteal phase, associated with diminished E2 in the follicular phase, to recur in 3 and 4 cycles within a twelve month period respectively in two out of a study group of four volunteers. All such cycles were of normal duration. The volunteers were young nursing students, a group, through stressful working conditions, at a potentially high risk of endocrine disturbance (Editorial 1982), and such data need not necessarily apply to infertile populations.

Where more than one test is applied to assess luteal function, difficulties can arise for, as shown by Annos et al (1980), use of the basal body temperature chart, plasma P and endometrial biopsy together may only be in agreement in one-third of cases casting doubt on the reliability of each individual test in diagnosing the abnormality. Others (Rosenfeld and Garcia 1976) are less sceptical

about these tests and claim a greater than 90% correlation of P measurement and endometrial biopsy in detection of ovulation. As Shangold et al (1983) observed there is a need, in the case of the LPD, to standardise criteria for diagnosis in order that incidences and recurrence rates of the abnormality can be studied accurately. Hull et al (1982) in attempting to define an acceptable serum P level compatible with ovulation in a large population undergoing basic infertility screening reported consistent results from cycle to cycle, though did not specify the number of patients this observation referred to. Their reported cumulative conception rate of 10% per cycle, consistent over two years, does suggest that, in most cases, the assessment of luteal function in the study cycle was truly representative of cyclical ovarian steroidogenesis.

The LUF has aroused a great deal of interest over the past few years. Ultrasound might be expected to provide a convenient and simple way of studying the persistence of LUF. Kerin et al (1983) found that, in 66 patients studied over 183 cycles, 8 women in a total of 9 cycles demonstrated LUF, as the authors defined it, using ultrasound as the method of investigation. These 8 women were re-examined over a total of 35 cycles and in only 1, a patient undergoing her fourth study cycle, was the LUF found to recur. Liukkonen et al (1984) found LUF in their study of a small number of patients undergoing ultrasonic evaluation over 3 cycles to occur exclusively in only 34% of the group. Hamilton et al (1985) in a large study found 27 patients demonstrating the LUF phenomenon, almost half of whom were undergoing induction of ovulation, mostly with clomiphene.They found that LUF did not recur in the patients with unexplained infertility but only in those with pelvic inflammatory disease or those undergoing induction of ovulation.

Precise figures for recurrence were not given. These data, together with the laparoscopic observations of Vanrell et al (1982), lend further weight to the thesis that one cyclical event is unlikely to be representative of all cycles in a patient, though Devroey et al (1983), using biochemical analyses of peritoneal fluid collected by culdocentesis, have taken the opposing view that in the case of LUF the abnormality tends to be repetitive.

To examine this question further, the combined resources of sequential ultrasound and serial biochemistry were employed. Spontaneously cycling women with unexplained infertility were studied over two intensively monitored cycles, in an attempt to ascertain the reproducibility of observed ovarian function.

## 6.2 Materials and Methods

The study population consisted of 26 patients with unexplained infertility of at least 3 years duration, as defined in chapter 4. All underwent detailed investigation over two complete cycles in a similar manner to that described earlier (section 4.2).

These patients had demonstrated an abnormality in their first cycle of investigation, and are included in the main study's analyses (Chapter 5). The study group comprised 26.5% of the 98 cycles, in 175 patients with unexplained infertility, in which ovarian function was observed to deviate from the normal control profiles described in chapter 2.

## Biochemistry

Areviously described (chapter 2) the analysis was orientated around the day of the LH peak and an assessment of the pituitary and ovarian hormone profiles made through comparison with normal controls. Particular attention was paid to events in the periovulatory period. To quantify follicular function at this time an E2 index was used, being the average of the sum of the E2 concentrations on days -2, -1, 0 and +1. The P indices (days +2 to +6) were also compared for the two cycles to evaluate early luteal function.

## Ultrasound

The day of the LH peak was again used to orientate analysis. Maximum FD was compared together with the nature of the ultrasonic profile as a whole from one cycle to the next. The relationship of the observation of follicular rupture to the gonadotrophin and ovarian steroid patterns was assessed and any differences from one month to the next noted.

## Statistics

Statistical analyses using Student's t-test (paired samples), Pearson's correlation, non-parametric methods (Wilcoxon rank sum test) and Chi-square test for frequencies were employed where appropriate.

## 6.3 Results

The age of the patients was in the range 21 to 39 years (median 30.5 years) and their median duration of infertility was 4 years (range 3 to 10 years).

The mean time span between the cycles of investigation was 3.6 months (SD 2.4 months) with a median value of 3 months (range 1 to 9 months). All patients therefore completed their evaluation within 1 year of the initial entry to the study (Table 6.1).

Table 6.2 shows the paired cycle characteristics of the patients under study. The denominators vary for the following reasons :

Three of the 26 patients failed to ovulate in the first study cycle. It is inappropriate therefore to consider their paired cycles in assessment of follicular and luteal phase duration. The remaining 23 cycles provide the data for comparison.

2 patients conceived during the second cycle and a calculation of luteal phase length, as with the 3 anovulatory patients, is impossible. 21 paired cycles are therefore compared for luteal phase length.

The patients who conceived are also excuded from the comparison of overall cycle length, but the anovulatory patients are included. This comparison comprises data from 24 cycles.

In the case of these 3 anovulatory patients neither an E2 nor a P index could be calculated and so the denominator for these paired

data is also 23 (Table 6.3).

Table 6.2 also shows the phase length data for the study cycles. As can be seen the figures are broadly similar with a median total cycle length of 28 days in both cycles. The minor differences observed did not reach statistical significance (Student's t-test : paired samples).

Table 6.3 shows the data on biochemical indices for the study cycles and again although minor differences were noted these were not significant. The ranges of values were similar in both groups.

Biochemical profiles

Examination of the biochemical profiles compared to normal data (Table 6.4), revealed that, of the 26 patients studied, 25 (96.2%) had an abnormality in at least 1 cycle. 14 (53.8%) revealed abnormal function in both cycles while 11 (47.2%) showed this in their first cycle only. The remaining patient exhibited normal biochemical profiles throughout both cycles.

Table 6.5 shows the nature of the biochemical abnormalities, cycle by cycle. The commonest observed abnormality was that of deficient luteal function, manifest as diminished P concentrations in the early post-ovulatory period. This phenomenon of PPS (section 5.2) was seen in 17 (68.0%) of the 25 abnormal first cycles. In the majority of cases P levels attained normal values by the mid-luteal phase (PPS-N), but in some P concentrations remained low throughout the luteal phase (PPS-S). Of the 14 abnormal second cycles, 10 (71.4%) involved PPS, a similar proportion to that found in the first

cycle. Other abnormalities observed included PFM (section 5.4), inappropriately high levels of LH (section 5.3) and anovulation. Other deviations from the normal control profiles, including the SLP, LFP, SFP (section 5.5), transient hyperprolactinaemia (PRL), and plateaued E2 levels in the periovulatory period i.e. no convincing E2 peak identifiable, were seen as isolated occurrences in either the first or second cycles.

Table 6.6 shows the type of biochemical abnormality in the 14 cycles where dual cycle abnormalities were revealed. As can be seen not all biochemical abnormalities were mutually exclusive.

These data provide insight into the risk of recurrence specific to each abnormality. Table 6.7 summarises this for the main abnormality sub-groups.

17 patients demonstrated PPS in the first cycle of whom 9 (52.9%) demonstrated abnormal ovarian function in their repeat cycle. In 8 cases, the PPS profile was repeated.

Of the 7 cycles demonstrating PFM, 5 (71.4%) elaborated abnormal biochemical profiles again, 4 of which repeated the PFM pattern.

3 (60%) of the 5 patients with the high LH profile and 2 of the 3 anovulatory patients demonstrated an abnormal biochemical profile in cycle 2 and in all cases the defect was similar to that of the preliminary cycle.

Ultrasonic profiles

Table 6.8 shows that of the 26 patients studied only 6 (23.1%) revealed normal ovarian function in both cycles. 9 (52.9%) of the 17 patients with abnormal ultrasonic profiles in the first cycle had normal patterns in the next. Where the first investigation cycle had demonstrated normal function (9 cycles), in only 3 cases was the second cycle found to be abnormal. Consistent normality or abnormality was found in 14 patients, amounting to 53.8% of the series.

Luteal cyst formation (section 5.1) was the commonest abnormality seen (table 6.9) comprising 10 of the 17 abnormalities in the first cycle and 6 of the 11 in the second. Poor follicular development (PFD) (section 5.4) was the next most common, followed by anovulation. A variety of other deviations from the control cycles' profiles were seen including multiple follicular development with associated twin ovulation, and development of a non-functional follicle prior to normal follicular development with normal biochemical function.

The ultrasonic abnormalities seen in the 8 patients with dual cycle problems are listed in table 6.10. These data are summarised in Table 6.11. Only 5 of the 10 patients (50%) with luteal cysts in the first cycle had atypical ultrasonic profiles in the next. 3 of these were again luteal cysts representing a 30.0% chance that the abnormality would be the same as that seen in the first cycle. One of the 3 patients who revealed PFD and 2 of the 3 anovulatory patients in cycle 1, demonstrated a second cycle abnormality, in both cases, the same ultrasonic phenomenon in the second cycle.

Table 6.12 shows the combined data of recurrence patterns for both ultrasonic and biochemical abnormalities. 17 of the patients in their first cycle had an ultrasonic abnormality and, although fewer revealed an abnormal profile in the second cycle, the difference was not significant. Biochemical abnormalities were found in nearly all the patients' first cycles but significantly less commonly in the second cycles (Chi-square = 10.3, $p < 0.001$).

16 patients in all experienced abnormalities in both cycles. Eight had U/S evidence of abnormal ovarian function in both, of whom 7 demonstrated dual biochemical disturbance as well. 14 patients had biochemical disturbances in both cycles. One patient in her first cycle exhibited deficient luteal P production despite a normal follicular growth pattern. In the second cycle she formed a luteal cyst but on this occasion her biochemical profile was normal (Table 6.13).

10 patients had an ultrasound scan performed on day 0 in both cycles and, as table 6.14 shows, there was no statistical difference observed between the two paired sets of data ($t = 0.32$, $p = 0.76$), though FD's did not correlate well from one cycle to the next ($r = 0.45$, $p = 0.19$).

16 patients developed follicles on the same side in both cycles, 11 on the right and 5 on the left. Of the remainder 4 grew their initial follicle on the right while 6 commenced on the left. The incidences of all four possible combinations are shown in table 6.15. There were no significant differences.

## 6.4 Discussion

This study represents a prospective analysis of ovarian function, using a protocol of intensive ultrasonic and biochemical surveillance over two cycles, closely related in time, on patients with UI. All of them, by definition, were cycling regularly without stimulation.

The data show that cycle phase length was consistent from cycle to cycle in these patients. The methodolgy of the study however permitted more detailed evaluation of cycle to cycle consistency of ovarian function. It is interesting that FD on day 0 in the paired cycles, although statistically similar did not corrrelate well from one cycle to the next, suggesting that the maximum FD in one cycle cannot be relied upon to be predictive of the periovulatory FD in future cycles.

All 26 patients showed an ultrasonic or biochemical variation from normal in the first cycle of study. They represent 26.5% of the patients demonstrating deviant ovarian function in the whole study group and might have been expected to demonstrate a high rate of abnormality in a second cycle of investigation. Only 14 (53.8%) of the series elaborated consecutive biochemically abnormal cycles and 8 (30.8%) consecutive U/S deviations. Combining U/S and biochemical data, 16 (61.5%) of the 26 patients exhibited aberrant ovarian function in the second cycle. This incidence is similar to the overall incidence of abnormality in the main study (Chapter 5) where 98 (56.0%) of 175 patients exhibited abnormal profiles (Chi-square = 0.10, $p = 0.75$). These data suggest that there is a consistency of chance of deviation from normal in patients with UI from cycle to

cycle. Data are required from a population of patients with UI who demonstrate normal ovarian function in a preliminary cycle, since their chance of deviant ovarian function may be less. This is unlikely to be the case since the main study population, selected only on the basis of their history of UI, was large (175 cycles), and consequently is unlikely to represent a biased group, at greater risk of repetitive abnormality.

The difference in incidences from one cycle to the next may be due to the sporadic nature of the abnormalities observed, but, as Moghissi and Wallach (1983) suggested, it is possible that the stress involved in attending for such investigations was less in the second cycle where patients had evolved a familiarity with the protocol of study. There is a need to carry out studies on the fertile population over a series of cycles to determine a meaningful expectation of normal or abnormal function, rather than rely on observations of doubtful significance in one cycle in isolation (Vanrell et al 1982).

Examination of the paired cycle patterns, in respect of specific abnormalities seen in the preliminary cycle, revealed similar risks of recidivism in the main sub-groups identified. 50% of the luteal cyst formers, 52.9% of the PPS and 60% of the high LH group elaborated abnormal patterns in the second cycle. It was interesting that not all repeated aberrant profiles were the same as in the preliminary cycles. Two of the 5 luteal cyst formers exhibited a different pattern of abnormality, but in 8 of the 9 cycles with PPS and 4 of the 5 cycles with PFM, the phenomena were repeated.

Reproducibility of ovarian function cannot be determined by reference to U/S profiles alone since, as the data from the present

study indicate, endocrine abnormalities may be found in the presence of a normal follicular growth profile. Polan et al (1982) found in a small study of 5 patients with ultrasonically observed abnormal ovarian function in a preliminary cycle that in 4 cases the next menstrual cycle was entirely normal. Had intensive biochemical analyses been performed on these cycles subtle abnormalities of ovarian function might have been found. Accurate evaluation of ovarian function must take both modes of investigation in to consideration.

Shepard et al (1977) observed that the finding of a single abnormality in an investigation cycle may have little prognostic importance for fertility. In the present study, two patients, both of whom had abnormal ovarian function in their first cycle, conceived in their second cycle. The first developed a luteal cyst in her first cycle, 16mm in diameter between days +5 and +8, associated with a P index of 87 and a short luteal phase of 11 days. She was the only patient who demonstrated a short luteal phase (SLP) in this series. The relevance of SLP to infertility remains controversial. Smith et al (1984) found a 9% incidence of SLP in a study of 95 patients with unexplained infertility but found this to be no different from the incidence in a similar number of healthy controls. It was suggested that in many cases of SLP the manifestation was due to premature menstrual bleeding in the face of normal P levels rather than a deficiency of P production by the corpus luteum. Although this patient's P index was normal and the maximum P value 14.0 ng/m, from day +7 onwards her levels dropped dramatically suggesting premature luteolysis. She exhibited no other biochemical clue as to why this might have occurred. In the cycle of conception two follicles were seen to develop and rupture, with normal biochemistry. A single fetus

developed and the pregnancy progressed uneventfully.

The second conception occurred in a patient who had transiently elevated PRL levels in her first cycle as an isolated abnormality, but in the second cycle, despite a normal follicular phase, exhibited PPS-N profile with a P index of 75. She unfortunately aborted at 7 weeks gestation. Histology of the aborted material confirmed the presence of chorionic villi. It is uncertain whether the cause of this patient's miscarriage was corpus luteum failure. She did not receive P supplementation which has been shown to have some possible therapeutic value in patients who have a history of recurrent abortion (Tho et al 1979) and perhaps this might have been helpful in her case. The material was not sent for genetic analysis which might have clarified the nature of the miscarriage.

Of the 17 patients with an ultrasonic abnormality in their first cycle, 8 (47.1%) exhibited an abnormality in the second cycle. In the case of luteal cyst formation, 6 of the 10 patients demonstrated a non-shrinkage pattern suggestive of LUF (section 5.1). Of these, only 1 (16.7%) demonstrated a LUF pattern in the second cycle. This figure, albeit based on small numbers, is lower than that quoted by Liukkonen et al (1984) but rather higher than the findings of Kerin et al (1983). Hamilton et al (1985) found the LUF to recur only in patients undergoing induction of ovulation or having pelvic inflammatory disease (PID), criteria for exclusion in the present study. Of the 4 patients demonstrating the cystic CL pattern of luteal cyst formation (section 5.1) in the first cycle, only 1 did so in the subsequent cycle.

Over half of the cases of PPS in cycle 1 were found to have a

biochemical abnormality in cycle 2, most of which were similar to that of the previous cycle. The data would suggest that infertile patients have a tendency for abnormal ovarian function, greater probably than in the general population, the exact nature of which may vary from cycle to cycle dependent on a variety of factors as yet not understood. Perhaps differences relate to receptor status within the follicle or pulsatility patterns of hypothalamic hormones in the early follicular phase or at the time of the LH surge. It is interesting that the more severe form of PPS recurred exclusively to the patients who had the abnormality in the first cycle, though one patient in cycle 2 with PPS-S had the milder P deficiency (PPS-N) in the first cycle.

Anovulatory cycles are unusual in patients with normal menstrual rhythm. It has been suggested (Aksel et al 1976, Aksel 1980) that high PRL levels may be implicated in LPD and that the so-called aluteal cycle may represent a severe form of the same phenomenon. None of the patients with anovulation had abnormalities of PRL secretion. Annos et al (1980) likewise found LPD only to be rarely associated with elevations in PRL.

In clinical terms, the inferences to be drawn from this study are that, although patients with prolonged UI may often exhibit abnormal ovarian function, aberration from normal is not necessarily consistent. Continued infertility is probably a function of the frequency with which such abnormalities occur, and since normal ovarian function can occur in these patients it is not surprising that some conceive spontaneously. (Hull et al 1985). To base therapeutic decisions on the information gained in a single cycle of investigation is unjustified, and in deciding on therapeutic

strategies, an approach which attempts to override all potential deviations from normal would best be employed. Techniques such as IVF and GIFT have already been used successfully in UI, and the approach of pituitary downregulation with GnRH agonists and subsequent ovulation induction with exogenous gonadotrophins has similar potential (Fleming et al 1982).

# CHAPTER 7 PERITONEAL FLUID STUDY

## 7.1 Introduction

In as many as 10% of cases of female subfertility abnormalities of the luteal phase are implicated. It has also been shown through studies using biochemistry, laparoscopy and ultrasound that in cases of unexplained infertilitythere may be an association with abnormalities of the luteal phase.

In 1978, using appropriately timed laparoscopy, Koninckx et al found that in 58% of patients with unexplained infertility, when the corpus luteum was examined carefully, no ovulation stigma could be found. Marik and Hulka (1978) also studied a similar population with laparoscopy and found a stigmatised corpus luteum in only 39% of their patients implying that luteinisation of the Graafian follicle without rupture, and with consequent entrapment of the ovum, might provide an explanation for many couples' failure to conceive.

Biochemical characterisation of P profiles in the luteal phase has also been shown to reveal abnormalities which conventional single sample analysis of luteal function would fail to elucidate. Thus Koninckx' group suggested that their luteinised unruptured follicle (LUF) patients demonstrated biochemical evidence of LPD both in terms of duration and overall quantity of P secretion similar to abnormalities demonstrated in patients with endometriosis (Brosens et al 1978). Others (Fleming et al 1981) have shown that patients with unexplained infertility reveal subtle abnormalities of reproductive function when

subjected to intensive cycle monitoring through daily analysis of of pituitary and ovarian hormones throughout the menstrual cycle. Commonest of these is deficient P production in the early luteal phase found in over 36% of the patients studied.

Diagnostic U/S has provided a further tool for investigation of unexplained infertility and several workers have described retained follicular cysts observed throughout the luteal phase both in unstimulated and stimulated cycles (Coulam et al 1982, Coutts et al 1982, Liukkonen et al 1984). It has been proposed that such phenomena might represent the LUF syndrome.

Peritoneal fluid (PF) is present in varying quantity throughout the menstrual cycle and Maathius, Van Look & Michie (1978) suggested that changes in the PF volume during the menstrual cycle relate to the cyclical activity of the ovaries. They found that the PF E2 and P concentrations were markedly increased following follicular rupture and that this may, in part, be due to release of follicular fluid containing high concentrations of these hormones. PF steroid levels were also much higher than the equivalent plasma steroid levels. Koninckx et al confirmed these findings (1980 JCEM, 1980 BJOGa & b) and went on to describe differences in the constituents of PF between cycles where an ovulation stigma was seen on the corpus luteum at laparoscopy and the 43% of their study cycles where no stigma could be identified. This led to their hypothesis that steroid hormone assays on PF could discriminate between the normal cycle and the LUF cycle. Others (Lesorgen et al 1984) have also suggested that this more objective evaluation of ovulation, rather than the more subjective assessment of stigma formation,

provides a helpful method of diagnosis of LUF.

Based on these reports other workers have studied the recurrence of these phenomena, avoiding the use of laparoscopy, either through measurement of peritoneal fluid steroids obtained at culdocentesis (Devroey et al 1983) or through ovarian ultrasonography in repeated cycles (Kerin et al 1983, Liukkonen et al 1984).

The significance of these phenomena is not yet clear in relation to unexplained infertility or endometriosis. The processes of of ovulation and corpus luteum formation and function have therefore been examined further using the combined resources of sequential plasma biochemistry, ovarian U/S and luteal phase laparoscopy with peritoneal fluid aspiration. This detailed study would usually be difficult, in that most patients being referred for detailed cycle analysis using ovarian U/S will already have undergone diagnostic laparoscopy. Thus, in offering such detailed investigation to patients with a likely diagnosis of unexplained infertility at an early stage in the couples' infertility investigations, a unique opportunity was presented to relate the findings from four different avenues of study.

## 7.2 Materials and Methods

The plan of investigation was for patients with potentially unexplained infertility to attend for blood sampling throughout an entire menstrual cycle. Ovarian U/S examinations were performed frequently from about the eighth day of the cycle onwards. Once a follicle greater than 12mm diameter was observed,

scans were performed daily until the characteristic shrinkage and infilling of the follicle as it became a corpus luteum was observed. Thereafter scans were performed every forty-eight hours until the day of laparoscopy. A NE4201 static scanner with a 3.5MHz probe was employed using the full bladder technique to visualise the ovaries.

Laparoscopy was timed to coincide with the early/mid luteal phase as determined by the U/S data. At operation the ovaries were thoroughly inspected to confirm the presence of the CL with or without stigma formation. Endometriosis, if present, was noted and classified according to the criteria of the American Fertility Society. Hydrotubation was performed and peritoneal fluid obtained by aspiration.

Twenty-four patients were studied, all of whom had normal menstrual rhythm and normal initial biochemical test results - plasma LH, FSH, Prolactin, testosterone and TSH measurements, together with a mid-luteal P concentration of at least 10ng/ml, suggestive of ovulation. They had nothing in their past medical or surgical history to suggest the likelihood of pelvic disease. The couples' only abnormality was a failure to conceive despite unprotected intercourse for a minimum of two years. All patients gave informed consent to undergo investigation and the study carried hospital ethical committee approval.

The daily venous blood samples were centrifuged and the plasmas stored at -20 C until analysis was carried out. Sensitive, specific and precise radioimmunoassays were performed (Coutts et al 1981) to determine the concentrations of FSH, LH,

PRL, E2 and P. Each patient's samples for the whole cycle were assayed in the same batch, as described in Chapter 2.

PF samples were centrifuged and the supernatants stored at -20 C until assays for E2 and P were performed.

Statistical analyses were carried out using linear regression analysis and the Wilcoxon rank sum test, where appropriate.

## 7.3 Results

Two of the twenty-four women were found to have extensive pelvic adhesions at laparoscopy due to inflammatory disease with resultant tubal occlusion and these are therefore excluded from further analysis. In the remaining twenty-two women the diagnosis of unexplained infertility was sustained and the data reported hereafter relate to this group of patients.

The age range of the patients was from 22 to 40 years (median 30 years) and the median duration of infertility 3 years (range 2 to 8 years). Laparoscopies were performed between days +2 and +12 of the cycle with reference to the day of the preceding LH peak (Day 0).

### Plasma biochemistry and ultrasonic profiles.

These are summarised in table 7.1.

In 16 cycles (72.7%) the pattern of ovarian function as

assessed by U/S and sequential blood sampling was normal, compared with the established normal cycle ranges (Chapter 2). All of these plus the remaining 6 cycles showed growth of a single dominant follicle, a classical mid-cycle surge of LH and rise of plasma P concentrations subsequently.

The 6 cycles where an abnormality was found are summarised in table 7.2.

All patients exhibited shrinkage of the dominant follicle following the LH surge but in one was the cystic nature of the follicle maintained during the luteal phase. Her biochemical profiles were normal. 2 patients showed abnormal ultrasonic profiles where the maximum pre-ovulatory FD was less than the lower 99.9% confidence limit of the mean of the control data (<17.1mm). One of these exhibited a deficient luteal phase P profile (PPS-S) whilst the other was biochemically normal. One patient with normal biochemistry had a large follicular growth pattern, with maximum FD more than two SD's above the control mean. One patient with an abnormal biochemical profile (PPS-N) had a normal ultrasound profile and one patient with normal biochemistry profiles had an apparently inactive contralateral ovarian cyst as well as the growing follicle.

Laparoscopy observations

At laparoscopy, a "corpus luteum" was seen in all patients with a definitive punctum identifiable in sixteen cases (72.7%) - the "punctum" group. In three cases (13.6%) there was equivocal evidence of punctum formation and in the remaining three patients

(13.6%) no stigma of ovulation could be identified. These were classified as luteinised unruptured follicles (LUF).

Ten patients were found to have endometriosis, but in all cases this was classified as mild disease. Areas involved included the uterosacral ligaments, the broad ligaments and the ovaries. In none was there any involvement of the fallopian tubes. Two of the LUF patients (66.6%) had endometriosis while 8 of the punctum group (50%) were affected.

The laparoscopy procedures were concentrated in the week following ovulation but extended to day +12 as a result of difficulties with theatre schedules (table 7.3). Throughout the full range of laparoscopy timings it was possible to define ovulation puncta. The LUF patients underwent laparoscopy on days +5, +6 and +9. Most of the "punctum" group had undergone laparoscopy by day +8, but in one patient definite stigma of ovulation was observed at laparoscopy on day +12.

Peritoneal fluid (PF) steroids

Peritoneal fluid was obtained in all cases. The amount of fluid available for collection from the Pouch of Douglas is influenced by the presence of loops of bowel or omentum in the pelvis and the degree of Trendelenberg tilt to which the patient is subjected. In view of this it is unlikely that the volume of PF aspirated is truly representative of the total amount of fluid present and consequently these volumes are not reported. It is assumed that the hormones measured are evenly distributed throughout the peritoneal fluid.

There was a wide range of PFE2 and PFP concentrations but only with PFP was a significant trend apparent in relation to timing of sampling following the LH peak (figures 7.1 & 7.2). This was more apparent after logarithmic transformation of the PFP data (figure 7.3). There was a significant correlation between the steroid levels in individual patients ($r = 0.816$; $p < 0.001$) (figure 7.4).

Plasma levels bore no relation to PF levels of the ovarian steroids (figures 7.5 & 7.6) ($r = 0.135$ & $0.297$). There was, however, a strong correlation between the PF : plasma ratios of E2 and P for individual patients (figure 7.7) ($r = 0.783$; $p < 0.001$). The P and E2 ratios correlated significantly with the timing of laparoscopy, though this was closer in relation to the P ratio than the E2 ratio (figures 7.8 & 7.9) ($r = 0.577$, $p < 0.01$; $r = 0.518$, $p < 0.05$).

There was considerable overlap between the punctum group and the LUF group in the range of PFE2 and PFP levels (table 7.4) with the values in the LUF group being in the lower part of the range for the punctum group. Where a punctum had been visualised the PF : plasma ratios of E2 and P tended to be higher than those seen in the LUF group but again considerable overlap was observed between the two groups. The differences observed did not achieve statistical significance (Wilcoxon Rank Sum Test).

Table 7.5 shows the PF steroid levels and PF:plasma steroid ratios in the 10 patients with signs of endometriosis, and the remaining 12 patients where no evidence of endometriosis could be

seen. Ranges of steroid values in both groups overlapped considerably with both PFE2 and PFP levels in the "endometriosis" group being mostly in the lower part of the range for the "no endometriosis" group. Steroid ratios in the "endometriosis" group were also lower than in the "no endometriosis" group, but the differences did not achieve statistical significance (Wilcoxon Rank Sum Test).

There was a stronger correlation between the PF steroid levels in individual patients in the "endometriosis" group ($r = 0.855$, $p < 0.001$) than in the "no endometriosis" group ($r = 0.799$, $p < 0.01$). Similarly steroid ratios were more closely correlated in individual patients in the "endometriosis" group ($r = 0.911$, $p < 0.001$) than in the "no endometriosis" group ($r = 0.739$, $p < 0.01$).

Since undergoing laparoscopy, six of the twenty-two patients have conceived (27.3%), two of whom have done so twice (table 7.6). One of these eight pregnancies resulted in a spontaneous abortion, the others all being delivered safely of healthy babies. These six women had a duration of infertility at the time of their laparoscopy in the range 24-39 months (median 32 months). These patients accounted for two of the ten cases with endometriosis (20%), four of the twelve without (33.3%), four of the sixteen cases with a punctum identified on the corpus luteum (25%), one of the three LUF patients (33.3%) and one of the three patients where there was equivocal evidence of punctum formation (33.3%).

In only one patient who subsequently conceived was their any

demonstrable biochemical abnormality during the study cycle. This was manifest as a subnormal plasma P rise in the early luteal phase (days +1 to +5) but subsequently normal progesterone production.

Ultrasonic profiles in all the patients who subsequently conceived were normal (table 7.6).

The patient who exhibited the greatest cycle abnormality had a dominant follicle 15.5mm diameter on day -1 (more than two standard deviations below the normal mean) and developed two small cysts in the early luteal phase. The luteal phase plasma P rise was markedly subnormal (P index 35) and P levels remained deficient throughout the luteal phase. The laparoscopic findings, on day +2 were unusual. The ovary contained a corpus luteum with a punctum at the lower pole, an endometriotic plaque centrally and a 1cm diameter cyst at the upper pole, aspiration of which produced 0.5ml of fluid. Aspiration of the corpus luteum which had been cystic on ultrasound on day +1 produced 0.3ml of fluid. The patient ovulated from the left ovary in this cycle but, as ultrasound had shown, had ovulated from the right side in the previous cycle. The steroid concentrations are shown in table 7.7. It is possible that the deficient P production after day +2 related to disturbance of the corpus luteum by aspiration or possibly the effect of general anaesthaesia (Soules et al 1980).

## 7.4 Discussion

The present literature on the abnormal luteal phase presents a confusing picture in terms of incidence, recurrence and

significance for fertility. This prospective study has confined itself to the study of patients with unexplained infertility, a group which is often mentioned in the literature in association with abnormalities of luteal function and more specifically the LUF phenomenon. Most previous studies in this area have related to mixed infertility groups.

In this series of patients, 72.7% of the population displayed normal ovarian function as determined by plasma biochemistry and ovarian U/S. The 13.6% incidence of LUF is similar to the low, one in six, incidence found by Kerin et al (1983) in the small group of patients with unexplained infertility in their study. Koninckx et al (1978) found a much higher incidence of LUF (41.6%) in the 32 patients they studied with unexplained infertility. This compared with the 93.8% incidence of normal corpus luteum and stigma formation in their "explained" infertile group.

The three examples of LUF diagnosed laparoscopically showed no unusual follicular growth patterns and follicular shrinkage and in-filling was observed in all cases. The ultrasonic equipment used was of a high quality with excellent resolution at the depth of field required and clear pictures of the ovaries were obtained. In terms of the ultrasonic detection of LUF these must be regarded as false negative results. No clear definition of the LUF syndrome exists using ultrasound. Kerin et al (1983) studying unstimulated cycles suggested the continued observation of the dominant follicle two days or more after the LH peak was diagnostic. Using these criteria a varied population of LUF's was revealed, some with diameters less than the "ovulatory" FD and

others with diameters greater than the "ovulatory" FD. Gibbons et al (1984) used a similar definition in studying a mixed population of both unstimulated and stimulated patients. Coulam et al (1982) described the ultrasonic development of intrafollicular echoes with failure of follicular shrinkage in stimulated cycles in four patients and suggested that this might represent the LUF syndrome. Some of the LUF's described expanded and reached quite sizeable dimensions. Liukkonen et al (1984) described the LUF phenomenon as the persistence of the dominant follicle following development of intrafollicular echoes but without ensuing shrinkage. Thus defined, in their unexplained infertility population of 37 patients, a 57% incidence of LUF was suspected. Laparoscopy was performed on twenty-two patients whose ultrasound profiles suggested the LUF phenomenon and in eighteen of these no ovulation stigma was found. Thus there were four false positive diagnoses of LUF using ultrasound and no false negatives. Biochemical data on follicular function were lacking in these two studies. The present study's failure to detect LUF using ultrasound in all the three cases diagnosed at laparoscopy may be due to the LUF structures having intrafollicular contents of sufficient density to mimic the natural processes of luteinisation observed in the normal cycle. Thus it would appear that while ultrasound would seem to be an attractive proposition for the study of the incidence and recurrence of the LUF syndrome its findings should be interpreted with caution in view of the possibility of false negatives.

Recent work also suggests that the ultrasonic observation of follicular shrinkage both in unstimulated (Craft et al 1980) and stimulated cycles (Stanger & Yovich 1984) need not necessarily

equate with ovum release. The incidence of retained oocytes in stimulated cycles may be as high as 60%.

It is disappointing that no ultrasonically observed luteal cysts were observed in this study and thus it is not possible to address the question as to whether such phenomena represent the LUF syndrome.

Caution is also appropriate in the use of PF steroid levels in the diagnosis of LUF without laparoscopy. Following ovulation PFE2 and PFP concentrations rise rapidly (Bernardus et al 1983, Koninckx et al 1980a, Koninckx et al 1980b) to levels where the PF:plasma concentration ratios of these hormones are high (Lesorgen et al 1984) particularly in the early luteal phase (Donnez, Langerock & Thomas 1982). The source of this fluid in part relates to spillage of intra-follicular fluid, rich in steroids (Mcnatty et al 1975, Zorn et al 1982, Loumaye, Donnez & Thomas 1985), and also to subsequent alterations in ovarian capillary permeability (Koninckx et al 1980a&b, Donnez et al 1982). In the LUF syndrome, it has been suggested that PF and plasma steroid concentrations tend to be similar. However, a very wide range of of PF steroid concentrations occur in women who exhibit ovulation stigmata. In this study the steroid ratios tended to be higher when a punctum was observed as compared with the small group of LUF patients, but there was considerable overlap between the two groups. Lesorgen et al (1984) suggested that biochemistry alone might discriminate between these two groups of patients but their criteria of diagnosis of stigma formation using a PF:plasma steroid ratio >3:1 would result in a very high false positive diagnosis of the LUF syndrome if applied

to the patients in this study. A similar overlap between LUF and normal cycles was also observed in the original publication by Koninckx et al (1980a) and in the report by Dhont et al (1984). This overlap implies that an attempt to diagnose LUF by low PF steroid levels alone may have high sensitivity (if an appropriate cut-off point is chosen) but will have poor specificity. The significant chance of false positive diagnoses will be particularly high in groups where LUF has a low prevalence. Restricting PF fluid sampling to the early part of the luteal phase might improve the specificity of the test since in this study group, as in others (Donnez et al 1982), the ratio tends to fall as the luteal phase progresses, but Dhont et al (1984) indicate from their data that considerable overlap in PFP concentrations between LUF and stigma cases occurs even in the first few days after ovulation.

The patients who were found to have endometriosis at laparoscopy tended to have lower PF steroid levels and ratios than those with no evidence of endometriosis. Brosens et al (1978) suggested the incidence of LUF in patients with endometriosis was high, and this would be an attractive theory to explain the observed differences in PF steroid levels in the two groups. However only two of the three LUF patients had endometriosis and the range of concentrations in the two groups was similar. Dhont et al (1984) failed to show a significant relationship between low PF steroid values and endometriosis. Since this is testing the correlation of values in a chronic condition with the single values obtained in an investigation cycle of what is potentially a cyclical variable it is not surprising that one might find conflicting results between

studies.

The findings by some workers of increased volumes of PF and elevated concentrations of PF prostanoids (Drake et al 1980, 1981, 1982 & 1983, Ylikorkala et al 1984, Badawy, Marshall & Cuenca 1985) in patients with endometriosis and unexplained infertility, which others (Koninckx et al 1980a, Rock et al 1982, Mudge et al 1985) have been unable to confirm, have fuelled the continuing controversy over the possible relationship between these clinical problems.

It has been suggested that failure to identify the stigma within the corpus luteum under laparoscopic study is not of immediate or prognostic importance. Marik and Hulka (1978) made the observation that re-epithelialisation of the stigma can occur within a few days of follicular rupture thus implying that the laparoscopic diagnosis of the LUF syndrome could only be made reliably in the early luteal phase. Others (Portuondo et al 1981) have biopsied the corpus luteum in patients with absent stigmata and failed to demonstrate an entrapped oocyte. Portuondo et al (1983) described four patients where conception occurred during the cycle of laparoscopy at which the corpus luteum was found bearing no sign of stigmatisation. Vanrell et al (1982) studied a population of women of proven fertility in the early luteal phase and found the ovulation stigma to be present in only 53% of the study group. On the basis of these data it has been suggested that the LUF syndrome may not be a primary cause of infertility, as one cyclical event may not be truly representative of all cycles. Ultrasonic studies on the recurrence of this phenomenon suggest that the LUF syndrome may be less prevalent than was

originally suspected. Kerin et al (1983) observed in their study population, most of whom did not have unexplained infertility, that LUF syndrome did not tend to recur with greater frequency than in the general population. Liukkonen et al (1984) in their unexplained infertility population found the abnormal ultrasound profile they described to occur in three consecutive cycles in only 34% of patients. Further work is required in this field for, if these ovarian events do cause infertility, is it by virtue of their undue frequency of occurrence, cycle by cycle?

In conclusion, this study, in a population of patients with relatively short durations of unexplained infertility, showed a lower incidence of cycle abnormality than previously reported figures in series involving patients with much longer durations of infertility (Coutts 1985). This method of study cannot therefore be recommended as a diagnostically definitive or economically justifiable technique of primary investigation in patients where the duration of infertility in most cases is likely to be comparatively low.

# CHAPTER 8 CONCLUSIONS

In this thesis ovarian function in women with unexplained infertility has been explored using the combined resources of ovarian ultrasound and sequential plasma biochemistry, comparing the findings in women with unexplained infertility with ultrasonic and endocrine data from normal fertile women.

The following conclusions can be drawn :

1. The relationships between the changes in circulating concentrations of gonadotrophins and ovarian steroids during the menstrual cycle were established in 43 cycles from normally cycling volunteers. Previously reported patterns of follicular growth, using identical ultrasound equipment, were confirmed. All volunteers developed a single dominant follicle which, following the mid-cycle LH peak, was seen to collapse and in-fill as the corpus luteum formed and P secretion increased.

2. Data generated in conception cycles suggested that, in terms of follicular growth and corpus luteum function, such cycles did not differ from the normal non-fertile cycle, justifying the use of non-conception data as a normal control. A sub-normal P profile was not a barrier to conception, although it may be associated with early embryonic loss, the cause of which is unclear.

3. In a population of patients (175) with unexplained infertility more than half (56%) demonstrated abnormalities of ovarian function.

4. The most commonly found ultrasonic abnormality was the formation of retained luteal phase cysts, seen in 23.4% of the cycles. Two distinct populations of luteal cyst cycles were identified on the basis of presence or absence of ultrasonic evidence of follicular shrinkage following the LH peak. Shrinkage of the dominant follicle prior to luteal cyst formation was generally associated with normal P production by the corpus luteum. These cysts were termed cystic corpora lutea. In the absence of ultrasonic evidence of shrinkage of the dominant follicle after the LH peak circulating P concentrations tended to be reduced. These cysts were termed luteinised unruptured follicles (LUF's). Discrimination between these 2 sub-groups of cyst formers, on the basis of ultrasonic profiles, could not be made in the follicular phase of the cycle. Detailed ultrasonic data of follicular dynamics immediately follwing the LH peak were required if the nature of the luteal cysts was to be determined accurately.

5. The associated hormone data could be interpreted in accordance with the 2 cell hypothesis of steroid production in the luteal phase of the cycle, with the ultrasonic differences observed possibly representing differences in vascularisation of the cysts. LUF cycles possibly represent a failure of the blood-follicle barrier to be broken down, decreasing availability to the granulosa lutein cells of precursors for steroid production, with a consequent reduction in secretion of products. Low follicular phase plasma FSH concentrations were not seen in the luteal cyst cycles, in contrast to previous reports in the literature in respect of luteal phase defects. Cycles associated

with normal P production in the early luteal phase (up to day +6) tended to have slightly higher than normal early follicular phase FSH concentrations. FSH concentrations in the mid-luteal phase of the cycle, in both types of cyst formers, tended to be elevated. This may be a consequence of differences in the secretion of inhibin-like products by the corpus luteum, or deviations from the normal in hypothalamic pulsatile control of gonadotrophin secretion by the pituitary. This would be an interesting avenue of research for the future.

6. Deficient P production in the early luteal phase (PPS) was identified in 51 (29.1%) of the patients under study, a similar proportion to that described previously (Fleming et al 1981). Elevated follicular phase FSH concentrations in PPS cycles suggested that the dominant follicles recruited may be abnormal, and do not derive from sub-normal follicular phase FSH profiles at any stage. It was hypothesised that low P production may be a consequence of one of two possible pathogenic pathways : the first where granulosa cell populations may be small, leading to decreased aromatase activity (low E2) and low inhibin-like activity (high FSH) in the follicular phase; and the second where LUF occurs, the integrity of the blood-follicle barrier failing to be breached.

7. Tonically elevated LH secretion was identified in 23 (13.1%) of the unexplained infertile patients. High LH profiles were associated with abnormalities of follicular dynamics in more than 2/3 of cases. Luteal cyst formation was commonly seen, with luteal phase defects seen in a high proportion of the remainder. Studies of LHRH pulsatility patterns may provide insight into

the pathophysiology of this disorder.

8. Sub-optimal follicular development was seen in association with reduced plasma concentrations of E2, but in some cases steroid concentrations were normal. Consideration of the follicular phase gonadotrophin profiles was essential to clarify the pathological processes involved.

9. Abnormalities of cycle phase length, namely the short luteal phase, the long follicular phase and the short follicular phase, were rare in patients with unexplained infertility. The majority of such cycles showed normal biochemical and ultrasonic profiles.

11. Abnormalities of ovarian function occurred with reduced frequency in women with relatively short (<3yrs) durations of unexplained infertility. Intensive cycle investigation could not be recommended as a diagnostically definitive, or economically justifiable technique of primary investigation in such patients.

12. The diagnosis of LUF by luteal phase laparoscopy i.e. absence of stigma of ovulation on the corpus luteum, did not correlate well with ultrasonic descriptions of the phenomenon. Ultrasound may have too high a false negative rate to permit its use as a tool of study of the incidence and recurrence of the LUF syndrome. Alternatively, subjective assessment of the presence or absence of an ovulation stigma was also imprecise when compared to the ultrasonic features of LUF described above.

13. Peritoneal fluid steroid concentrations in women who exhibited

ovulation stigmata varied enormously, and considerable overlap between normal and laparoscopically diagnosed LUF cycles existed.

14. Neither ultrasound nor biochemistry, in isolation, was ideal to evaluate ovarian function. When ultrasonic follicular dynamics appeared to be normal, in a single cycle of investigation, it was likely that in a repeated examination the pattern would again be normal. This was not the case with the hormone profiles, since, in some cases, abnormalities of steroid production were identified in the absence of ultrasonic deviations from normal.

15. Ovarian function, as assessed by detailed biochemistry and ultrasonic examinations, may change from cycle to cycle, and thus the implications for long term fertility of finding an isolated abnormality remain unsolved. Therapeutic decision making in unexplained infertility remains difficult, and must only be considered after observing recidivism of an abnormality.

16. Since variation in the abnormalities described could occur from cycle to cycle, designing therapy to correct a single pattern of abnormality is unjustified. The different abnormalities may be a manifestation of a fundamental disturbance in ovarian function, best approached through a strategy which attempts to override all potential deviations from normal. In vitro fertilization or GIFT might be suitable, or the approach of pituitary down-regulation with GnRH agonists and subsequent ovulation induction with exogenous gonadotrophins.

# REFERENCES


Abdulla, U., Diver, M.J., Hipkin, L.J. & Davis, J.C. (1983) Plasma progesterone levels as an index of ovulation. British Journal of Obstetrics and Gynaecology, 90, 543-548.

Abraham, G.E., Maroulis, G.B. & Marshall, J.R. (1974) Evaluation of ovulation and corpus luteum function using measurements of plasma progesterone. Obstetrics and Gynaecology, 44, 522-525.

Adams, J., Polson, D.W., Abdulwahid, N., Morris, D.V., Franks, S., Mason, H.D., Tucker, M., Price, J. & Jacobs, H.S. (1985) Multifollicular ovaries : clinical and endocrine features and response to pulsatile gonadotrophin releasing hormone. Lancet, ii, 1375-1379.

Adejuwon, C.A., Faunde, A., Segal, S.J. & Alvares-Sanches, F. (1984) Serum prolactin profiles of the normal human conceptual cycle. International Journal of Gynaecology and Obstetrics, 22, 213-216.

Aksel, S., Wiebe, H., Tyson, J. & Jones, G.S. (1976) Hormonal findings associated with aluteal cycles. Obstetrics and Gynaecology, 48, 598-602.

Aksel, S. (1980) Sporadic and recurrent luteal phase defects in cyclic women : comparison with normal cycles. Fertility and Sterility, 33, 372-377.

Aksel, S. (1981) Hormonal characteristics of long cycles in fertile women. Fertility and Sterility, 36, 521-523.

Aksel, S. (1987) Thou shalt luteinize, not rupture. Fertility and Sterility, 47, 762-764.

Andino, N.A., Bidot, C., Valdes, M. & Machado, A.J. (1985) Chromatographic pattern of circulating prolactin in ovulatory hyperprolactinaemia. Fertility and Sterility, 44, 600-605.

Andrews, W.C. (1979) Luteal phase defects. Fertility and Sterility, 32, 501-509.

Annos, T., Thompson, I.E. & Taymor, M.L. (1980) Luteal phase deficiency and infertility : difficulties encountered in diagnosis and treatment. Obstetrics and Gynaecology, 55, 705-710.

Badawy, S.Z.A., Marshall, L. & Cuenca, V. (1985) Peritoneal fluid prostaglandins in various stages of the menstrual cycle : role in infertile patients with endometriosis. International Journal of Fertility, 30, 48-52.

Bahamondes, L., Saboya, W., Tambascia, M. & Trevisan, M. (1979) Galactorrhoea, infertility and short luteal phases in hyperprolactinaemic women : early stage of amenorrhoea-galactorrhoea. Fertility and Sterility, 32, 476-477.

Baird, D.T. & Fraser, I.S. (1974) Blood production and ovarian secretion rates of oestradiol and oestrone in women throughout the menstrual cycle. Journal of Clinical Endocrinology and Metabolism, 38, 1009-1017.

Baird, D.T., Baker, T.G., McNatty, K.P. & Neal, P. (1975) Relationship between the secretion of the corpus luteum and the length of the follicular phase of the ovarian cycle. Journal of Reproduction and Fertility, 45, 611-619.

Baird, D.T. (1985) Control of luteolysis. In The Luteal Phase, ed. Jeffcoate, S.L. Ch. 2, pp 25-42. Chichester : John Wiley.

Baird, D.T. (1988) Gonadal hormones : endocrine and paracrine effects. Simpson symposia, 1, 9-10. (Abstract)

Baker, H.W.G., Burger, H.G., de Kretser, D.M., Hudson, B., Rennie, G.C. & Straffon, W.G.E. (1985) Testicular vein ligation and fertility in men with varicoceles. British Medical Journal, 291, 1678-1680.

Balasch, J., Vanrell, J.A., Creus, M., Marquez, M., & Gonzalez-Merlo, J. (1985) The endometrial biopsy for diagnosis of luteal phase deficiency. Fertility and Sterility, 44, 699-701.

Balasch, J., Creus, M. & Vanrell, J.A. (1986) Luteal function after delayed ovulation. Fertility and Sterility, 45, 342-344.

Barnea, E.R., Holford, T.R. & McInnes, D.R.A. (1985) Long term prognosis of infertile couples with normal basic investigations : a life-table analysis. Obstetrics and Gynaecology, 66, 24-26.

Bayard, F., Damilano, S., Robel, P. & Baulieu, E.E. (1978) Cytoplasmic and nuclear estradiol and progesterone receptors in human endometrium. Journal of Clinical Endocrinology and Metabolism, 46, 635-648.

Bernardus, R.E., van Dop, P.A., van Kessel, H. & Schoemaker, J. (1983) New evidence for the existence of the luteinised unruptured follicle syndrome as a cause of infertility : a case report. Fertility and Sterility, 39, 376-378.

Bioeffects Committee of the American Institute of Ultrasound in Medicine. (1984) Safety considerations for diagnostic ultrasound. AIUM Publications, 4405 E-W Highway, Suite 504, Bethesda, MD 20814, U.S.A.

Bomsel-Helmreich, O. (1985) Ultrasound and the pre-ovulatory human follicle. Oxford Reviews of Reproductive Biology, 7, 1-72.

Breitenecker, G., Friedrich, F. & Kemeter, P. (1978) Further investigations on the maturation and degeneration of human ovarian follicles and their oocytes. Fertility and Sterility, 29, 336-341.

Broom, T.J., Mathews, C.D., Cooke, I.D., Ralph, M.M., Seamark, R.F. & Cox, L.W. (1981) Endocrine profiles and fertility status of human menstrual cycles of varying follicular phase length. Fertility and Sterility, 36, 194-200.

Brosens, I.A., Konninckx, P.R. & Corveleyn, P.A. (1978) A study of plasma progesterone, oestradiol 17-B, prolactin and LH levels, and the luteal phase appearance of the ovaries in patients with endometriosis and infertility. British Journal of Obstetrics and Gynaecology, 85, 246-250.

Bryce, R.L., Shuter, B., Sinosich, M.J., Stiel, J.N., Picker, R.H. & Saunders, D.M. (1982) The value of ultrasound, gonadotrophin and estradiol measurements for precise ovulation prediction. Fertility and Sterility, 37, 42-45.

Carr, B.R., Sadler, R.K., Rochelle, D.B., Stalmach, M.A., Macdonald, P.C & Simpson, E.R. (1981) Plasma lipoprotein regulation of progesterone biosynthesis by human corpus luteum tissue in organ culture. Journal of Clinical Endocrinology and Metabolism, 52, 875-881.

Cheesman, K.L., Cheesman, S.D., Chatterton, R.T. & Cohen, M.R. (1983) Alterations in progesterone metabolism and luteal function in infertile women with endometriosis. Fertility and Sterility, 40, 590-595.

Clarke, G.N., Stojanoff, A., Cauchi, M.N., McBain, J.C., Speirs, A.L. & Johnston, W.I.H. (1984) Detection of anti-spermatozoal antibodies of IgA class in cervical mucus. American Journal of Reproductive Biology, 5, 61-65.

Cook, C.L., Rao, Ch. V. & Yussman, M.A. (1983) Plasma gonadotrophin and sex steroid hormone levels during the early, mid-follicular and mid-luteal phases of women with luteal phase defects. Fertility and Sterility, 40, 45-48.

Corenblum, B., Pairaudeau, N. & Schewchuk, A.B. (1976) Prolactin hypersecretion and short luteal phase defects. Obstetrics and Gynaecology, 4, 486-488.

Coulam, C.B., Hill, L.M. & Breckle, R. (1982) Ultrasonic evidence for luteinisation of unruptured pre-ovulatory follicles. Fertility and Sterility, 37, 524-529.

Coulam, C.B., Hill, L.M. & Breckle, R. (1983) Ultrasonic assessment of subsequent unexplained infertility after ovulation induction. British Journal of Obstetrics and Gynaecology, 90, 460-467.

Coutts, J.R.T., Gaukroger, J.M., Samad-Kader, A. & Macnaughton, M.C. (1981) Steroidogenesis by the human Graafian follicle. In Functional Morphology of the Human Ovary, ed. Coutts, J.R.T. Ch. 5, pp 53-72. Lancaster : M.T.P. press.

Coutts, J.R.T., Adam, A.H. & Fleming, R. (1982) The deficient luteal phase may represent an anovulatory cycle. Clinical Endocrinology (Oxford), 17, 384-394.

Coutts, J.R.T. (1985) The abnormal luteal phase. In The Luteal Phase, ed. Jeffcoate, S.L. Ch. 7, pp 101-114. London : John Wiley.

Craft, I., Shelton, K., Yovich, J. & Smith, D. (1980) Ovum retention in the human. Fertility and Sterility, 34, 537-541.

Dalton. M.E., Bromham, D.R., Ambrose, C.L., Osborne, J. & Dalton, K.D. (1987) Nasal absorption of progesterone in women. British Journal of Obstetrics and Gynaecology, 94, 84-88.

Daly, D.C., Soto-Albors, C., Walters, C., Ying, Y. & Riddick, D.H. (1985) Ultrasonic evidence of luteinised unruptured follicle syndrome in unexplained infertility. Fertility and Sterility, 43, 62-65.

De Crespigny, L.Ch., O'Herlihy, C. & Robinson, H.P. (1981) Ultrasonic observation of the mechanisms of human ovulation. American Journal of Obstetrics and Gynaecology, 139, 636-639.

Devroey, P., Temmerman, M., Verhoeven, N., Naaktgeboren, N., Heip, J., Amy, J.J. & Van Steirteghem, A.C. (1983) Recurrence of the luteinised unruptured follicle. British Journal of Obstetrics and Gynaecology, 90, 381-382.

Del Pozo, E., Wyss, H., Tolis, G., Alcaniz, J., Campano, A. & Naftolin, F. (1979) Prolactin and deficient luteal function. Obstetrics and Gynaecology, 53, 282-286.

Dhont, M., Serreyn, R., Duvivier, P., Vanluchene, E., Deboever, J. & Vandekerckhove, D. (1984) Ovulation stigma and concentration of progesterone and estradiol in peritoneal fluid : relation with fertility and endometriosis. Fertility and Sterility, 41, 872-877.

DiZerega, G.S. & Hodgen, G.D. (1981) Follicular phase treatment of luteal phase dysfunction. Fertility and Sterility, 35, 428-432.

DiZerega, G.S. & Hodgen, G.D. (1981) Luteal phase dysfunction infertility : a sequel to aberrant folliculogenesis. Fertility and Sterility, 35, 489-499.

Dlugi, A.M., Laufer, N., DeCherney, A.H., Maclusky, N.J., Haseltine, F.P., Polan, M.L., Mezer, H.C., Tarlatzis, B. & Naftolin, F. (1984) The periovukatory and luteal phase of conception cycles following in-vitro fertilization and embryo transfer. Fertility and Sterility, 41, 530-537.

Dodson, K.S., Coutts, J.R.T. & Macnaughton, M.C. (1975a) Plasma sex steroid and gonadotrophin patterns in human menstrual cycles. British Journal of Obstetrics and Gynaecology, 82, 602-614.

Dodson, K.S., Macnaughton, M.C. & Coutts, J.R.T. (1975b) Infertility in women with apparently ovulatory cycles. I. Comparison of their plasma sex steroid and gonadotrophin profiles with those in the normal cycle. British Journal of Obstetrics and Gynaecology, 82, 615-624.

Dodson, K.S., Macnaughton, M.C. & Coutts, J.R.T. (1975c) Infertility in women with apparently ovulatory cycles. II. The effects of clomiphene treatment on the profiles of gonadotrophins and sex steroid hormones in peripheral plasma. British Journal of Obstetrics and Gynaecology, 82, 625-633.

Donald, I. (1963) Use of ultrasonics in diagnosis of abdominal swellings. British Medical Journal, 2, 1154-1155.

Donnez, J., Langerock, S. & Thomas, K. (1982) Peritoneal fluid volume and 17 beta estradiol and progesterone concentrations in ovulatory, anovulatory and post-menopausal women. Obstetrics and Gynaecology, 59, 687-692.

Downs, K.A. & Gibson, M. (1983) Clomiphene citrate therapy for luteal phase defect. Fertility and Sterility, 39, 34-38.

Drake, T., O'Brien, W., Grunert, G. & Metz, S. (1980) Peritoneal fluid volumes in endometriosis. Fertility and Sterility, 34, 280-281.

Drake, T.S., O'Brien, W.F., Ramwell, P.W. & Metz, S.A. (1981) Peritoneal fluid thromboxane B2 and 6-keto PGF1-alpha in endometriosis. American Journal of Obstetrics and Gynaecology, 140, 401-404.

Drake, T.S., O'Brien, W.F. & Ramwell, P.W. (1982) Elevated peritoneal fluid prostanoids in unexplained infertility : a possible biochemical marker for microscopic endometriosis. Fertility and Sterility, 37, 302-303.

Drake, T.S., O'Brien, W.F. & Ramwell, P.W. (1983) Peritoneal fluid prostanoids in unexplained infertility. American Journal of Obstetrics and Gynaecology, 147, 63-64.

Duck, F.A., Starrit, H.C., Aindow, J.D., Perkins, M.A. & Hawkins, A.J. (1985) The output of pulse echo ultrasound equipment : a survey of powers, pressures and intensities. British Journal of Radiology, 58, 989-1001.

Duignan, N.M. (1976) Polycystic ovarian disease. British Journal of Obstetrics and Gynaecology, 83, 593-602.

Editorial (1982) Running, Jumping and ... Amenorrhoea. Lancet, ii, 638-640.

Edmonds, D.K., Lindsay, K.S., Miller, J.F., Williamson, E. & Wood, P.J. (1982) Early embryonic mortality in women. Fertility and Sterility, 38, 447-453.

Eissa, M.K., Obhrai, M.S., Docker, M.F., Lynch, S.S., Sawers, R.H. & Newton, J.R. (1986) Follicular growth and endocrine profiles in spontaneous and induced conception cycles. Fertility and Sterility, 45, 191-195.

Eissa, M.K., Sawers, R.S., Docker, M.F., Lynch, S.S. & Newton, J.R. (1987) Characteristics and incidence of dysfunctional ovulation patterns detected by ultrasound. Fertility and Sterility, 47, 603-612.

European Federation of Societies for Ultrasound in Medicine and Biology (1984) Statement. Safety of ultrasound. Journal of Perinatal Medicine, 12, 289.

Fleischer, A.C., Herbert, C., Maxon, W. & Hackeloer, B.J. (1984) Correspondance. Premature ovulation after ovarian ultrasonography. British Journal of Obstetrics and Gynaecology, 91, 602-604.

Fleming, R., Craig, A., England, P., Macnaughton, M.C. & Coutts, J.R.T. (1978) Influence of hyperprolactinaemia on ovarian function in infertile women with normal menstrual rhythm. Journal of Endocrinology, 77, 14P-15P (abstract).

Fleming, R., Carswell, W., Black, W.P., Macnaughton, M.C., Craig, A., Fergusson, C. & Coutts, J.R.T. (1981) The deficient corpus luteum as a cause of infertility. In Functional Morphology of the Human Ovary, ed. Coutts, J.R.T. Ch. 17, pp 205-220. Lancaster : M.T.P. press.

Fleming, R., Adam, A.H., Barlow, D.H., Black, W.P., Macnaughton, M.C. & Coutts, J.R.T. (1982) A new systematic treatment for infertile women with abnormal hormone profiles. British Journal of Obstetrics and Gynaecology, 89, 80-83.

Fleming, R. & Coutts, J.R.T. (1982) Effects of clomiphene treatment on infertile women with normal menstrual rhythm. British Journal of Obstetrics and Gynaecology, 89, 749-753.

Fleming, R., Hamilton, M.P.R., Haxton, M.J. & Coutts, M.J. (1985) Blockade of the LH surge and direct control of ovarian function in women with functioning pituitaries. In Gamete Quality and Fertility Regulation, ed. Rolland, R., Heineman, M.J., Hillier, S.G. & Vemer, H. Excerpta Medica, International Congress Series, 658 pp 197-204. Amsterdam : Elsevier Science Publishers.

Fleming, R., Yates, R.W.S., Haxton, M.J., Coutts, J.R.T., Hamilton, M.P.R. & Conaghan, C. (1987) Ovulation induction using the combination of buserilin and exogenous gonadotrophins in women with functional pituitaries. British Journal of Clinical Practice, 48, 34S-39S

Funduk-Kurjak, B. & Kurjak, A. (1982) Ultrasound monitoring of follicular maturation and ovulation in normal menstrual cycle and in ovulation induction. Acta Obstetrica Gynaecologica Scandinavica, 61, 329-335.

Garcea, N., Campo, S., Siccardi, P., Panetta, V., Venneri, M. & Dargenio, R. (1983) Effect of drug induced hyper- and hypoprolactinaemia on human corpus luteum. Acta Eurologica Fertilitas, 14, 35-40.

Garcia, J.E., Acosta, A.A., Hsiu, J-G. & Jones, H.W.Jr. (1984) Advanced endometrial maturation after ovulation induction with human menopausal gonadotropin/human chorionic gonadotropin for in-vitro-fertilisation. Fertility and Sterility, 41, 31-35.

Gautray, J.P., de Brux, J., Tajchner, G., Robel, P. & Mouren, M. (1981) Clinical investigation of the menstrual cycle. III. Clinical, endometrial and endocrine aspects of luteal defect. Fertility and Sterility, 35, 296-303.

Gerhard, I. & Runnebaum, B. (1982) The hCG test : an approach to luteal insufficiency. European Journal of Obstetrics and Gynaecology and Reproductive Biology, 14, 101-114.

Gibbons, W.E., Buttram, V.C. & Rossavik, I.K. (1984) The observed incidence of luteinised unruptured follicle syndrome in a population of women undergoing ovulation monitoring by ultrasound. Fertility and Sterility, 41, 19S.

Glazener, C.M.A., Bailey, I. & Hull, M.G.R. (1985) Effectiveness of vaginal administration of progesterone. British Journal of Obstetrics and Gynaecology, 92, 364-368.

Glazener, C.M.A., Kelly, N.J. & Hull, M.G.R. (1987) Prolactin measurement in the investigation of infertility in women with a normal menstrual cycle. British Journal of Obstetrics and Gynaecology, 94, 535-538.

Grant, A. (1981) Abnormal luteal function in endometriosis. Fertility and Sterility, 35, 592.

Hackeloer, B.J., Fleming, R., Robinson, H.P., Adam, A.H. & Coutts, J.R.T. (1979) Correlation of ultrasonic and endocrinologic assessment of human follicular development. American Journal of Obstetrics and Gynaecology, 135, 122-128.

Hamilton, C.J.C.M., Wetzels, L.C.G., Evers, J.L.H., Hoogland, H.J., Muijtjens, A. & De Haan, J. (1985) Follicle growth curves and hormonal patterns in patients with the luteinized unruptured follicle syndrome. Fertility and Sterility, 43, 541-548.

Hammond, M.G. & Talbert, L.M. (1982) Clomiphene citrate therapy of infertile women with low luteal phase progesterone llevels. Obstetrics and Gynaecology, 59, 275-279.

Hattori, Y., Yoshida, T., Suzuki, H., Takashima, Y. & Noda, K. (1982) Endocrinological studies and clomiphene therapy of luteal insufficiency. Asia Oceanica Journal of Obstetrics and Gynaecology, 8, 19-27.

Haxton, M.J., Fleming, R., Hamilton, M.P.R., Yates, R.W., Black, W.P. & Coutts, J.R.T. (1987) "Unexplained infertility" results of secondary investigation in 95 couples. British Journal of Obstetrics and Gynaecology, 94, 539-542.

Healy, D.L., Schenken, R.S., Lynch, A., Williams, R.F. & Hodgen, G.F. (1984) Pulsatile progesterone secretion : its relevance to clinical evaluation of corpus luteum function. Fertility and Sterility, 41, 114-121.

Hillier, S.G. (1981) A consideration of the roles of ovarian C19 steroid aromatase and 5-alpha reductase enzymic activities in the local control of follicular development in the human ovary. In Functional Morphology of the Human Ovary, ed. Coutts, J.R.T. Ch. 8, pp 94-101. Lancaster : M.T.P. Press.

Hillier, S.G. & Wickings, E.J. (1985) Cellular aspects of corpus luteum function. In The Luteal Phase, ed. Jeffcoate, S.L. Ch. 1, pp 1-23. London : John Wiley.

Hoff, J.D., Quigley, M.E. & Yen, S.S.C. (1983) Hormonal dynamics at mid-cycle : a re-evaluation. Journal of Clinical Endocrinology and Metabolism, 57, 792-796.

Holtz, G., Williamson, H.O., Mathur, R.S., Landgrebe, S.C. & Moore, E.E. (1985) Luteinized unruptured follicle syndrome in mild endometriosis : assessment with biochemical parameters. Journal of Reproductive Medicine, 9, 643-645.

Huang, K.E., Muechler, E.K. & Bonfiglio, T.A. (1984) Follicular phase treatment of luteal phase defect with follicle stimulating hormone in infertile women. Obstetrics and Gynaecology, 64, 32-36.

Hull, M.G.R., Savage, P.E., Bromham, D.R., Ismail, A.A.A. & Morris, A.F. (1982) The value of a single serum progesterone measurement in the mid-luteal phase as a criterion of a potentially fertile cycle ("ovulation") derived from treated and untreated conception cycles. Fertility and Sterility, 37, 355-360.

Hull, M.G.R., Glazener, C.M.A., Kelly, N.J., Conway, D.I., Foster, P.A., Hinton, R.A., Coulson, C., Lambert, P.A., Watt, E.M. & Desai, K.M. (1985) Population study of causes, treatment and outcome of infertility. British Medical Journal, 291, 1693-1697.

Israel, S.L., Mishell, D.R., Stone, S.C., Thorneycroft, I.H. & Moyer, D.L. (1972) Single luteal phase serum progesterone assay as an indicator of ovulation. American Journal of Obstetrics and Gynaecology, 112, 1043-1046.

Jacobson, A. & Marshall. J.R. (1980) Detrimental effect of endometrial biopsies on pregnancy rate following human menopausal gonadotropin/human chorionic gonadotropin induced ovulation. Fertility and Sterility, 33, 602-604.

Jasczak, S.E. (1983) Anovulatory luteal cycles in primates. Contraception, 27, 505-514.

Jewelewicz, R. (1975) Management of infertility resulting from anovulation. American Journal of Obstetrics and Gynaecology, 122, 909-920.

Jones, G.S. & Delfs, E. (1951) Endocrine patterns in term pregnancies following abortion. Journal of the American Medical Association, 146, 1212-1218.

Jones, G.S., Maffezoli, R.D., Strott, G.A., Ross, G.T. & Kaplan, G. (1970) Pathophysiology of reproductive failure after clomiphene induced ovulation. American Journal of Obstetrics and Gynaecology, 108, 847-867.

Jones, G.S. (1976) The luteal phase defect. Fertility and Sterility, 27, 351-356.

Kato, H., Ueda, K., Tsutsui, H., Miyauchi, F. & Torigoe, T. (1982) Role of the non-gravid part of the uterus in the regulation of corpus luteum function in pregnant rats. Endocrinology, 111, 2020-2024.

Kauppila, A., Leinonen, P., Vihko, R. & Ylostalo, P. (1982) Metoclopramide induced hyperprolactinaemia impairs ovarian follicle maturation and corpus luteum function in women. Journal of Clinical Endocrinology and Metabolism, 54, 955-960.

Keller, D.W., Wiest, W.G., Askin, F.B., Johnson, L.W. & Strickler, R.C. Pseudocorpus luteum deficiency : a local defect of progesterone action on endometrial stroma. Journal of Clinical Endocrinology and Metabolism, 48, 127-132.

Kemman, E. & Jones, J.R. (1983) Sequential clomiphene citrate-menotropin therapy for induction or enhancement of ovulation. Fertility and Sterility, 39, 772-779.

Kerin, J.F., Edmonds, D.K., Warnes, G.M., Cox, L.W., Seamark, R.F., Mathews, C.D., Young, G.B. & Baird, D.T. (1981) Morphological and functional relations of Graafian follicle growth to ovulation in women using ultrasonic, laparoscopic and biochemical measurements. British Journal of Obstetrics and Gynaecology, 88, 81-90.

Kerin, J.F., Kirby, C., Morris, D., McEvoy, M., Ward, B. & Cox, L.W. (1983) Incidence of the luteinised unruptured follicle phenomenon in cycling women. Fertility and Sterility, 40, 620-626.

Killick, S. & Elstein, M. (1987) Pharmacologic production of luteinized unruptured follicles by prostaglandin synthetase inhibitors. Fertility and Sterility, 47, 773-777.

Kletzky, O.A., Nakamura, R.M., Thorneycroft, I.H. & Mishell, D.R. (1975) Lognormal distribution of gonadotropins and steroid values in the normal menstrual cycle. American Journal of Obstetrics and Gynaecology, 121, 688-694.

Koninckx, P.R., Goddeeris, P.G., Lauweryns, J.M., De Hertogh, R.C. & Brosens, I.A. (1977) Accuracy of endometrial biopsy dating in relation to the mid-cycle luteinising hormone peak. Fertility and Sterility, 28, 443-445.

Koninckx, P.R., De Moor, P. & Brosens, I.A. (1978) Delayed onset of luteinisation as a cause of infertility. Fertility and Sterility, 29, 266-269.

Koninckx, P.R., De Moor, P. & Brosens, I.A. (1980) Diagnosis of the luteinised unruptured follicle syndrome by steroid hormone assays on peritoneal fluid. British Journal of Obstetrics and Gynaecology, 87, 929-934.

Koninckx, P.R., Renaer, M. & Brosens, I.A. (1980) Origin of peritoneal fluid in women : an ovarian exudation product. British Journal of Obstetrics and Gynaecology, 87, 177-183.

Koninckx, P.R., Heyns, W., Verhoeven, G., Van Baelen, H., Lissens, W.D., De Moor, P. & Brosens, I.A. (1980) Biochemical characterisation of peritoneal fluid in women during the menstrual cycle. Journal of Clinical Endocrinology and Metabolism, 51, 1239-1244.

Koninckx, P.R. & Brosens, I.A. (1982) The luteinised unruptured follicle sysndrome. Obstetrical and Gynaecological Annual, 11, 175-186.

Kratochwil, A., Jentsch, K. & Bresina, K. (1973) Ultraschallanatomie des weilblichen beckens und ihre klinische bedeutung. Archiven Gynaekologie, 214, 273.

Kusuda, M., Nakamura, G., Matsukuma, M., Kurano, A. (1983) Corpus luteum insufficiency as a cause of nidatory failure. Acta Obstetrica Gynaecologica Scandinavica, 62, 199-205.

Laborde, N., Carril, M., Chevakoff, S., Croxatto, H.D., Pedroya, E. & Rosner, J.M. (1976) The secretion of progesterone during the periovulatory period in women with certified ovulation. Journal of Clinical Endocrinology and Metabolism, 43, 1157-1163.

Laufer, N., Navot, D. & Schenker, J.G. (1982) The pattern of luteal phase plasma progesterone and estradiol in fertile cycles. American Journal of Obstetrics and Gynaecology, 143, 808-813.

Lenton, E.A., Weston, G.A. & Cooke, I.D. (1977) Problems in using basal body temperature recordings in an infertility clinic. British Medical Journal, 1, 803-805.

Lenton, E.A., Adams, M. & Cooke, I.D. (1978) Plasma steroid and gonadotrophin profiles in ovulatory but infertile women. Clinical Endocrinology, 8, 241-255.

Lenton, E. A., Brook, L.M., Sobowale, O. & Cooke, I.D. (1979) Prolactin concentrations in normal menstrual cycles and cinception cycles. Clinical Endocrinology, 10, 383-391.

Lenton, E.A. & Cooke, I.D. (1981) Investigation and assessment of the infertile woman by comparison with the endocrine parameters of a fertile cycle. INSERM, 103, 387-408.

Lenton, E.A., Sulaiman, R., Sobowale, O. & Cooke, I.D. (1982) The human menstrual cycle : plasma concentrations of prolactin, LH, FSH, estradiol and progesterone inj conceiving and non-conceiving women. Journal of Reproduction and Fertilty, 65, 131-139.

Lenton, E.A., Harper, R., Smith, S.K. & Cooke, I.D. (1984) Follicular growth abnormalities in women with unexplained infertility. Presented at IIIrd World Congress of In-Vitro Fertilization and Embryo Transfer, Helsinki : Abstract 9.

Lenton, E.A., Landgren, B-M., Sexton, C. & Harper, R. (1984) Normal variation in the length of the follicular phase of the menstrual cycle - effect of chronological age. British Journal of Obstetrics and Gynaecology, 91, 681-684.

Lesorgen, P.R., Wu, C.H., Green, P.J., Gocial, B. & Lerner, L.J. (1984) Peritoneal fluid and serum steroids in infertility patients. Fertility and Sterility, 42, 237-242.

Liukkonen, S., Koskimies, A.I., Tenhunen, A. & Ylostalo, P. (1984) Diagnosis of luteinised unruptured follicle (LUF) syndrome by ultrasound. Fertility and Sterility, 41, 26-30.

Loumaye, E., Donnez, J. & Thomas, K. (1985) Ovulation instantaneously modifies women's peritoneal fluid characteristics : a demonstration from an in-vitro fertilization program. Fertility and Sterility, 44, 827-829.

McBain, J.C. & Pepperell, R. (1987) Unexplained infertility. In The Infertile Couple, 2nd edition, ed. Pepperell, R.J., Hudson, B. & Wood, C. Ch. 8, pp 208-232. Melbourne : Churchill Livingstone.

McNatty, K.P., Sawers, R.S. & McNeilly, A.S. (1974) A possible role for prolactin in control of steroid secretion by the human Graafian follicle. Nature, 250, 653-655.

McNatty, K.P., Hunter, W.M., McNeilly, A.S. & Sawers, R.S. (1975) Changes in the concentration of pituitary and steroid hormones in the follicular fluid of human Graafian follicles throughout the menstrual cycle. Journal of Endocrinology, 64, 555-571.

McNatty, K.P. & Sawers, R.S. (1975) Relationship between the endocrine environment within the Graafian follicle and the subsequent role of progesterone secretion by human granulosa cells in vitro. Journal of Endocrinology, 66, 391-400.

McNatty, K.P. (1979) Relationship between plasma prolactin and the endocrine microenvironment of the developng human antral follicle. Fertility and Sterility, 32, 433-438.

McNatty, K.P., Moore-Smith, D., Makris, A., Osathanondh, R. & Ryan, K.J. (1979) The microenvironment of the human antral follicle : interrelationships among the steroid levels in antral fluid, the population of granulosa cells and the status of the human oocyte in vivo and in vitro. Journal of Clinical Endocrinology and Metabolism, 49, 851-860.

Macnaughton, M.C., Samad-Kader, A., Gaukroger, J.M. & Coutts, J.R.T. (1981) Steroid hormone production by the human corpus luteum. In Functional Morphology of the Human Ovary, ed Coutts, J.R.T. Ch.12, pp 137-156. Lancaster : M.T.P. Press.

McNay, M.B. & Fleming, J.E.E. (1984) The safety of diagnostic ultrasound. British Journal of Hospital Medicine, July, 35-38.

McNeilly, A.S., Glasier, A.S., Jonassen, J. & Howie, P.W. (1982) Evidence for direct inhibition of ovarian function by prolactin. Journal of Reproduction and Fertility, 65, 559-569.

McRae, M.A., Blasco, L. & Lyttle, C.R. (1984) Serum hormones and their receptors in women with normal and inadequate corpus luteum function. Fertility and Sterility, 42, 58-63.

Maathuis, J.B., Van Look, P.F.A. & Michie, E.A. (1978) Changes in volume, total protein and ovarian steroid concentrations of peritoneal fluid throughout the human menstrual cycle. Journal of Endocrinology, 76, 123-133.

Marik, J. & Hulka, J. (1978) Luteinized unruptured follicle syndrome : a subtle cause of infertility. Fertility and Sterility, 29, 270-274.

Marut, E.L., Huang, S.C. & Hodgen, G.D. (1983) Distinguishing the steroidogenic roles of granulosa and theca cells of the dominant ovarian follicle and corpus luteum. Journal of Clinical Endocrinology and Metabolism, 57, 925-930.

Mathews, C.D. & Peek, J.C. (1987) Artificial insemination - donor and husband. In The Infertile Couple, ed. Pepperell, R.J., Hudson, B. & Wood, C. Ch. 9, pp 233-262. Melbourne, Churchill Livingstone.

Moghissi, K.S. & Wallach, E.E. (1983) Unexplained infertility. Fertility and Sterility, 39, 5-21.

Molloy, B.G., El Shiekh, M.A.A., Chapman, C., Oakey, R., Hancock, K.W. & Glass, M.R. (1984) Pathological mechanisms in polycystic ovary syndrome : modulation of LH pulsatility by progesterone. British Journal of Obstetrics and Gynaecology, 91, 457-465.

Mudge, T.J. (1982) The luteinized unruptured follicle sysndrome. Clinical Reproduction and Fertility, 1, 243-244.

Mudge, T.J., James, M.J., Jones, W.J. & Walsh, J.A. (1985) Peritoneal fluid 6-keto prostaglandin F1-alpha levels in women with endometriosis. American Journal of Obstetrics and Gynaecology, 152, 901-904.

Muhlenstedt, D., Bohnet, H.G., Hanker, J.P. & Schneider, H.P.G. (1978) Short luteal phase and prolactin. International Journal of Fertility, 23, 213-218.

Nitschke-Dabelstein, S., Hackeloer, B.J. & Sturm, G. (1981) Ovulation and corpus luteum formation observed by ultrasonography. Ultrasound in Medicine and Biology, 7, 33-39.

Noyes, R.W., Hertig, A. & Rock, J. (1950) Dating the endometrial biopsy. Fertility and Sterility, 1, 3-25.

O'Herlihy, C., De Crespigny, L. Ch. & Robinson, H.P. (1980a) Monitoring ovarian follicular development with real-time ultrasound. British Journal of Obstetrics and Gynaecology, 87, 613-618.

O'Herlihy, C., De Crespigny, L.Ch., Lopata, A., Johnston, I., Hoult, I. & Robinson, H.P. (1980b) Pre-ovulatory follicular size : a comparison of ultrasound and laparoscopic measurements. Fertility and Sterility, 34, 24-26.

O'Herlihy, C., Robinson, H.P. & De Crespigny, L.Ch. (1980c) Mittelschmerz is a pre-ovulatory symptom. British Medical Journal, 280, 986.

O'Herlihy, C., Pepperell, R.J. & Robinson, H.P. (1982) Ultrasound timing of human chorionic gonadotropin administration in clomiphene stimulated cycles. Obstetrics and Gynaecology, 59, 40-45.

O'Herlihy, C., Evans, J.H., Brown, J.B., De Crespigny, L.Ch. & Robinson, H.P. (1982) Use of ultrasound in monitoring ovulation induction with human pituitary gonadotropins. Obstetrics and Gynaecology, 60, 577-582.

Olive, D.L. & Haney, A.F. (1986) Endometriosis-associated infertility : a critical review of therapeutic approaches. Obstetrical and Gynaecological Survey, 41, 538-555.

Padilla, S.L., Person, G.K., McDonough, P.G. & Reindollar, R.H. (1985) The efficacy of bromocriptine in patients with ovulatory dysfunction and normoprolactinaemic galactorrhoea. Fertility and Sterility, 44, 695-698.

Papiernik, E., Spira, A., Bomsel-Helmreich, O & Lebel, S. (1979) Ovarian overripeness and intra-uterine growth retardation. Lancet, ii, 1025-1026.

Pauerstein, C.J., Eddy, C.A., Croxatto, H.D., Hess, R., Siler-khodr, T.M. & Croxatto, H.B. (1978) Temporal relationship of oestrogen, progesterone and luteinizing hormone levels to ovulation in women and infrahuman primates. American Journal of Obstetrics and Gynaecology, 130, 876-886.

Pepperell, R.J. & McBain, J.C. (1985) Unexplained infertility : a review. British Journal of Obstetrics and Gynaecology, 92, 569-580.

Perez, R.J., Plurad, A.V. & Palladino, V.S. (1981) The relationships of the corpus luteum and the endometrium in infertile patients. Fertility and Sterility, 35, 423-427.

Picker, R.H., Smith, D.H., Tucker, M.H. & Saunders, D.M. (1983) Ultrasonic signs of imminent ovulation. Journal of Clinical Ultrasound, 11, 1-2.

Polan, M.L., Totora, M., Caldwell, B.V., DeCherney, A.H., Haseltine, A.H. & Kase, N. (1982) Abnormal ovarian cycles as diagnosed by ultrasound and serum oestradiol levels. Fertility and Sterility, 37, 342-347.

Portuondo, J.A., Agustin, A., Herran, C. & Echanojauregui, A.D. (1981) The corpus luteum in infertile patients found during laparoscopy. Fertility and Sterility, 36, 37-40.

Portuondo, J.A., Pena, J., Otaola, C. & Echanojauregui, A.D. (1983) Absence of ovulation stigma in the conception cycle. International Journal of Fertility, 28, 52-54.

Quagliarello, J. & Arny, M. (1986) Inaccuracy of basal body temperature charts in predicting urinary luteinising hormone surges. Fertility and Sterility, 45, 334-337.

Queenan, J.T., O'Brien, G.D., Bains, L.M., Simpson, J., Collins, W.P. & Campbell, S. (1980) Ultrasound scanning of ovaries to detect ovulation in women. Fertility and Sterility, 34, 99-105.

Radwanska, E. & Swyer, G.I.M. (1974) Plasma progesterone estimation in infertile women under treatment with clomiphene and chorionic gonadotrophin. Journal of Obstetrics and Gynaecology of the British Commonwealth, 81, 107-112.

Renaud, R.L., Macer, J., Dervain, I., Ehret, M-C., Aron, C., Plas-Roser, S., Spira, A. & Pollack, H. (1980) Echographic study of follicular maturation and ovulation during the normal menstrual cycle. Fertility and Sterility, 33, 272-276.

Robertson, R.D., Picker, R.H., Wilson, P.C. & Saunders, D.M. (1979) The assessment of ovulation by ultrasound and plasma oestradiol measurements. Obstetrics and Gynaecology, 54, 686-691.

Rock, J.A., Dubin, N.H., Ghodgaonkar, R.B., Bergquist, C.A., Erozan, Y.S. & Kimball, Ali. (1982) Cul-de-sac fluid in women with endometriosis : fluid volume and prostanoid concentration during the proliferative phase of the cycle - days 8-12. Fertility and Sterility, 37, 747-750.

Rosenberg, S.M., Luciano, A.A. & Riddick, D.H. (1980) The luteal phase defect : the relative frequency of an encouraging response to treatment with vaginal progesterone. Fertility and Sterility, 34, 17-20.

Rosenfeld, D.L. & Garcia, C. (1976) A comparison of endometrial histology with simultaneous plasma progesterone determinations in infertile women. Fertility and Sterility, 27, 1256-1266.

Ross, G.T., Cargille, C.M., Lipsett, M.B., Rayford, P.L., Marshall, J.R., Strott, C.A. & Robbard, D. (1970) Pituitary and gonadal hormones in women during spontaneous and induced ovulatory cycles. Recent Progress in Hormone Research, 26, 1-62.

Sallam, H.N., Marinho, A.O., Collins, W.P., Rodeck, C.H. & Campbell, S. (1982) Monitoring gonadotrophin therapy by real-time ultrasonic scanning of ovarian follicles. British Journal of Obstetrics and Gynaecology, 89, 155-159.

Sallam, H.N., Whitehead, M.I. & Collins, W.P. (1983) Incidence of mature follicles in spontaneous and induced ovarian cycles. (letter) Lancet, i, 357.

Sarris, S., Swyer, G.I.M., McGarrigle, H.H.G., Lawrence, D.M., Little, V. & Lachelin, G.C.L. (1978) Prolactin and luteal insufficiency. Clinical Endocrinology, 9, 543-547.

Saunders, D.M., Hunter, J.C., Haase, H.R. & Wilson, G.R. (1979) Treatment of luteal phase inadequacy with bromocriptine. Obstetrics and Gynaecology, 53, 287-289.

Seppala, M., Hirvonen, E. & Ranta, T. (1976) Hyperprolactinaemia and luteal insufficiency. Lancet, i, 229-230.

Shangold, M., Berkeley, A. & Gray, J. (1983) Both mid-luteal serum progesterone levels and late luteal endometrial histology should be assessed in all infertile women. Fertility and Sterility, 40, 627-630.

Shepard, M.K. & Senturia, Y.D. (1977) Comparison of serum progesterone and endometrial biopsy for confirmation of ovulation and evaluation of luteal function. Fertility and Sterility, 28, 541-548.

Sherman, B.M. & Korenman, S.G. (1974) Measurement of plasma LH, FSH, estradiol and progesterone in disorders of the human menstrual cycle : the short luteal phase. Journal of Clinical Endocrinology and Metabolism, 38, 89-93.

Sherman, B.M. & Korenman, S.G. (1974) Measurement of plasma LH, FSH, estradiol and progesterone in disorders of the human menstrual cycle : the inadequate luteal phase. Journal of Clinical Endocrinology and Metabolism, 39, 145-149.

Shulman, S. (1986) Infertility as caused by sperm antibodies. Gynaecological and Obstetrical Investigation, 22, 113-127.

Sir, T., Alba, F., Kohen, P., Navarro, V. & Devoto, L. (1987) Hormonal and ultrasound profile of luteinized unruptured follicle following pulsatile gonadotrophin releasing hormone infusion. Case report. British Journal of Obstetrics and Gynaecology, 94, 791-794.

Smith, D.H., Picker, R.H., Sinosich, M. & Saunders, D.M. (1980) Assessment of ovulation by ultrasound and estradiol levels during spontaneous and induced cycles. Fertility and Sterility, 33, 387-390.

Smith, D.H., Picker, R.H., Sinosich, M.J., Saunders, D.M. & Grudzinskas, J.G. (1983) Effects of clomiphene administration on ovarian function as measured by estradiol and ultrasound. Obstetrics and Gynaecology, 61, 695-697.

Smith, S.K., Lenton, E.A. & Cooke, I.D. (1983) Pre-menstrual levels of 17B-oestradiol and progesterone in plasma in cycles of short and normal luteal phase length. Clinical Reproduction and Fertility, 2, 261-267.

Smith, S.K., Lenton, E.A., Landgren, B-M. & Cooke, I.D. (1984) The short luteal phase and infertility. British Journal of Obstetrics and Gynaecology, 91, 1120-1122.

Sobowale, O., Lenton, E.A., Francis, B. & Cooke, I.D. (1978) Comparison of plasma steroid and gonadotrophin profiles in spontaneous cycles in which conception did and did not occur. British Journal of Obstetrics and Gynaecology, 85, 460-467.

Soules, M.R., Wiebe, R.H., Aksel, S. & Hammond, C.B. (1977) The diagnosis and therapy of luteal phase deficiency. Fertility and Sterility, 28, 1033-1037.

Soules, M.R., Sutton, G.P., Hammond, C.B. & Haney, A.F. (1980) Endocrine changes at operation under general anaesthesia : reproductive hormone fluctuations in young women. Fertility and Sterility, 33, 364-371.

Soules, M.R., Hughes, C.R., Aksel, S., Tyrey, L. & Hammond, C.B. (1981) The function of the corpus luteum of pregnancy in ovulatory dysfunction and luteal phase deficiency. Fertility and Sterility, 36, 31-36.

Soules, M.R., Steiner, R.A., Clifton, D.K., Cohen, N.L., Aksel, S. & Bremner, W.J. (1984) Progesterone modulation of pulsatile luteinizing hormone secretion in normal women. Journal of Clinical Endocrinology and Metabolism, 58, 378-383.

Soules, M.R., Steiner, R.A., Clifton, D.K. & Bremner, W.J. (1984) Abnormal patterns of pulsatile luteinizing hormone in women with luteal phase deficiency. Obstetrics and Gynaecology, 63, 626-629.

Stanger, J.D. & Yovich, J.L. (1984) Failure of human oocyte release at ovulation. Fertility and Sterility, 41, 827-832.

Stanger, J.D. & Yovich, J.L. (1985) Reduced in-vitro fertilisation of human oocytes from patients with raised basal luteinizing hormone levels during the follicular phase. British Journal of Obstetrics and Gynaecology, 92, 385-393.

Stouffer, R.L. & Hodgen, G.D. (1980) Induction of luteal phase defects in rhesus monkeys by follicular fluid administration at the onset of the menstrual cycle. Journal of Clinical Endocrinology and Metabolism, 51, 669-671.

Stouffer, R.L., Hodgen, G.D., Ottobre, A.C. & Christian, C.D. (1984) Follicular fluid treatment during the follicular versus luteal phase of the menstrual cycle : effects on corpus luteum function. Journal of Clinical Endocrinology and Metabolism, 58, 1027-1033.

Tan, G.J., Tweedale, R. & Biggs, J.S.G. (1982) Oxytocin may play a role in the control of the human corpus luteum. Journal of Endocrinology, 95, 65-70.

Taylor, P.J., Leader, A. & Pattinson, H.A. (1985) Unexplained infertility : a reappraisal. International Journal of Fertility, 30, 53-56.

Templeton, A.A. & Penney, G.C. (1982) The incidence, characteristics and prognosis of patients whose infertility is unexplained. Fertility and Sterility, 37, 175-182.

Testart, J., Thebault, A., Souderes, E. & Frydman, R. (1982) Premature ovulation after ovarian ultrasonography. British Journal of Obstetrics and Gynaecology, 89, 694-700.

Tho, P.T., Byrd, J.R. & McDonough, P.G. (1979) Etiologies and subsequent reproductive performance of 100 couples with recurrent abortion. Fertility and Sterility, 32, 389-395.

Thomas, E.J. & Cooke, I.D. (1987) Successful treatment of asymptomatic endometriosis : does it benefit infertile women. British Medical Journal, 294, 1117-1119.

Van Hall, E.V. & Mastboom, J.L. (1969) Luteal phase insufficiency in patients treated with clomiphene. American Journal of Obstetrics and Gynaecology, 103, 165-171.

Vanrell, J.A., Balasch, J., Fuster, J.S. & Fuster, R. (1982) Ovulation stigma in fertile women. Fertility and Sterility, 37, 712-713.

Vanrell, J.A.. & Balasch, J. (1983) Prolactin in the evaluation of luteal phase in infertility. Fertility and Sterility, 39, 30-33.

Verkauf, B.S. (1983) The incidence and outcome of single factor, multifactorial, and unexplained imfertility. American Journal of Obstetrics and Gynaecology, 147, 175-181.

Wathes, D.C. & Swann, R.W. (1982) Is oxytocin an ovarian hormone? Nature, 297, 225-227.

Wentz, A.C. (1982) Diagnosing luteal phase inadequacy. Fertility and Sterility, 37, 334-335.

Whittaker, P.G., Taylor, A. & Lind, T. (1983) Unsuspected pregnancy loss in healthy women. Lancet, i, 1126-1127.

Ylikorkala, O., Koskimies, A., Laatkainen, T., Tenhunen, A. & Viinikka, L. (1984) Peritoneal fluid prostaglandins in endometriosis, tubal disorders and unexplained infertility. Obstetrics and Gynaecology, 63, 616-620.

Ylostalo, P., Ronnberg, L. & Jouppila, P. (1979) Measurement of the ovarian follicle by ultrasound in ovulation induction. Fertility and Sterility, 31, 651-655.

Yovich, J.L., McColm, S.C., Yovich, J.M. & Matson, P.L. (1985) Early luteal serum progesterone concentrations are higher in pregnancy cycles. Fertility and Sterility, 44, 185-189.

Yovich, J.L., Stanger, J.D., Yovich, J.M., Tuvik, A.I. & Turner, S.R. (1985) Hormonal profiles in the follicular phase, luteal phase and first trimester of pregnancies arising from in-vitro fertilisation. British Journal of Obstetrics and Gynaecology, 92; 374-384.

Zegers-Hochschild, F., Lira, C.G., Parada, M. & Lorenzini, E.A. (1984) A comparative study of the follicular growth profile in conception and non-conception cycles. Fertility and Sterility, 41, 244-247.

Zimmerman, R., Bohnet, H.G., Werise, H.C. & Leidenberger, F.A. (1984) Preliminary report about a modified gonadotropin (human menopausal gonadotropin/human chorionic gonadotropin) treatment in infertile patients with premature luteinization. Fertility and Sterility, 41, 714-718.

Zorn, J.R., Roger, M., Savage, M. & Grenier, J. (1982) Steroid hormone levels in peritoneal fluid during the periovulatory period. Fertility and Sterility, 38, 162-165.

**********

# THE USE OF OVARIAN ULTRASOUND AND BIOCHEMISTRY IN THE INVESTIGATION AND MANAGEMENT OF THE FEMALE PARTNER IN COUPLES WITH UNEXPLAINED INFERTILITY

(2 VOLUMES)

VOLUME II

(Figures & Tables)

Mark Patrick Rogers HAMILTON ©

M.B.Ch.B., M.R.C.O.G.

Thesis submitted to
The University of Glasgow
for the degree of
Doctor of Medicine

Original research carried out in the
University Department of Obstetrics & Gynaecology,
Glasgow Royal Infirmary
&
Department of Midwifery,
Queen Mother's Hospital, Glasgow

November 1988

CHAPTER 2

ESTABLISHMENT OF NORMAL RANGES

## 5.2 POOR PROGESTERONE SURGE (PPS)

## 5.3 HIGH LH



## 5.4 POOR FOLLICULAR MATURATION

- Poor Follicular Maturation (PFM)
- Poor Follicular Development (PFD)

## 5.5 ABNORMALITIES OF CYCLE PHASE LENGTH

- Short Luteal Phase (SLP)
- Long Follicular Phase (LFP)
- Short Follicular Phase (SFP)

## CHAPTER 6

## CYCLE TO CYCLE VARIATION IN OVARIAN FUNCTION

CHAPTER 7

PERITONEAL FLUID STUDY



**********

Table 2.1

Radio-immuno assay technical details

| Hormone | 17-B estradiol | Progesterone | FSH | LH |
|---|---|---|---|---|
| Antigen | estradiol-6-O-carboxymethyl oxime | Progesterone -11 alpha-hemisuccinate | FSH | hCG |
| Major cross reactions | Oestriol (11%) | Deoxycorticosterone (11%) | None | hCG (100%) |
| | Oestrone (1.2%) | 20 alpha dihydroprogesterone (1.2%) | | |
| Precision of Assay inter- | 11.3% | 11.8% | 8.1% | 7.4% |
| Precision of Assay intra- | 10.2% | 9.2% | 3.8% | 4.2% |
| Minimum Sensitivity | 10pg/ml | 20pg/ml | 1IU/l | 2IU/l |

(Coutts et al 1981)

Table 2.2

Controls

Patient/cycle characteristics

| | Nos | Mean | SD | SEM | Median | Range |
|---|---|---|---|---|---|---|
| AGE (Years) | | | | | | |
| | 43 | 26.4 | 4.2 | 0.6 | 26 | 18-36 |
| FOLLICULAR PHASE (Days) | | | | | | |
| | 43 | 14.3 | 2.9 | 0.4 | 14 | 10-21 |
| LUTEAL PHASE (Days) | | | | | | |
| | 43 | 15.1 | 1.0 | 0.2 | 15 | 13-17 |
| CYCLE LENGTH (Days) | | | | | | |
| | 43 | 29.5 | 3.1 | 0.5 | 29 | 24-35 |

Table 2.3

Group 1 (U/S) vs Group 2 (U/S + Bioch)

Follicular diameters (mm)

| | Gp. | Mean | SD | n | t | p |
|---|---|---|---|---|---|---|
| Day -5 | 1 | 11.5 | 2.15 | 4 | 1.09 | >0.1 |
| | 2 | 13.0 | 2.3 | 10 | | |
| Day -4 | 1 | 13.1 | 1.9 | 8 | 1.93 | >0.05 |
| | 2 | 14.8 | 1.6 | 8 | | |
| Day -3 | 1 | 16.1 | 3.7 | 11 | 0.46 | >0.1 |
| | 2 | 15.4 | 2.0 | 7 | | |
| Day -2 | 1 | 17.5 | 3.4 | 12 | 0.60 | >0.5 |
| | 2 | 18.3 | 2.3 | 9 | | |
| Day -1 | 1 | 19.6 | 2.9 | 11 | 0.58 | >0.5 |
| | 2 | 20.2 | 2.0 | 12 | | |
| Day 0 | 1 | 19.9 | 5.2 | 11 | 0.42 | >0.5 |
| | 2 | 20.6 | 1.7 | 11 | | |

Table 2.4

Group 2 (Biochemistry & U/S) vs. Group 3 (Biochemistry)

Plasma E2 concentrations (pg/ml)

| | Group | mean | SD | Nos. | t | p |
|---|---|---|---|---|---|---|
| Day -8 | 2 | 85 | 10.3 | 13 | 0.78 | >0.1 |
| | 3 | 92 | 30.1 | 11 | | |
| Day -4 | 2 | 122 | 21.9 | 15 | 2.61 | >0.01 |
| | 3 | 148 | 29.7 | 12 | | |
| Day -3 | 2 | 153 | 35.4 | 15 | 1.53 | >0.1 |
| | 3 | 176 | 42.8 | 12 | | |
| Day -2 | 2 | 192 | 46.3 | 15 | 1.03 | >0.1 |
| | 3 | 215 | 67.6 | 11 | | |
| Day -1 | 2 | 216 | 48.7 | 15 | 1.34 | >0.1 |
| | 3 | 244 | 62.4 | 12 | | |
| Day 0 | 2 | 189 | 42.9 | 14 | 1.60 | >0.1 |
| | 3 | 223 | 64.2 | 12 | | |
| Day +1 | 2 | 130 | 32.8 | 16 | 1.70 | >0.1 |
| | 3 | 107 | 40.4 | 12 | | |
| Day +2 | 2 | 137 | 32.8 | 16 | 2.24 | >0.02 |
| | 3 | 112 | 23.7 | 12 | | |
| Day +8 | 2 | 171 | 53.2 | 16 | 0.58 | >0.5 |
| | 3 | 160 | 46.2 | 11 | | |
| E2 Index | 2 | 182 | 21.8 | 16 | 1.10 | >0.1 |
| | 3 | 194 | 37.1 | 12 | | |

Table 2.5

Group 2 (Bioch & U/S) vs Group 3 (Bioch)

Plasma P concentrations (ng/ml)

| | Group | mean | SD | Nos | t | p |
|---|---|---|---|---|---|---|
| Day 0 | 2 | 0.8 | 0.5 | 10 | 2.00 | >0.05 |
| | 3 | 1.2 | 0.3 | 11 | | |
| Day +1 | 2 | 1.7 | 0.9 | 16 | 2.00 | >0.05 |
| | 3 | 2.3 | 0.7 | 12 | | |
| Day +2 | 2 | 3.3 | 0.9 | 15 | 5.35 | <0.001 |
| | 3 | 5.7 | 1.5 | 12 | | |
| Day +3 | 2 | 7.6 | 3.8 | 16 | 1.40 | >0.1 |
| | 3 | 9.4 | 2.7 | 12 | | |
| Day +4 | 2 | 12.1 | 5.2 | 15 | 1.62 | >0.1 |
| | 3 | 15.1 | 4.2 | 12 | | |
| Day +5 | 2 | 17.0 | 4.9 | 16 | 0.45 | >0.5 |
| | 3 | 17.9 | 5.6 | 12 | | |
| Day +6 | 2 | 18.1 | 5.9 | 16 | 0.86 | >0.1 |
| | 3 | 20.0 | 5.7 | 12 | | |
| P Index (Sum +2-+6) | 2 | 58.5 | 16.5 | 16 | 1.94 | >0.05 |
| | 3 | 70.6 | 16.1 | 12 | | |

Table 2.6

Group 2 (Bioch & U/S) vs Group 3 (Bioch)

Plasma FSH concentrations (IU/l)

| | Group | mean | SD | Nos | t | p |
|---|---|---|---|---|---|---|
| Day -5 | 2 | 4.7 | 2.3 | 15 | 0.32 | >0.5 |
| | 3 | 4.4 | 2.4 | 12 | | |
| Day -2 | 2 | 4.6 | 3.6 | 16 | 1.40 | >0.1 |
| | 3 | 3.3 | 1.5 | 11 | | |
| Day -1 | 2 | 6.2 | 5.1 | 15 | 0.93 | >0.1 |
| | 3 | 4.6 | 3.4 | 12 | | |
| Day 0 | 2 | 10.4 | 4.4 | 14 | 0.42 | >0.5 |
| | 3 | 11.2 | 5.2 | 12 | | |
| Day +1 | 2 | 8.2 | 5.9 | 16 | 1.47 | >0.1 |
| | 3 | 5.2 | 1.9 | 9 | | |
| Day +2 | 2 | 4.5 | 2.3 | 15 | 0.45 | >0.5 |
| | 3 | 5.1 | 4.5 | 12 | | |
| Day +8 | 2 | 2.4 | 1.2 | 13 | 0.43 | >0.5 |
| | 3 | 2.2 | 1.1 | 12 | | |

Table 2.7

Group 2 (Bioch & U/S) vs Group 3 (Bioch)

Plasma LH concentrations (IU/l)

| | Group | mean | SD | Nos. | t | p |
|---|---|---|---|---|---|---|
| Day -5 | 2 | 8.7 | 3.3 | 15 | 0.98 | >0.1 |
| | 3 | 7.5 | 3.1 | 12 | | |
| Day -2 | 2 | 10.9 | 4.6 | 16 | 0.51 | >0.5 |
| | 3 | 10.1 | 2.1 | 11 | | |
| Day -1 | 2 | 19.5 | 11.9 | 15 | 0.70 | >0.1 |
| | 3 | 16.9 | 5.3 | 12 | | |
| Day 0 | 2 | 62.9 | 21.6 | 14 | 0.03 | >0.5 |
| | 3 | 63.2 | 29.7 | 12 | | |
| Day +1 | 2 | 27.7 | 16.4 | 16 | 0.62 | >0.5 |
| | 3 | 23.5 | 17.1 | 10 | | |
| Day +2 | 2 | 13.4 | 6.1 | 15 | 1.45 | >0.1 |
| | 3 | 10.6 | 3.2 | 12 | | |
| Day +8 | 2 | 6.4 | 3.1 | 13 | 0.20 | >0.5 |
| | 3 | 6.1 | 4.5 | 12 | | |

Table 2.8

Controls

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 23 | 75.0 | 79.7 | 21.3 | 4.4 | 70.5 | 88.8 |
| -9 | 24 | 90.0 | 87.9 | 17.0 | 3.5 | 80.7 | 95.1 |
| -8 | 26 | 88.0 | 87.2 | 23.9 | 4.7 | 77.6 | 96.8 |
| -7 | 27 | 95.0 | 92.5 | 22.0 | 4.2 | 83.8 | 101.2 |
| -6 | 24 | 100.0 | 100.3 | 21.1 | 4.3 | 91.4 | 109.2 |
| -5 | 28 | 115.0 | 114.5 | 27.6 | 5.2 | 103.8 | 125.2 |
| -4 | 27 | 130.0 | 133.2 | 28.3 | 5.4 | 122.0 | 144.4 |
| -3 | 27 | 150.0 | 162.9 | 39.8 | 7.7 | 147.2 | 178.6 |
| -2 | 26 | 202.5 | 201.6 | 56.3 | 11.0 | 178.9 | 224.3 |
| -1 | 27 | 220.0 | 228.4 | 55.8 | 10.7 | 206.4 | 250.4 |
| 0 | 26 | 210.0 | 204.6 | 55.4 | 10.9 | 182.2 | 227.0 |
| +1 | 28 | 124.0 | 120.4 | 37.5 | 7.1 | 105.9 | 134.9 |
| +2 | 28 | 107.5 | 109.5 | 28.8 | 5.4 | 98.4 | 120.6 |
| +3 | 28 | 125.0 | 129.2 | 44.5 | 8.4 | 112.0 | 146.4 |
| +4 | 28 | 135.0 | 139.5 | 42.3 | 8.0 | 123.1 | 155.9 |
| +5 | 27 | 150.0 | 150.3 | 43.3 | 8.3 | 133.2 | 167.4 |
| +6 | 28 | 145.0 | 159.1 | 46.7 | 8.8 | 141.0 | 177.2 |
| +7 | 27 | 160.0 | 159.6 | 41.2 | 7.9 | 143.3 | 175.9 |
| +8 | 27 | 155.0 | 166.6 | 49.9 | 9.6 | 146.9 | 186.3 |
| +9 | 26 | 168.0 | 165.6 | 50.3 | 9.9 | 145.3 | 185.9 |
| +10 | 20 | 134.0 | 138.2 | 53.6 | 11.9 | 113.3 | 163.1 |
| +11 | 16 | 102.5 | 116.2 | 53.0 | 13.3 | 88.0 | 144.4 |
| +12 | 16 | 105.0 | 108.1 | 36.9 | 9.2 | 88.4 | 127.8 |
| +13 | 14 | 79.0 | 85.5 | 33.3 | 9.0 | 66.1 | 104.9 |
| +14 | 6 | 80.0 | 89.7 | 31.3 | 13.0 | 56.2 | 123.2 |

FIGURE 2.1

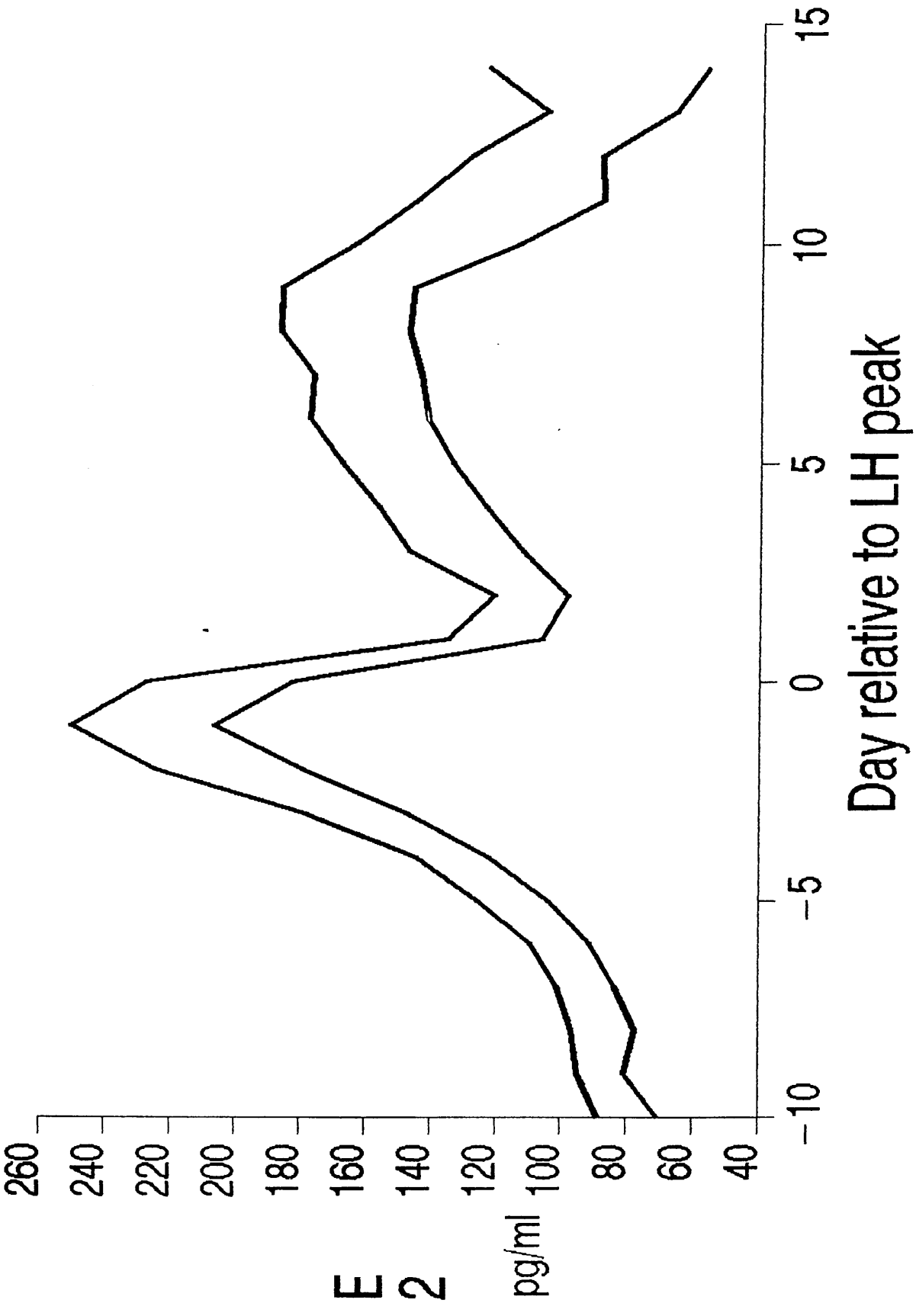

Controls plasma E2
95% confidence limits of mean
E 2
pg/ml
260
240
220
200
180
160
140
120
100
80
60
40
−10
−5
0
5
10
15
Day relative to LH peak

Table 2.9

Controls

E2 Index (pg/ml)

| | | Actual | Corrected (%) |
|---|---|---|---|
| Mean | | 186.9 | 100.0 |
| SD | | 29.4 | 15.7 |
| SEM | | 5.6 | 3.0 |
| 95% | low | 175.5 | 93.9 |
| | high | 198.3 | 106.1 |

Table 2.10

Controls

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| 0 | 21 | 0.9 | 1.0 | 0.4 | 0.1 | 0.8 | 1.2 |
| +1 | 28 | 1.9 | 2.0 | 0.8 | 0.2 | 1.7 | 2.3 |
| +2 | 27 | 4.0 | 4.3 | 1.7 | 0.3 | 3.6 | 5.0 |
| +3 | 28 | 8.4 | 8.4 | 3.4 | 0.7 | 7.1 | 9.7 |
| +4 | 27 | 14.0 | 13.4 | 4.9 | 1.0 | 11.4 | 15.4 |
| +5 | 28 | 17.0 | 17.4 | 5.2 | 1.0 | 15.4 | 19.4 |
| +6 | 28 | 18.9 | 18.9 | 5.8 | 1.1 | 16.7 | 21.1 |
| +7 | 28 | 19.1 | 19.0 | 5.2 | 1.0 | 17.0 | 21.0 |
| +8 | 28 | 18.5 | 18.3 | 6.0 | 1.1 | 16.0 | 20.6 |
| +9 | 26 | 14.8 | 15.6 | 6.6 | 1.3 | 12.9 | 18.3 |
| +10 | 19 | 12.2 | 11.6 | 6.9 | 1.6 | 8.3 | 14.9 |
| +11 | 17 | 5.4 | 6.0 | 3.9 | 0.9 | 4.0 | 8.0 |
| +12 | 16 | 1.9 | 3.5 | 3.9 | 1.0 | 1.4 | 5.6 |
| +13 | 13 | 1.2 | 2.3 | 2.5 | 0.7 | 0.8 | 3.8 |
| +14 | 8 | 0.9 | 1.5 | 1.4 | 0.5 | 0.4 | 2.6 |

FIGURE 2.2

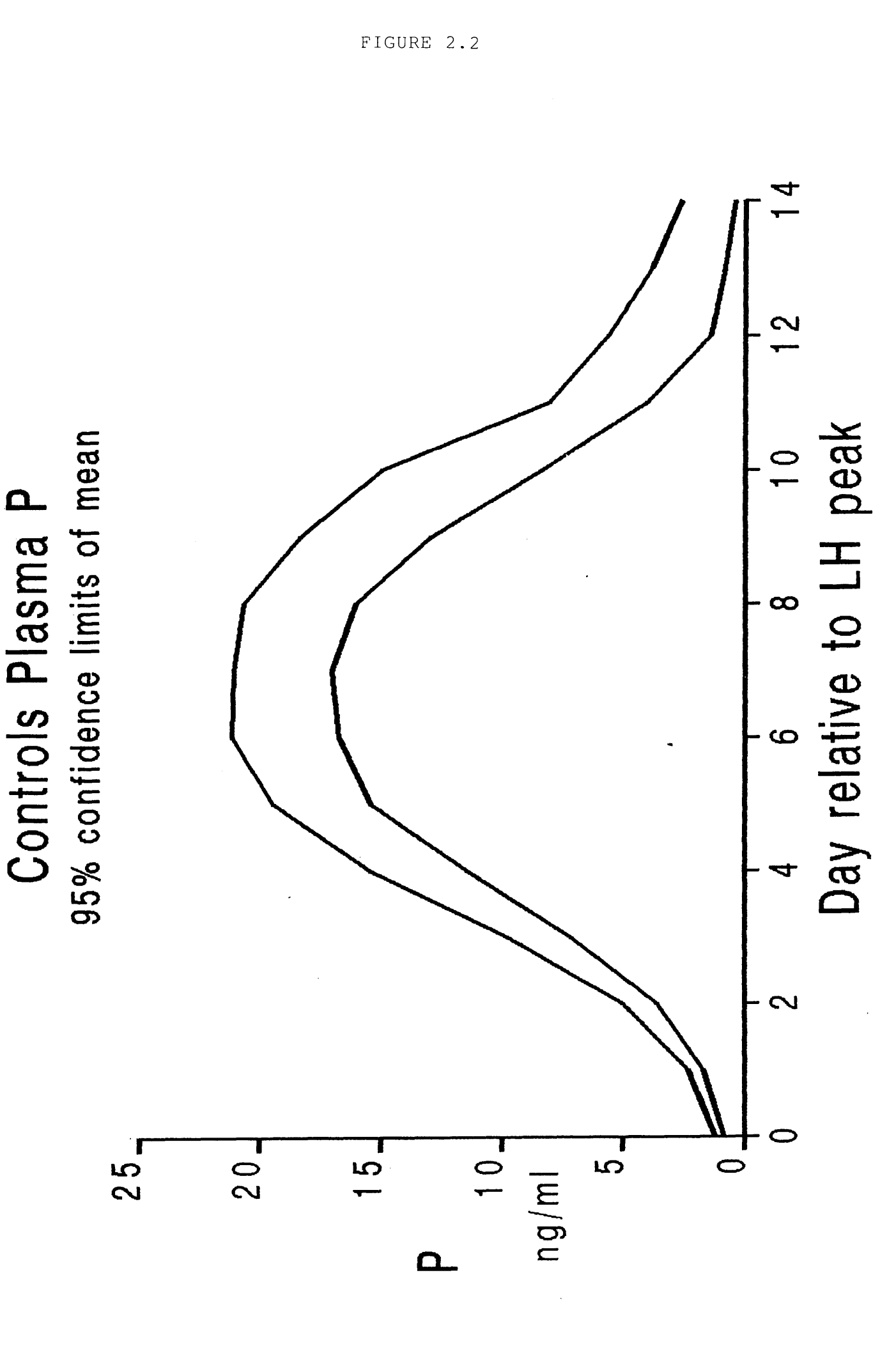

Controls Plasma P
95% confidence limits of mean
P
ng/ml
25
20
15
10
5
0
0
2
4
6
8
10
12
14
Day relative to LH peak

Table 2.11

Controls

P Index (ng/ml)

| | | Actual | Corrected |
|---|---|---|---|
| Nos | | 28 | 28 |
| Mean | | 63.7 | 100.0 |
| SD | | 17.2 | 27.0 |
| SEM | | 3.3 | 5.1 |
| 95% | low | 56.9 | 89.5 |
| | high | 70.5 | 110.5 |
| 99% | low | 54.8 | 85.9 |
| | high | 72.6 | 114.1 |

Table 2.12

Controls

Plasma FSH concentrations (IU/1)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 24 | 5.2 | 5.4 | 2.1 | 0.4 | 4.5 | 6.3 |
| -9 | 25 | 5.0 | 5.7 | 1.9 | 0.4 | 4.9 | 6.5 |
| -8 | 25 | 5.5 | 6.0 | 2.6 | 0.5 | 4.9 | 7.1 |
| -7 | 27 | 4.7 | 5.4 | 2.2 | 0.4 | 4.5 | 6.3 |
| -6 | 26 | 4.1 | 4.7 | 2.0 | 0.4 | 3.9 | 5.5 |
| -5 | 27 | 4.2 | 4.6 | 2.3 | 0.4 | 3.7 | 5.5 |
| -4 | 26 | 3.6 | 4.2 | 2.1 | 0.4 | 3.3 | 5.1 |
| -3 | 25 | 3.3 | 3.5 | 1.8 | 0.4 | 2.8 | 4.2 |
| -2 | 27 | 3.4 | 4.1 | 2.9 | 0.6 | 2.9 | 5.3 |
| -1 | 27 | 3.8 | 5.5 | 4.4 | 0.9 | 3.7 | 7.3 |
| 0 | 26 | 11.5 | 10.8 | 4.7 | 0.9 | 8.9 | 12.7 |
| +1 | 25 | 4.5 | 7.1 | 5.0 | 1.0 | 4.9 | 9.2 |
| +2 | 27 | 4.3 | 4.8 | 3.4 | 0.7 | 3.5 | 6.1 |
| +3 | 28 | 3.6 | 4.4 | 3.3 | 0.6 | 3.1 | 5.7 |
| +4 | 26 | 3.3 | 3.8 | 1.9 | 0.4 | 3.0 | 4.6 |
| +5 | 26 | 2.7 | 3.2 | 1.7 | 0.3 | 2.5 | 3.9 |
| +6 | 26 | 2.1 | 2.7 | 1.3 | 0.3 | 2.2 | 3.2 |
| +7 | 24 | 2.0 | 2.3 | 1.2 | 0.2 | 1.8 | 2.8 |
| +8 | 25 | 2.1 | 2.3 | 1.1 | 0.2 | 1.8 | 2.8 |
| +9 | 25 | 1.8 | 2.0 | 1.1 | 0.2 | 1.6 | 2.4 |
| +10 | 20 | 1.9 | 2.0 | 1.1 | 0.2 | 1.5 | 2.5 |
| +11 | 17 | 1.9 | 2.1 | 1.2 | 0.3 | 1.5 | 2.5 |
| +12 | 17 | 2.3 | 2.6 | 1.8 | 0.4 | 1.7 | 3.5 |
| +13 | 13 | 2.9 | 3.2 | 2.2 | 0.6 | 1.9 | 4.5 |
| +14 | 9 | 3.5 | 3.9 | 2.6 | 0.9 | 1.9 | 5.9 |

FIGURE 2.3

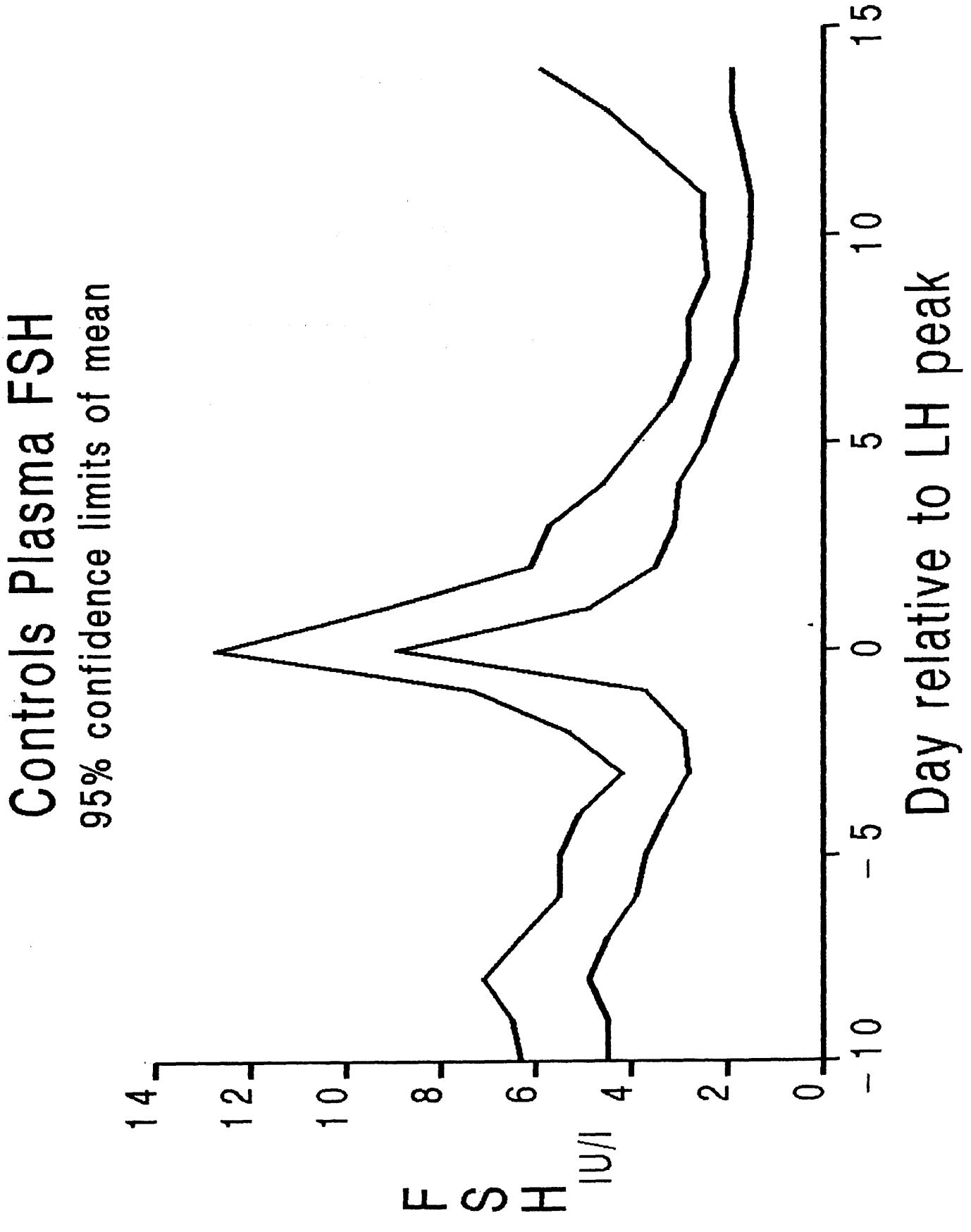

Controls Plasma FSH
95% confidence limits of mean
FSH IU/l
14
12
10
8
6
4
2
0
−10
−5
0
5
10
15
Day relative to LH peak

Table 2.13

Controls

Plasma LH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 24 | 7.3 | 8.2 | 3.9 | 0.8 | 6.6 | 9.8 |
| -9 | 25 | 8.0 | 8.3 | 3.0 | 0.6 | 7.0 | 9.6 |
| -8 | 25 | 8.4 | 8.9 | 3.5 | 0.7 | 7.5 | 10.3 |
| -7 | 27 | 8.3 | 8.7 | 3.3 | 0.6 | 7.4 | 10.0 |
| -6 | 26 | 7.7 | 8.2 | 3.1 | 0.6 | 6.9 | 9.5 |
| -5 | 27 | 8.1 | 8.1 | 3.2 | 0.6 | 6.8 | 9.4 |
| -4 | 26 | 7.7 | 7.7 | 2.5 | 0.5 | 6.7 | 8.7 |
| -3 | 25 | 8.6 | 8.9 | 3.7 | 0.8 | 7.4 | 10.4 |
| -2 | 27 | 10.0 | 10.6 | 3.7 | 0.7 | 9.1 | 12.1 |
| -1 | 27 | 16.5 | 18.3 | 9.5 | 1.8 | 14.6 | 22.0 |
| 0 | 26 | 73.5 | 63.0 | 25.1 | 4.9 | 52.9 | 73.1 |
| +1 | 26 | 18.7 | 26.1 | 16.5 | 3.2 | 19.4 | 32.8 |
| +2 | 27 | 11.6 | 12.1 | 5.1 | 0.9 | 10.2 | 14.0 |
| +3 | 28 | 11.1 | 11.3 | 4.9 | 1.0 | 9.2 | 13.2 |
| +4 | 26 | 9.8 | 10.8 | 5.4 | 1.0 | 8.6 | 13.0 |
| +5 | 26 | 8.1 | 8.5 | 4.1 | 0.8 | 6.8 | 10.2 |
| +6 | 26 | 6.7 | 8.7 | 5.6 | 1.1 | 6.4 | 11.0 |
| +7 | 24 | 5.3 | 6.2 | 4.4 | 0.9 | 4.3 | 8.1 |
| +8 | 25 | 5.7 | 6.2 | 3.8 | 0.8 | 4.6 | 7.8 |
| +9 | 25 | 6.3 | 6.8 | 4.2 | 0.8 | 5.1 | 8.5 |
| +10 | 19 | 5.4 | 6.0 | 3.5 | 0.8 | 4.3 | 7.7 |
| +11 | 18 | 4.6 | 5.4 | 2.9 | 0.7 | 4.0 | 6.8 |
| +12 | 17 | 5.7 | 6.8 | 4.0 | 1.0 | 4.7 | 8.9 |
| +13 | 13 | 7.0 | 9.4 | 7.0 | 2.0 | 5.1 | 13.7 |
| +14 | 8 | 6.6 | 6.7 | 2.6 | 0.9 | 4.5 | 8.9 |

FIGURE 2.4

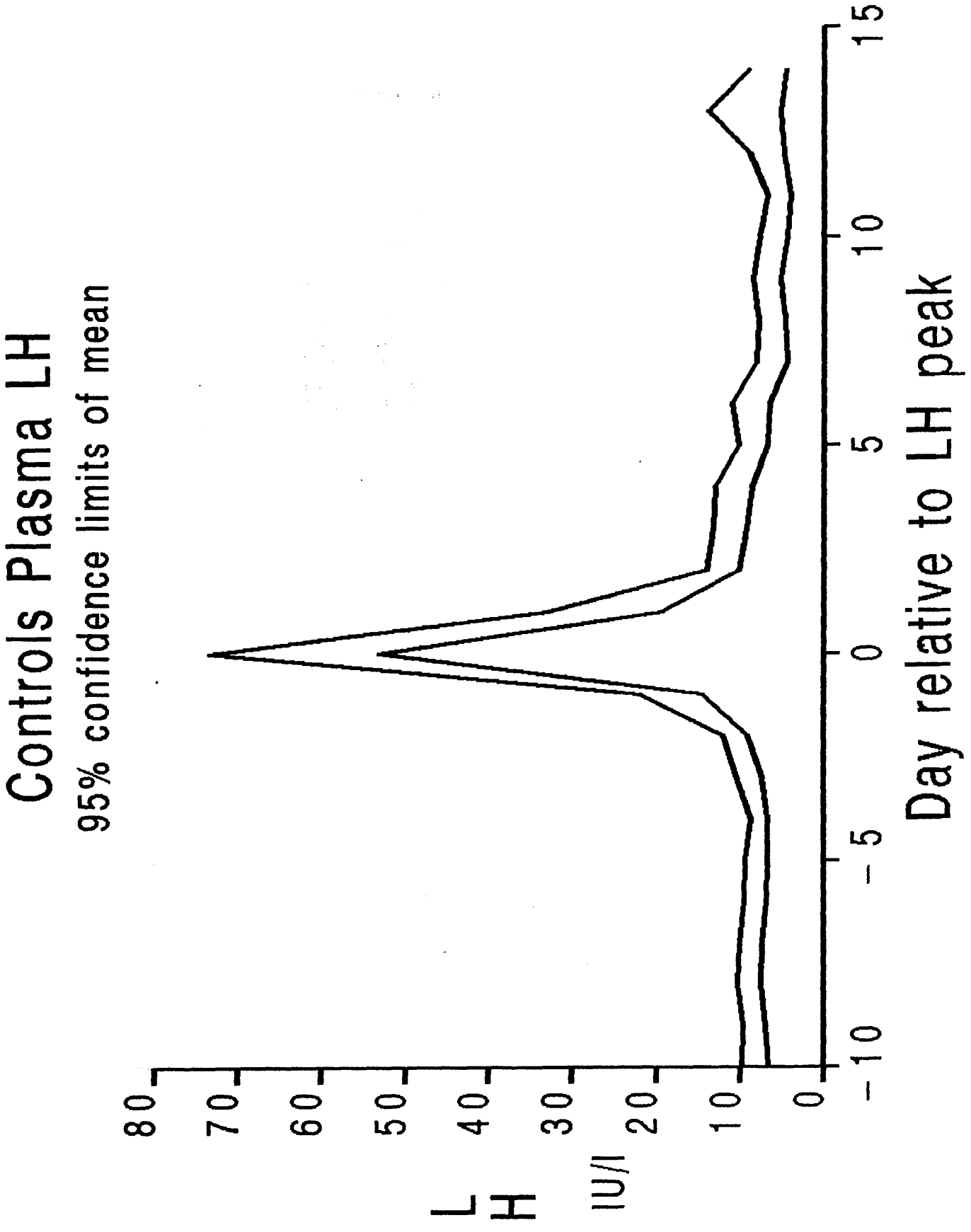

Controls Plasma LH
95% confidence limits of mean
LH IU/l
80
70
60
50
40
30
20
10
0
−10
−5
0
5
10
15
Day relative to LH peak

Table 2.14

Controls

Plasma LH : FSH ratio

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 24 | 1.4 | 1.6 | 0.8 | 0.2 | 1.2 | 2.0 |
| -9 | 25 | 1.5 | 1.6 | 0.9 | 0.2 | 1.2 | 2.0 |
| -8 | 25 | 1.6 | 1.7 | 0.7 | 0.1 | 1.5 | 1.9 |
| -7 | 27 | 1.7 | 1.8 | 0.8 | 0.2 | 1.4 | 2.2 |
| -6 | 26 | 1.8 | 2.0 | 1.1 | 0.2 | 1.6 | 2.4 |
| -5 | 27 | 1.9 | 2.2 | 1.3 | 0.3 | 1.6 | 2.8 |
| -4 | 26 | 1.9 | 2.3 | 1.5 | 0.3 | 1.7 | 2.9 |
| -3 | 25 | 2.8 | 2.9 | 1.6 | 0.3 | 2.3 | 3.5 |
| -2 | 27 | 3.0 | 3.3 | 1.6 | 0.3 | 2.7 | 3.9 |
| -1 | 27 | 4.5 | 4.4 | 2.4 | 0.5 | 3.4 | 5.4 |
| 0 | 26 | 6.1 | 6.6 | 3.8 | 0.7 | 5.2 | 8.0 |
| +1 | 25 | 3.9 | 4.2 | 2.5 | 0.5 | 3.2 | 5.2 |
| +2 | 27 | 2.9 | 3.2 | 1.8 | 0.3 | 2.6 | 3.8 |
| +3 | 28 | 2.9 | 3.2 | 1.5 | 0.3 | 2.6 | 3.8 |
| +4 | 26 | 3.0 | 3.2 | 1.7 | 0.3 | 2.6 | 3.8 |
| +5 | 26 | 2.8 | 2.9 | 1.4 | 0.3 | 2.3 | 3.5 |
| +6 | 26 | 3.1 | 3.3 | 1.9 | 0.4 | 2.5 | 4.1 |
| +7 | 24 | 2.9 | 2.9 | 1.4 | 0.3 | 2.3 | 3.5 |
| +8 | 25 | 3.2 | 2.9 | 1.2 | 0.2 | 2.5 | 3.3 |
| +9 | 25 | 3.7 | 3.8 | 2.0 | 0.4 | 3.0 | 4.6 |
| +10 | 18 | 3.0 | 3.3 | 1.9 | 0.4 | 2.5 | 4.1 |
| +11 | 16 | 2.5 | 2.7 | 1.6 | 0.4 | 1.9 | 3.5 |
| +12 | 16 | 2.3 | 2.9 | 1.9 | 0.5 | 1.9 | 3.9 |
| +13 | 12 | 2.0 | 3.1 | 3.1 | 0.9 | 1.1 | 5.1 |
| +14 | 8 | 1.5 | 1.9 | 1.0 | 0.4 | 1.0 | 2.8 |

FIGURE 2.5

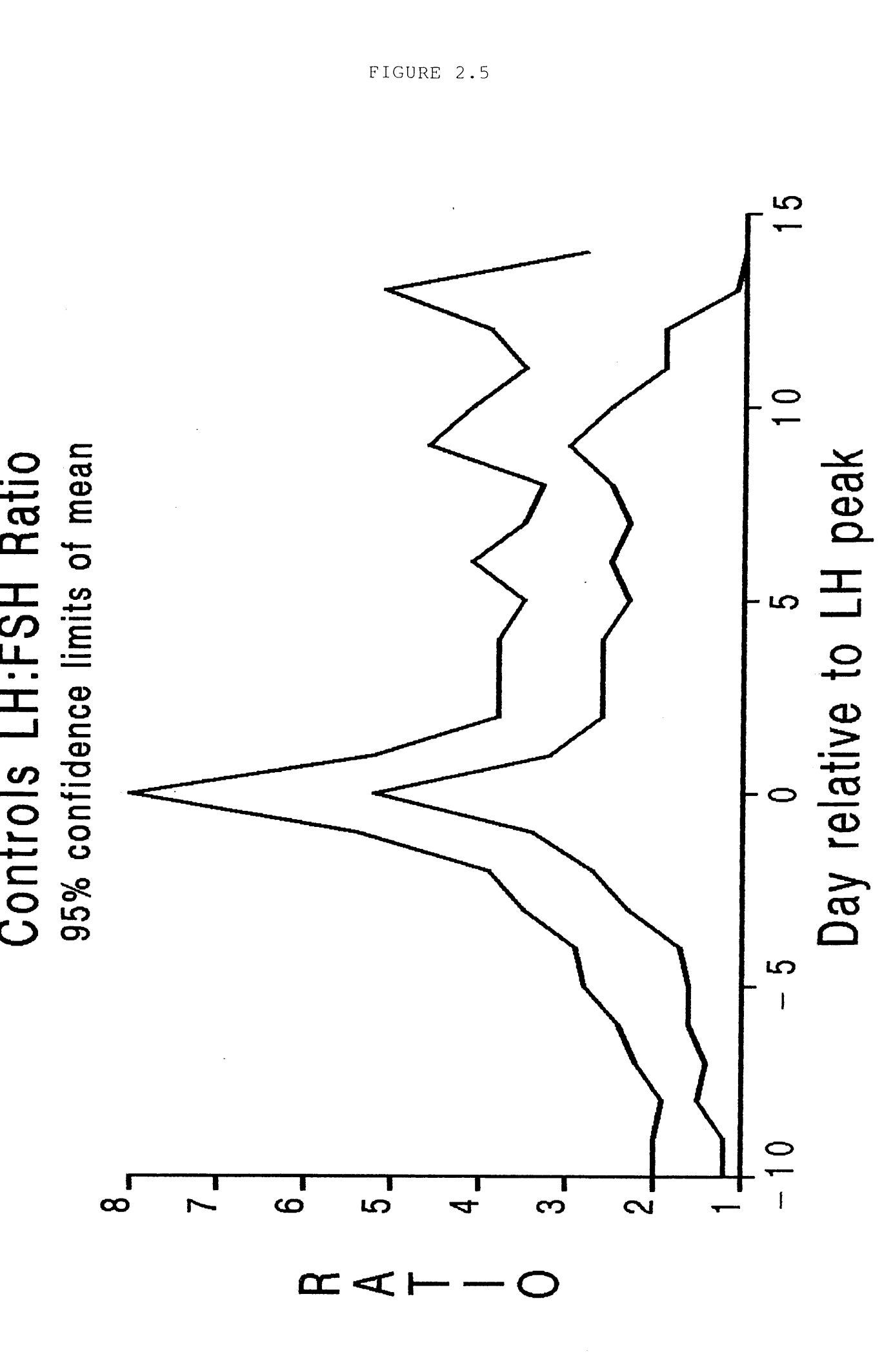

Controls LH:FSH Ratio
95% confidence limits of mean
RATIO
8
7
6
5
4
3
2
1
-10
-5
0
5
10
15
Day relative to LH peak

Table 2.15

Controls

Follicular diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -8 | 4 | 10.0 | 10.5 | 1.0 | 0.5 | 8.9 | 12.1 |
| -7 | 5 | 10.0 | 9.8 | 1.1 | 0.5 | 8.4 | 11.2 |
| -6 | 6 | 12.0 | 12.3 | 2.3 | 1.0 | 9.9 | 14.7 |
| -5 | 15 | 13.0 | 12.5 | 2.4 | 0.6 | 11.2 | 13.8 |
| -4 | 16 | 14.3 | 13.9 | 1.9 | 0.5 | 12.9 | 14.9 |
| -3 | 18 | 15.5 | 15.8 | 3.1 | 0.7 | 14.3 | 17.3 |
| -2 | 21 | 18.0 | 17.8 | 3.0 | 0.6 | 16.5 | 19.1 |
| -1 | 23 | 20.0 | 19.9 | 2.4 | 0.5 | 18.8 | 21.0 |
| 0 | 22 | 21.0 | 20.2 | 3.8 | 0.8 | 18.5 | 21.9 |
| +1 | 16 | 19.0 | 18.0 | 5.2 | 1.4 | 15.1 | 20.9 |
| +2 | 12 | 16.5 | 16.1 | 4.3 | 1.4 | 13.0 | 19.2 |
| +3 | 12 | 12.0 | 13.0 | 1.7 | 1.0 | 8.7 | 17.3 |
| +4 | 11 | 9.0 | 9.0 | 1.0 | 0.6 | 6.5 | 11.5 |

FIGURE 2.6

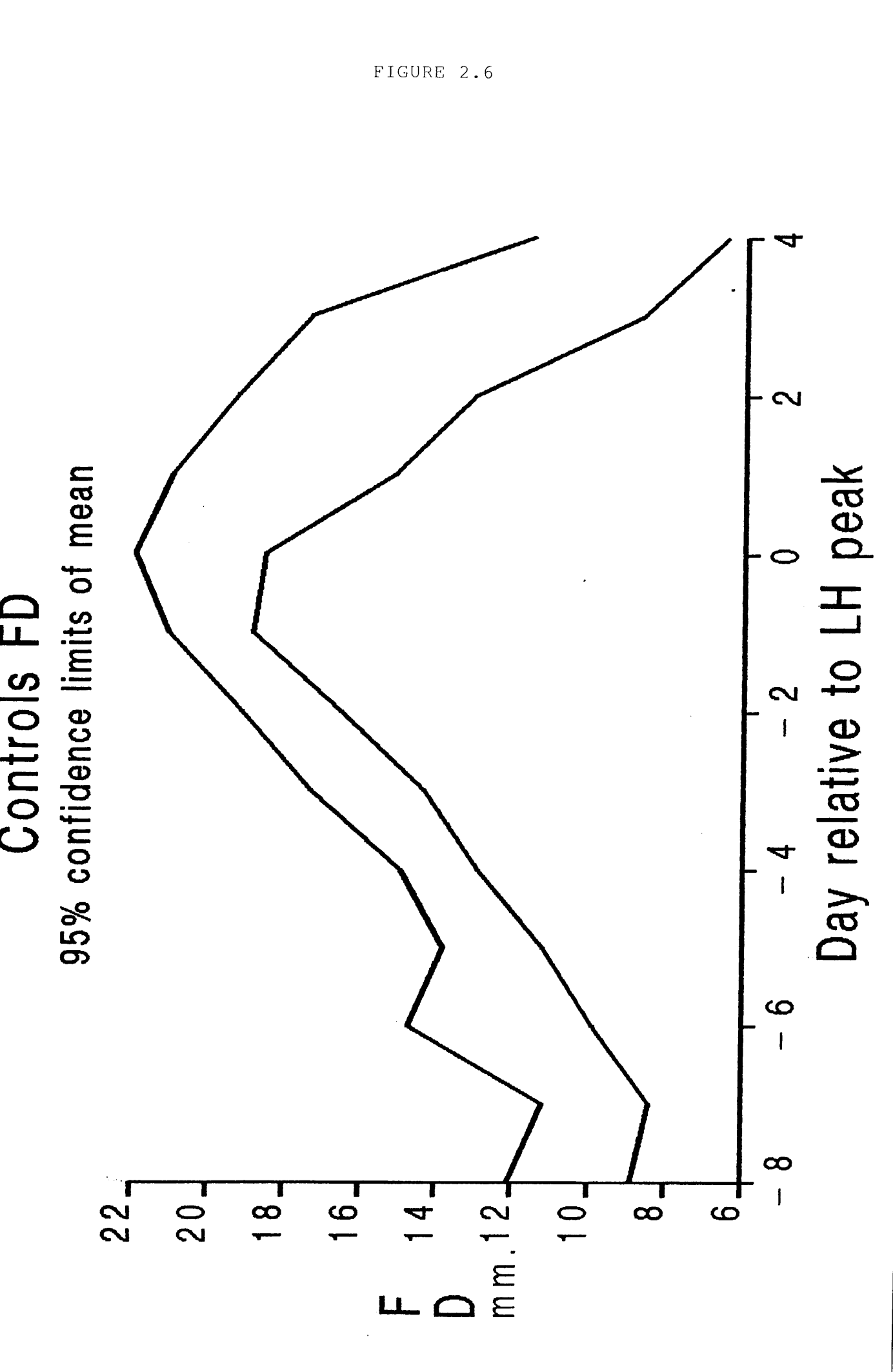

Controls FD
95% confidence limits of mean
FD mm.
22
20
18
16
14
12
10
8
6
-8
-6
-4
-2
0
2
4
Day relative to LH peak

FIGURE 2.7

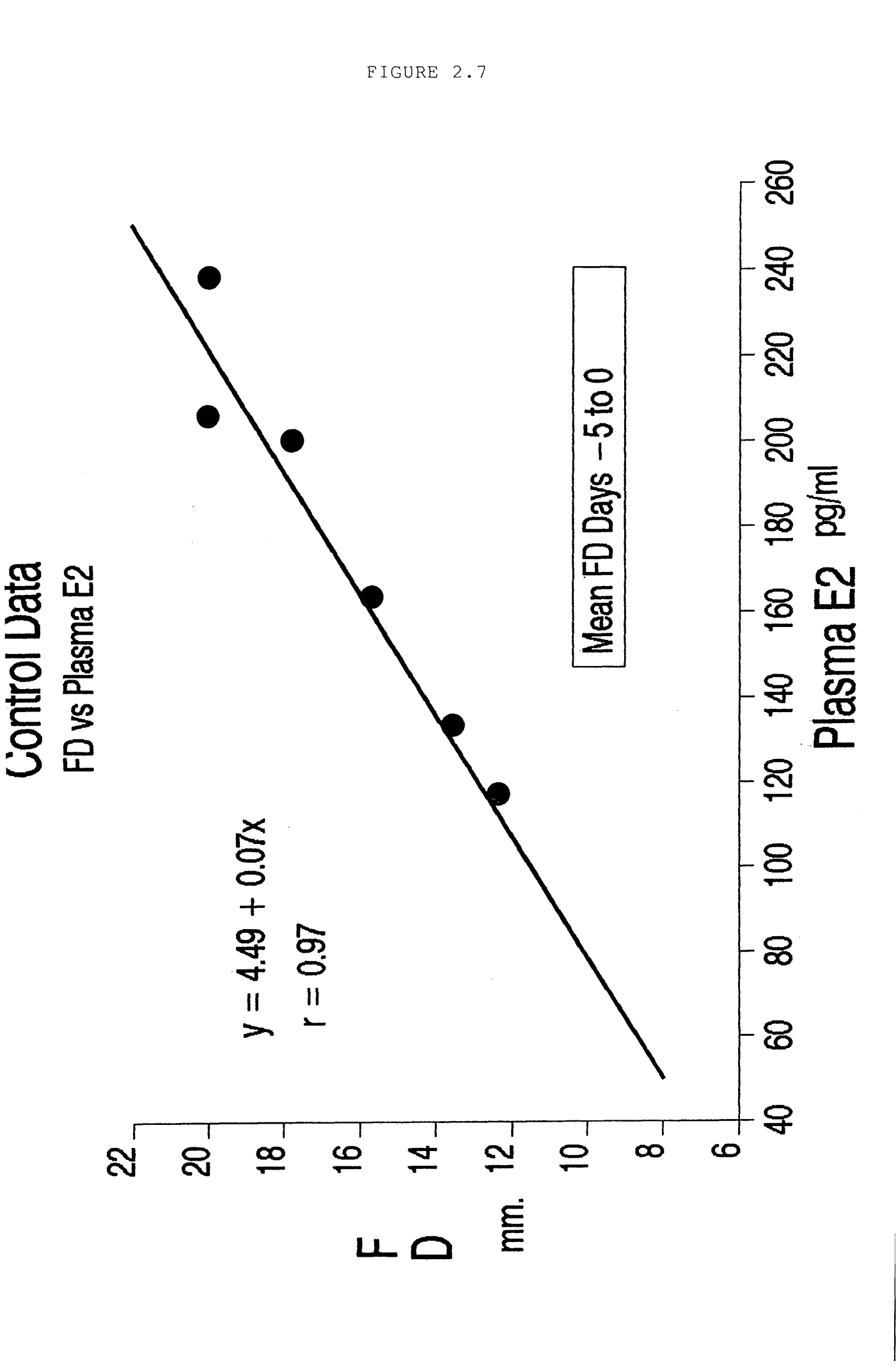

Control Data
FD vs Plasma E2
y = 4.49 + 0.07x
r = 0.97
Mean FD Days −5 to 0
FD mm.
Plasma E2 pg/ml
22
20
18
16
14
12
10
8
6
40
60
80
100
120
140
160
180
200
220
240
260

FIGURE 2.8

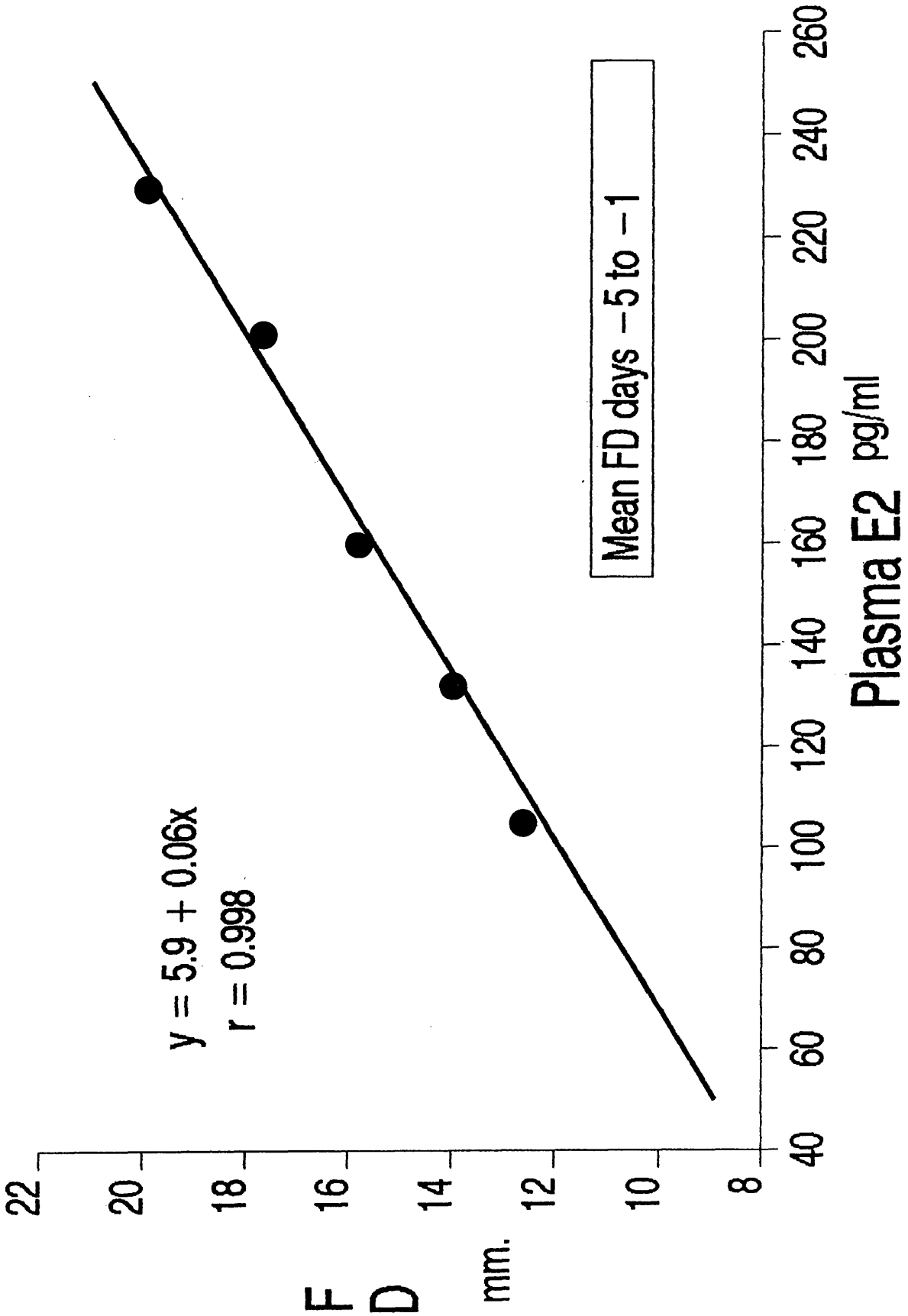

Control Data
FD vs Plasma E2
y = 5.9 + 0.06x
r = 0.998
Mean FD days −5 to −1
FD mm.
Plasma E2 pg/ml
22
20
18
16
14
12
10
8
40
60
80
100
120
140
160
180
200
220
240
260

Table 3.1

Conceptions

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -9 | 8 | 85.0 | 86.3 | 8.3 | 2.95 | 79.5 | 93.1 | |
| -8 | 10 | 87.5 | 87.8 | 18.3 | 5.79 | 74.7 | 100.9 | |
| -7 | 10 | 105.0 | 96.3 | 24.1 | 7.62 | 79.1 | 113.5 | |
| -6 | 10 | 97.5 | 99.3 | 25.1 | 7.94 | 81.3 | 117.3 | |
| -5 | 11 | 120.0 | 110.7 | 28.7 | 8.65 | 91.4 | 130.0 | |
| -4 | 10 | 119.0 | 129.6 | 40.9 | 12.90 | 100.4 | 158.8 | |
| -3 | 10 | 167.5 | 163.0 | 40.8 | 12.90 | 133.8 | 192.2 | |
| -2 | 10 | 217.5 | 240.3 | 86.2 | 27.23 | 178.7 | 301.9 | |
| -1 | 11 | 220.0 | 238.0 | 62.8 | 18.93 | 195.8 | 280.2 | |
| 0 | 11 | 220.0 | 230.9 | 31.4 | 9.47 | 209.8 | 252.0 | |
| +1 | 11 | 153.0 | 153.0 | 27.6 | 8.32 | 134.7 | 171.5 | |
| +2 | 11 | 120.0 | 113.6 | 39.4 | 11.88 | 87.1 | 140.1 | |
| +3 | 11 | 105.0 | 116.4 | 34.7 | 10.46 | 93.1 | 139.7 | |
| +4 | 11 | 140.0 | 142.1 | 47.3 | 14.26 | 110.3 | 173.9 | |
| +5 | 10 | 142.5 | 155.0 | 55.3 | 17.49 | 115.4 | 194.6 | |
| +6 | 11 | 155.0 | 159.0 | 30.7 | 9.26 | 138.4 | 179.6 | |
| +7 | 11 | 160.0 | 162.5 | 27.5 | 8.29 | 143.7 | 181.3 | |
| +8 | 11 | 170.0 | 181.8 | 37.9 | 13.43 | 151.9 | 211.7 | |
| +9 | 11 | 170.0 | 165.9 | 24.3 | 7.33 | 149.6 | 182.2 | |
| +10 | 9 | 195.0 | 186.4 | 45.6 | 15.20 | 151.3 | 221.5 | a |
| +11 | 8 | 185.0 | 199.4 | 72.9 | 25.77 | 138.5 | 260.3 | b |
| +12 | 5 | 200.0 | 220.0 | 60.4 | 27.01 | 145.0 | 295.0 | c |
| +13 | 3 | 210.0 | 216.7 | 11.4 | 6.58 | 188.4 | 245.0 | c |
| +14 | 2 | 266.5 | 266.5 | 47.4 | 33.52 | - | - | |

Significance (Wilcoxon Rank Sum Test) in comparison with controls

a = $p < 0.05$
b = $p < 0.01$
c = $p < 0.001$

FIGURE 3.1

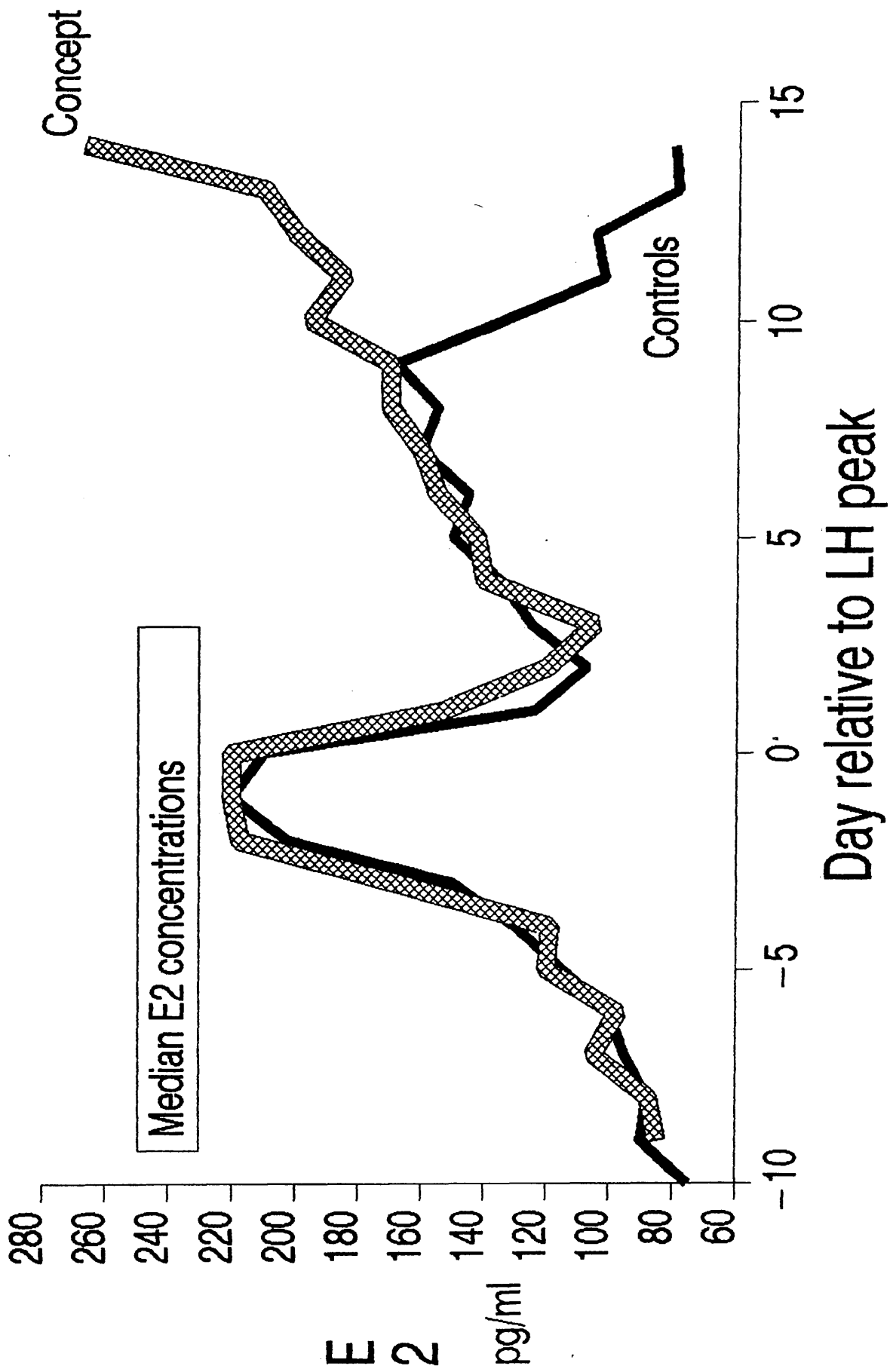

Conceptions
Concept
Controls
Median E2 concentrations
E 2
pg/ml
280
260
240
220
200
180
160
140
120
100
80
60
−10
−5
0
5
10
15
Day relative to LH peak

Table 3.2

Conceptions

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| 0 | 10 | 1.0 | 0.9 | 0.2 | 0.06 | 0.8 | 1.0 | |
| +1 | 11 | 1.6 | 1.9 | 0.7 | 0.21 | 1.4 | 2.4 | |
| +2 | 11 | 3.9 | 4.0 | 1.5 | 0.44 | 3.0 | 5.0 | |
| +3 | 11 | 8.4 | 9.2 | 3.5 | 1.06 | 6.8 | 11.6 | |
| +4 | 10 | 13.7 | 13.2 | 3.1 | 0.99 | 11.0 | 15.4 | |
| +5 | 11 | 17.0 | 19.0 | 7.0 | 2.10 | 14.3 | 23.7 | |
| +6 | 11 | 20.6 | 20.5 | 8.1 | 2.45 | 15.0 | 26.0 | |
| +7 | 10 | 21.8 | 21.3 | 7.3 | 2.31 | 16.1 | 26.5 | |
| +8 | 11 | 18.4 | 20.0 | 6.9 | 2.07 | 15.4 | 24.6 | |
| +9 | 10 | 16.7 | 16.1 | 6.7 | 2.10 | 11.3 | 20.9 | |
| +10 | 9 | 18.3 | 20.2 | 9.4 | 3.14 | 13.0 | 27.2 | a |
| +11 | 8 | 17.8 | 20.8 | 10.0 | 3.53 | 12.5 | 29.1 | b |
| +12 | 7 | 20.0 | 24.7 | 11.0 | 4.17 | 14.5 | 34.9 | b |
| +13 | 6 | 29.5 | 29.9 | 8.2 | 3.36 | 21.3 | 38.5 | b |
| P index | 11 | 105.5 | 105.0 | 33.6 | 10.13 | 82.4 | 127.6 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.02$
b = $p < 0.001$

FIGURE 3.2

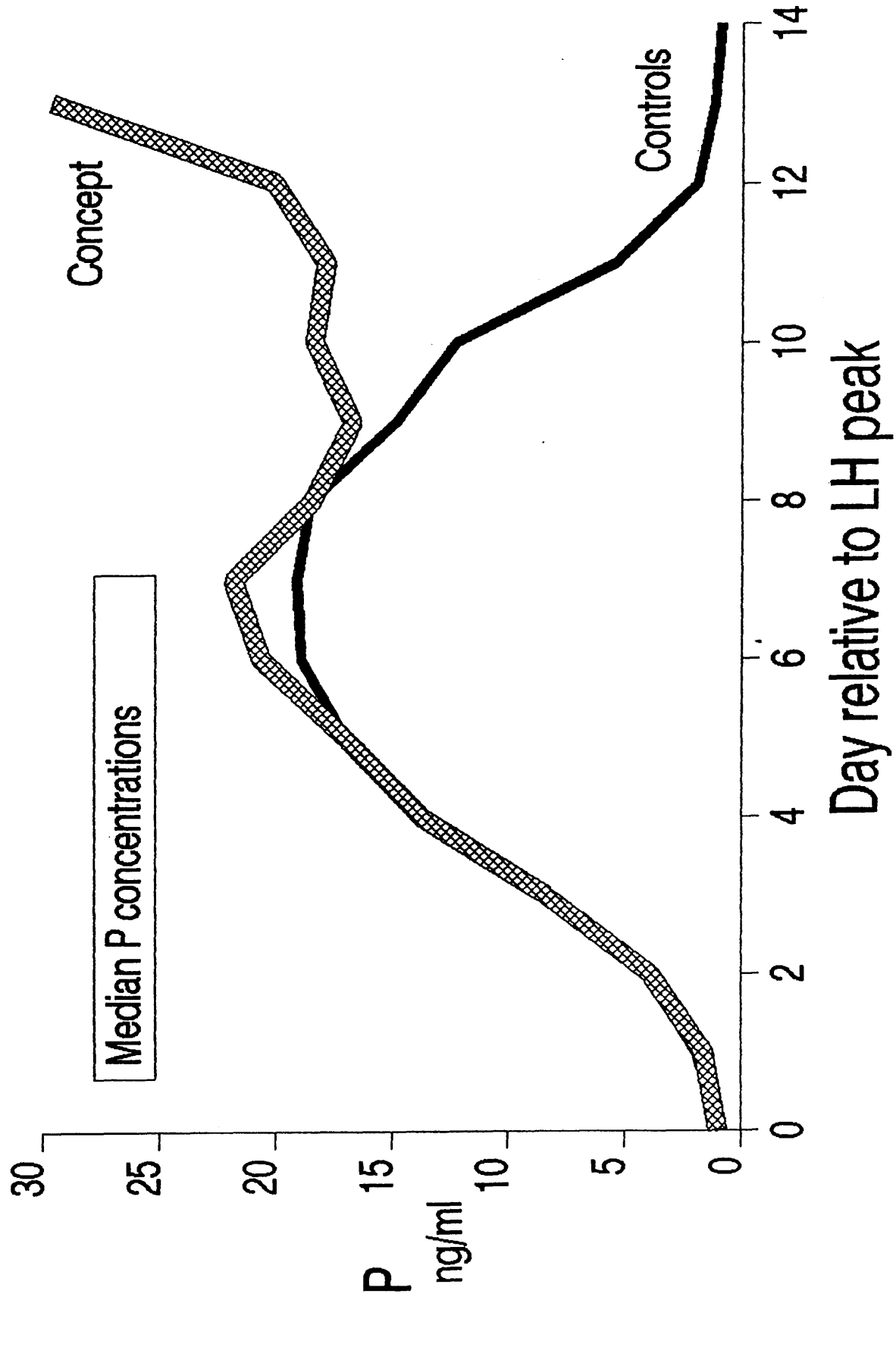

Conceptions
Median P concentrations
Concept
Controls
P ng/ml
30
25
20
15
10
5
0
0
2
4
6
8
10
12
14
Day relative to LH peak

Table 3.3

Conceptions

Plasma FSH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -9 | 8 | 5.0 | 6.0 | 3.0 | 1.06 | 3.5 | 8.5 |
| -8 | 9 | 5.5 | 5.8 | 2.6 | 0.85 | 3.8 | 7.8 |
| -7 | 8 | 5.3 | 4.9 | 1.8 | 0.63 | 3.4 | 6.4 |
| -6 | 9 | 4.2 | 4.4 | 1.3 | 0.43 | 3.4 | 5.4 |
| -5 | 10 | 3.7 | 4.1 | 2.0 | 0.62 | 2.7 | 5.5 |
| -4 | 9 | 3.1 | 3.3 | 1.2 | 0.41 | 2.4 | 4.2 |
| -3 | 8 | 2.9 | 3.0 | 1.1 | 0.40 | 2.1 | 3.9 |
| -2 | 10 | 2.6 | 2.9 | 1.1 | 0.36 | 2.1 | 3.7 |
| -1 | 10 | 3.1 | 3.1 | 0.9 | 0.30 | 2.4 | 3.8 |
| 0 | 10 | 9.6 | 9.8 | 3.1 | 0.99 | 7.6 | 12.0 |
| +1 | 10 | 8.0 | 8.9 | 6.0 | 1.91 | 4.6 | 13.2 |
| +2 | 10 | 4.4 | 4.3 | 1.4 | 0.43 | 3.3 | 5.3 |
| +3 | 10 | 3.1 | 3.1 | 1.4 | 0.44 | 2.1 | 4.1 |
| +4 | 9 | 2.7 | 2.9 | 1.4 | 0.47 | 1.8 | 4.0 |
| +5 | 9 | 2.4 | 2.5 | 1.1 | 0.36 | 1.7 | 3.3 |
| +6 | 9 | 1.8 | 2.0 | 1.0 | 0.35 | 1.2 | 2.8 |
| +7 | 8 | 1.7 | 1.9 | 1.0 | 0.37 | 1.0 | 2.8 |
| +8 | 8 | 1.6 | 1.9 | 1.1 | 0.39 | 1.0 | 2.8 |
| +9 | 8 | 1.3 | 1.5 | 0.9 | 0.32 | 0.7 | 2.3 |
| +10 | 3 | 1.3 | 1.4 | 0.2 | 0.13 | 0.8 | 2.0 |
| +11 | 2 | 1.1 | 1.1 | 0.7 | 0.50 | - | - |
| +12 | 3 | 1.3 | 1.3 | 0.5 | 0.26 | 0.2 | 2.4 |
| +13 | 3 | 1.6 | 1.4 | 0.5 | 0.27 | 0.2 | 2.6 |
| +14 | 2 | 1.4 | 1.4 | 0.8 | 0.59 | - | - |

No significant differences in comparison with controls
(Wilcoxon rank sum test)

FIGURE 3.3

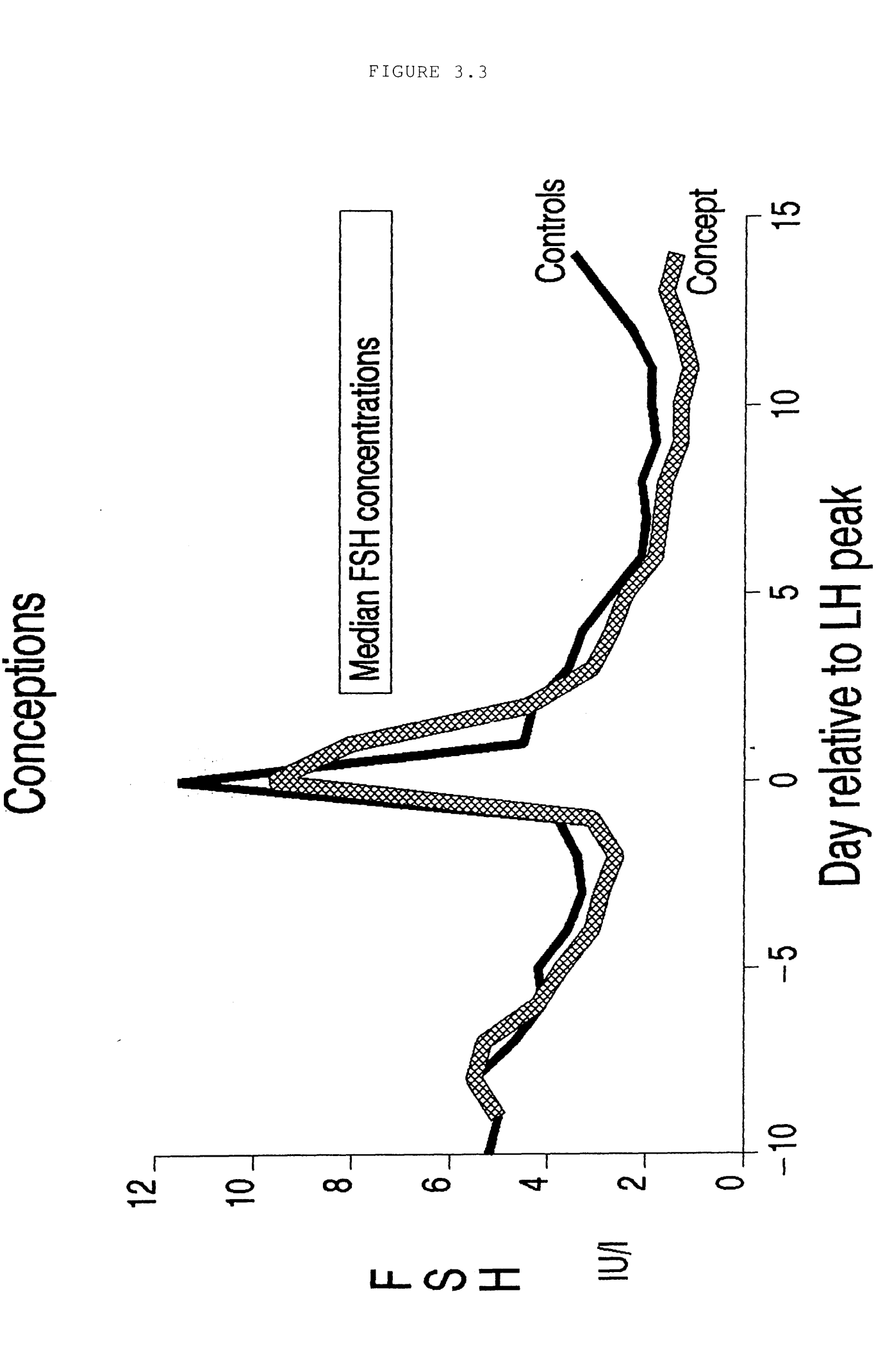

Conceptions
Median FSH concentrations
Controls
Concept
FSH IU/l
12
10
8
6
4
2
0
-10
-5
0
5
10
15
Day relative to LH peak

Table 3.4

Conceptions

Plasma LH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -9 | 8 | 7.1 | 7.9 | 5.1 | 1.82 | 3.6 | 12.2 | |
| -8 | 9 | 8.4 | 7.8 | 4.2 | 1.40 | 4.6 | 11.0 | |
| -7 | 9 | 7.9 | 8.3 | 4.3 | 1.43 | 5.0 | 11.6 | |
| -6 | 8 | 8.6 | 9.0 | 5.2 | 1.54 | 5.4 | 12.6 | |
| -5 | 10 | 8.3 | 8.9 | 5.3 | 1.89 | 4.6 | 13.2 | |
| -4 | 9 | 7.9 | 6.6 | 3.2 | 1.06 | 4.2 | 9.0 | |
| -3 | 7 | 7.2 | 6.8 | 4.4 | 1.68 | 2.7 | 10.9 | |
| -2 | 10 | 10.0 | 9.6 | 4.4 | 1.40 | 6.4 | 12.8 | |
| -1 | 10 | 13.7 | 13.8 | 5.0 | 1.57 | 10.2 | 17.4 | |
| 0 | 10 | 73.5 | 65.4 | 28.6 | 9.03 | 45.0 | 85.4 | |
| +1 | 10 | 43.6 | 36.3 | 17.0 | 5.37 | 24.2 | 48.4 | |
| +2 | 10 | 15.7 | 14.1 | 7.0 | 2.23 | 9.1 | 19.1 | |
| +3 | 10 | 12.5 | 11.0 | 6.3 | 1.98 | 6.5 | 15.5 | |
| +4 | 9 | 8.0 | 8.4 | 3.5 | 1.16 | 5.7 | 11.1 | |
| +5 | 9 | 7.9 | 8.9 | 4.0 | 1.35 | 5.8 | 12.0 | |
| +6 | 9 | 8.3 | 9.4 | 6.3 | 2.09 | 4.6 | 14.2 | |
| +7 | 9 | 4.7 | 7.4 | 5.3 | 1.77 | 3.3 | 11.5 | |
| +8 | 9 | 7.2 | 8.1 | 5.3 | 1.76 | 4.0 | 12.2 | |
| +9 | 9 | 6.4 | 7.2 | 4.6 | 1.52 | 3.7 | 10.7 | |
| +10 | 4 | 7.7 | 6.4 | 2.7 | 1.34 | 2.1 | 10.7 | |
| +11 | 4 | 8.7 | 8.0 | 2.3 | 1.18 | 4.2 | 11.8 | |
| +12 | 3 | 18.0 | 17.0 | 1.7 | 1.00 | 12.7 | 21.3 | a |
| +13 | 4 | 23.5 | 21.2 | 6.6 | 3.28 | 10.8 | 31.6 | a |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.001$

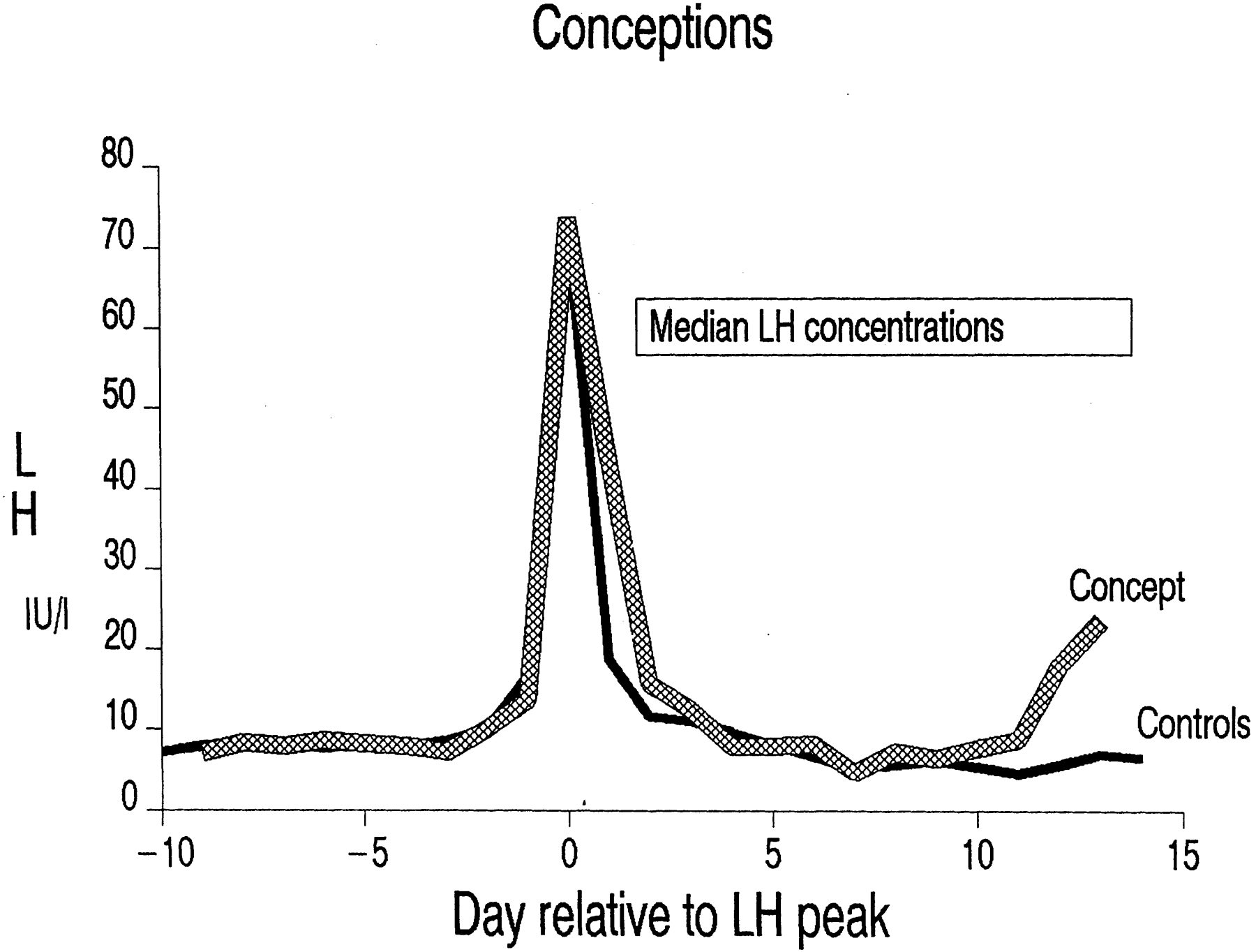

Conceptions
Median LH concentrations
LH IU/l
80
70
60
50
40
30
20
10
0
−10
−5
0
5
10
15
Concept
Controls
Day relative to LH peak

FIGURE 3.4

Table 3.5

Conceptions

Follicular Diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -4 | 4 | 14.8 | 14.6 | 0.48 | 0.24 | 13.8 | 15.4 |
| -3 | 2 | 14.8 | 14.8 | 3.18 | 2.25 | - | - |
| -2 | 6 | 16.0 | 15.8 | 0.75 | 0.31 | 15.0 | 16.6 |
| -1 | 6 | 18.5 | 18.8 | 1.86 | 1.32 | 15.4 | 22.2 |
| 0 | 8 | 20.8 | 20.8 | 1.46 | 0.52 | 19.6 | 22.0 |
| +1 | 7 | 20.5 | 20.2 | 2.91 | 1.10 | 17.5 | 22.9 |
| +2 | 3 | 16.0 | 16.5 | 6.76 | 3.90 | - | - |

No significant differences in comparison with controls
(Wilcoxon Rank Sum Test)

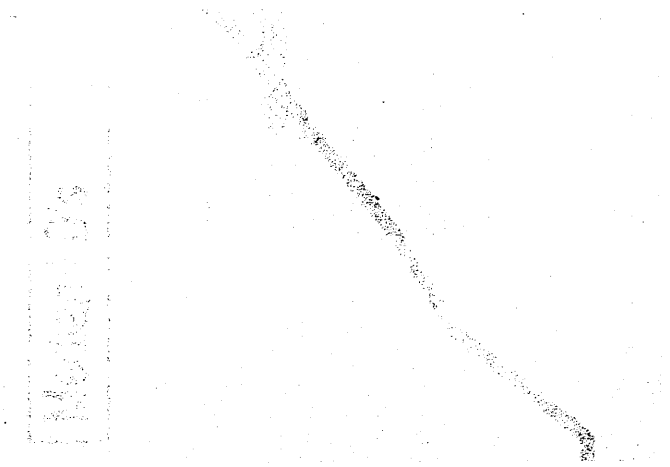


FIGURE 3.5

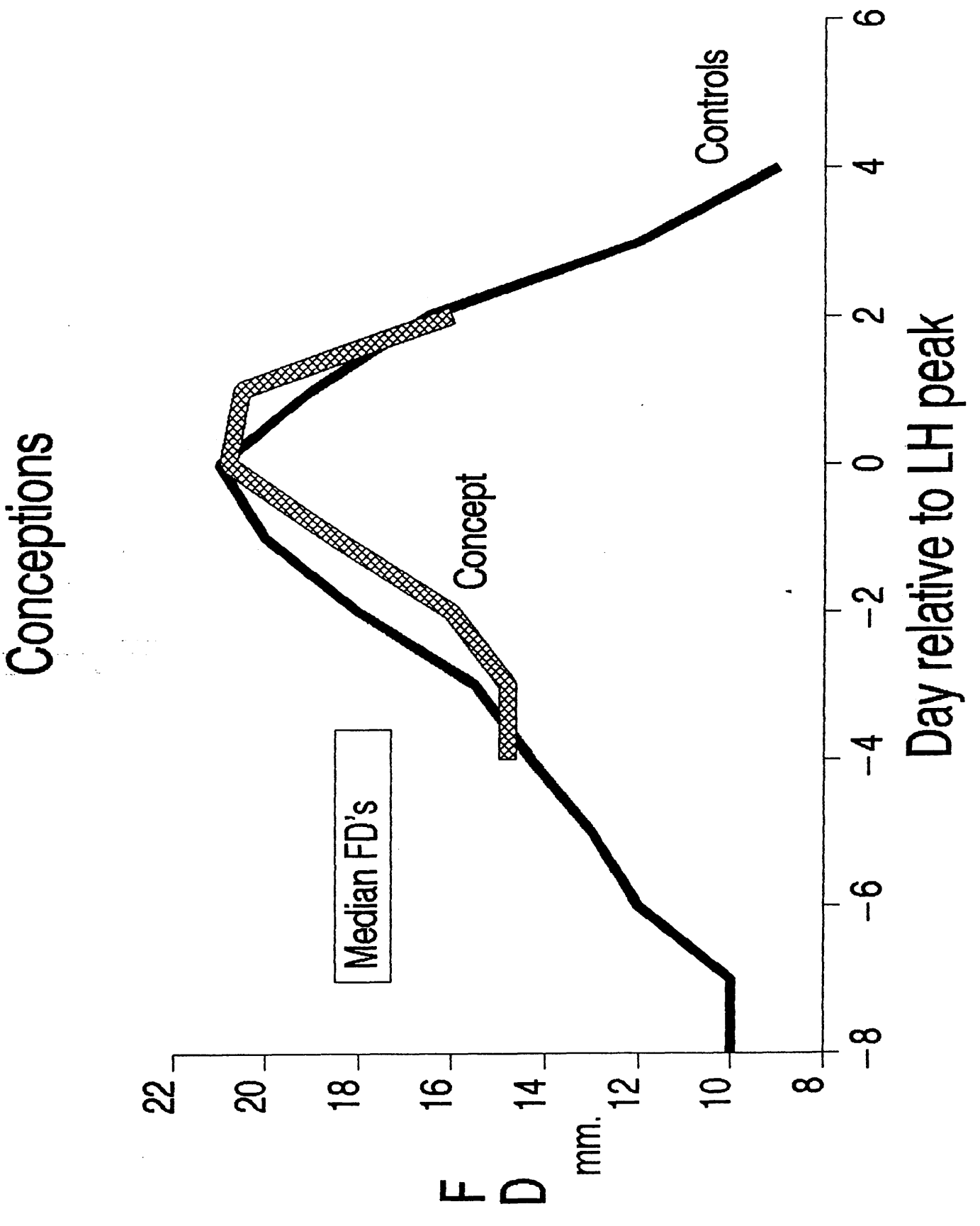

Conceptions
Median FD's
Concept
Controls
FD mm.
22
20
18
16
14
12
10
8
−8
−6
−4
−2
0
2
4
6
Day relative to LH peak

Table 5.1.1

Luteal Cyst Formers

Patient/cycle characteristics

| | Nos | Mean | SD | SEM | Median | Range | |
|---|---|---|---|---|---|---|---|
| AGE (Years) | | | | | | | |
| All cysts | 41 | 29.7 | 4.2 | 0.7 | 29 | 22-39 | a |
| Shrinkers | 21 | 30.3 | 4.6 | 1.0 | 30 | 22-39 | a |
| Non-shrinkers | 20 | 29.1 | 3.8 | 0.8 | 29 | 24-38 | a |
| >20mm | 30 | 29.2 | 3.9 | 0.7 | 29 | 22-38 | a |
| <20mm | 11 | 31.3 | 4.8 | 1.4 | 30 | 23-39 | a |
| Normal PI | 10 | 30.8 | 4.9 | 1.5 | 31 | 23-39 | a |
| Low PI | 31 | 29.4 | 4.0 | 0.7 | 29 | 22-38 | a |
| FOLLICULAR PHASE (Days) | | | | | | | |
| All cysts | 41 | 14.6 | 3.4 | 0.5 | 14 | 8-27 | |
| Shrinkers | 21 | 14.3 | 3.1 | 0.7 | 14 | 11-25 | |
| Non-shrinkers | 20 | 14.9 | 3.8 | 0.9 | 14.5 | 8-27 | |
| >20mm | 30 | 14.8 | 3.2 | 0.6 | 15 | 8-27 | |
| <20mm | 11 | 13.9 | 4.0 | 1.2 | 13 | 11-25 | |
| Normal PI | 10 | 13.5 | 2.1 | 0.7 | 13 | 11-17 | |
| Low PI | 31 | 14.5 | 3.7 | 0.7 | 15 | 8-27 | |
| LUTEAL PHASE (Days) | | | | | | | |
| All cysts | 41 | 15.0 | 1.6 | 0.3 | 15 | 11-18 | |
| Shrinkers | 21 | 14.9 | 1.8 | 0.4 | 15 | 11-17 | |
| Non-shrinkers | 20 | 15.2 | 1.5 | 0.3 | 15 | 12-18 | |
| >20mm | 30 | 15.1 | 1.6 | 0.3 | 15 | 12-18 | |
| <20mm | 11 | 14.9 | 1.6 | 0.5 | 15 | 11-17 | |
| Normal PI | 10 | 14.7 | 0.9 | 0.3 | 15 | 14-16 | |
| Low PI | 31 | 15.2 | 1.8 | 0.3 | 15 | 11-18 | |
| CYCLE LENGTH (Days) | | | | | | | |
| All cysts | 41 | 29.6 | 3.9 | 0.6 | 30 | 22-44 | |
| Shrinkers | 21 | 29.2 | 3.8 | 0.8 | 29 | 22-41 | |
| Non-shrinkers | 20 | 30.1 | 4.0 | 0.9 | 30 | 25-44 | |
| >20mm | 30 | 29.9 | 3.5 | 0.6 | 30 | 25-44 | |
| <20mm | 11 | 28.8 | 4.9 | 1.5 | 27 | 22-41 | |
| Normal PI | 10 | 28.2 | 2.1 | 0.7 | 27 | 26-32 | |
| Low PI | 31 | 30.1 | 4.2 | 0.8 | 30 | 22-44 | |

No significant inter-group differences.
Significance in comparison with controls : a = $p < 0.001$
(Wilcoxon Rank Sum Test)

Table 5.1.2

Large Cysts (>20mm)

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 20 | 75.0 | 77.0 | 16.7 | 3.7 | 69.6 | 84.4 | |
| -9 | 21 | 80.0 | 77.0 | 17.9 | 3.9 | 69.2 | 84.8 | a |
| -8 | 24 | 80.0 | 79.0 | 17.9 | 3.7 | 71.6 | 86.4 | i |
| -7 | 25 | 85.0 | 86.2 | 17.2 | 3.4 | 79.4 | 93.0 | |
| -6 | 25 | 85.0 | 89.5 | 20.8 | 4.2 | 81.1 | 97.9 | i |
| -5 | 26 | 107.5 | 109.5 | 22.4 | 4.4 | 100.6 | 118.2 | |
| -4 | 28 | 107.5 | 123.4 | 38.8 | 7.3 | 108.8 | 138.0 | |
| -3 | 28 | 140.0 | 144.6 | 43.0 | 8.1 | 128.4 | 160.8 | |
| -2 | 28 | 166.5 | 181.3 | 50.2 | 9.5 | 162.3 | 200.3 | |
| -1 | 27 | 230.0 | 216.0 | 51.2 | 9.9 | 196.2 | 235.8 | |
| 0 | 30 | 191.5 | 196.2 | 54.3 | 9.9 | 176.4 | 216.0 | i |
| +1 | 28 | 140.0 | 139.1 | 42.7 | 8.1 | 122.9 | 155.3 | |
| +2 | 30 | 121.5 | 121.2 | 30.4 | 5.6 | 110.0 | 132.4 | |
| +3 | 30 | 135.0 | 136.2 | 28.7 | 5.2 | 125.8 | 146.6 | |
| +4 | 29 | 140.0 | 145.7 | 44.6 | 8.3 | 129.1 | 152.8 | |
| +5 | 30 | 135.0 | 151.4 | 52.1 | 9.5 | 132.4 | 170.4 | |
| +6 | 28 | 140.0 | 148.9 | 49.2 | 9.3 | 130.3 | 167.5 | |
| +7 | 29 | 147.5 | 154.2 | 45.0 | 8.4 | 137.4 | 171.0 | |
| +8 | 28 | 142.5 | 153.7 | 47.2 | 8.9 | 135.9 | 171.5 | |
| +9 | 26 | 137.5 | 158.3 | 70.8 | 13.9 | 130.5 | 186.1 | |
| +10 | 25 | 135.0 | 147.3 | 55.4 | 11.1 | 125.1 | 169.5 | |
| +11 | 27 | 133.0 | 143.4 | 57.1 | 11.0 | 121.4 | 165.4 | |
| +12 | 26 | 125.0 | 127.2 | 51.9 | 10.2 | 106.8 | 147.6 | |
| +13 | 24 | 115.0 | 108.6 | 41.0 | 8.4 | 91.8 | 125.4 | |
| +14 | 22 | 97.5 | 97.1 | 30.9 | 6.6 | 83.9 | 110.3 | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls | Small Cysts |
|---|---|---|
| $p < 0.05$ | a | i |

Table 5.1.3

Small Cysts (<20mm)

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 9 | 75.0 | 73.3 | 12.5 | 4.2 | 63.7 | 82.9 |
| -9 | 10 | 77.5 | 80.5 | 21.8 | 6.9 | 64.9 | 96.1 |
| -8 | 10 | 87.5 | 96.0 | 27.8 | 8.8 | 86.1 | 115.9 |
| -7 | 10 | 80.0 | 90.8 | 24.9 | 7.9 | 82.9 | 108.7 |
| -6 | 11 | 105.0 | 110.3 | 31.6 | 9.5 | 88.8 | 131.8 |
| -5 | 11 | 115.0 | 119.6 | 32.0 | 9.6 | 97.9 | 141.3 |
| -4 | 11 | 133.0 | 140.3 | 36.9 | 11.1 | 115.2 | 165.4 |
| -3 | 11 | 153.0 | 167.4 | 47.7 | 14.4 | 134.9 | 199.9 |
| -2 | 11 | 195.0 | 199.5 | 59.6 | 18.0 | 158.8 | 240.2 |
| -1 | 10 | 245.0 | 246.0 | 53.7 | 17.0 | 207.6 | 284.4 |
| 0 | 11 | 235.0 | 236.2 | 38.2 | 11.5 | 220.2 | 252.2 |
| +1 | 11 | 130.0 | 143.6 | 39.8 | 12.0 | 116.9 | 170.3 |
| +2 | 11 | 120.0 | 118.0 | 36.7 | 11.1 | 93.3 | 142.7 |
| +3 | 11 | 120.0 | 131.5 | 33.8 | 10.2 | 108.8 | 154.2 |
| +4 | 11 | 130.0 | 159.6 | 56.6 | 17.1 | 121.5 | 197.7 |
| +5 | 11 | 148.0 | 162.1 | 48.5 | 14.6 | 129.6 | 194.6 |
| +6 | 9 | 145.0 | 160.3 | 53.2 | 17.7 | 119.5 | 201.1 |
| +7 | 11 | 155.0 | 165.5 | 36.6 | 11.0 | 141.0 | 190.0 |
| +8 | 11 | 165.0 | 175.7 | 45.7 | 13.8 | 145.0 | 206.4 |
| +9 | 11 | 165.0 | 172.1 | 51.4 | 15.5 | 137.6 | 206.6 |
| +10 | 11 | 163.0 | 164.2 | 44.1 | 13.3 | 134.6 | 193.8 |
| +11 | 11 | 145.0 | 149.4 | 36.6 | 11.0 | 124.9 | 173.9 |
| +12 | 9 | 135.0 | 144.8 | 61.2 | 20.4 | 98.7 | 190.9 |
| +13 | 9 | 125.0 | 134.4 | 54.6 | 18.2 | 93.2 | 175.6 |
| +14 | 9 | 93.0 | 125.7 | 75.6 | 25.2 | 68.7 | 182.7 |

No significant differences with controls (Wilcoxon Rank Sum Test)

FIGURE 5.1.1

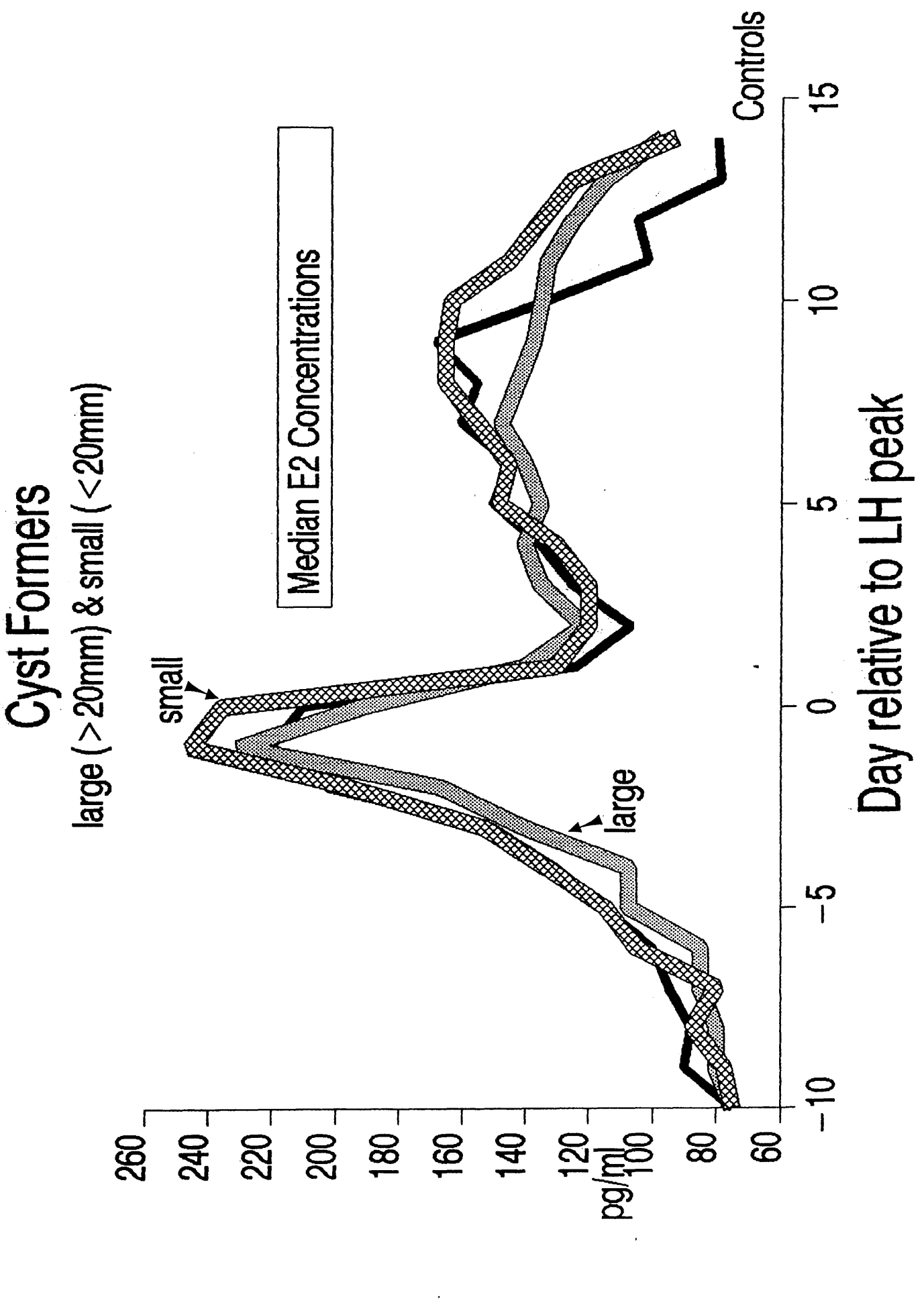

Cyst Formers
large (>20mm) & small (<20mm)
Median E2 Concentrations
small
large
Controls
pg/ml
260
240
220
200
180
160
140
120
100
80
60
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.1.4

Large Cysts (>20mm)

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | | |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 19 | 1.0 | 1.0 | 0.7 | 0.2 | 0.6 | 1.4 | | |
| +1 | 27 | 1.3 | 1.6 | 1.3 | 0.3 | 1.0 | 2.2 | | |
| +2 | 29 | 3.1 | 3.4 | 2.9 | 0.5 | 2.4 | 4.4 | | |
| +3 | 30 | 4.9 | 5.4 | 3.7 | 0.7 | 4.0 | 6.8 | b | |
| +4 | 29 | 6.6 | 7.6 | 4.3 | 0.8 | 6.0 | 9.2 | c | |
| +5 | 30 | 11.1 | 11.2 | 5.7 | 1.0 | 9.2 | 11.2 | c | i |
| +6 | 28 | 15.7 | 15.1 | 7.0 | 1.3 | 12.4 | 17.8 | a | |
| +7 | 29 | 17.2 | 17.8 | 7.5 | 1.4 | 14.9 | 20.7 | | |
| +8 | 29 | 16.6 | 15.9 | 6.9 | 1.3 | 13.2 | 18.6 | | |
| +9 | 26 | 14.6 | 15.9 | 7.4 | 1.5 | 12.3 | 19.0 | | |
| +10 | 25 | 16.4 | 14.8 | 6.9 | 1.4 | 11.9 | 17.7 | | |
| +11 | 27 | 13.4 | 12.9 | 7.2 | 1.4 | 10.0 | 15.8 | c | |
| +12 | 26 | 8.9 | 9.5 | 6.0 | 1.2 | 7.0 | 12.0 | b | |
| +13 | 24 | 5.4 | 5.7 | 4.9 | 1.0 | 3.6 | 7.8 | a | |
| +14 | 22 | 2.4 | 3.3 | 3.3 | 0.7 | 1.8 | 4.8 | | |
| P index | 30 | 66.0 | 67.4 | 31.3 | 5.7 | 55.7 | 79.1 | c | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls | Small Cysts |
|---|---|---|
| p <0.05 | a | i |
| p <0.01 | b | |
| p <0.001 | c | |

Table 5.1.5

Small Cysts (<20mm)

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| 0 | 7 | 0.8 | 0.8 | 0.4 | 0.2 | 0.3 | 1.3 | |
| +1 | 10 | 1.1 | 1.5 | 0.8 | 0.3 | 0.8 | 2.2 | |
| +2 | 11 | 2.7 | 3.0 | 1.6 | 0.5 | 1.9 | 4.1 | a |
| +3 | 11 | 4.2 | 5.1 | 2.0 | 0.6 | 4.8 | 6.4 | b |
| +4 | 11 | 9.2 | 9.7 | 3.9 | 1.2 | 7.0 | 12.4 | a |
| +5 | 11 | 13.4 | 15.4 | 6.1 | 1.8 | 11.4 | 19.4 | |
| +6 | 9 | 18.0 | 18.2 | 7.5 | 2.5 | 12.4 | 24.0 | |
| +7 | 11 | 17.6 | 19.1 | 5.2 | 1.6 | 15.6 | 22.7 | |
| +8 | 11 | 18.0 | 18.5 | 5.7 | 1.7 | 14.7 | 22.3 | |
| +9 | 11 | 19.2 | 16.9 | 5.4 | 1.6 | 13.3 | 20.2 | |
| +10 | 11 | 15.0 | 13.9 | 5.9 | 1.8 | 9.9 | 17.7 | |
| +11 | 11 | 11.6 | 12.7 | 7.5 | 2.3 | 7.6 | 17.8 | b |
| +12 | 9 | 8.4 | 8.4 | 3.7 | 1.2 | 5.6 | 11.2 | b |
| +13 | 9 | 5.0 | 4.5 | 2.5 | 0.8 | 2.7 | 6.3 | |
| +14 | 9 | 1.6 | 2.1 | 1.4 | 0.9 | 0.9 | 3.3 | |
| P index | 11 | 84.0 | 80.0 | 26.7 | 8.1 | 62.1 | 97.9 | a |

Significance (Wilcoxon Rank Sum Test) in comparison with :

Controls

p <0.05 a
P <0.01 b

FIGURE 5.1.2

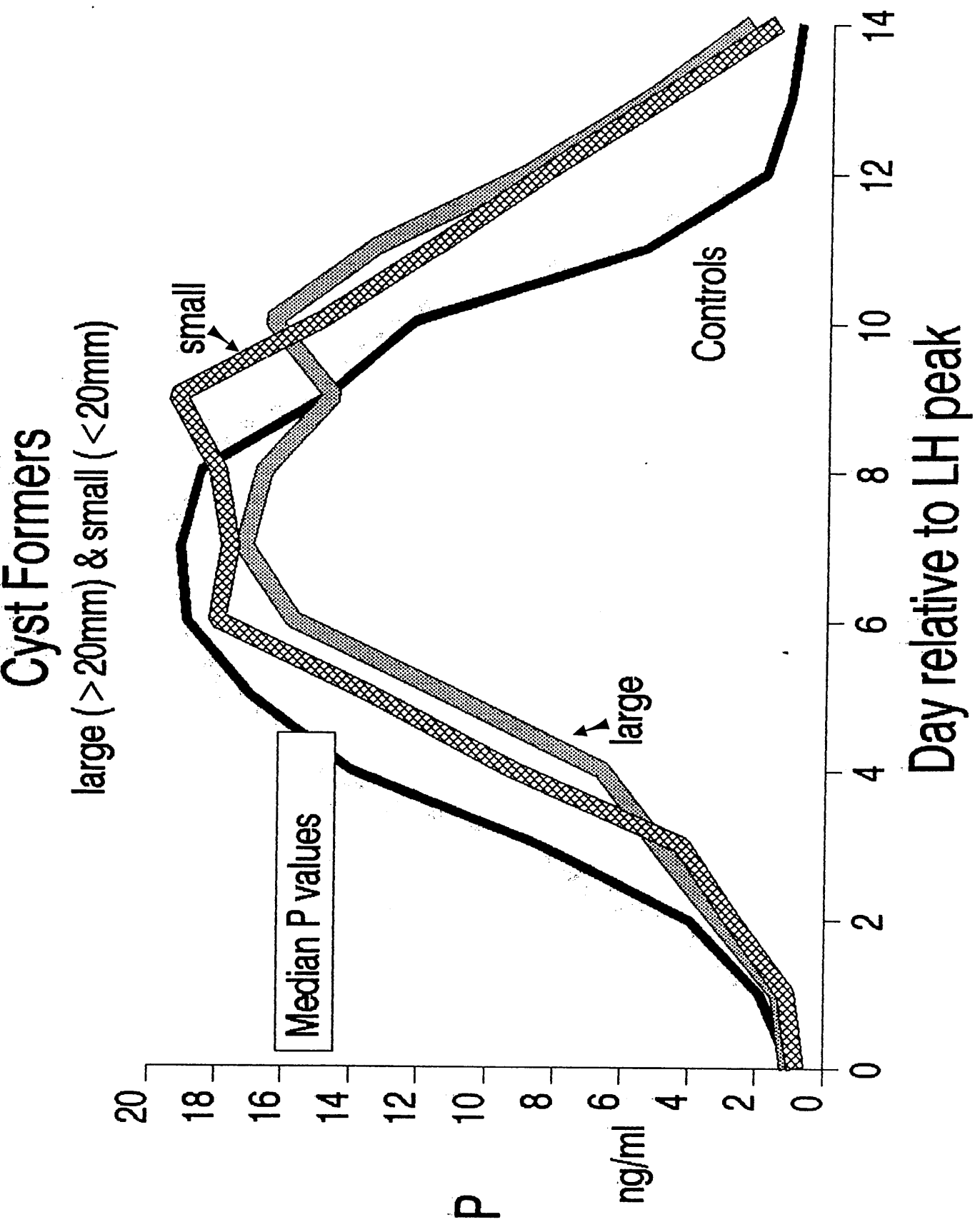

Cyst Formers
large (>20mm) & small (<20mm)
small
large
Controls
Median P values
P
ng/ml
Day relative to LH peak
0
2
4
6
8
10
12
14
16
18
20

Table 5.1.6

Large Cysts (>20mm)

Plasma LH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 18 | 8.8 | 8.9 | 4.0 | 0.9 | 6.9 | 10.9 | |
| -9 | 21 | 7.6 | 8.8 | 5.8 | 1.3 | 6.2 | 11.4 | |
| -8 | 24 | 7.3 | 8.9 | 5.6 | 1.1 | 6.5 | 11.3 | |
| -7 | 24 | 7.6 | 9.4 | 5.4 | 1.1 | 7.1 | 11.7 | |
| -6 | 25 | 9.4 | 9.5 | 4.4 | 0.9 | 7.7 | 11.3 | |
| -5 | 27 | 9.1 | 8.9 | 4.2 | 0.8 | 7.2 | 10.6 | |
| -4 | 27 | 6.9 | 7.6 | 3.7 | 0.7 | 6.1 | 9.1 | |
| -3 | 27 | 8.7 | 10.7 | 4.7 | 0.9 | 8.8 | 12.6 | |
| -2 | 27 | 9.8 | 10.7 | 4.7 | 0.9 | 8.8 | 12.6 | |
| -1 | 26 | 18.5 | 21.9 | 13.0 | 2.6 | 7.7 | 18.3 | |
| 0 | 29 | 66.0 | 61.7 | 18.0 | 3.3 | 54.9 | 68.5 | i |
| +1 | 28 | 19.0 | 24.2 | 14.6 | 2.8 | 18.5 | 29.9 | |
| +2 | 29 | 13.0 | 13.5 | 7.1 | 1.3 | 10.8 | 16.2 | |
| +3 | 30 | 14.0 | 14.1 | 6.4 | 1.2 | 11.7 | 16.5 | |
| +4 | 28 | 9.6 | 14.7 | 10.5 | 2.0 | 6.4 | 14.6 | |
| +5 | 30 | 9.9 | 12.1 | 7.0 | 1.3 | 9.5 | 14.7 | |
| +6 | 27 | 9.0 | 9.7 | 6.2 | 1.2 | 7.2 | 12.2 | |
| +7 | 30 | 7.9 | 9.1 | 6.0 | 1.1 | 6.9 | 11.3 | |
| +8 | 26 | 5.8 | 7.4 | 4.6 | 0.9 | 5.5 | 9.3 | |
| +9 | 25 | 8.8 | 9.7 | 7.7 | 1.5 | 6.5 | 12.9 | |
| +10 | 25 | 6.7 | 7.4 | 5.0 | 1.0 | 2.9 | 7.1 | |
| +11 | 26 | 6.0 | 7.6 | 5.2 | 1.0 | 5.6 | 9.6 | |
| +12 | 23 | 7.6 | 7.8 | 4.5 | 0.9 | 5.9 | 9.7 | |
| +13 | 23 | 7.1 | 6.7 | 2.9 | 0.6 | 5.5 | 7.9 | |
| +14 | 19 | 7.2 | 7.6 | 2.6 | 0.5 | 6.5 | 8.7 | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

Small Cysts

p <0.05 i

No significant differences from controls.

Table 5.1.7

Small Cysts (<20mm)

Plasma LH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 8 | 8.1 | 9.4 | 6.1 | 2.2 | 4.2 | 14.6 |
| -9 | 9 | 6.3 | 8.0 | 5.1 | 1.7 | 4.1 | 11.9 |
| -8 | 9 | 9.5 | 10.0 | 7.6 | 2.5 | 4.3 | 15.7 |
| -7 | 9 | 9.1 | 8.4 | 5.4 | 1.8 | 4.0 | 12.8 |
| -6 | 10 | 8.0 | 9.8 | 6.5 | 2.1 | 5.0 | 14.6 |
| -5 | 10 | 7.4 | 9.0 | 6.2 | 2.0 | 4.5 | 13.5 |
| -4 | 10 | 8.6 | 9.0 | 5.7 | 1.8 | 4.9 | 13.1 |
| -3 | 9 | 7.8 | 8.2 | 5.2 | 1.7 | 4.3 | 12.1 |
| -2 | 10 | 10.0 | 10.2 | 6.0 | 1.9 | 5.9 | 14.5 |
| -1 | 10 | 18.5 | 21.1 | 12.7 | 4.0 | 12.1 | 30.1 |
| 0 | 10 | 42.5 | 45.7 | 22.7 | 7.2 | 29.4 | 62.0 |
| +1 | 10 | 28.5 | 27.7 | 12.8 | 4.0 | 18.7 | 36.7 |
| +2 | 10 | 11.5 | 12.1 | 5.1 | 1.6 | 8.5 | 15.7 |
| +3 | 10 | 8.3 | 10.2 | 7.1 | 2.2 | 5.2 | 15.2 |
| +4 | 10 | 9.4 | 12.5 | 7.0 | 2.2 | 7.5 | 17.5 |
| +5 | 10 | 7.0 | 8.9 | 5.7 | 3.2 | 1.7 | 16.1 |
| +6 | 8 | 11.2 | 12.2 | 7.3 | 2.6 | 6.1 | 18.3 |
| +7 | 10 | 6.5 | 8.3 | 6.3 | 2.0 | 3.8 | 12.8 |
| +8 | 10 | 5.3 | 8.4 | 7.8 | 2.5 | 2.7 | 14.1 |
| +9 | 10 | 3.7 | 6.1 | 6.2 | 2.0 | 1.6 | 10.6 |
| +10 | 10 | 6.4 | 6.9 | 6.0 | 1.9 | 2.6 | 11.2 |
| +11 | 10 | 4.3 | 5.0 | 4.2 | 1.3 | 2.1 | 7.9 |
| +12 | 8 | 5.0 | 6.1 | 4.8 | 1.7 | 2.1 | 10.1 |
| +13 | 8 | 8.1 | 7.2 | 5.1 | 1.8 | 2.9 | 11.5 |
| +14 | 8 | 7.1 | 6.7 | 4.6 | 1.6 | 2.9 | 10.5 |

No significant differences from controls.

FIGURE 5.1.3

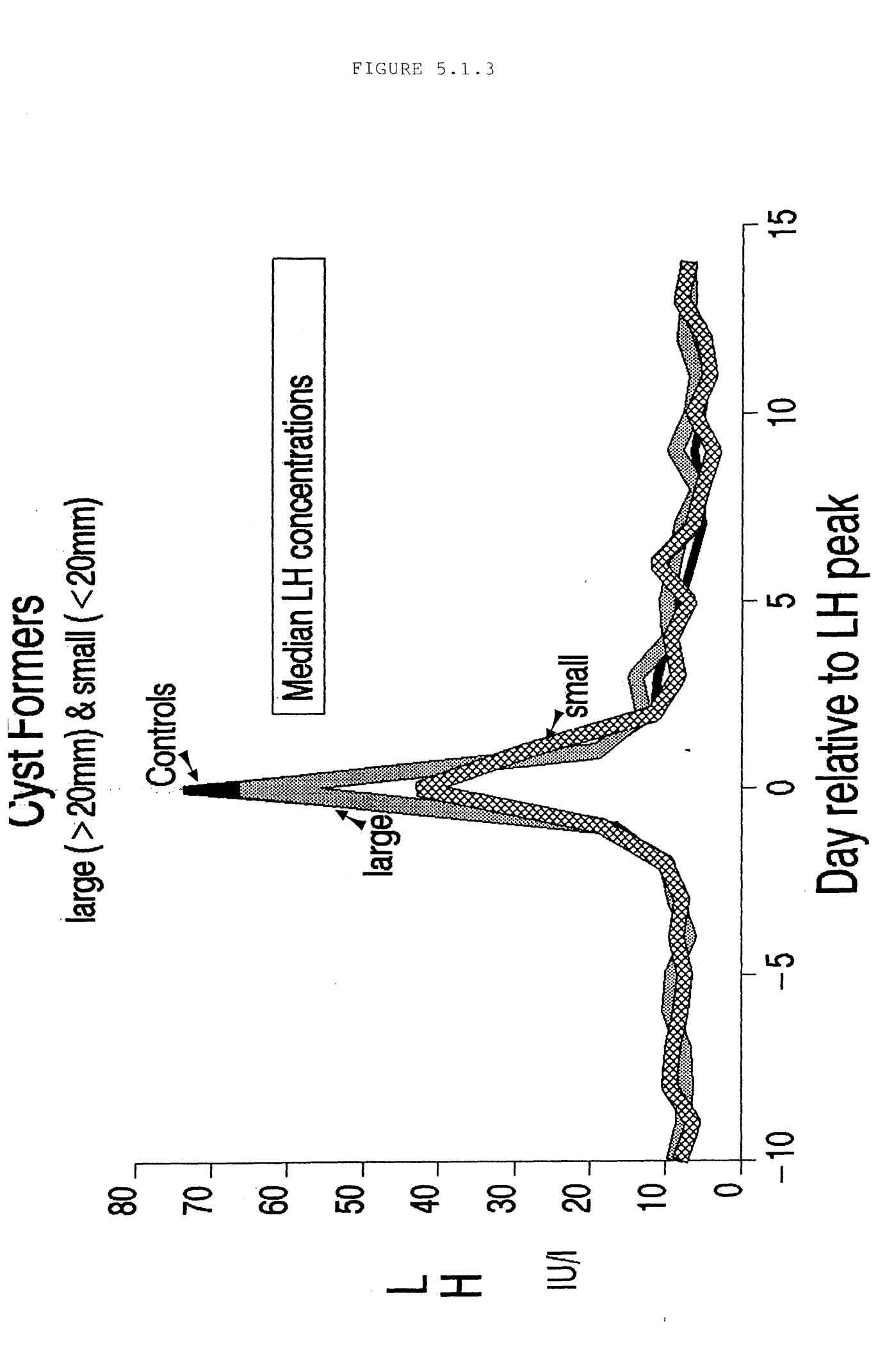

Cyst Formers
large (>20mm) & small (<20mm)
Median LH concentrations
Controls
large
small
LH IU/l
80
70
60
50
40
30
20
10
0
-10
-5
0
5
10
15
Day relative to LH peak

Table 5.1.8

Large Cysts (>20mm)

Plasma FSH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 18 | 6.8 | 7.3 | 2.5 | 0.6 | 6.0 | 8.6 | b |
| -9 | 21 | 6.9 | 7.2 | 2.7 | 0.6 | 5.9 | 8.5 | a |
| -8 | 24 | 6.2 | 6.7 | 3.5 | 0.7 | 5.3 | 8.1 | |
| -7 | 24 | 5.5 | 5.9 | 2.6 | 0.5 | 4.9 | 6.9 | |
| -6 | 25 | 5.3 | 5.9 | 2.2 | 0.4 | 5.1 | 6.7 | a |
| -5 | 27 | 5.6 | 5.0 | 1.5 | 0.3 | 4.4 | 5.6 | |
| -4 | 28 | 4.3 | 4.2 | 1.1 | 0.2 | 3.8 | 4.6 | |
| -3 | 28 | 3.8 | 3.8 | 1.3 | 0.2 | 3.4 | 4.2 | |
| -2 | 28 | 4.0 | 3.8 | 1.1 | 0.2 | 3.4 | 4.2 | |
| -1 | 27 | 4.6 | 5.0 | 2.1 | 0.4 | 4.2 | 5.8 | |
| 0 | 30 | 14.0 | 13.5 | 6.0 | 1.1 | 11.3 | 15.7 | |
| +1 | 29 | 7.6 | 7.9 | 4.3 | 0.8 | 6.3 | 9.5 | |
| +2 | 28 | 5.3 | 6.1 | 3.9 | 0.7 | 4.7 | 7.5 | |
| +3 | 30 | 4.4 | 5.1 | 3.0 | 0.5 | 4.1 | 6.1 | |
| +4 | 28 | 4.6 | 4.9 | 3.2 | 0.6 | 3.7 | 6.1 | |
| +5 | 30 | 4.0 | 4.4 | 3.1 | 0.6 | 3.2 | 5.6 | |
| +6 | 27 | 3.6 | 4.0 | 2.6 | 0.5 | 3.0 | 5.0 | a |
| +7 | 30 | 3.5 | 3.7 | 2.9 | 0.5 | 2.7 | 4.7 | a |
| +8 | 28 | 3.2 | 3.4 | 2.5 | 0.5 | 2.4 | 4.4 | a |
| +9 | 24 | 3.0 | 3.7 | 2.7 | 0.6 | 2.5 | 4.9 | c |
| +10 | 25 | 2.6 | 3.6 | 3.0 | 0.6 | 2.4 | 4.8 | a |
| +11 | 27 | 2.7 | 3.2 | 2.4 | 0.5 | 2.2 | 4.2 | |
| +12 | 26 | 2.8 | 3.3 | 2.3 | 0.5 | 2.3 | 4.3 | |
| +13 | 24 | 2.8 | 3.7 | 2.7 | 0.6 | 2.5 | 4.9 | |
| +14 | 19 | 4.2 | 4.9 | 3.2 | 0.7 | 3.5 | 6.3 | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

Controls

| | |
|---|---|
| p <0.05 | a |
| p <0.02 | b |
| p <0.01 | c |

No significant differences from small cysts.

Table 5.1.9

Small Cysts (<20mm)

Plasma FSH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 8 | 7.1 | 7.6 | 4.4 | 1.6 | 3.8 | 11.4 | |
| -9 | 9 | 8.3 | 8.4 | 4.4 | 1.5 | 4.9 | 11.9 | b |
| -8 | 9 | 6.8 | 7.7 | 4.0 | 1.3 | 4.7 | 10.7 | |
| -7 | 9 | 5.5 | 8.1 | 4.3 | 1.4 | 4.9 | 11.3 | b |
| -6 | 10 | 7.1 | 7.7 | 4.4 | 1.4 | 4.5 | 10.9 | c |
| -5 | 10 | 6.6 | 6.8 | 3.6 | 1.1 | 4.3 | 9.3 | a |
| -4 | 10 | 5.4 | 5.5 | 2.3 | 0.7 | 3.9 | 7.1 | |
| -3 | 9 | 4.0 | 4.6 | 1.9 | 0.6 | 3.2 | 6.0 | |
| -2 | 10 | 4.0 | 4.5 | 1.8 | 0.6 | 3.1 | 5.9 | |
| -1 | 10 | 5.7 | 6.0 | 3.0 | 0.9 | 4.0 | 8.0 | |
| 0 | 10 | 13.5 | 10.5 | 5.8 | 1.8 | 6.4 | 14.6 | |
| +1 | 10 | 10.7 | 11.1 | 4.6 | 1.5 | 7.7 | 14.5 | a |
| +2 | 10 | 7.5 | 7.3 | 3.0 | 0.9 | 5.3 | 9.3 | a |
| +3 | 10 | 5.4 | 5.2 | 2.0 | 0.6 | 3.8 | 6.6 | |
| +4 | 10 | 4.6 | 4.7 | 1.5 | 0.5 | 3.6 | 5.8 | |
| +5 | 10 | 3.4 | 3.8 | 1.4 | 0.4 | 2.9 | 4.7 | |
| +6 | 8 | 3.4 | 3.6 | 0.9 | 1.3 | 0.5 | 6.7 | |
| +7 | 10 | 2.8 | 2.9 | 1.0 | 0.3 | 2.2 | 3.6 | |
| +8 | 10 | 2.8 | 2.9 | 1.2 | 0.4 | 2.0 | 3.8 | |
| +9 | 10 | 2.5 | 2.5 | 1.0 | 0.3 | 1.8 | 3.2 | |
| +10 | 10 | 2.5 | 2.6 | 0.8 | 0.3 | 1.9 | 3.3 | |
| +11 | 10 | 2.3 | 2.3 | 0.8 | 0.3 | 1.6 | 3.0 | |
| +12 | 8 | 2.5 | 2.7 | 1.2 | 0.4 | 1.8 | 3.6 | |
| +13 | 8 | 2.7 | 3.3 | 2.0 | 0.7 | 1.6 | 5.0 | |
| +14 | 8 | 3.7 | 4.4 | 3.0 | 1.1 | 1.9 | 6.9 | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

Controls

| | |
|---|---|
| p <0.05 | a |
| p <0.02 | b |
| p <0.01 | c |

FIGURE 5.1.4

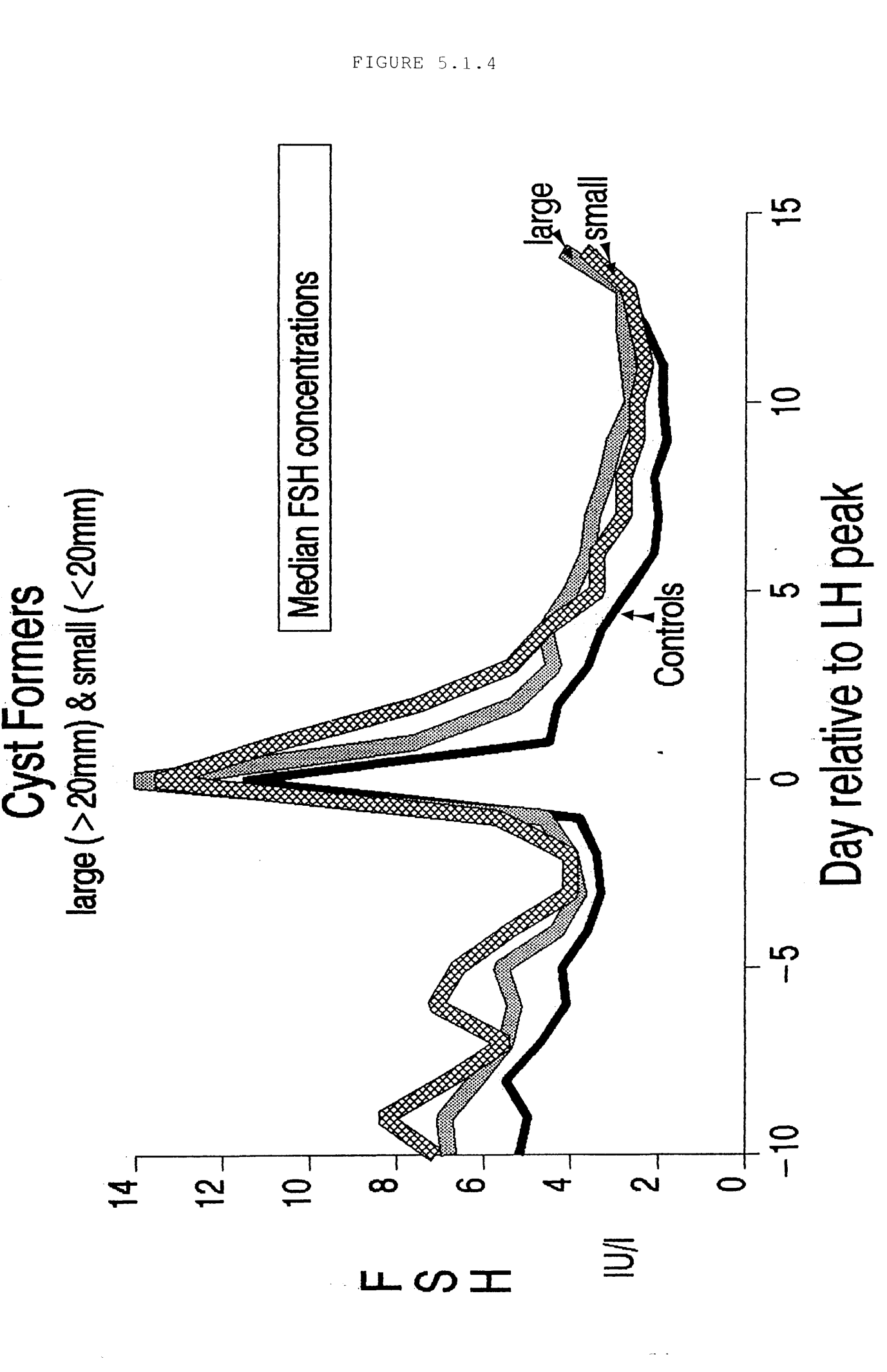

Cyst Formers
large (>20mm) & small (<20mm)
Median FSH concentrations
large
small
Controls
FSH
IU/l
14
12
10
8
6
4
2
0
-10
-5
0
5
10
15
Day relative to LH peak

Table 5.1.10

Large Cysts (>20mm)

Follicular Diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -5 | 7 | 11.0 | 11.1 | 2.8 | 1.1 | 8.4 | 13.8 | |
| -4 | 11 | 13.8 | 14.1 | 2.6 | 0.8 | 12.3 | 15.9 | |
| -3 | 11 | 13.5 | 14.8 | 3.7 | 1.1 | 12.3 | 17.3 | |
| -2 | 12 | 16.0 | 17.1 | 3.8 | 1.1 | 14.7 | 19.5 | |
| -1 | 13 | 18.2 | 18.2 | 2.8 | 0.8 | 16.5 | 19.9 | |
| 0 | 20 | 20.3 | 20.3 | 3.3 | 0.7 | 18.8 | 21.8 | |
| +1 | 19 | 20.0 | 21.1 | 5.6 | 1.2 | 18.4 | 23.8 | |
| +2 | 17 | 24.0 | 23.7 | 4.0 | 1.0 | 21.6 | 25.8 | |
| +3 | 21 | 26.0 | 25.7 | 5.3 | 1.2 | 23.2 | 28.2 | |
| +4 | 15 | 27.0 | 26.7 | 6.1 | 1.6 | 23.3 | 30.1 | |
| +5 | 18 | 26.0 | 26.9 | 6.0 | 1.4 | 23.9 | 29.9 | |
| +6 | 12 | 28.5 | 29.5 | 8.6 | 2.5 | 24.0 | 35.0 | |
| +7 | 13 | 28.0 | 29.1 | 6.4 | 1.8 | 25.2 | 33.0 | |
| +8 | 13 | 30.0 | 31.8 | 10.8 | 3.0 | 25.3 | 38.3 | |
| Cyst size | 31 | 29.5 | 30.4 | 8.4 | 1.5 | 27.3 | 33.5 | a |

Significance (Wilcoxon Rank Sum Test) in comparison with :

Small Cysts

p <0.001 a

No significant differences in FD's in comparison with controls or small cyst formers.

Table 5.1.11

Small Cysts (<20mm)

Follicular Diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -5 | 3 | 16.0 | 15.0 | 3.6 | 2.1 | 6.0 | 24.0 |
| -4 | 5 | 12.0 | 13.9 | 3.2 | 1.4 | 10.0 | 17.8 |
| -3 | 4 | 15.0 | 15.5 | 1.4 | 0.7 | 13.3 | 17.7 |
| -2 | 7 | 17.0 | 16.8 | 2.2 | 0.8 | 14.8 | 18.8 |
| -1 | 7 | 21.0 | 20.6 | 1.7 | 0.6 | 19.1 | 22.1 |
| 0 | 10 | 21.0 | 21.6 | 3.4 | 1.1 | 19.1 | 24.1 |
| +1 | 6 | 18.0 | 17.8 | 3.2 | 1.3 | 14.5 | 21.1 |
| +2 | 7 | 16.5 | 17.7 | 3.8 | 1.4 | 14.3 | 21.1 |
| +3 | 5 | 16.5 | 15.9 | 3.4 | 1.5 | 11.7 | 20.1 |
| +4 | 7 | 17.0 | 16.3 | 2.1 | 0.8 | 14.3 | 18.3 |
| +5 | 2 | 16.5 | 16.5 | 0.7 | 0.5 | 10.1 | 22.6 |
| +6 | 9 | 15.0 | 15.3 | 1.4 | 0.5 | 14.1 | 16.5 |
| +7 | 3 | 17.0 | 17.2 | 1.3 | 0.8 | 13.8 | 20.6 |
| +8 | 4 | 17.5 | 18.0 | 1.4 | 0.7 | 15.8 | 20.2 |
| Cyst size | 11 | 16.0 | 16.2 | 1.4 | 0.4 | 15.3 | 17.1 |

No significant differences in comparison with controls (Wilcoxon Rank Sum Test)

FIGURE 5.1.5

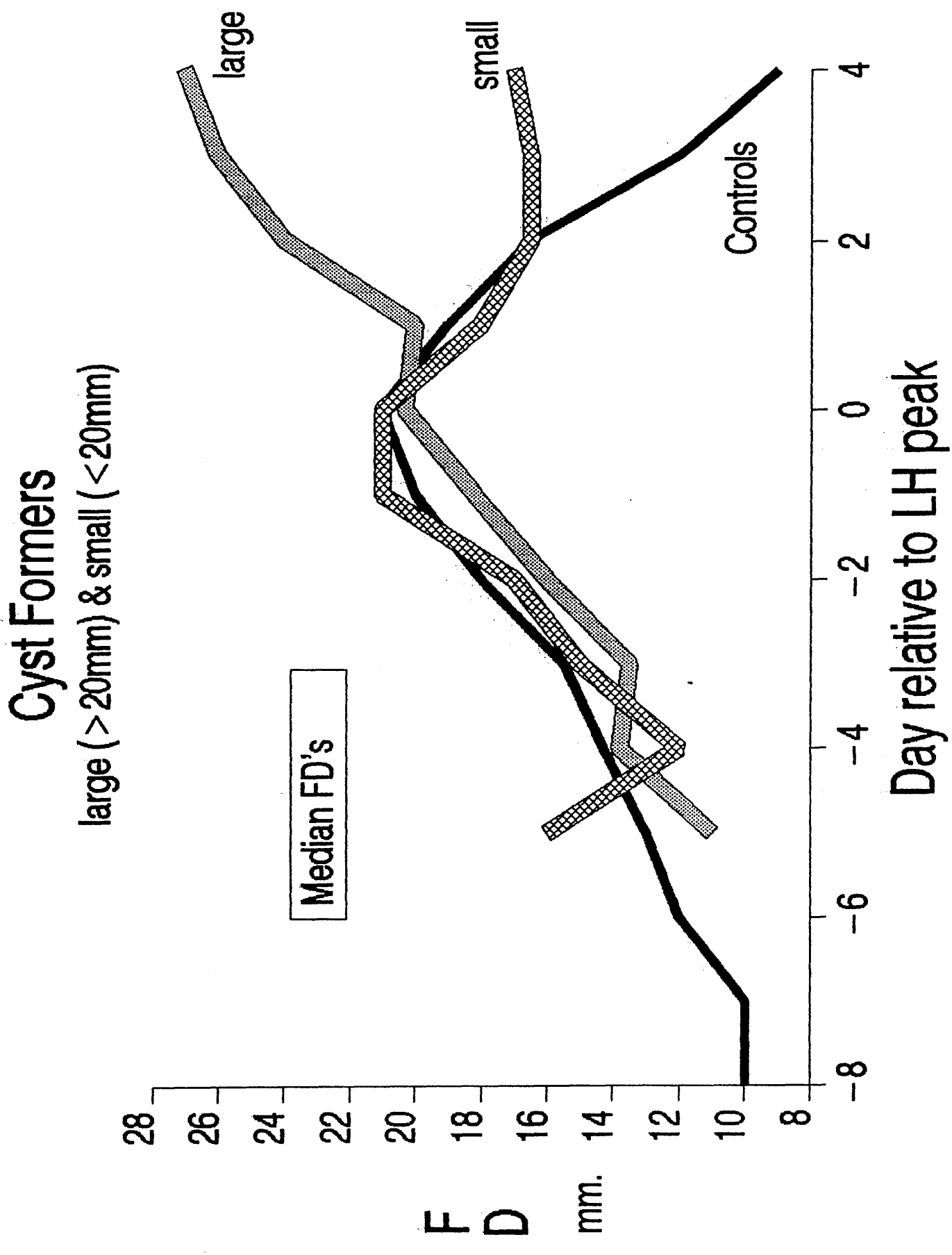

Cyst Formers
large (>20mm) & small (<20mm)
Median FD's
large
small
Controls
FD mm.
28
26
24
22
20
18
16
14
12
10
8
-8
-6
-4
-2
0
2
4
Day relative to LH peak

Table 5.1.12

All Cysts (shrinkers)

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 16 | 72.5 | 73.1 | 15.7 | 3.9 | 64.8 | 81.4 |
| -9 | 17 | 80.0 | 77.9 | 23.1 | 5.6 | 66.0 | 89.8 |
| -8 | 18 | 80.0 | 84.2 | 19.8 | 4.7 | 74.3 | 94.1 |
| -7 | 18 | 85.0 | 87.9 | 21.9 | 5.2 | 76.9 | 98.9 |
| -6 | 19 | 95.0 | 102.8 | 28.8 | 6.6 | 88.9 | 116.7 |
| -5 | 20 | 105.0 | 119.3 | 27.4 | 6.1 | 106.5 | 132.1 |
| -4 | 19 | 120.0 | 133.5 | 37.3 | 8.6 | 115.4 | 151.6 |
| -3 | 20 | 150.0 | 155.8 | 40.5 | 9.1 | 136.8 | 174.8 |
| -2 | 19 | 195.0 | 193.4 | 53.6 | 12.3 | 167.6 | 219.2 |
| -1 | 18 | 230.0 | 227.2 | 51.5 | 12.1 | 201.7 | 252.7 |
| 0 | 21 | 220.0 | 218.1 | 42.7 | 9.3 | 198.7 | 237.5 |
| +1 | 20 | 135.0 | 139.3 | 34.3 | 7.7 | 123.2 | 155.4 |
| +2 | 21 | 123.0 | 118.6 | 29.1 | 6.3 | 105.5 | 131.7 |
| +3 | 21 | 125.0 | 130.9 | 28.9 | 6.3 | 117.8 | 144.0 |
| +4 | 21 | 130.0 | 154.3 | 48.4 | 10.6 | 132.2 | 176.4 |
| +5 | 21 | 135.0 | 151.2 | 42.0 | 9.2 | 132.0 | 170.4 |
| +6 | 18 | 137.5 | 150.7 | 45.7 | 10.8 | 127.9 | 173.5 |
| +7 | 21 | 155.0 | 159.0 | 41.9 | 9.1 | 140.0 | 178.0 |
| +8 | 21 | 155.0 | 163.0 | 44.8 | 9.8 | 142.6 | 183.4 |
| +9 | 19 | 150.0 | 155.9 | 47.7 | 10.9 | 133.0 | 178.8 |
| +10 | 20 | 145.0 | 155.3 | 52.6 | 11.8 | 130.6 | 180.0 |
| +11 | 20 | 140.0 | 137.9 | 38.1 | 8.5 | 120.1 | 155.7 |
| +12 | 16 | 127.5 | 130.2 | 55.5 | 13.9 | 101.1 | 159.3 |
| +13 | 16 | 112.5 | 116.3 | 49.7 | 12.4 | 86.1 | 142.7 |
| +14 | 15 | 91.5 | 111.4 | 62.5 | 16.1 | 76.9 | 145.9 |

No significant differences from controls and non- shrinkers.
(Wilcoxon Rank Sum Test)

Table 5.1.13

All Cysts (non-shrinkers)

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 13 | 80.0 | 79.2 | 14.8 | 4.1 | 70.2 | 88.2 |
| -9 | 14 | 77.5 | 78.3 | 13.0 | 3.5 | 70.8 | 85.8 |
| -8 | 16 | 87.5 | 83.8 | 15.8 | 3.9 | 75.4 | 92.2 |
| -7 | 17 | 85.0 | 87.1 | 17.1 | 4.1 | 78.3 | 95.9 |
| -6 | 17 | 85.0 | 88.1 | 20.5 | 5.0 | 77.5 | 98.7 |
| -5 | 17 | 105.0 | 104.4 | 21.3 | 5.2 | 93.5 | 115.3 |
| -4 | 20 | 115.0 | 123.2 | 39.9 | 8.9 | 104.5 | 141.9 |
| -3 | 19 | 140.0 | 145.9 | 49.8 | 11.4 | 121.9 | 169.9 |
| -2 | 20 | 168.0 | 179.6 | 52.7 | 11.8 | 154.9 | 204.3 |
| -1 | 19 | 235.0 | 221.1 | 55.5 | 12.7 | 194.3 | 247.9 |
| 0 | 20 | 191.5 | 195.2 | 61.2 | 13.7 | 166.6 | 223.8 |
| +1 | 19 | 145.0 | 141.6 | 48.8 | 11.2 | 118.1 | 165.1 |
| +2 | 20 | 116.5 | 122.2 | 35.0 | 7.8 | 105.8 | 138.6 |
| +3 | 20 | 137.5 | 139.2 | 30.9 | 6.9 | 124.7 | 153.7 |
| +4 | 19 | 140.0 | 144.2 | 47.9 | 11.0 | 121.1 | 167.3 |
| +5 | 20 | 135.0 | 157.5 | 59.7 | 13.3 | 129.6 | 185.4 |
| +6 | 19 | 150.0 | 152.6 | 54.4 | 12.5 | 136.8 | 168.4 |
| +7 | 19 | 155.0 | 155.3 | 44.7 | 10.3 | 133.8 | 176.8 |
| +8 | 18 | 142.5 | 156.3 | 51.1 | 12.0 | 130.9 | 181.7 |
| +9 | 18 | 155.0 | 169.2 | 80.6 | 19.0 | 129.1 | 209.3 |
| +10 | 16 | 140.0 | 148.9 | 53.1 | 13.3 | 120.6 | 177.2 |
| +11 | 18 | 136.5 | 153.2 | 63.6 | 15.0 | 121.6 | 184.8 |
| +12 | 19 | 130.0 | 133.1 | 54.3 | 12.5 | 106.9 | 159.3 |
| +13 | 17 | 115.0 | 115.1 | 43.0 | 10.4 | 93.0 | 137.2 |
| +14 | 16 | 97.5 | 99.7 | 31.9 | 8.0 | 82.7 | 116.7 |

No significant differences from controls.
(Wilcoxon Rank Sum Test)

FIGURE 5.1.6

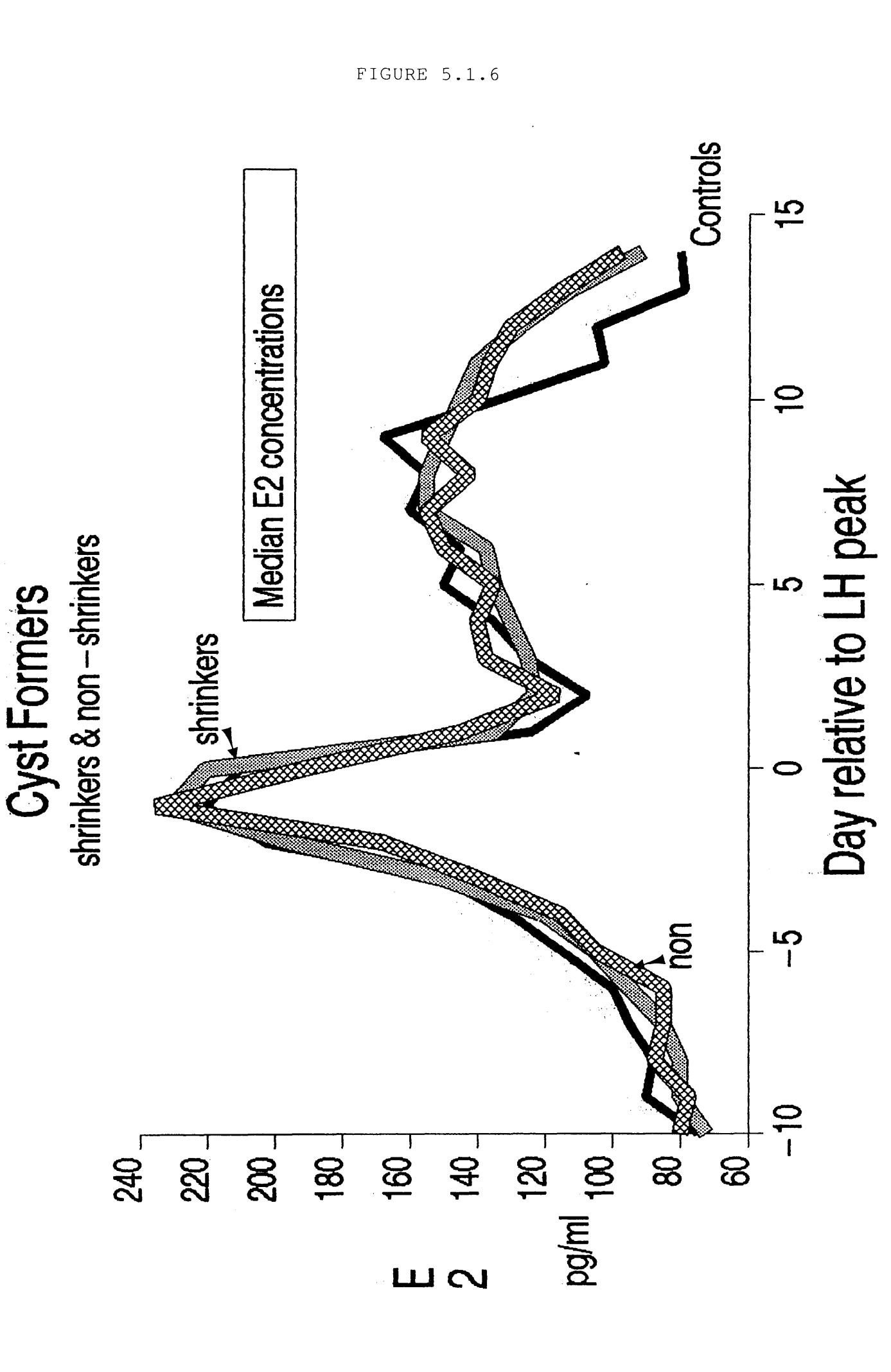

Cyst Formers
shrinkers & non – shrinkers
Median E2 concentrations
shrinkers
non
Controls
E 2
pg/ml
240
220
200
180
160
140
120
100
80
60
–10
–5
0
5
10
15
Day relative to LH peak

Table 5.1.14

All Cysts (shrinkers)

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | | |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 14 | 0.9 | 0.9 | 0.7 | 0.2 | 0.5 | 1.3 | | |
| +1 | 19 | 1.4 | 1.7 | 1.4 | 0.3 | 1.1 | 2.3 | | |
| +2 | 21 | 3.1 | 3.8 | 3.3 | 0.7 | 2.3 | 5.3 | | |
| +3 | 21 | 5.3 | 6.2 | 3.8 | 0.8 | 4.5 | 7.9 | | |
| +4 | 21 | 10.6 | 10.3 | 3.8 | 0.8 | 8.6 | 12.0 | a | |
| +5 | 21 | 14.2 | 15.8 | 5.6 | 1.2 | 13.3 | 18.3 | a | iii |
| +6 | 18 | 18.0 | 19.5 | 6.6 | 1.6 | 16.1 | 22.9 | | iii |
| +7 | 21 | 19.2 | 20.4 | 5.1 | 1.1 | 18.1 | 22.7 | | ii |
| +8 | 21 | 18.0 | 18.9 | 5.6 | 1.3 | 16.2 | 21.6 | | i |
| +9 | 19 | 19.2 | 18.0 | 6.3 | 1.4 | 15.1 | 20.9 | | i |
| +10 | 20 | 16.4 | 15.5 | 7.0 | 1.6 | 12.2 | 18.8 | | |
| +11 | 20 | 14.7 | 14.0 | 7.7 | 1.7 | 10.4 | 17.6 | c | |
| +12 | 16 | 10.4 | 9.6 | 4.5 | 1.1 | 7.3 | 11.9 | c | |
| +13 | 16 | 5.3 | 5.0 | 3.1 | 0.8 | 3.3 | 6.7 | b | |
| +14 | 15 | 2.1 | 2.9 | 2.6 | 0.7 | 1.4 | 4.4 | | |
| P index | 21 | 84.0 | 86.0 | 28.1 | 6.1 | 73.2 | 98.8 | | iii |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls | Non-shrinkers |
|---|---|---|
| p <0.05 | a | i |
| p <0.02 | b | |
| p <0.01 | | ii |
| p <0.001 | c | iii |

Table 5.1.15

All Cysts (non-shrinkers)

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| 0 | 12 | 1.0 | 1.0 | 0.6 | 0.2 | 0.6 | 1.4 | |
| +1 | 18 | 1.2 | 1.4 | 0.7 | 0.2 | 1.0 | 1.8 | b |
| +2 | 19 | 2.8 | 2.7 | 1.3 | 0.3 | 2.1 | 3.3 | c |
| +3 | 20 | 4.1 | 4.4 | 2.4 | 0.5 | 3.3 | 5.5 | d |
| +4 | 19 | 5.6 | 5.8 | 3.4 | 0.8 | 4.2 | 7.4 | d |
| +5 | 20 | 8.2 | 8.8 | 4.1 | 0.9 | 6.9 | 10.7 | d |
| +6 | 19 | 10.4 | 12.5 | 5.9 | 1.4 | 9.7 | 15.3 | d |
| +7 | 19 | 14.4 | 15.6 | 7.8 | 1.8 | 11.8 | 19.4 | |
| +8 | 19 | 10.8 | 14.2 | 6.9 | 1.6 | 10.9 | 17.5 | a |
| +9 | 18 | 13.2 | 14.3 | 7.0 | 1.6 | 10.8 | 17.8 | |
| +10 | 16 | 13.4 | 13.2 | 6.0 | 1.5 | 10.0 | 16.4 | |
| +11 | 18 | 11.1 | 11.6 | 6.5 | 1.5 | 8.4 | 14.8 | c |
| +12 | 19 | 8.2 | 8.9 | 6.3 | 1.4 | 5.9 | 11.9 | c |
| +13 | 17 | 4.0 | 5.7 | 5.3 | 1.3 | 3.0 | 8.4 | a |
| +14 | 16 | 1.1 | 3.0 | 3.2 | 0.8 | 1.3 | 4.7 | |
| P index | 20 | 53.5 | 54.8 | 24.1 | 5.4 | 43.5 | 66.1 | d |

Significance (Wilcoxon Rank Sum Test) in comparison with :

Controls

| | |
|---|---|
| p <0.05 | a |
| p <0.02 | b |
| p <0.01 | c |
| p <0.001 | d |

FIGURE 5.1.7

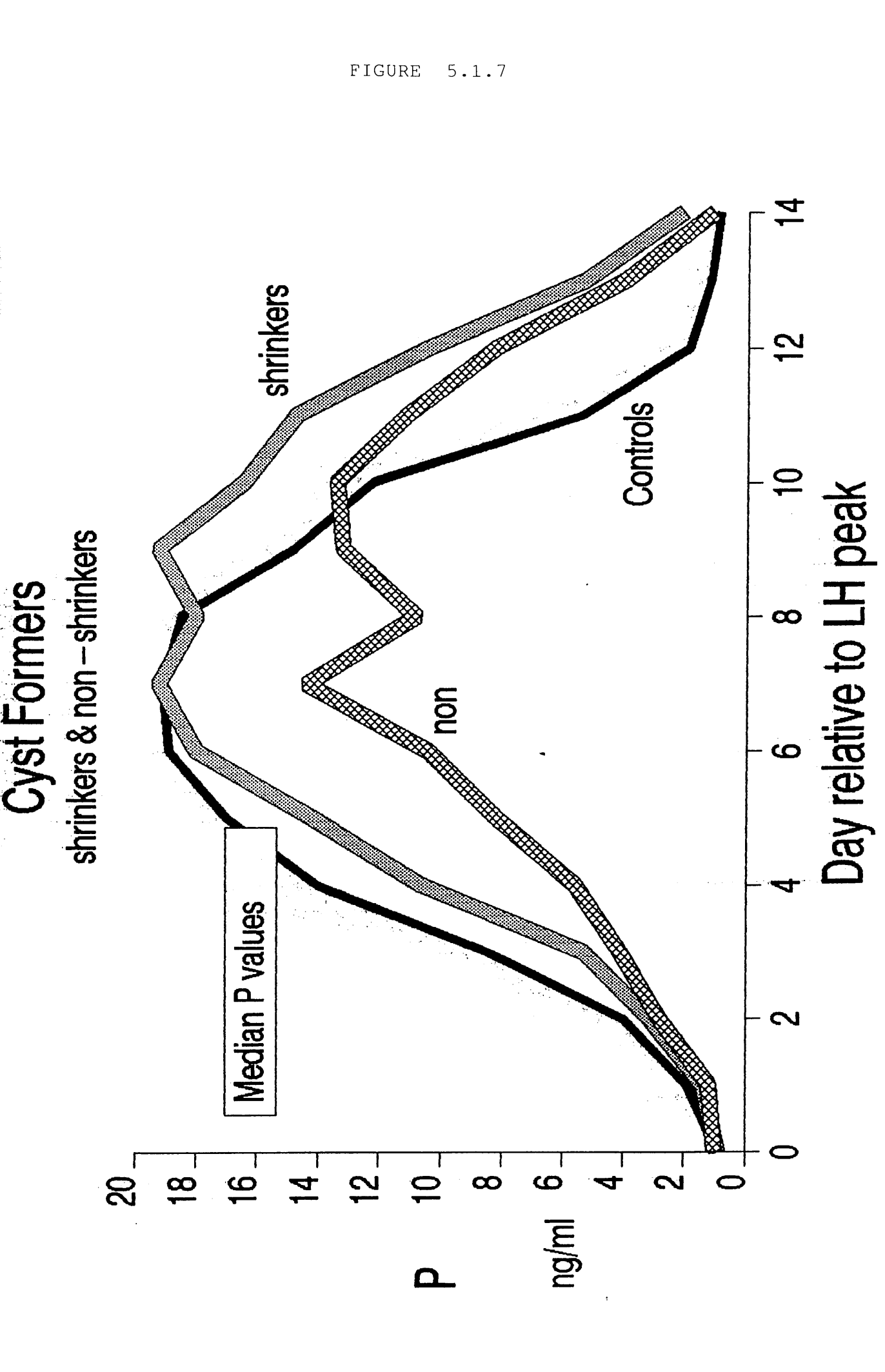

Cyst Formers
shrinkers & non – shrinkers
Median P values
shrinkers
non
Controls
P
ng/ml
20
18
16
14
12
10
8
6
4
2
0
0
2
4
6
8
10
12
14
Day relative to LH peak

Table 5.1.16

All Cysts (shrinkers)

Plasma LH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 14 | 7.0 | 8.9 | 5.2 | 1.4 | 5.9 | 11.9 |
| -9 | 16 | 6.5 | 8.2 | 5.7 | 1.4 | 5.2 | 11.2 |
| -8 | 17 | 7.4 | 9.1 | 6.2 | 1.5 | 5.9 | 12.3 |
| -7 | 17 | 7.4 | 9.2 | 6.4 | 1.5 | 6.0 | 12.4 |
| -6 | 18 | 7.0 | 9.6 | 5.9 | 1.4 | 5.2 | 14.0 |
| -5 | 19 | 6.2 | 8.2 | 5.5 | 1.3 | 5.5 | 10.9 |
| -4 | 17 | 6.6 | 7.5 | 4.7 | 1.1 | 5.2 | 9.8 |
| -3 | 17 | 7.0 | 7.4 | 4.0 | 1.0 | 5.3 | 9.5 |
| -2 | 17 | 8.1 | 9.8 | 4.9 | 1.2 | 7.3 | 12.3 |
| -1 | 17 | 19.0 | 20.7 | 13.4 | 3.2 | 13.9 | 27.5 |
| 0 | 19 | 50.0 | 54.7 | 21.6 | 4.9 | 44.4 | 65.0 |
| +1 | 18 | 25.5 | 28.4 | 14.0 | 3.2 | 21.6 | 35.2 |
| +2 | 19 | 12.0 | 12.2 | 5.6 | 1.3 | 9.5 | 14.9 |
| +3 | 20 | 12.5 | 12.5 | 7.1 | 1.6 | 9.2 | 15.8 |
| +4 | 20 | 10.0 | 14.2 | 11.3 | 2.5 | 9.0 | 19.4 |
| +5 | 20 | 8.1 | 9.6 | 6.0 | 1.3 | 6.9 | 12.3 |
| +6 | 16 | 11.0 | 10.2 | 6.7 | 1.7 | 6.6 | 13.8 |
| +7 | 20 | 5.9 | 7.7 | 5.6 | 1.3 | 5.0 | 10.4 |
| +8 | 18 | 4.1 | 7.4 | 6.6 | 1.6 | 4.0 | 10.8 |
| +9 | 17 | 3.8 | 7.2 | 7.2 | 1.7 | 3.6 | 10.8 |
| +10 | 19 | 4.5 | 5.7 | 4.8 | 1.1 | 3.4 | 8.0 |
| +11 | 18 | 4.4 | 5.8 | 5.2 | 1.2 | 3.3 | 8.3 |
| +12 | 13 | 4.9 | 5.7 | 4.2 | 1.2 | 3.1 | 8.3 |
| +13 | 15 | 7.6 | 7.4 | 4.0 | 1.0 | 5.3 | 9.5 |
| +14 | 13 | 7.2 | 7.4 | 3.9 | 1.1 | 5.0 | 9.8 |

No significant differences from controls and non-shrinkers.
(Wilcoxon Rank Sum Test)

Table 5.1.17

All Cysts (non-shrinkers)

Plasma LH concentrations (IU/1)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 12 | 9.9 | 9.3 | 4.0 | 1.2 | 6.8 | 11.8 |
| -9 | 14 | 8.3 | 9.0 | 5.4 | 1.4 | 5.9 | 12.1 |
| -8 | 16 | 7.4 | 9.4 | 6.2 | 1.5 | 6.1 | 12.7 |
| -7 | 16 | 8.7 | 9.1 | 4.0 | 1.0 | 7.0 | 11.2 |
| -6 | 17 | 9.7 | 9.5 | 4.1 | 1.0 | 7.4 | 11.6 |
| -5 | 18 | 9.7 | 9.7 | 3.6 | 0.9 | 7.9 | 11.5 |
| -4 | 20 | 7.0 | 8.3 | 3.9 | 0.9 | 6.5 | 10.1 |
| -3 | 19 | 9.4 | 10.8 | 6.2 | 1.4 | 7.8 | 13.8 |
| -2 | 20 | 10.0 | 11.2 | 5.1 | 1.1 | 8.8 | 13.6 |
| -1 | 19 | 19.0 | 22.5 | 12.4 | 2.9 | 16.5 | 28.5 |
| 0 | 20 | 63.0 | 60.4 | 19.2 | 4.3 | 51.5 | 69.3 |
| +1 | 20 | 18.0 | 22.3 | 14.0 | 3.1 | 15.8 | 28.8 |
| +2 | 20 | 14.5 | 14.0 | 7.6 | 1.7 | 10.5 | 17.5 |
| +3 | 20 | 13.0 | 12.7 | 6.0 | 1.3 | 9.9 | 15.5 |
| +4 | 18 | 11.0 | 14.1 | 7.7 | 1.8 | 10.3 | 17.9 |
| +5 | 20 | 10.5 | 13.0 | 7.2 | 1.6 | 9.6 | 16.4 |
| +6 | 19 | 9.0 | 10.3 | 6.4 | 1.5 | 7.2 | 13.4 |
| +7 | 20 | 8.4 | 10.1 | 6.3 | 1.4 | 7.2 | 13.0 |
| +8 | 18 | 5.8 | 7.9 | 4.4 | 1.0 | 5.7 | 10.1 |
| +9 | 18 | 8.9 | 10.1 | 7.5 | 1.8 | 6.4 | 13.8 |
| +10 | 16 | 8.7 | 9.1 | 5.3 | 1.3 | 6.3 | 11.9 |
| +11 | 18 | 6.0 | 7.9 | 4.8 | 1.1 | 5.5 | 10.3 |
| +12 | 18 | 7.8 | 8.5 | 4.6 | 1.1 | 6.2 | 10.8 |
| +13 | 16 | 7.0 | 6.3 | 3.0 | 0.8 | 4.7 | 7.8 |
| +14 | 14 | 7.2 | 7.3 | 2.6 | 0.7 | 5.8 | 8.8 |

No significant differences from controls.
(Wilcoxon Rank Sum Test)

FIGURE 5.1.8

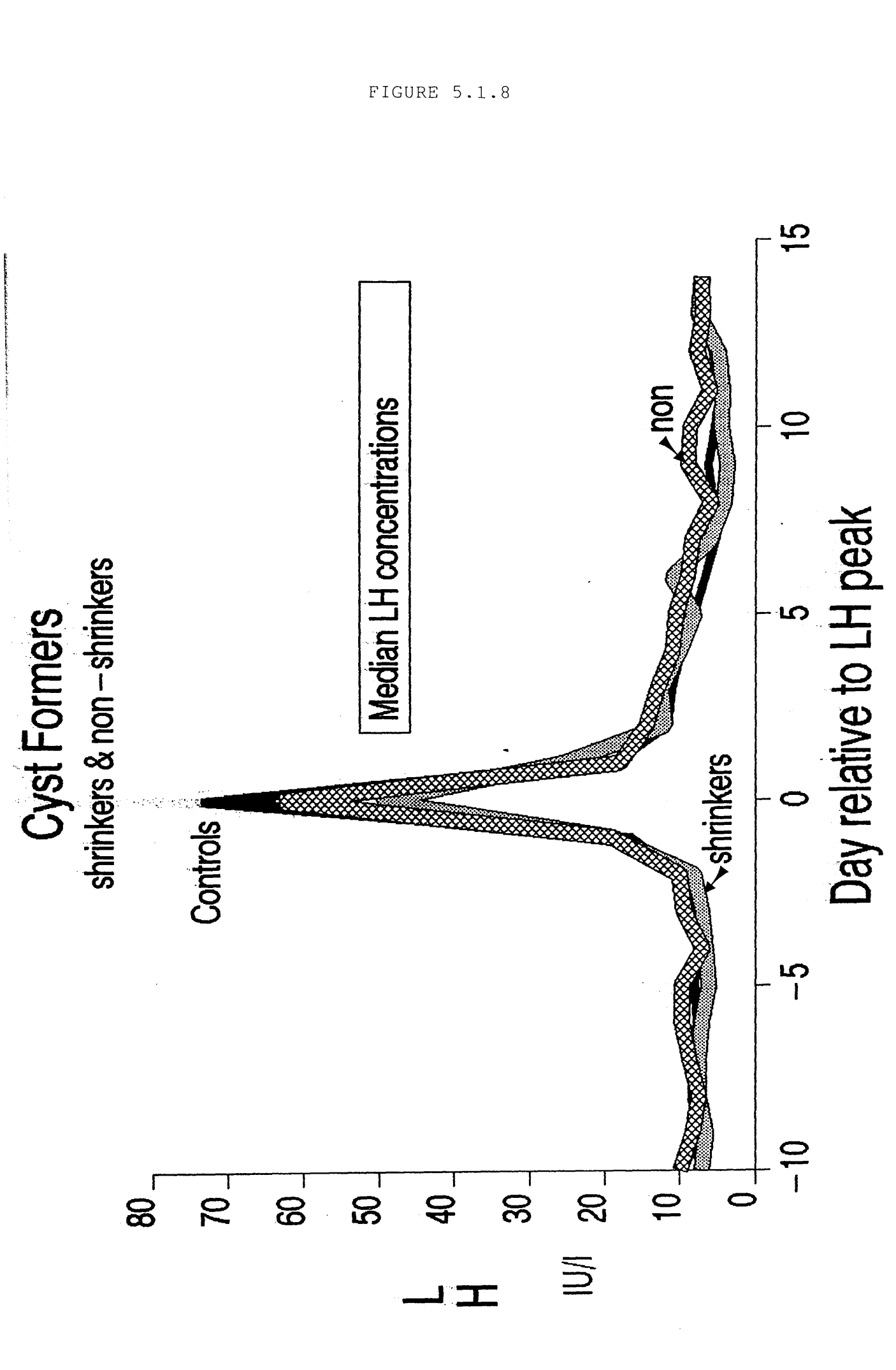

Cyst Formers
shrinkers & non-shrinkers
Median LH concentrations
Controls
non
shrinkers
LH IU/l
80
70
60
50
40
30
20
10
0
-10
-5
0
5
10
15
Day relative to LH peak

Table 5.1.18

All Cysts (shrinkers)

Plasma FSH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | | |
|---|---|---|---|---|---|---|---|---|---|
| -10 | 14 | 7.4 | 7.3 | 3.8 | 1.0 | 5.1 | 9.5 | | |
| -9 | 16 | 8.6 | 8.3 | 4.0 | 1.0 | 6.2 | 10.4 | c | |
| -8 | 17 | 6.8 | 7.6 | 4.3 | 1.0 | 5.5 | 9.7 | | |
| -7 | 17 | 7.5 | 7.8 | 3.9 | 0.9 | 5.9 | 9.7 | b | i |
| -6 | 18 | 6.9 | 7.3 | 3.5 | 0.8 | 5.6 | 9.0 | c | |
| -5 | 19 | 6.4 | 6.0 | 2.8 | 0.7 | 4.5 | 7.5 | | |
| -4 | 18 | 5.4 | 5.1 | 1.9 | 0.5 | 4.0 | 6.2 | | i |
| -3 | 18 | 3.8 | 4.1 | 1.6 | 0.4 | 3.3 | 4.9 | | |
| -2 | 18 | 4.3 | 4.2 | 1.5 | 0.3 | 3.6 | 4.8 | | |
| -1 | 18 | 5.4 | 5.6 | 2.6 | 0.6 | 4.3 | 6.9 | | |
| 0 | 20 | 13.0 | 11.4 | 5.1 | 1.1 | 9.1 | 13.7 | | |
| +1 | 19 | 9.3 | 9.8 | 4.3 | 1.0 | 7.7 | 11.9 | | |
| +2 | 19 | 6.4 | 6.3 | 2.9 | 0.7 | 4.8 | 7.8 | | |
| +3 | 20 | 5.0 | 5.2 | 2.7 | 0.6 | 3.9 | 6.5 | | |
| +4 | 20 | 4.9 | 4.7 | 2.1 | 0.5 | 3.7 | 5.7 | | |
| +5 | 20 | 3.4 | 3.9 | 1.8 | 0.4 | 3.1 | 4.7 | | |
| +6 | 16 | 3.4 | 3.8 | 1.6 | 0.4 | 2.9 | 4.7 | a | |
| +7 | 20 | 3.0 | 2.8 | 1.2 | 0.3 | 2.2 | 3.4 | | |
| +8 | 20 | 2.8 | 2.9 | 1.3 | 0.3 | 2.3 | 3.5 | | |
| +9 | 16 | 2.6 | 2.8 | 1.2 | 0.3 | 2.2 | 3.4 | a | |
| +10 | 19 | 2.7 | 2.9 | 2.1 | 0.5 | 1.8 | 4.0 | | |
| +11 | 19 | 2.3 | 2.7 | 1.3 | 0.3 | 2.1 | 3.3 | | |
| +12 | 14 | 2.5 | 2.9 | 1.6 | 0.7 | 1.4 | 4.4 | | |
| +13 | 15 | 2.8 | 3.5 | 2.1 | 0.5 | 2.4 | 4.6 | | |
| +14 | 13 | 4.2 | 4.8 | 3.2 | 0.9 | 2.8 | 6.8 | | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls | Non-shrinkers |
|---|---|---|
| p <0.05 | a | i |
| p <0.02 | b | |
| p <0.01 | c | |

Table 5.1.19

All Cysts (non-shrinkers)

Plasma FSH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 12 | 7.2 | 7.5 | 2.2 | 0.6 | 6.1 | 8.9 | c |
| -9 | 14 | 6.3 | 6.7 | 2.0 | 0.5 | 5.6 | 7.8 | |
| -8 | 16 | 6.0 | 6.3 | 2.7 | 0.7 | 4.8 | 7.8 | |
| -7 | 16 | 5.3 | 5.2 | 1.7 | 0.4 | 4.3 | 6.1 | |
| -6 | 17 | 5.2 | 5.4 | 2.1 | 0.5 | 4.3 | 6.5 | |
| -5 | 18 | 5.5 | 4.9 | 1.5 | 0.4 | 4.1 | 5.7 | |
| -4 | 20 | 4.2 | 4.1 | 0.7 | 0.2 | 3.8 | 4.4 | |
| -3 | 19 | 3.9 | 3.8 | 1.3 | 0.3 | 3.2 | 4.4 | |
| -2 | 20 | 3.8 | 3.7 | 1.2 | 0.3 | 3.1 | 4.3 | |
| -1 | 19 | 4.5 | 5.0 | 2.2 | 0.5 | 4.0 | 6.0 | |
| 0 | 20 | 14.0 | 14.2 | 6.7 | 1.5 | 11.1 | 17.3 | a |
| +1 | 20 | 7.0 | 7.8 | 4.7 | 1.0 | 5.6 | 10.0 | |
| +2 | 19 | 4.7 | 6.4 | 4.4 | 1.0 | 4.3 | 8.5 | |
| +3 | 20 | 4.1 | 5.1 | 2.9 | 0.7 | 3.7 | 6.5 | |
| +4 | 18 | 3.9 | 5.0 | 3.6 | 0.8 | 3.2 | 6.8 | |
| +5 | 20 | 4.0 | 4.6 | 3.6 | 0.8 | 2.9 | 6.3 | |
| +6 | 19 | 3.3 | 4.1 | 2.8 | 0.6 | 2.7 | 5.5 | a |
| +7 | 20 | 3.6 | 4.2 | 3.3 | 0.7 | 2.7 | 5.7 | b |
| +8 | 18 | 3.0 | 3.7 | 2.9 | 0.7 | 2.3 | 5.1 | a |
| +9 | 18 | 2.9 | 3.8 | 3.1 | 0.7 | 2.3 | 5.3 | b |
| +10 | 16 | 3.0 | 3.8 | 3.0 | 0.8 | 2.2 | 5.4 | b |
| +11 | 18 | 2.7 | 3.3 | 2.8 | 0.7 | 1.9 | 4.7 | |
| +12 | 19 | 2.6 | 3.2 | 2.5 | 0.6 | 2.0 | 4.4 | |
| +13 | 17 | 2.7 | 3.7 | 2.9 | 0.7 | 2.2 | 5.2 | |
| +14 | 14 | 3.7 | 4.8 | 3.2 | 0.8 | 3.0 | 6.6 | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

Controls

| | |
|---|---|
| p <0.05 | a |
| p <0.02 | b |
| p <0.01 | c |

FIGURE 5.1.9

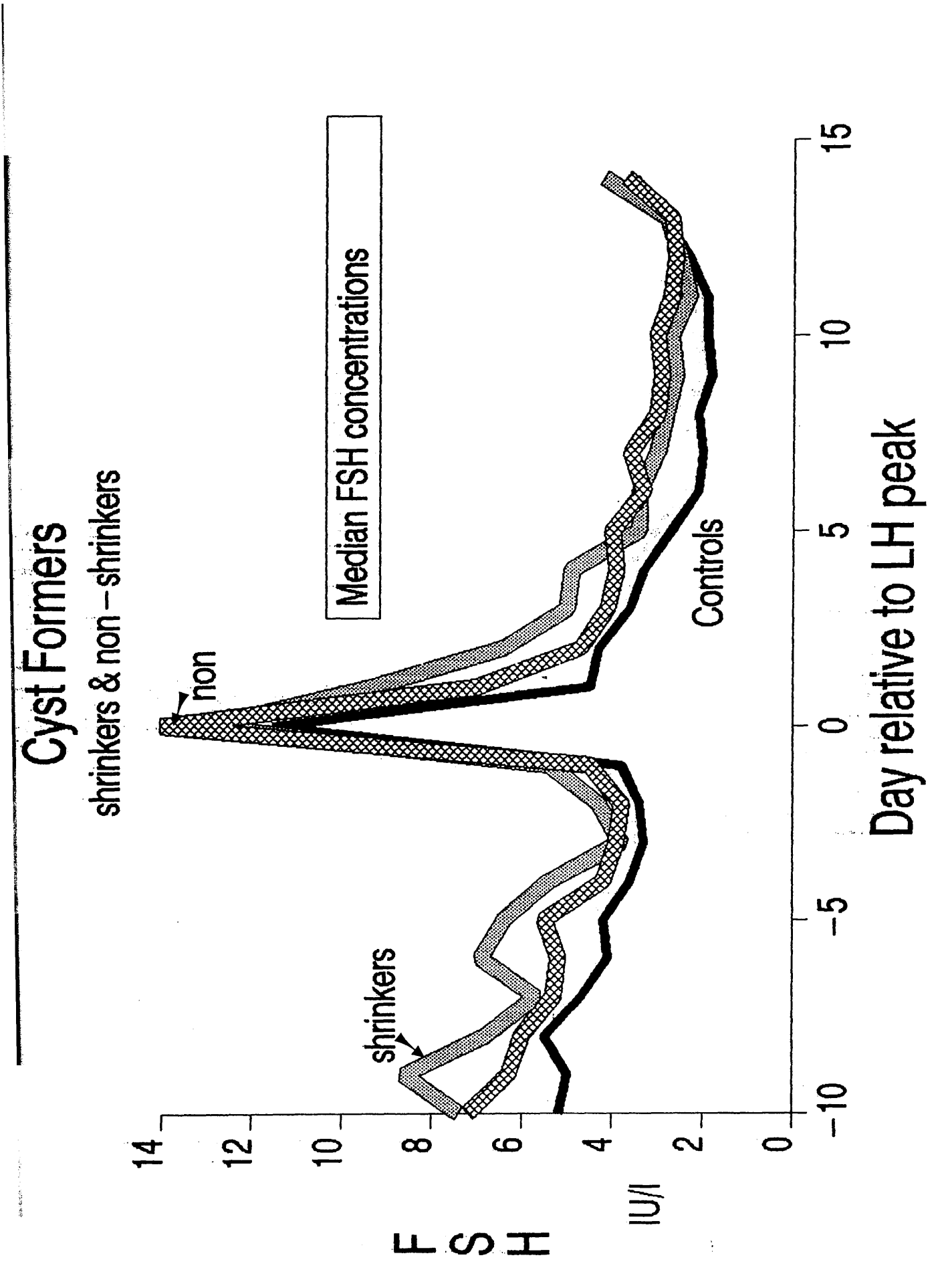

Cyst Formers
shrinkers & non–shrinkers
Median FSH concentrations
non
shrinkers
Controls
FSH
IU/l
14
12
10
8
6
4
2
0
–10
–5
0
5
10
15
Day relative to LH peak

Table 5.1.20

All Cysts (shrinkers)

Follicular Diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -5 | 6 | 11.8 | 12.6 | 3.8 | 1.5 | 8.7 | 16.5 | |
| -4 | 8 | 14.0 | 14.8 | 3.5 | 1.2 | 12.0 | 17.6 | |
| -3 | 6 | 14.8 | 14.6 | 1.8 | 0.7 | 12.8 | 16.4 | |
| -2 | 11 | 16.5 | 16.8 | 3.4 | 1.0 | 14.6 | 19.0 | |
| -1 | 9 | 19.5 | 20.0 | 2.1 | 0.7 | 18.4 | 21.6 | |
| 0 | 19 | 20.5 | 21.4 | 3.0 | 0.7 | 19.9 | 22.9 | |
| +1 | 15 | 19.0 | 18.7 | 3.6 | 0.9 | 16.8 | 20.6 | i |
| +2 | 13 | 19.3 | 19.4 | 3.7 | 1.0 | 17.2 | 21.6 | iii |
| +3 | 13 | 18.5 | 21.0 | 6.0 | 1.7 | 16.3 | 24.7 | ii |
| +4 | 13 | 19.0 | 19.6 | 4.7 | 1.3 | 16.8 | 22.4 | iv |
| +5 | 8 | 21.0 | 21.6 | 4.0 | 1.1 | 19.0 | 24.2 | ii |
| +6 | 12 | 15.5 | 17.3 | 4.1 | 1.2 | 14.7 | 19.9 | iv |
| +7 | 7 | 18.5 | 20.7 | 4.8 | 1.8 | 16.3 | 25.1 | iv |
| +8 | 10 | 19.0 | 22.5 | 7.2 | 2.3 | 17.3 | 27.7 | iii |
| Cyst size | 21 | 18.5 | 20.4 | 5.7 | 1.2 | 17.8 | 23.0 | iv |

Significance (Wilcoxon Rank Sum Test) in comparison with :

Non-shrinkers

| | |
|---|---|
| p <0.05 | i |
| p <0.02 | ii |
| p <0.01 | iii |
| p <0.001 | iv |

No significant differences from controls.

Table 5.1.21

All Cysts (non-shrinkers)

Follicular Diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -5 | 4 | 9.5 | 11.8 | 3.3 | 1.7 | 6.5 | 17.1 |
| -4 | 8 | 13.8 | 13.3 | 1.4 | 0.5 | 12.1 | 14.5 |
| -3 | 9 | 14.0 | 15.2 | 3.9 | 1.3 | 12.2 | 18.2 |
| -2 | 8 | 16.3 | 17.3 | 3.1 | 1.1 | 14.7 | 19.6 |
| -1 | 11 | 18.0 | 18.2 | 2.9 | 0.9 | 16.2 | 20.2 |
| 0 | 11 | 19.5 | 19.6 | 3.5 | 1.1 | 17.2 | 23.0 |
| +1 | 10 | 21.0 | 22.9 | 6.5 | 2.1 | 18.2 | 27.6 |
| +2 | 11 | 25.5 | 24.9 | 4.1 | 1.2 | 22.2 | 27.6 |
| +3 | 13 | 26.0 | 26.6 | 5.4 | 1.5 | 23.4 | 29.8 |
| +4 | 9 | 28.0 | 28.9 | 6.5 | 2.2 | 23.9 | 33.9 |
| +5 | 12 | 31.0 | 28.8 | 6.4 | 1.9 | 24.7 | 32.9 |
| +6 | 9 | 31.0 | 31.7 | 8.7 | 2.9 | 25.0 | 38.4 |
| +7 | 9 | 33.0 | 31.6 | 5.4 | 1.8 | 27.4 | 35.8 |
| +8 | 7 | 37.0 | 37.2 | 10.2 | 3.9 | 27.7 | 46.7 |
| Cyst size | 20 | 33.0 | 33.1 | 8.4 | 1.9 | 29.1 | 37.1 |

No significant differences from controls.
(Wilcoxon Rank Sum Test)

FIGURE 5.1.10

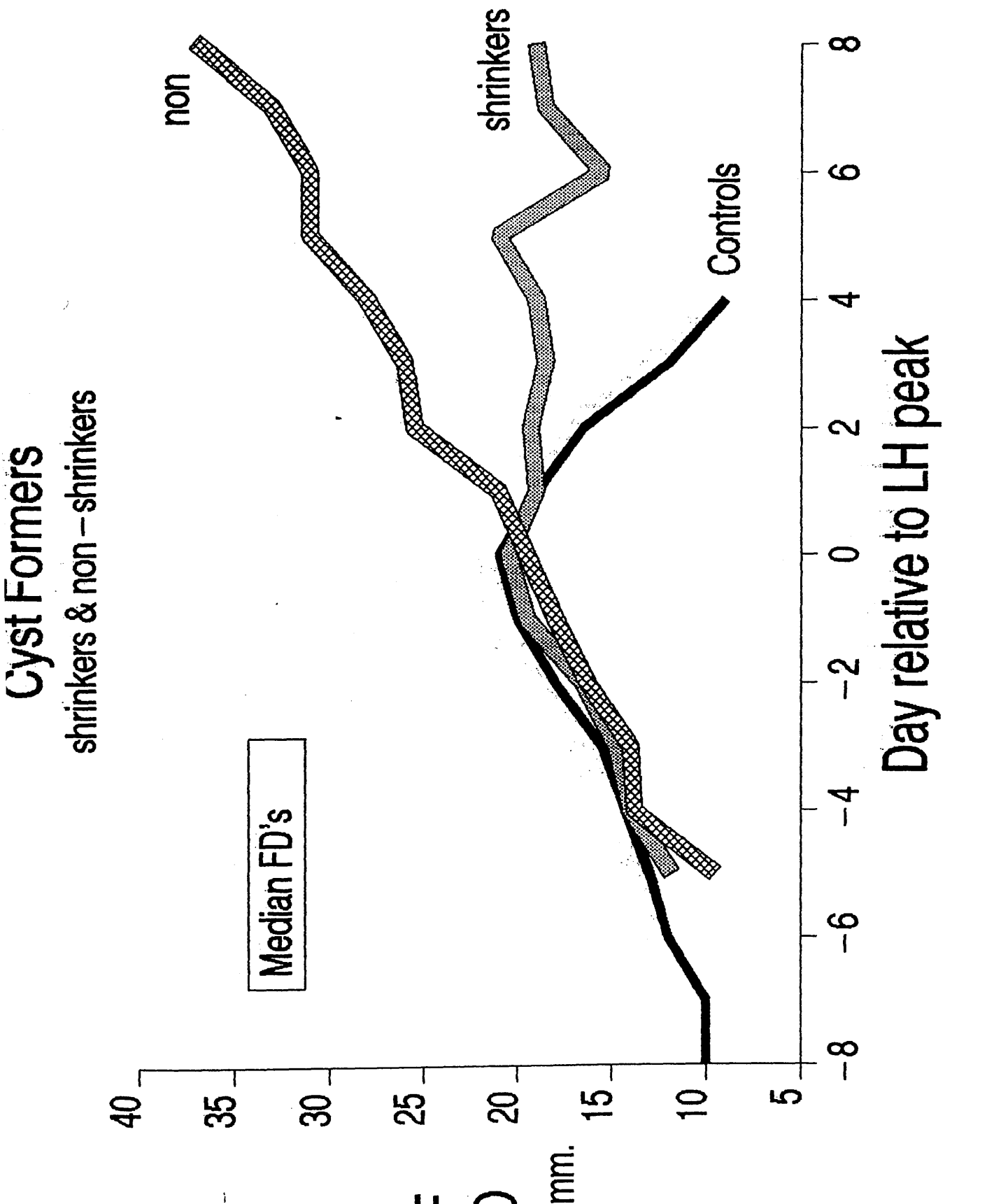

Cyst Formers
shrinkers & non – shrinkers
Median FD's
non
shrinkers
Controls
FD mm.
40
35
30
25
20
15
10
5
-8
-6
-4
-2
0
2
4
6
8
Day relative to LH peak

Table 5.1.22

All Cysts (low P index)

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | | |
|---|---|---|---|---|---|---|---|---|---|
| -10 | 22 | 75.0 | 77.0 | 15.9 | 3.4 | 69.9 | 84.1 | | |
| -9 | 23 | 80.0 | 80.0 | 19.1 | 4.0 | 71.7 | 88.3 | | |
| -8 | 24 | 82.5 | 87.9 | 21.7 | 4.4 | 78.8 | 97.0 | | |
| -7 | 26 | 90.0 | 89.1 | 20.9 | 4.1 | 80.7 | 97.5 | | |
| -6 | 26 | 95.0 | 96.8 | 26.4 | 5.2 | 86.1 | 107.5 | | |
| -5 | 28 | 110.0 | 112.5 | 26.9 | 5.1 | 102.0 | 123.0 | | |
| -4 | 29 | 120.0 | 127.9 | 39.1 | 7.3 | 112.9 | 142.9 | | |
| -3 | 29 | 140.0 | 147.3 | 45.6 | 8.5 | 129.9 | 164.7 | | |
| -2 | 29 | 168.0 | 176.9 | 47.7 | 8.9 | 158.7 | 195.1 | | |
| -1 | 27 | 235.0 | 220.4 | 51.6 | 9.9 | 200.0 | 240.8 | | |
| 0 | 31 | 208.0 | 205.5 | 45.3 | 8.1 | 189.0 | 222.0 | | |
| +1 | 29 | 140.0 | 143.8 | 42.5 | 7.9 | 127.6 | 160.0 | a | |
| +2 | 30 | 125.0 | 128.1 | 30.8 | 5.6 | 116.6 | 139.6 | a | ii |
| +3 | 31 | 135.0 | 140.3 | 31.2 | 5.6 | 128.9 | 151.7 | | i |
| +4 | 31 | 145.0 | 156.7 | 50.9 | 9.1 | 138.1 | 175.3 | | |
| +5 | 31 | 135.0 | 159.2 | 55.5 | 10.0 | 138.8 | 179.6 | | |
| +6 | 27 | 150.0 | 159.6 | 52.0 | 10.0 | 139.0 | 180.2 | | |
| +7 | 29 | 150.0 | 162.1 | 45.4 | 8.4 | 144.9 | 179.3 | | |
| +8 | 30 | 157.5 | 163.1 | 50.5 | 9.2 | 144.3 | 181.9 | | |
| +9 | 28 | 150.0 | 169.8 | 71.2 | 13.5 | 142.1 | 197.5 | | |
| +10 | 27 | 145.0 | 156.2 | 55.3 | 10.6 | 134.4 | 178.0 | | |
| +11 | 29 | 140.0 | 148.9 | 54.6 | 10.1 | 128.2 | 169.6 | | |
| +12 | 25 | 135.0 | 139.1 | 57.2 | 11.4 | 115.6 | 162.6 | | |
| +13 | 24 | 112.5 | 121.2 | 42.3 | 8.6 | 94.7 | 139.0 | b | |
| +14 | 22 | 107.5 | 108.4 | 42.7 | 9.1 | 89.5 | 127.3 | | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls | Normal P Index |
|---|---|---|
| p <0.05 | a | i |
| p <0.02 | b | ii |

Table 5.1.23

All Cysts (normal P index)

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 8 | 72.5 | 75.6 | 16.4 | 5.8 | 61.9 | 89.3 |
| -9 | 9 | 75.0 | 75.6 | 19.6 | 6.5 | 70.6 | 90.6 |
| -8 | 10 | 82.5 | 74.5 | 21.8 | 6.9 | 58.9 | 90.1 |
| -7 | 9 | 83.0 | 83.1 | 14.1 | 4.7 | 72.3 | 93.9 |
| -6 | 10 | 90.0 | 93.3 | 26.0 | 8.2 | 74.8 | 111.8 |
| -5 | 10 | 107.5 | 111.5 | 21.5 | 6.8 | 96.1 | 126.9 |
| -4 | 10 | 131.5 | 129.1 | 38.8 | 12.3 | 101.3 | 156.9 |
| -3 | 10 | 154.0 | 161.6 | 43.6 | 13.8 | 130.4 | 192.8 |
| -2 | 10 | 212.5 | 214.0 | 59.8 | 18.9 | 171.2 | 256.8 |
| -1 | 10 | 230.0 | 234.0 | 54.9 | 17.4 | 194.6 | 273.4 |
| 0 | 10 | 215.0 | 211.6 | 75.2 | 23.8 | 157.8 | 265.4 |
| +1 | 10 | 135.0 | 130.0 | 37.6 | 11.9 | 103.1 | 156.9 |
| +2 | 10 | 105.0 | 101.6 | 24.5 | 7.8 | 84.0 | 119.2 |
| +3 | 10 | 115.0 | 118.4 | 17.2 | 5.5 | 106.0 | 130.8 |
| +4 | 9 | 122.5 | 125.0 | 22.6 | 7.5 | 107.7 | 142.3 |
| +5 | 10 | 135.0 | 139.1 | 29.2 | 9.2 | 118.3 | 159.9 |
| +6 | 10 | 125.0 | 130.3 | 36.9 | 11.7 | 103.8 | 156.8 |
| +7 | 9 | 140.0 | 143.9 | 35.4 | 11.8 | 116.7 | 171.1 |
| +8 | 10 | 150.0 | 145.8 | 34.6 | 10.9 | 121.1 | 170.5 |
| +9 | 9 | 125.0 | 139.2 | 35.0 | 11.7 | 112.2 | 166.2 |
| +10 | 9 | 128.0 | 141.2 | 42.2 | 13.4 | 110.3 | 172.1 |
| +11 | 9 | 120.0 | 133.1 | 41.0 | 13.7 | 101.5 | 164.7 |
| +12 | 10 | 110.0 | 113.3 | 42.6 | 13.4 | 83.0 | 143.6 |
| +13 | 9 | 90.0 | 100.9 | 53.5 | 17.8 | 59.9 | 141.9 |
| +14 | 9 | 80.0 | 97.9 | 63.2 | 21.1 | 49.2 | 146.6 |

No siginificant differences in comparison with controls.
(Wilcoxon Rank Sum Test)

FIGURE 5.1.11

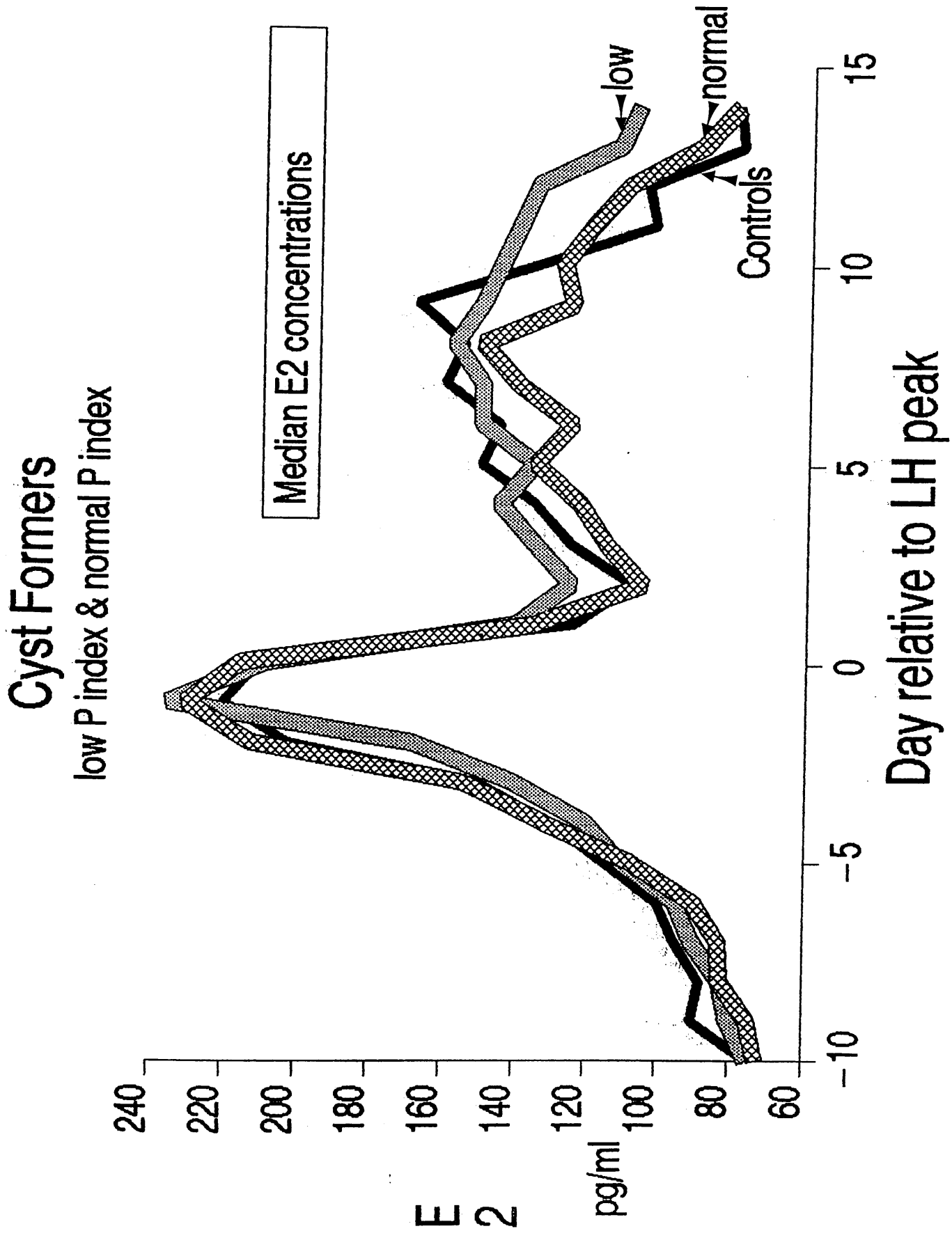

Cyst Formers
low P index & normal P index
Median E2 concentrations
low
normal
Controls
E 2
pg/ml
240
220
200
180
160
140
120
100
80
60
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.1.24

All Cysts (low P index)

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | | |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 17 | 0.9 | 0.9 | 0.5 | 0.1 | 0.7 | 1.1 | | |
| +1 | 27 | 1.2 | 1.4 | 0.7 | 0.1 | 1.2 | 1.6 | b | |
| +2 | 30 | 2.6 | 2.6 | 1.2 | 0.2 | 2.2 | 3.0 | c | ii |
| +3 | 31 | 3.8 | 4.2 | 1.8 | 0.3 | 3.6 | 4.8 | c | iii |
| +4 | 31 | 6.2 | 6.7 | 3.1 | 0.6 | 5.5 | 7.9 | c | iii |
| +5 | 30 | 11.6 | 9.7 | 3.7 | 0.7 | 8.3 | 11.1 | c | iii |
| +6 | 27 | 13.1 | 12.8 | 5.0 | 1.0 | 10.7 | 14.9 | c | iii |
| +7 | 30 | 16.1 | 15.6 | 5.8 | 1.1 | 13.4 | 17.8 | a | iii |
| +8 | 30 | 15.5 | 14.6 | 5.8 | 1.1 | 12.4 | 16.8 | a | iii |
| +9 | 28 | 14.6 | 13.9 | 5.9 | 1.1 | 11.7 | 16.1 | | iii |
| +10 | 27 | 13.2 | 13.2 | 6.4 | 1.2 | 10.7 | 15.7 | | i |
| +11 | 29 | 11.6 | 11.7 | 7.0 | 1.3 | 9.0 | 14.4 | b | |
| +12 | 25 | 8.4 | 8.6 | 4.8 | 1.0 | 6.5 | 10.7 | b | |
| +13 | 24 | 4.7 | 5.8 | 4.8 | 1.0 | 3.7 | 7.9 | a | |
| +14 | 22 | 1.6 | 3.2 | 3.3 | 1.6 | -0.3 | 6.7 | | |
| P index | 31 | 62.0 | 57.5 | 19.5 | 3.5 | 50.4 | 64.6 | c | iii |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls | Normal P index |
|---|---|---|
| p <0.05 | a | i |
| p <0.01 | b | ii |
| p <0.001 | c | iii |

Table 5.1.25

All Cysts (normal P index)

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| 0 | 9 | 0.9 | 1.0 | 0.8 | 0.3 | 0.3 | 1.7 | |
| +1 | 10 | 1.7 | 2.0 | 1.8 | 0.6 | 0.6 | 3.4 | |
| +2 | 10 | 3.3 | 5.3 | 4.2 | 1.3 | 2.4 | 8.2 | |
| +3 | 10 | 7.0 | 8.6 | 4.5 | 1.4 | 5.4 | 11.8 | |
| +4 | 9 | 14.3 | 13.8 | 2.0 | 0.7 | 12.2 | 15.4 | |
| +5 | 10 | 18.7 | 20.2 | 5.0 | 1.6 | 16.6 | 23.8 | |
| +6 | 10 | 24.4 | 24.2 | 5.0 | 1.6 | 20.6 | 27.8 | b |
| +7 | 10 | 25.4 | 25.6 | 3.9 | 1.2 | 22.9 | 28.3 | d |
| +8 | 10 | 24.8 | 22.7 | 5.2 | 1.7 | 18.9 | 26.5 | a |
| +9 | 9 | 25.5 | 23.3 | 3.7 | 1.2 | 20.5 | 26.1 | c |
| +10 | 9 | 16.6 | 18.4 | 5.5 | 1.8 | 14.2 | 22.6 | b |
| +11 | 9 | 18.4 | 16.7 | 6.8 | 2.3 | 11.4 | 22.0 | d |
| +12 | 10 | 9.0 | 10.9 | 6.9 | 2.2 | 5.9 | 15.9 | c |
| +13 | 9 | 5.2 | 4.3 | 2.5 | 0.8 | 2.5 | 6.1 | |
| +14 | 9 | 2.1 | 2.3 | 1.7 | 0.6 | 0.9 | 3.7 | |
| P index | 10 | 101.0 | 111.8 | 18.6 | 5.9 | 98.5 | 125.1 | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

Controls

| | |
|---|---|
| p <0.05 | a |
| p <0.02 | b |
| p <0.01 | c |
| p <0.001 | d |

FIGURE 5.1.12

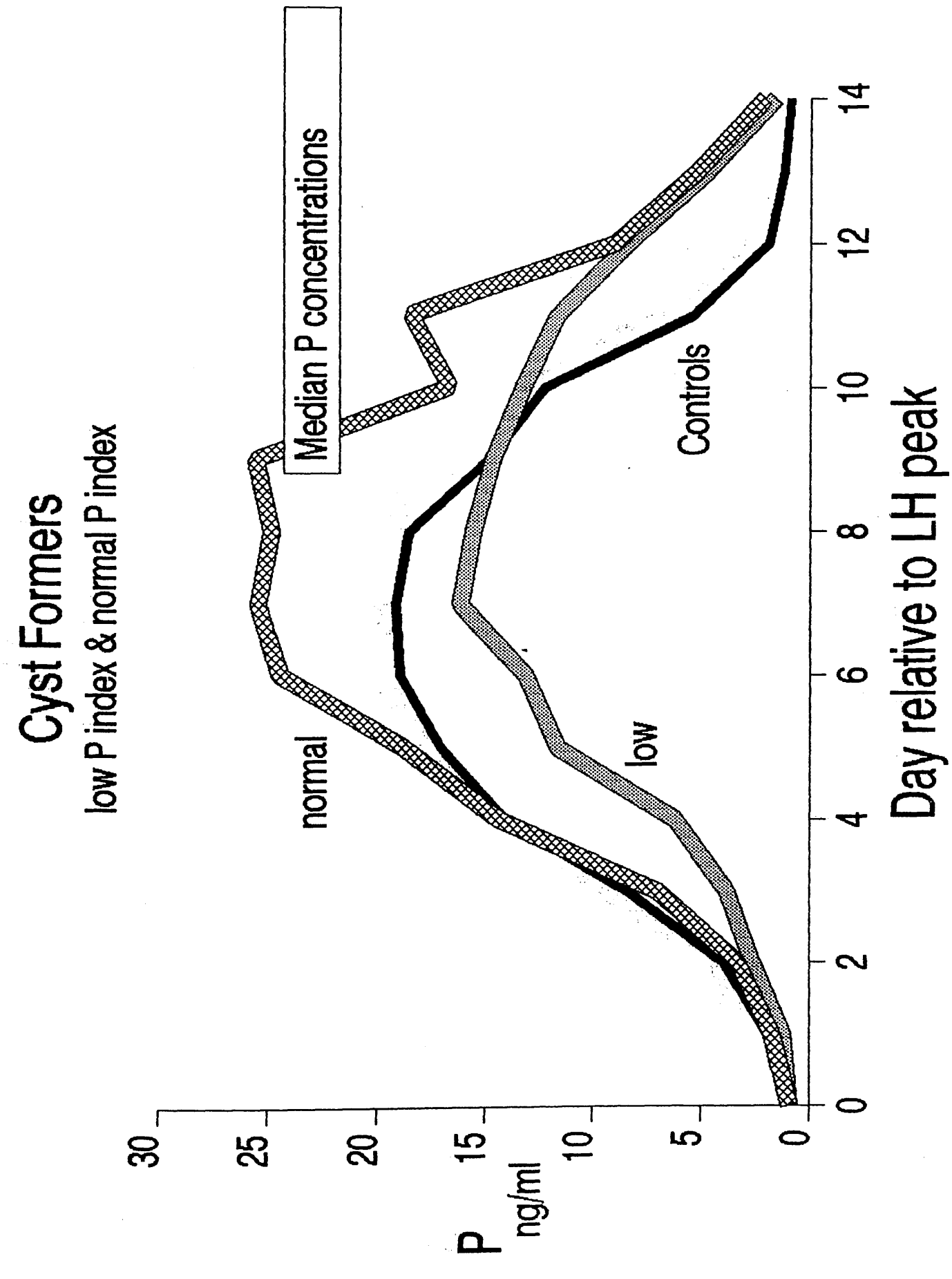

Cyst Formers
low P index & normal P index
Median P concentrations
normal
low
Controls
P ng/ml
30
25
20
15
10
5
0
0
2
4
6
8
10
12
14
Day relative to LH peak

Table 5.1.26

All Cysts (low P index)

Plasma LH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 20 | 9.1 | 9.0 | 4.9 | 1.1 | 6.7 | 11.3 |
| -9 | 22 | 7.8 | 8.3 | 5.2 | 1.1 | 6.0 | 10.6 |
| -8 | 23 | 7.1 | 9.6 | 6.7 | 1.4 | 6.7 | 12.5 |
| -7 | 24 | 7.4 | 8.3 | 4.8 | 1.0 | 6.2 | 10.4 |
| -6 | 25 | 9.2 | 9.2 | 4.9 | 1.0 | 7.1 | 11.3 |
| -5 | 27 | 7.7 | 8.6 | 4.8 | 0.9 | 6.7 | 10.5 |
| -4 | 28 | 7.0 | 8.2 | 4.5 | 0.9 | 6.4 | 10.0 |
| -3 | 27 | 8.9 | 9.5 | 6.2 | 1.2 | 7.0 | 12.0 |
| -2 | 28 | 10.0 | 11.0 | 5.1 | 1.0 | 8.9 | 13.1 |
| -1 | 27 | 19.0 | 23.6 | 13.8 | 2.7 | 18.0 | 29.2 |
| 0 | 30 | 67.5 | 60.0 | 19.3 | 3.5 | 52.8 | 67.2 |
| +1 | 29 | 23.0 | 25.1 | 11.7 | 2.2 | 20.6 | 29.6 |
| +2 | 30 | 12.0 | 12.8 | 6.9 | 1.3 | 10.1 | 13.5 |
| +3 | 30 | 14.0 | 14.0 | 7.1 | 1.3 | 11.3 | 16.7 |
| +4 | 29 | 10.0 | 13.5 | 8.1 | 1.5 | 10.4 | 16.6 |
| +5 | 29 | 9.8 | 11.8 | 7.4 | 1.4 | 8.9 | 14.7 |
| +6 | 26 | 9.6 | 10.3 | 6.8 | 1.3 | 7.6 | 13.0 |
| +7 | 30 | 9.4 | 9.3 | 6.2 | 1.1 | 7.1 | 11.5 |
| +8 | 28 | 5.5 | 8.1 | 6.0 | 1.1 | 5.8 | 10.4 |
| +9 | 26 | 5.7 | 8.9 | 7.6 | 1.5 | 5.8 | 12.0 |
| +10 | 26 | 7.0 | 7.4 | 5.2 | 1.0 | 5.3 | 9.5 |
| +11 | 28 | 5.5 | 6.5 | 4.9 | 0.9 | 4.7 | 8.3 |
| +12 | 23 | 7.6 | 7.2 | 4.5 | 0.9 | 5.3 | 9.1 |
| +13 | 22 | 6.1 | 6.0 | 3.7 | 0.8 | 4.3 | 7.7 |
| +14 | 19 | 6.9 | 6.7 | 3.4 | 0.8 | 5.0 | 8.4 |

No significant differences from controls and normal P index cycles.
(Wilcoxon Rank Sum Test)

Table 5.1.27

All Cysts (normal P index)

Plasma LH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 6 | 8.0 | 9.3 | 3.8 | 1.6 | 5.2 | 13.4 |
| -9 | 8 | 6.4 | 9.4 | 6.5 | 2.3 | 4.0 | 14.8 |
| -8 | 10 | 7.1 | 8.2 | 4.6 | 1.4 | 5.0 | 11.4 |
| -7 | 9 | 11.0 | 11.5 | 6.3 | 2.1 | 6.7 | 16.3 |
| -6 | 10 | 9.0 | 10.4 | 5.3 | 1.7 | 6.6 | 15.2 |
| -5 | 10 | 9.0 | 9.7 | 4.6 | 1.5 | 6.3 | 13.1 |
| -4 | 9 | 7.4 | 7.1 | 3.4 | 1.1 | 4.6 | 9.6 |
| -3 | 9 | 7.5 | 8.1 | 2.3 | 0.8 | 6.3 | 9.9 |
| -2 | 9 | 8.8 | 9.2 | 4.4 | 1.5 | 5.7 | 12.7 |
| -1 | 9 | 13.0 | 15.7 | 6.3 | 2.1 | 10.9 | 20.5 |
| 0 | 9 | 50.0 | 49.7 | 22.7 | 7.6 | 32.2 | 67.2 |
| +1 | 8 | 13.0 | 27.9 | 20.4 | 7.2 | 10.9 | 44.9 |
| +2 | 10 | 16.0 | 14.4 | 5.8 | 1.8 | 10.3 | 18.5 |
| +3 | 10 | 10.5 | 10.5 | 4.7 | 1.5 | 7.1 | 13.9 |
| +4 | 9 | 12.0 | 16.2 | 13.9 | 4.6 | 5.6 | 26.8 |
| +5 | 10 | 8.0 | 10.2 | 4.8 | 1.5 | 6.8 | 13.6 |
| +6 | 9 | 10.0 | 10.1 | 5.9 | 2.0 | 5.5 | 14.7 |
| +7 | 10 | 6.3 | 7.8 | 5.3 | 1.7 | 4.0 | 11.6 |
| +8 | 8 | 4.7 | 6.3 | 3.9 | 1.2 | 3.5 | 9.1 |
| +9 | 8 | 3.8 | 7.4 | 7.5 | 2.7 | 1.0 | 13.8 |
| +10 | 9 | 4.5 | 6.9 | 5.8 | 1.9 | 2.5 | 11.3 |
| +11 | 8 | 7.4 | 8.3 | 5.5 | 1.9 | 3.8 | 12.8 |
| +12 | 8 | 6.3 | 7.9 | 4.9 | 1.7 | 3.9 | 11.9 |
| +13 | 9 | 8.7 | 8.7 | 2.3 | 0.8 | 6.9 | 10.5 |
| +14 | 8 | 9.3 | 8.8 | 2.3 | 0.8 | 6.9 | 10.7 |

No significant differences from controls.
(Wilcoxon Rank Sum Test)

FIGURE 5.1.13

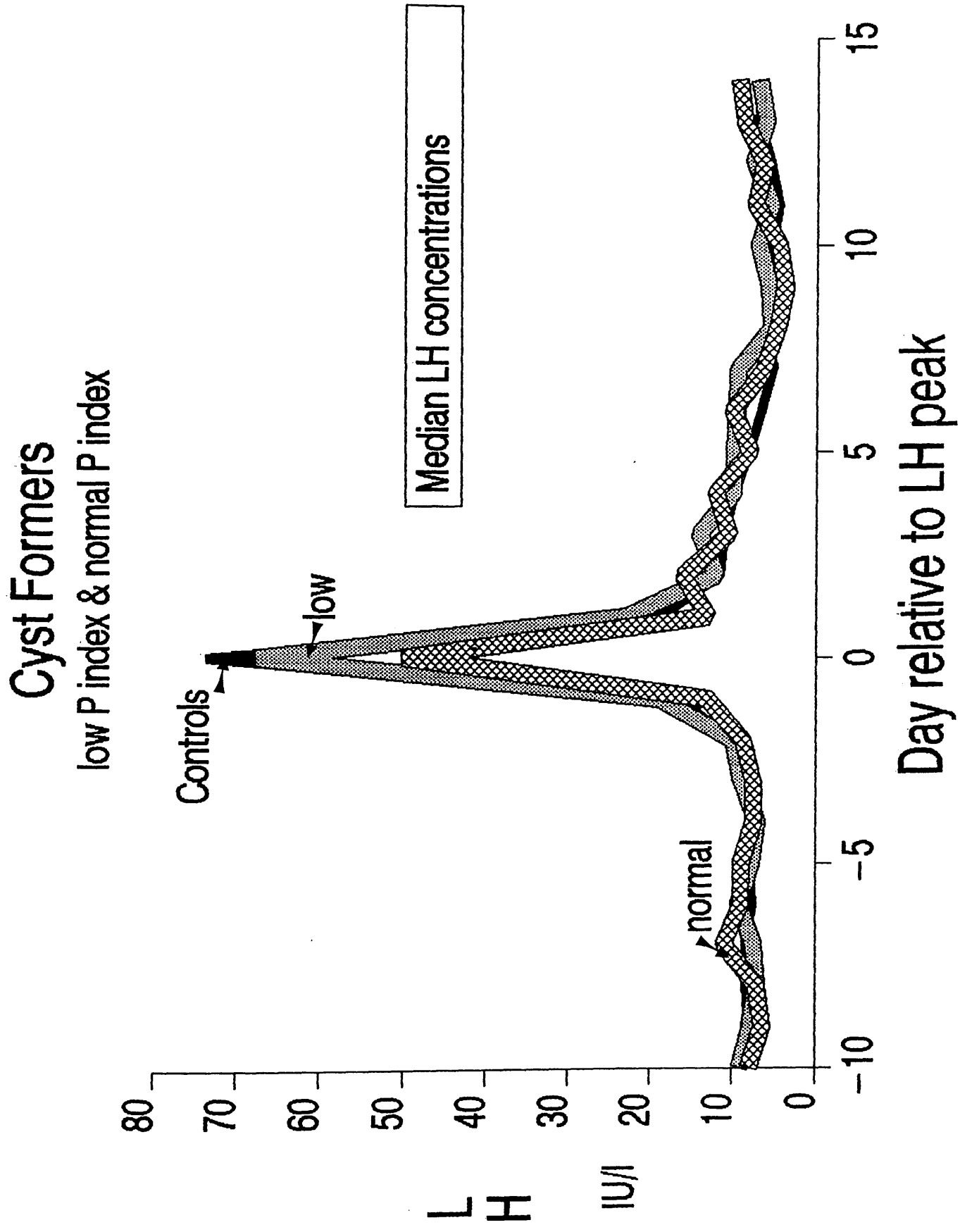

Cyst Formers
low P index & normal P index
Median LH concentrations
Controls
low
normal
L H IU/l
80
70
60
50
40
30
20
10
0
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.1.28

All Cysts (low P index)

Plasma FSH concentrations (IU/1)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | | |
|---|---|---|---|---|---|---|---|---|---|
| -10 | 20 | 6.8 | 7.1 | 2.9 | 0.6 | 5.8 | 8.4 | a | |
| -9 | 22 | 6.3 | 6.6 | 2.5 | 0.5 | 5.6 | 7.6 | | ii |
| -8 | 23 | 5.9 | 6.3 | 2.9 | 0.6 | 5.1 | 7.5 | | |
| -7 | 24 | 5.5 | 5.8 | 2.2 | 0.5 | 4.8 | 6.8 | | i |
| -6 | 25 | 5.2 | 6.0 | 3.1 | 0.6 | 4.8 | 7.2 | | |
| -5 | 27 | 5.5 | 5.4 | 2.6 | 0.5 | 4.4 | 6.4 | | |
| -4 | 28 | 4.5 | 4.4 | 1.6 | 0.3 | 3.8 | 5.0 | | |
| -3 | 26 | 3.9 | 3.9 | 1.4 | 0.3 | 3.3 | 4.5 | | |
| -2 | 28 | 4.0 | 4.0 | 1.4 | 0.3 | 3.4 | 4.6 | | |
| -1 | 27 | 5.1 | 5.4 | 2.5 | 0.5 | 4.4 | 6.4 | | |
| 0 | 30 | 13.0 | 13.0 | 6.1 | 1.1 | 10.8 | 15.2 | | |
| +1 | 29 | 8.0 | 8.5 | 4.5 | 0.8 | 6.9 | 10.1 | | |
| +2 | 27 | 5.7 | 6.3 | 3.8 | 0.7 | 4.9 | 7.7 | | |
| +3 | 30 | 4.6 | 5.1 | 2.6 | 0.5 | 4.1 | 6.1 | | |
| +4 | 29 | 5.1 | 4.9 | 2.9 | 0.5 | 3.9 | 6.9 | | |
| +5 | 30 | 3.8 | 4.4 | 3.0 | 0.5 | 3.4 | 5.4 | | |
| +6 | 26 | 3.5 | 4.0 | 2.5 | 0.5 | 3.0 | 5.0 | a | |
| +7 | 30 | 3.5 | 3.7 | 2.8 | 0.5 | 2.7 | 4.7 | a | |
| +8 | 28 | 3.2 | 3.5 | 2.5 | 0.5 | 2.5 | 4.5 | a | |
| +9 | 27 | 3.2 | 3.6 | 2.6 | 0.5 | 2.6 | 4.6 | b | |
| +10 | 26 | 2.8 | 3.3 | 2.5 | 0.5 | 2.3 | 4.3 | a | |
| +11 | 28 | 2.4 | 3.0 | 2.3 | 0.4 | 2.2 | 3.8 | | |
| +12 | 24 | 2.7 | 3.2 | 2.3 | 0.5 | 2.2 | 4.2 | | |
| +13 | 23 | 2.8 | 3.6 | 2.7 | 0.6 | 2.4 | 4.8 | | |
| +14 | 19 | 3.6 | 4.4 | 3.0 | 0.7 | 2.9 | 5.9 | | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls | Normal P index |
|---|---|---|
| p <0.05 | a | i |
| p <0.01 | b | ii |

Table 5.1.29

All Cysts (normal P index)

Plasma FSH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 6 | 8.1 | 8.4 | 4.0 | 1.6 | 4.3 | 12.5 | a |
| -9 | 8 | 9.2 | 10.1 | 4.0 | 1.4 | 6.8 | 13.4 | c |
| -8 | 10 | 9.1 | 8.5 | 4.8 | 1.5 | 5.1 | 11.9 | |
| -7 | 9 | 9.9 | 8.5 | 4.6 | 1.5 | 5.0 | 12.0 | a |
| -6 | 10 | 7.6 | 7.3 | 2.6 | 0.8 | 5.5 | 9.1 | b |
| -5 | 10 | 6.6 | 5.7 | 1.7 | 0.5 | 4.6 | 6.8 | |
| -4 | 10 | 4.9 | 4.5 | 2.0 | 0.6 | 3.1 | 5.9 | |
| -3 | 10 | 3.6 | 3.9 | 1.7 | 0.5 | 2.8 | 5.0 | |
| -2 | 10 | 3.8 | 3.8 | 1.3 | 0.4 | 2.9 | 4.7 | |
| -1 | 10 | 4.4 | 4.8 | 1.9 | 0.6 | 3.4 | 6.2 | |
| 0 | 10 | 13.5 | 12.1 | 6.1 | 1.9 | 7.8 | 16.4 | |
| +1 | 10 | 9.8 | 9.4 | 5.0 | 1.6 | 5.8 | 13.0 | |
| +2 | 9 | 6.9 | 6.4 | 3.0 | 1.0 | 4.1 | 8.7 | |
| +3 | 10 | 4.9 | 5.4 | 3.2 | 1.0 | 3.1 | 7.7 | |
| +4 | 9 | 4.3 | 4.7 | 3.0 | 1.0 | 2.4 | 7.0 | |
| +5 | 10 | 3.4 | 3.8 | 2.4 | 0.7 | 2.2 | 5.4 | |
| +6 | 9 | 3.3 | 3.7 | 1.7 | 0.6 | 2.3 | 5.1 | |
| +7 | 10 | 3.2 | 2.9 | 1.1 | 0.4 | 2.0 | 3.8 | |
| +8 | 10 | 3.0 | 2.6 | 0.9 | 0.3 | 1.9 | 4.3 | |
| +9 | 7 | 2.3 | 2.6 | 0.8 | 0.3 | 1.9 | 3.3 | |
| +10 | 9 | 2.7 | 3.4 | 2.9 | 1.0 | 1.1 | 5.7 | |
| +11 | 9 | 2.3 | 2.9 | 1.6 | 0.5 | 1.7 | 4.1 | |
| +12 | 10 | 3.8 | 3.1 | 1.6 | 0.5 | 2.0 | 4.2 | |
| +13 | 9 | 4.1 | 3.8 | 2.2 | 0.7 | 2.2 | 5.4 | |
| +14 | 8 | 4.5 | 5.6 | 3.4 | 1.2 | 2.8 | 8.4 | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

Controls

| | |
|---|---|
| p <0.02 | a |
| p <0.01 | b |
| p <0.001 | c |

FIGURE 5.1.14

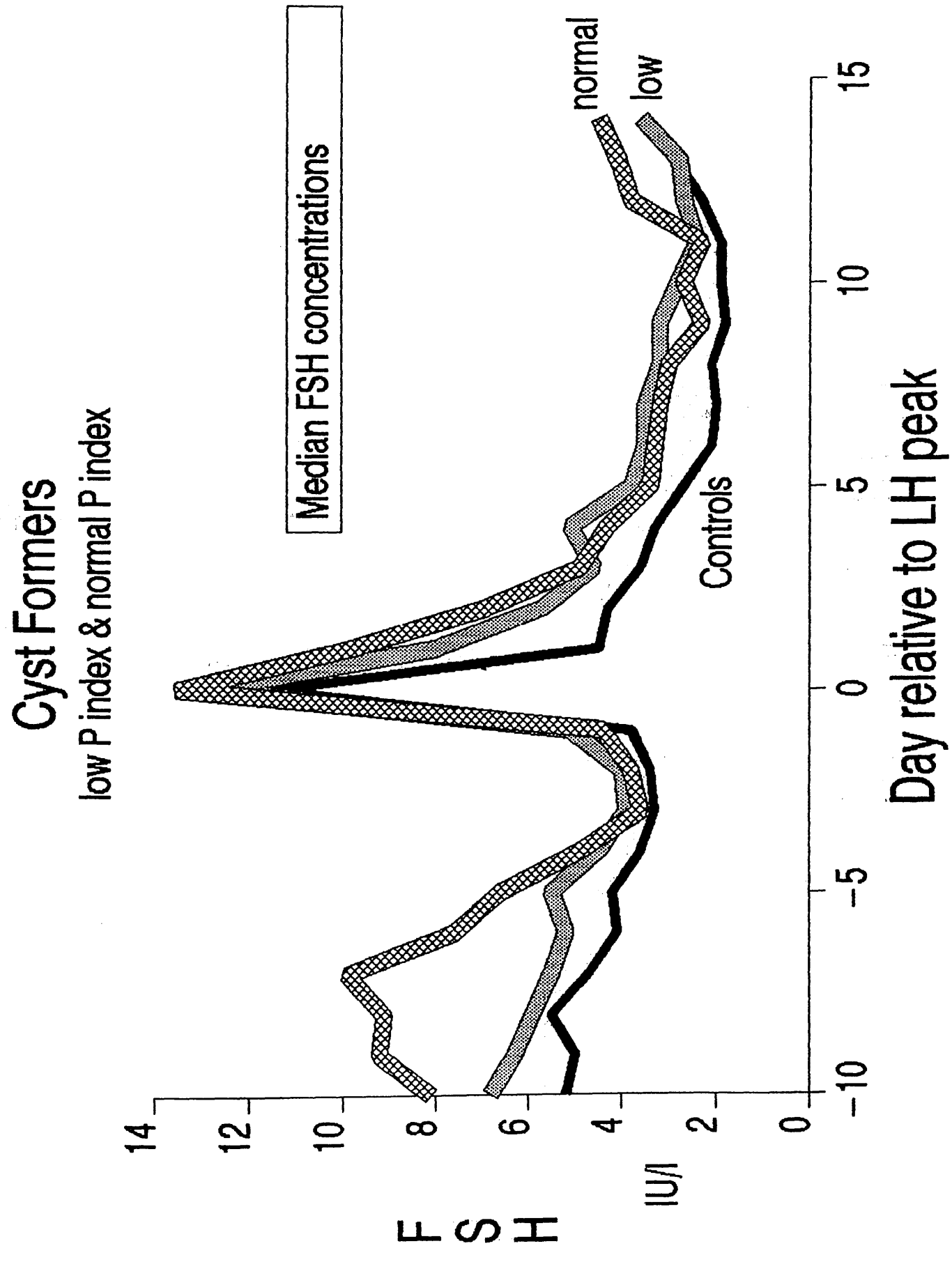

Cyst Formers
low P index & normal P index
Median FSH concentrations
normal
low
Controls
FSH
IU/l
14
12
10
8
6
4
2
0
-10
-5
0
5
10
15
Day relative to LH peak

Table 5.1.30

All Cysts (low P index)

Follicular Diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | | |
|---|---|---|---|---|---|---|---|---|---|
| -5 | 7 | 11.0 | 11.7 | 3.9 | 1.5 | 8.0 | 15.4 | | |
| -4 | 11 | 13.0 | 13.5 | 2.3 | 0.7 | 11.9 | 15.1 | | |
| -3 | 11 | 15.0 | 15.1 | 3.7 | 1.1 | 12.6 | 17.6 | | |
| -2 | 12 | 16.3 | 16.9 | 2.9 | 0.8 | 15.1 | 18.7 | | |
| -1 | 16 | 18.8 | 18.3 | 2.4 | 0.6 | 17.5 | 19.6 | | ii |
| 0 | 21 | 20.0 | 19.9 | 3.3 | 0.7 | 18.4 | 21.4 | | i |
| +1 | 17 | 19.0 | 20.1 | 6.0 | 1.4 | 17.1 | 23.1 | | |
| +2 | 18 | 21.0 | 22.4 | 5.0 | 1.2 | 19.9 | 24.9 | a | |
| +3 | 19 | 26.0 | 24.6 | 6.9 | 1.6 | 21.2 | 28.0 | b | |
| +4 | 19 | 23.0 | 23.7 | 7.6 | 1.7 | 20.1 | 27.3 | b | |
| +5 | 13 | 26.0 | 27.4 | 7.0 | 1.9 | 23.3 | 31.5 | | |
| +6 | 17 | 21.0 | 24.2 | 10.2 | 2.5 | 18.9 | 29.5 | | |
| +7 | 12 | 29.5 | 28.6 | 7.5 | 2.2 | 23.8 | 33.4 | | |
| +8 | 13 | 27.5 | 29.4 | 12.0 | 3.3 | 22.2 | 36.6 | | |
| Cyst size | 31 | 27.0 | 27.8 | 10.4 | 1.9 | 23.9 | 31.7 | | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls | Normal P index |
|---|---|---|
| p <0.05 | | i |
| p <0.01 | a | ii |
| p <0.001 | b | |

Table 5.1.31

All Cysts (normal P index)

Follicular diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -5 | 3 | 12.5 | 13.5 | 2.2 | 1.3 | 7.9 | 19.1 | |
| -4 | 5 | 15.0 | 15.4 | 3.4 | 1.5 | 11.2 | 19.6 | |
| -3 | 4 | 13.5 | 14.5 | 1.6 | 0.8 | 12.0 | 17.0 | |
| -2 | 7 | 17.0 | 17.2 | 4.0 | 1.5 | 13.5 | 20.9 | |
| -1 | 4 | 22.3 | 22.0 | 1.2 | 0.6 | 20.1 | 23.9 | |
| 0 | 9 | 21.5 | 22.6 | 2.6 | 0.9 | 20.5 | 24.7 | |
| +1 | 8 | 22.0 | 20.9 | 3.8 | 1.4 | 17.6 | 24.2 | |
| +2 | 6 | 19.8 | 20.4 | 4.0 | 1.6 | 16.3 | 24.5 | |
| +3 | 7 | 20.5 | 21.5 | 3.4 | 1.3 | 18.3 | 24.7 | a |
| +4 | 3 | 22.0 | 21.3 | 2.1 | 1.2 | 16.1 | 26.5 | a |
| +5 | 7 | 21.0 | 23.1 | 4.9 | 1.9 | 18.5 | 27.7 | |
| +6 | 3 | 20.0 | 22.3 | 6.8 | 3.9 | 5.5 | 39.1 | |
| +7 | 3 | 22.5 | 23.0 | 4.8 | 2.8 | 11.0 | 35.0 | |
| +8 | 4 | 24.5 | 25.8 | 8.4 | 4.2 | 12.4 | 39.2 | |
| Cyst size | 10 | 20.5 | 23.0 | 5.4 | 1.7 | 19.2 | 26.8 | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls |
|---|---|
| p <0.001 | a |

FIGURE 5.1.15

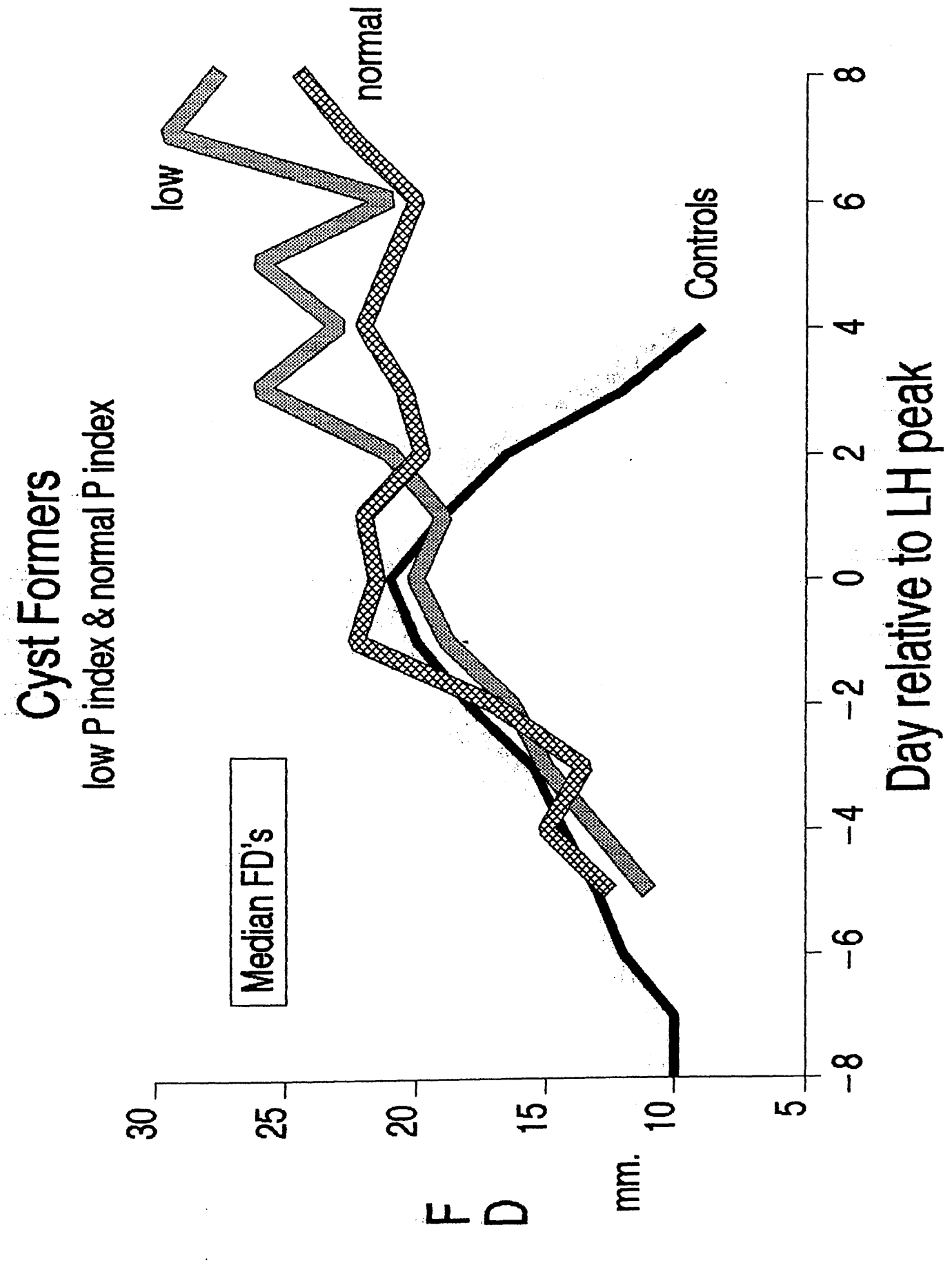

Cyst Formers
low P index & normal P index
Median FD's
low
normal
Controls
F D
mm.
30
25
20
15
10
5
-8
-6
-4
-2
0
2
4
6
8
Day relative to LH peak

Table 5.1.32

Large Cysts (>20mm shrinkers)

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 7 | 65.0 | 72.9 | 20.2 | 7.6 | 54.2 | 91.6 |
| -9 | 7 | 80.0 | 74.3 | 26.2 | 9.9 | 50.1 | 98.5 |
| -8 | 8 | 72.5 | 69.4 | 19.0 | 6.7 | 53.5 | 85.3 |
| -7 | 8 | 87.5 | 84.4 | 18.4 | 6.5 | 69.0 | 99.8 |
| -6 | 8 | 95.0 | 92.5 | 22.4 | 7.9 | 73.8 | 111.2 |
| -5 | 9 | 120.0 | 118.9 | 22.6 | 7.5 | 101.5 | 136.3 |
| -4 | 8 | 118.0 | 124.1 | 38.3 | 13.5 | 92.1 | 156.1 |
| -3 | 9 | 140.0 | 141.7 | 25.4 | 8.5 | 122.2 | 161.2 |
| -2 | 8 | 185.0 | 185.6 | 46.2 | 16.4 | 146.9 | 224.3 |
| -1 | 8 | 195.0 | 203.8 | 39.8 | 14.1 | 170.5 | 237.1 |
| 0 | 10 | 198.0 | 198.3 | 39.9 | 12.6 | 169.8 | 226.8 |
| +1 | 9 | 135.0 | 133.9 | 27.5 | 9.2 | 112.8 | 155.0 |
| +2 | 10 | 126.5 | 119.3 | 19.6 | 6.2 | 105.3 | 133.3 |
| +3 | 10 | 127.5 | 130.3 | 24.2 | 7.7 | 113.0 | 147.6 |
| +4 | 10 | 130.0 | 148.5 | 39.7 | 12.5 | 120.1 | 176.9 |
| +5 | 10 | 130.0 | 139.3 | 31.7 | 10.0 | 116.6 | 162.0 |
| +6 | 9 | 125.0 | 141.1 | 37.5 | 12.5 | 112.3 | 169.9 |
| +7 | 10 | 127.5 | 152.0 | 48.0 | 15.2 | 117.6 | 186.4 |
| +8 | 10 | 137.5 | 149.0 | 41.4 | 13.1 | 119.4 | 178.6 |
| +9 | 8 | 122.5 | 133.8 | 33.4 | 11.8 | 105.9 | 161.7 |
| +10 | 9 | 125.0 | 144.4 | 62.5 | 20.8 | 96.3 | 192.5 |
| +11 | 9 | 120.0 | 123.9 | 37.0 | 12.3 | 95.5 | 152.3 |
| +12 | 7 | 110.0 | 111.4 | 44.5 | 16.8 | 70.2 | 152.6 |
| +13 | 7 | 90.0 | 92.9 | 32.9 | 12.4 | 62.5 | 123.3 |
| +14 | 6 | 90.0 | 90.0 | 29.8 | 12.2 | 58.7 | 121.3 |

No significant difference from controls and non-shrinkers.
(Wilcoxon Rank Sum Test)

Table 5.1.33

Large cysts (>20mm non-shrinkers)

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 13 | 80.0 | 79.2 | 14.8 | 4.1 | 70.2 | 88.2 |
| -9 | 14 | 77.5 | 78.3 | 13.0 | 3.5 | 70.8 | 85.8 |
| -8 | 16 | 87.5 | 83.8 | 15.8 | 3.9 | 75.4 | 92.2 |
| -7 | 17 | 85.0 | 87.1 | 17.1 | 4.1 | 78.3 | 95.9 |
| -6 | 17 | 85.0 | 88.1 | 20.5 | 5.0 | 77.5 | 98.7 |
| -5 | 17 | 105.0 | 104.4 | 21.3 | 5.2 | 93.5 | 115.3 |
| -4 | 20 | 115.0 | 123.2 | 39.9 | 8.9 | 104.5 | 141.9 |
| -3 | 19 | 140.0 | 145.9 | 49.8 | 11.4 | 121.9 | 169.9 |
| -2 | 20 | 168.0 | 179.6 | 52.7 | 11.8 | 154.9 | 204.3 |
| -1 | 19 | 235.0 | 221.1 | 55.5 | 12.7 | 194.3 | 247.9 |
| 0 | 20 | 191.5 | 195.2 | 61.2 | 13.7 | 166.6 | 223.8 |
| +1 | 19 | 145.0 | 141.6 | 48.8 | 11.2 | 118.1 | 165.1 |
| +2 | 20 | 116.5 | 122.2 | 35.0 | 7.8 | 105.8 | 138.6 |
| +3 | 20 | 137.5 | 139.2 | 30.9 | 6.9 | 124.7 | 153.7 |
| +4 | 19 | 140.0 | 144.2 | 47.9 | 11.0 | 121.1 | 167.3 |
| +5 | 20 | 135.0 | 157.5 | 59.7 | 13.3 | 129.6 | 185.4 |
| +6 | 19 | 150.0 | 152.6 | 54.4 | 12.5 | 136.8 | 168.4 |
| +7 | 19 | 155.0 | 155.3 | 44.7 | 10.3 | 133.8 | 176.8 |
| +8 | 18 | 142.5 | 156.3 | 51.1 | 12.0 | 130.9 | 181.7 |
| +9 | 18 | 155.0 | 169.2 | 80.6 | 19.0 | 129.1 | 209.3 |
| +10 | 16 | 140.0 | 148.9 | 53.1 | 13.3 | 120.6 | 177.2 |
| +11 | 18 | 136.5 | 153.2 | 63.6 | 15.0 | 121.6 | 184.8 |
| +12 | 19 | 130.0 | 133.1 | 54.3 | 12.5 | 106.9 | 159.3 |
| +13 | 17 | 115.0 | 115.1 | 43.0 | 10.4 | 93.0 | 137.2 |
| +14 | 16 | 97.5 | 99.7 | 31.9 | 8.0 | 82.7 | 116.7 |

No significant difference from controls.
(Wilcoxon Rank Sum Test)

FIGURE 5.1.16

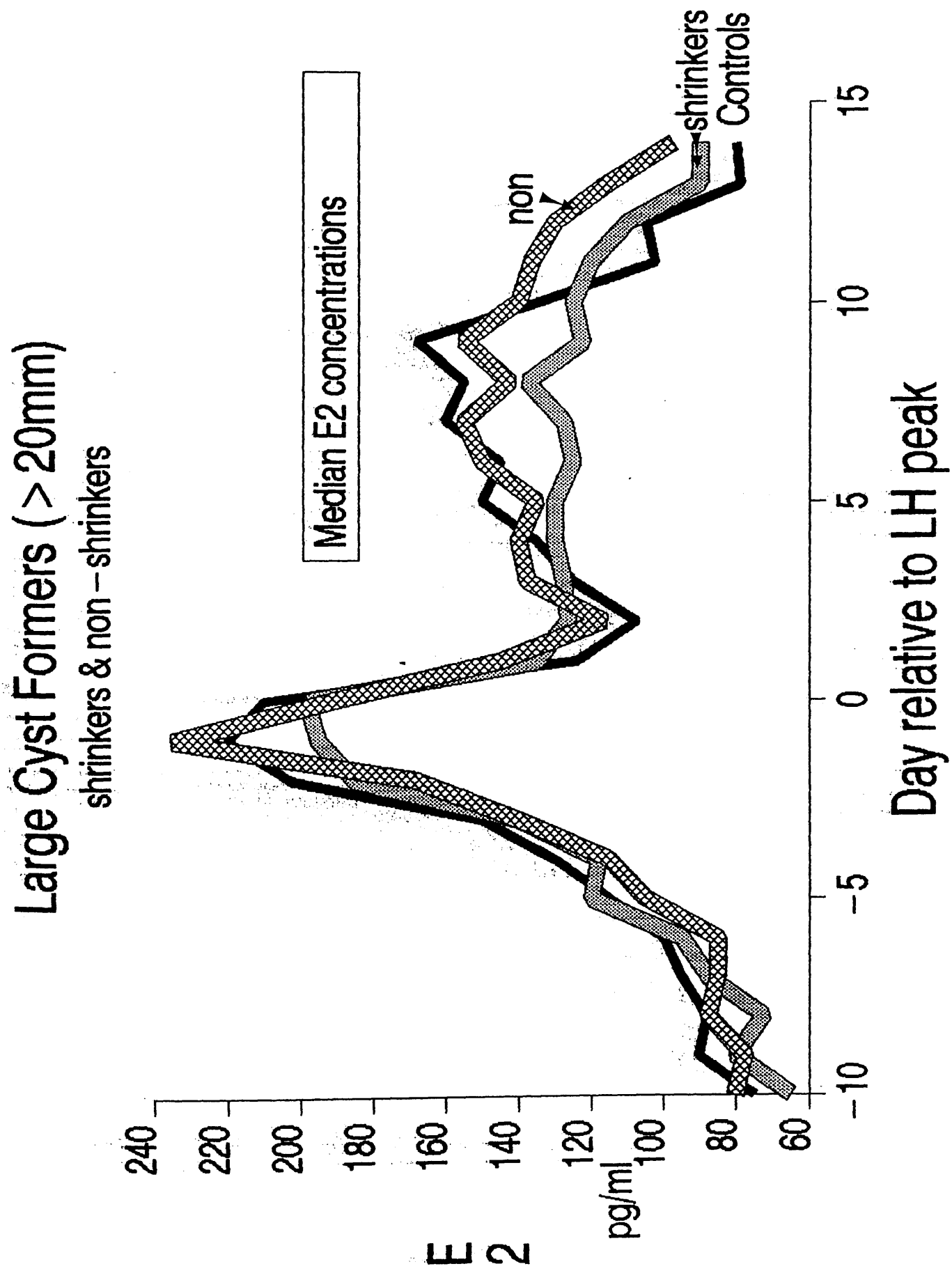

Large Cyst Formers (>20mm)
shrinkers & non – shrinkers
Median E2 concentrations
non
shrinkers
Controls
E2
pg/ml
240
220
200
180
160
140
120
100
80
60
-10
-5
0
5
10
15
Day relative to LH peak

Table 5.1.34

Large Cysts (>20mm shrinkers)

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | | |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 7 | 0.8 | 1.1 | 0.9 | 0.3 | 0.3 | 1.9 | | |
| +1 | 9 | 1.4 | 1.9 | 1.9 | 0.6 | 0.4 | 3.4 | | |
| +2 | 10 | 3.2 | 4.7 | 4.4 | 1.4 | 1.6 | 7.8 | | |
| +3 | 10 | 5.8 | 7.4 | 5.0 | 1.6 | 3.9 | 10.9 | | i |
| +4 | 10 | 11.1 | 11.1 | 3.7 | 1.2 | 8.5 | 13.7 | | iii |
| +5 | 10 | 15.8 | 16.2 | 5.4 | 1.7 | 12.4 | 20.0 | | iii |
| +6 | 9 | 21.2 | 20.7 | 5.7 | 1.9 | 16.3 | 25.1 | | ii |
| +7 | 10 | 21.0 | 22.0 | 4.9 | 1.5 | 18.5 | 25.5 | | i |
| +8 | 10 | 18.4 | 19.3 | 5.7 | 1.8 | 15.2 | 23.4 | | |
| +9 | 8 | 20.5 | 19.6 | 7.4 | 2.6 | 13.4 | 25.8 | | |
| +10 | 9 | 16.8 | 17.6 | 7.9 | 2.6 | 11.5 | 23.7 | | |
| +11 | 9 | 15.4 | 15.6 | 8.2 | 2.7 | 9.3 | 21.9 | b | |
| +12 | 7 | 12.8 | 11.1 | 5.2 | 2.0 | 6.3 | 15.9 | b | |
| +13 | 7 | 5.4 | 5.7 | 3.9 | 1.5 | 2.1 | 9.3 | a | |
| +14 | 6 | 2.7 | 4.1 | 3.6 | 1.5 | 0.0 | 8.2 | | |
| P index | 10 | 90.0 | 92.5 | 29.4 | 9.3 | 71.5 | 113.5 | | iii |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls | Non-shrinkers |
|---|---|---|
| p <0.05 | a | i |
| p <0.01 | | ii |
| p <0.001 | b | iii |

Table 5.1.35

Large Cysts (>20mm non-shrinkers)

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| 0 | 12 | 1.0 | 1.0 | 0.6 | 0.2 | 0.6 | 1.4 | |
| +1 | 18 | 1.2 | 1.4 | 0.7 | 0.2 | 1.0 | 1.8 | b |
| +2 | 19 | 2.8 | 2.7 | 1.3 | 0.3 | 2.1 | 3.3 | c |
| +3 | 20 | 4.1 | 4.4 | 2.4 | 0.5 | 3.3 | 5.5 | d |
| +4 | 19 | 5.6 | 5.8 | 3.4 | 0.8 | 4.2 | 7.4 | d |
| +5 | 20 | 8.2 | 8.8 | 4.1 | 0.9 | 6.9 | 10.7 | d |
| +6 | 19 | 10.4 | 12.5 | 5.9 | 1.4 | 9.7 | 15.3 | d |
| +7 | 19 | 14.4 | 15.6 | 7.8 | 1.8 | 11.8 | 19.4 | |
| +8 | 19 | 10.8 | 14.2 | 6.9 | 1.6 | 10.9 | 17.5 | a |
| +9 | 18 | 13.2 | 14.3 | 7.0 | 1.6 | 10.8 | 17.8 | |
| +10 | 16 | 13.4 | 13.2 | 6.0 | 1.5 | 10.0 | 16.4 | |
| +11 | 18 | 11.1 | 11.6 | 6.5 | 1.5 | 8.4 | 14.8 | c |
| +12 | 19 | 8.2 | 8.9 | 6.3 | 1.4 | 5.9 | 11.9 | c |
| +13 | 17 | 4.0 | 5.7 | 5.3 | 1.3 | 3.0 | 8.4 | a |
| +14 | 16 | 1.1 | 3.0 | 3.2 | 0.8 | 1.3 | 4.7 | |
| P index | 20 | 53.5 | 54.8 | 24.1 | 5.4 | 43.5 | 66.1 | d |

Significance (Wilcoxon Rank Sum Test) in comparison with :

Controls

| | |
|---|---|
| p <0.05 | a |
| p <0.02 | b |
| p <0.01 | c |
| p <0.001 | d |

FIGURE 5.1.17

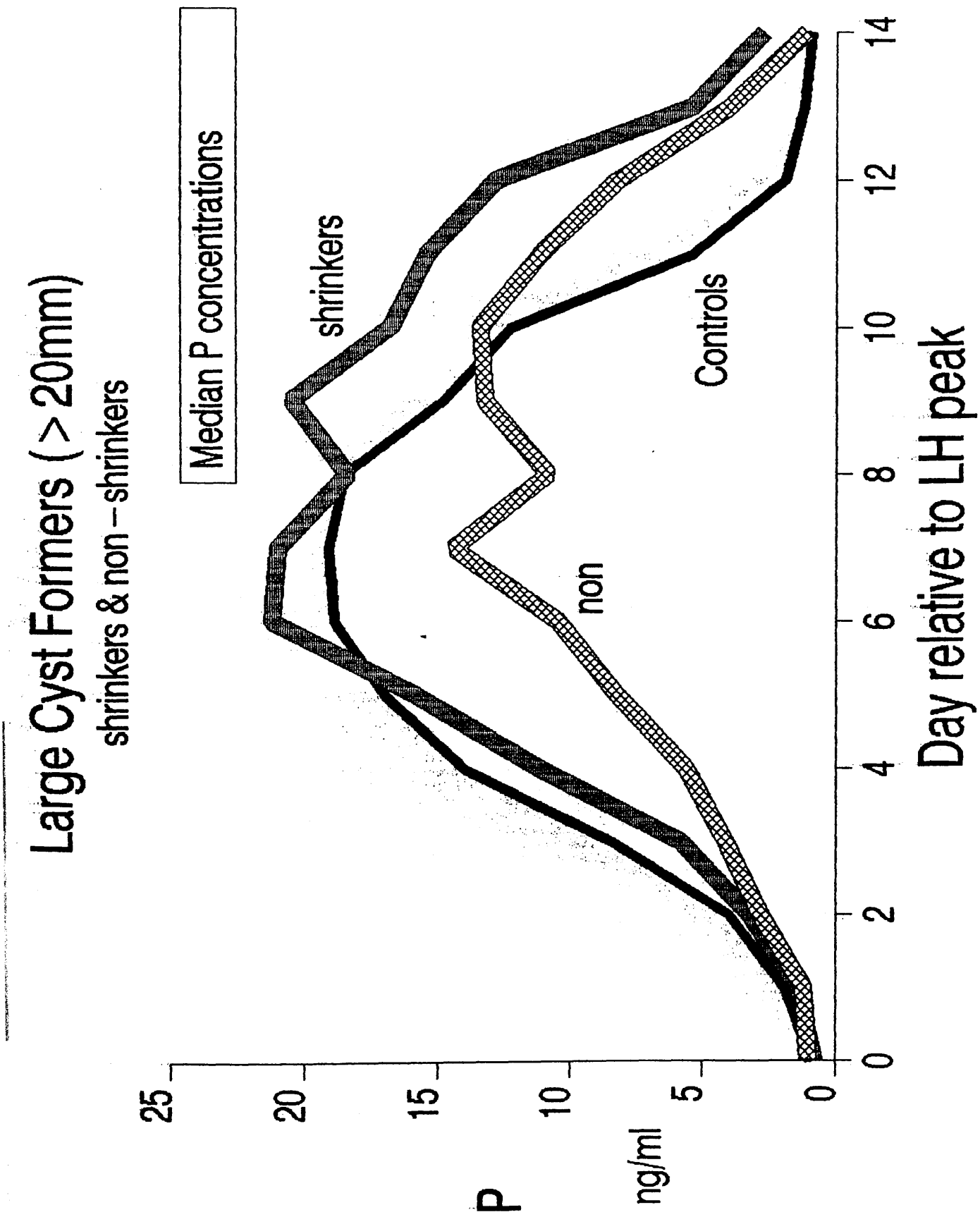

Large Cyst Formers (>20mm)
shrinkers & non – shrinkers
Median P concentrations
shrinkers
non
Controls
P
ng/ml
25
20
15
10
5
0
0
2
4
6
8
10
12
14
Day relative to LH peak

Table 5.1.36

Large Cysts (>20mm shrinkers)

Plasma LH concentrations (IU/1)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 6 | 7.0 | 8.2 | 4.4 | 1.8 | 3.6 | 12.8 |
| -9 | 7 | 6.5 | 8.5 | 6.8 | 2.6 | 2.2 | 14.7 |
| -8 | 8 | 7.5 | 8.0 | 4.3 | 1.5 | 4.4 | 11.6 |
| -7 | 8 | 6.2 | 10.1 | 7.6 | 2.7 | 3.7 | 16.5 |
| -6 | 8 | 6.9 | 9.3 | 5.4 | 1.9 | 4.8 | 13.8 |
| -5 | 9 | 5.4 | 7.2 | 4.9 | 1.6 | 3.2 | 11.4 |
| -4 | 7 | 4.9 | 5.7 | 2.1 | 0.8 | 3.8 | 7.6 |
| -3 | 8 | 6.8 | 6.5 | 2.1 | 0.7 | 4.7 | 8.3 |
| -2 | 7 | 8.1 | 9.2 | 3.3 | 1.3 | 6.1 | 12.3 |
| -1 | 7 | 13.0 | 20.0 | 15.3 | 5.8 | 5.9 | 34.1 |
| 0 | 9 | 73.0 | 64.8 | 15.8 | 5.3 | 52.7 | 76.9 |
| +1 | 8 | 25.0 | 29.1 | 16.1 | 5.7 | 15.6 | 42.6 |
| +2 | 9 | 12.0 | 12.4 | 6.4 | 2.1 | 7.5 | 17.3 |
| +3 | 10 | 15.0 | 14.7 | 6.8 | 2.2 | 9.8 | 19.6 |
| +4 | 10 | 15.5 | 15.8 | 14.7 | 4.6 | 5.3 | 26.3 |
| +5 | 10 | 8.8 | 10.3 | 6.5 | 2.1 | 5.6 | 15.0 |
| +6 | 8 | 8.0 | 8.2 | 5.9 | 2.1 | 3.3 | 13.1 |
| +7 | 10 | 7.3 | 7.1 | 5.1 | 1.6 | 3.4 | 10.8 |
| +8 | 8 | 4.1 | 4.9 | 4.1 | 1.5 | 1.5 | 8.3 |
| +9 | 7 | 3.8 | 8.7 | 8.7 | 3.3 | 0.7 | 16.7 |
| +10 | 9 | 4.4 | 5.3 | 2.7 | 0.9 | 3.3 | 7.3 |
| +11 | 8 | 5.8 | 6.8 | 6.4 | 2.3 | 1.5 | 12.1 |
| +12 | 5 | 4.9 | 5.0 | 3.2 | 1.4 | 1.0 | 9.0 |
| +13 | 7 | 7.2 | 7.6 | 2.6 | 1.0 | 5.2 | 10.0 |
| +14 | 5 | 7.2 | 8.4 | 2.5 | 1.1 | 5.4 | 11.4 |

No significant differences from controls and non-shrinkers.
(Wilcoxon Rank Sum Test)

Table 5.1.37

Large Cysts (>20mm non-shrinkers)

Plasma LH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 12 | 9.9 | 9.3 | 4.0 | 1.2 | 6.8 | 11.8 |
| -9 | 14 | 8.3 | 9.0 | 5.4 | 1.4 | 5.9 | 12.1 |
| -8 | 16 | 7.4 | 9.4 | 6.2 | 1.5 | 6.1 | 12.7 |
| -7 | 16 | 8.7 | 9.1 | 4.0 | 1.0 | 7.0 | 11.2 |
| -6 | 17 | 9.7 | 9.5 | 4.1 | 1.0 | 7.4 | 11.6 |
| -5 | 18 | 9.7 | 9.7 | 3.6 | 0.9 | 7.9 | 11.5 |
| -4 | 20 | 7.0 | 8.3 | 3.9 | 0.9 | 6.5 | 10.1 |
| -3 | 19 | 9.4 | 10.8 | 6.2 | 1.4 | 7.8 | 13.8 |
| -2 | 20 | 10.0 | 11.2 | 5.1 | 1.1 | 8.8 | 13.6 |
| -1 | 19 | 19.0 | 22.5 | 12.4 | 2.9 | 16.5 | 28.5 |
| 0 | 20 | 63.0 | 60.4 | 19.2 | 4.3 | 51.5 | 69.3 |
| +1 | 20 | 18.0 | 22.3 | 14.0 | 3.1 | 15.8 | 28.8 |
| +2 | 20 | 14.5 | 14.0 | 7.6 | 1.7 | 10.5 | 17.5 |
| +3 | 20 | 13.0 | 12.7 | 6.0 | 1.3 | 9.9 | 15.5 |
| +4 | 18 | 11.0 | 14.1 | 7.7 | 1.8 | 10.3 | 17.9 |
| +5 | 20 | 10.5 | 13.0 | 7.2 | 1.6 | 9.6 | 16.4 |
| +6 | 19 | 9.0 | 10.3 | 6.4 | 1.5 | 7.2 | 13.4 |
| +7 | 20 | 8.4 | 10.1 | 6.3 | 1.4 | 7.2 | 13.0 |
| +8 | 18 | 5.8 | 7.9 | 4.4 | 1.0 | 5.7 | 10.1 |
| +9 | 18 | 8.9 | 10.1 | 7.5 | 1.8 | 6.4 | 13.8 |
| +10 | 16 | 8.7 | 9.1 | 5.3 | 1.3 | 6.3 | 11.9 |
| +11 | 18 | 6.0 | 7.9 | 4.8 | 1.1 | 5.5 | 10.3 |
| +12 | 18 | 7.8 | 8.5 | 4.6 | 1.1 | 6.2 | 10.8 |
| +13 | 16 | 7.0 | 6.3 | 3.0 | 0.8 | 4.7 | 7.8 |
| +14 | 14 | 7.2 | 7.3 | 2.6 | 0.7 | 5.8 | 8.8 |

No significant differences from controls.
(Wilcoxon Rank Sum Test)

FIGURE 5.1.18

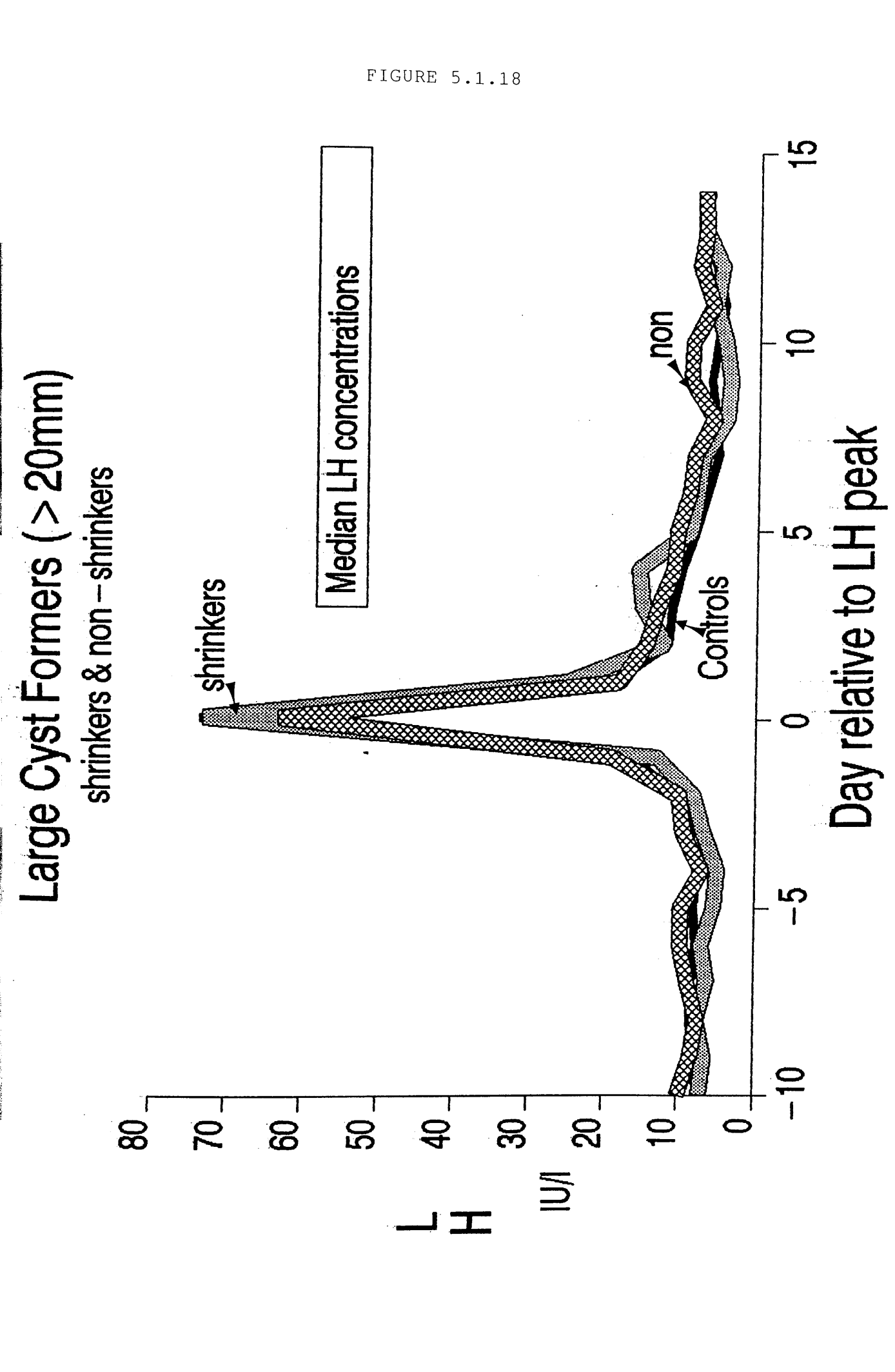

Large Cyst Formers (>20mm)
shrinkers & non – shrinkers
Median LH concentrations
shrinkers
non
Controls
LH IU/l
80
70
60
50
40
30
20
10
0
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.1.38

Large Cysts (>20mm shrinkers)

Plasma FSH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | | |
|---|---|---|---|---|---|---|---|---|---|
| -10 | 6 | 6.6 | 6.9 | 3.1 | 1.3 | 3.6 | 10.2 | | |
| -9 | 7 | 8.8 | 8.1 | 3.8 | 1.4 | 4.6 | 11.6 | a | |
| -8 | 8 | 6.3 | 7.5 | 4.8 | 1.7 | 3.5 | 11.5 | | |
| -7 | 8 | 6.3 | 7.5 | 3.6 | 1.3 | 4.5 | 10.5 | | i |
| -6 | 8 | 6.1 | 7.0 | 2.1 | 0.7 | 5.3 | 8.7 | c | |
| -5 | 9 | 5.5 | 5.1 | 1.3 | 0.4 | 4.1 | 6.1 | | |
| -4 | 8 | 4.9 | 4.7 | 1.4 | 0.5 | 3.5 | 5.9 | | |
| -3 | 9 | 3.4 | 3.7 | 1.2 | 0.4 | 2.7 | 4.7 | | |
| -2 | 8 | 4.3 | 3.9 | 1.0 | 0.4 | 3.0 | 4.8 | | |
| -1 | 8 | 5.1 | 5.0 | 2.0 | 0.7 | 3.3 | 6.7 | | |
| 0 | 10 | 13.0 | 12.3 | 4.5 | 1.4 | 9.1 | 15.5 | | |
| +1 | 9 | 8.1 | 8.2 | 3.6 | 1.2 | 5.4 | 11.0 | | |
| +2 | 9 | 4.8 | 5.3 | 2.6 | 0.9 | 3.3 | 7.3 | | |
| +3 | 10 | 4.7 | 5.2 | 3.3 | 1.0 | 2.8 | 7.6 | | |
| +4 | 10 | 5.5 | 4.8 | 2.7 | 0.8 | 3.0 | 6.6 | | |
| +5 | 10 | 3.6 | 4.0 | 2.2 | 0.7 | 2.4 | 5.6 | | |
| +6 | 8 | 3.4 | 3.9 | 2.1 | 0.7 | 2.1 | 5.8 | | |
| +7 | 10 | 3.0 | 2.7 | 1.3 | 0.4 | 1.7 | 3.7 | | |
| +8 | 10 | 3.1 | 2.9 | 1.5 | 0.5 | 1.8 | 4.0 | | |
| +9 | 6 | 3.4 | 3.4 | 1.5 | 0.6 | 1.8 | 5.0 | b | |
| +10 | 9 | 3.2 | 3.3 | 3.0 | 1.0 | 1.0 | 5.6 | | |
| +11 | 9 | 3.1 | 2.7 | 1.9 | 0.6 | 1.2 | 4.2 | | |
| +12 | 7 | 3.9 | 3.4 | 1.8 | 0.7 | 1.7 | 5.1 | | |
| +13 | 7 | 4.0 | 3.8 | 2.3 | 0.9 | 1.7 | 5.9 | | |
| +14 | 5 | 4.2 | 5.4 | 3.7 | 1.7 | 0.8 | 10.0 | | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls | Non-shrinkers |
|---|---|---|
| p <0.05 | a | i |
| p <0.02 | b | |
| p <0.01 | c | |

Table 5.1.39

Large Cysts (>20mm non-shrinkers)

Plasma FSH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 12 | 7.2 | 7.5 | 2.2 | 0.6 | 6.1 | 8.9 | c |
| -9 | 14 | 6.3 | 6.7 | 2.0 | 0.5 | 5.6 | 7.8 | |
| -8 | 16 | 6.0 | 6.3 | 2.7 | 0.7 | 4.8 | 7.8 | |
| -7 | 16 | 5.3 | 5.2 | 1.7 | 0.4 | 4.3 | 6.1 | |
| -6 | 17 | 5.2 | 5.4 | 2.1 | 0.5 | 4.3 | 6.5 | |
| -5 | 18 | 5.5 | 4.9 | 1.5 | 0.4 | 4.1 | 5.7 | |
| -4 | 20 | 4.2 | 4.1 | 0.7 | 0.2 | 3.8 | 4.4 | |
| -3 | 19 | 3.9 | 3.8 | 1.3 | 0.3 | 3.2 | 4.4 | |
| -2 | 20 | 3.8 | 3.7 | 1.2 | 0.3 | 3.1 | 4.3 | |
| -1 | 19 | 4.5 | 5.0 | 2.2 | 0.5 | 4.0 | 6.0 | |
| 0 | 20 | 14.0 | 14.2 | 6.7 | 1.5 | 11.1 | 17.3 | a |
| +1 | 20 | 7.0 | 7.8 | 4.7 | 1.0 | 5.6 | 10.0 | |
| +2 | 19 | 4.7 | 6.4 | 4.4 | 1.0 | 4.3 | 8.5 | |
| +3 | 20 | 4.1 | 5.1 | 2.9 | 0.7 | 3.7 | 6.5 | |
| +4 | 18 | 3.9 | 5.0 | 3.6 | 0.8 | 3.2 | 6.8 | |
| +5 | 20 | 4.0 | 4.6 | 3.6 | 0.8 | 2.9 | 6.3 | |
| +6 | 19 | 3.3 | 4.1 | 2.8 | 0.6 | 2.7 | 5.5 | a |
| +7 | 20 | 3.6 | 4.2 | 3.3 | 0.7 | 2.7 | 5.7 | b |
| +8 | 18 | 3.0 | 3.7 | 2.9 | 0.7 | 2.3 | 5.1 | a |
| +9 | 18 | 2.9 | 3.8 | 3.1 | 0.7 | 2.3 | 5.3 | b |
| +10 | 16 | 3.0 | 3.8 | 3.0 | 0.8 | 2.2 | 5.4 | b |
| +11 | 18 | 2.7 | 3.3 | 2.8 | 0.7 | 1.9 | 4.7 | |
| +12 | 19 | 2.6 | 3.2 | 2.5 | 0.6 | 2.0 | 4.4 | |
| +13 | 17 | 2.7 | 3.7 | 2.9 | 0.7 | 2.2 | 5.2 | |
| +14 | 14 | 3.7 | 4.8 | 3.2 | 0.8 | 3.0 | 6.6 | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

Controls

| | |
|---|---|
| p <0.05 | a |
| p <0.02 | b |
| p <0.01 | c |

FIGURE 5.1.19

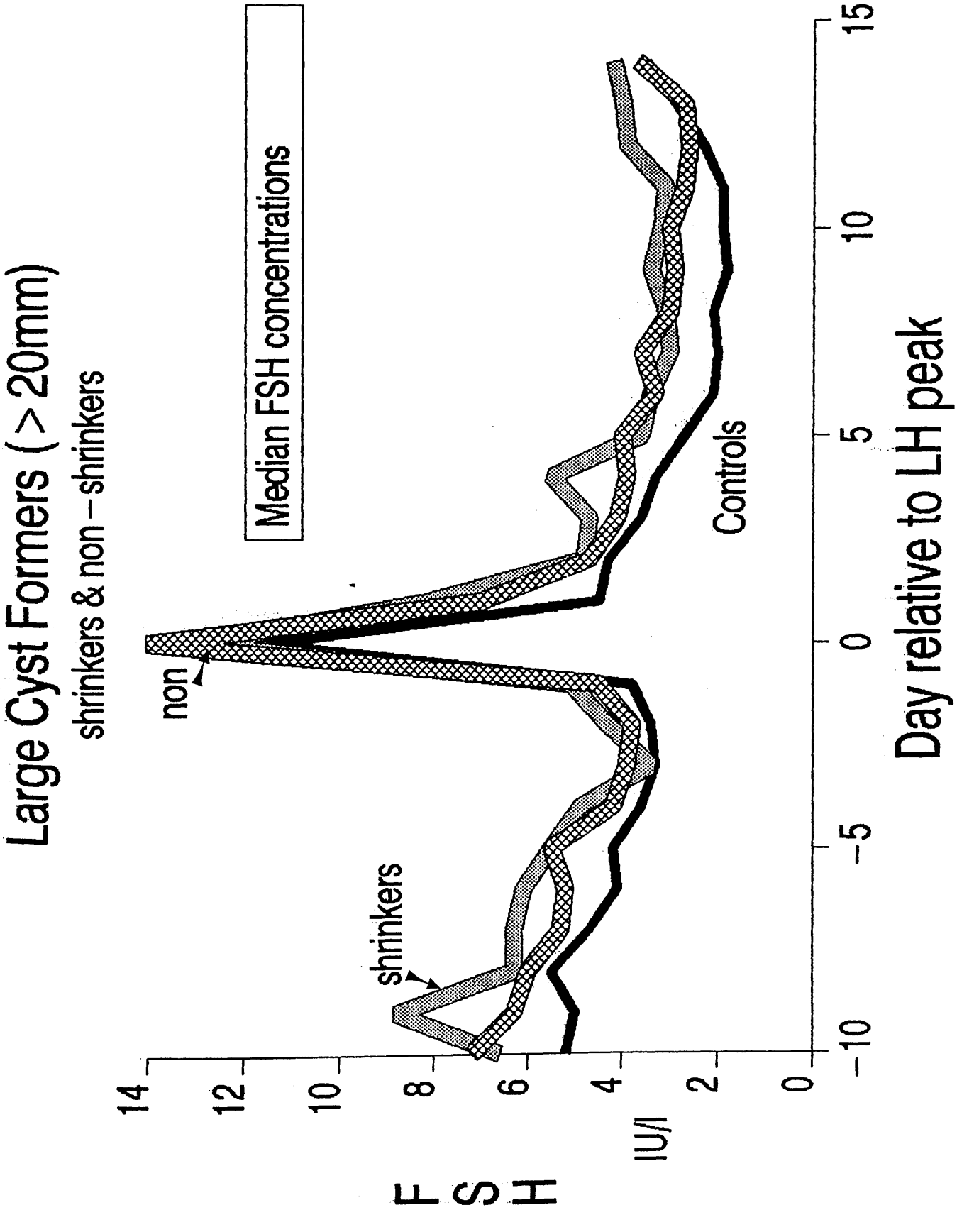

Large Cyst Formers (>20mm)
shrinkers & non-shrinkers
Median FSH concentrations
non
shrinkers
Controls
FSH
IU/l
14
12
10
8
6
4
2
0
-10
-5
0
5
10
15
Day relative to LH peak

Table 5.1.40

Large Cysts (>20mm shrinkers)

Follicular Diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | | |
|---|---|---|---|---|---|---|---|---|---|
| -5 | 3 | 10.0 | 10.2 | 2.3 | 1.3 | 4.6 | 15.8 | | |
| -4 | 3 | 15.0 | 16.3 | 4.2 | 2.4 | 6.0 | 26.6 | | |
| -3 | 2 | 12.8 | 12.8 | 1.1 | 0.8 | 3.3 | 22.3 | | |
| -2 | 4 | 15.0 | 16.9 | 5.4 | 2.7 | 8.3 | 25.5 | | |
| -1 | 2 | 17.8 | 17.8 | 2.5 | 1.8 | - | - | | |
| 0 | 9 | 20.5 | 21.2 | 2.8 | 0.9 | 19.0 | 23.4 | | |
| +1 | 9 | 19.0 | 19.2 | 3.9 | 1.3 | 16.2 | 22.2 | | |
| +2 | 6 | 20.5 | 21.3 | 2.8 | 1.1 | 18.4 | 24.2 | a | |
| +3 | 8 | 23.5 | 24.2 | 5.1 | 1.8 | 19.9 | 28.5 | b | |
| +4 | 6 | 22.0 | 24.0 | 4.0 | 1.8 | 19.0 | 29.0 | b | |
| +5 | 6 | 23.5 | 23.3 | 2.9 | 1.2 | 20.3 | 26.3 | | |
| +6 | 3 | 21.0 | 23.0 | 4.4 | 2.5 | 12.2 | 33.8 | | |
| +7 | 4 | 24.3 | 23.4 | 4.8 | 2.4 | 15.7 | 31.1 | | i |
| +8 | 6 | 24.5 | 25.5 | 8.0 | 2.4 | 19.2 | 31.8 | | i |
| Cyst size | 10 | 23.8 | 25.0 | 5.1 | 1.6 | 21.4 | 28.6 | | ii |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls | Non-shrinkers |
|---|---|---|
| p <0.05 | | i |
| p <0.02 | a | |
| p <0.01 | | ii |
| p <0.001 | b | |

Table 5.1.41

Large Cysts (>20mm non-shrinkers)

Follicular Diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -5 | 4 | 9.5 | 11.8 | 3.3 | 1.7 | 6.5 | 17.1 | |
| -4 | 8 | 13.8 | 13.3 | 1.4 | 0.5 | 12.1 | 14.5 | |
| -3 | 9 | 14.0 | 15.2 | 3.9 | 1.3 | 12.2 | 18.2 | |
| -2 | 8 | 16.3 | 17.3 | 3.1 | 1.1 | 14.7 | 19.6 | |
| -1 | 11 | 18.0 | 18.2 | 2.9 | 0.9 | 16.2 | 20.2 | |
| 0 | 11 | 19.5 | 19.6 | 3.5 | 1.1 | 17.2 | 23.0 | |
| +1 | 10 | 21.0 | 22.9 | 6.5 | 2.1 | 18.2 | 27.6 | a |
| +2 | 11 | 25.5 | 24.9 | 4.1 | 1.2 | 22.2 | 27.6 | b |
| +3 | 13 | 26.0 | 26.6 | 5.4 | 1.5 | 23.4 | 29.8 | b |
| +4 | 9 | 28.0 | 28.9 | 6.5 | 2.2 | 23.9 | 33.9 | b |
| +5 | 12 | 31.0 | 28.8 | 6.4 | 1.9 | 24.7 | 32.9 | |
| +6 | 9 | 31.0 | 31.7 | 8.7 | 2.9 | 25.0 | 38.4 | |
| +7 | 9 | 33.0 | 31.6 | 5.4 | 1.8 | 27.4 | 35.8 | |
| +8 | 7 | 37.0 | 37.2 | 10.2 | 3.9 | 27.7 | 46.7 | |
| Cyst size | 20 | 33.0 | 33.1 | 8.4 | 1.9 | 29.1 | 37.1 | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

Controls

p <0.05 a
p <0.001 b

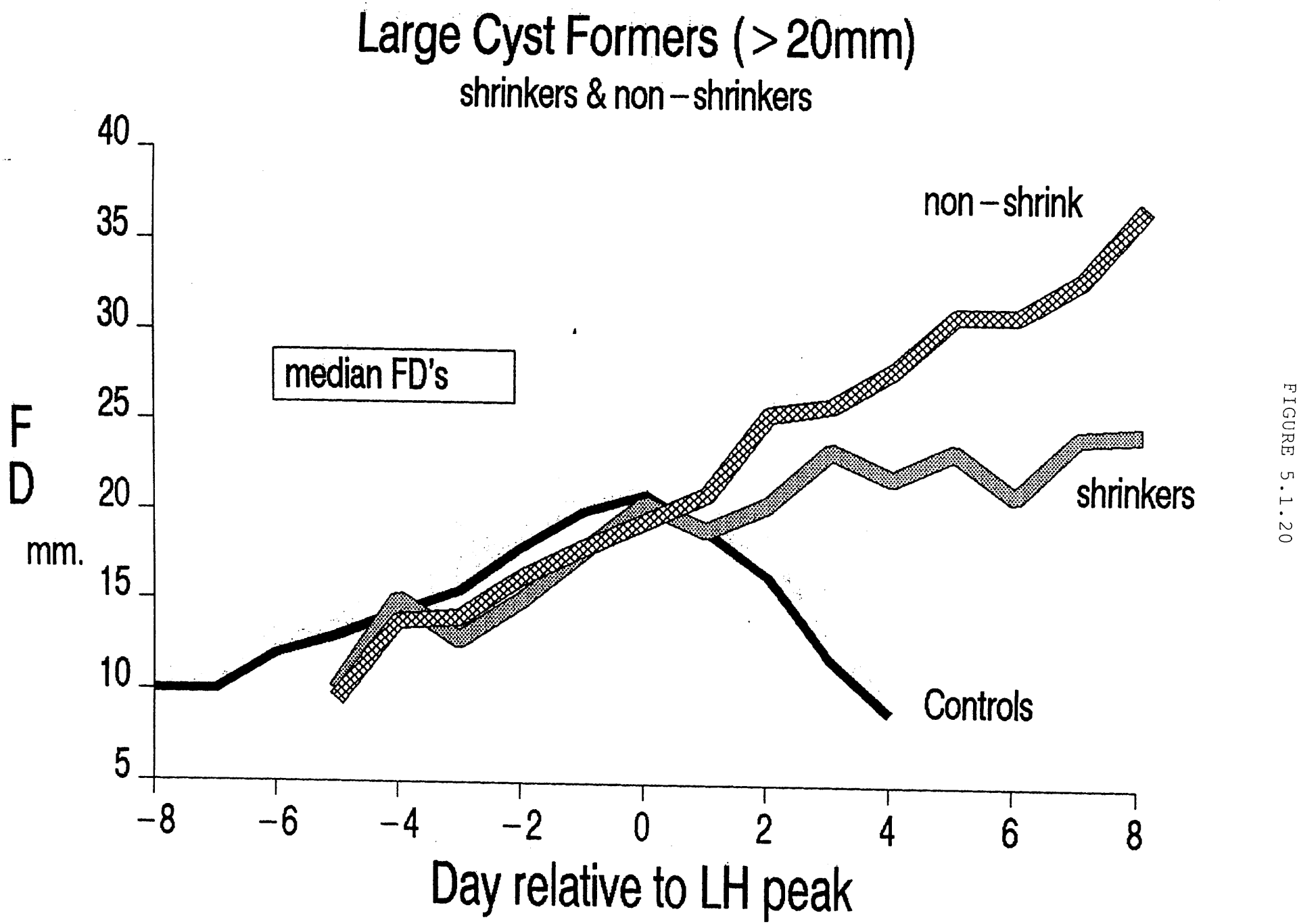

Large Cyst Formers (>20mm)
shrinkers & non-shrinkers
40
35
30
25
20
15
10
5
F
D
mm.
median FD's
non-shrink
shrinkers
Controls
-8
-6
-4
-2
0
2
4
6
8
Day relative to LH peak

FIGURE 5.1.20

Table 5.1.42

Large Cysts (>20mm low P index)

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 15 | 75.0 | 78.7 | 16.7 | 4.3 | 69.4 | 88.0 | |
| -9 | 16 | 77.5 | 78.2 | 16.8 | 4.2 | 69.3 | 87.1 | |
| -8 | 17 | 85.0 | 83.8 | 15.0 | 3.6 | 76.1 | 91.5 | i |
| -7 | 19 | 90.0 | 88.5 | 18.1 | 4.2 | 79.8 | 97.2 | |
| -6 | 18 | 85.0 | 90.7 | 22.5 | 5.3 | 79.5 | 101.9 | |
| -5 | 19 | 105.0 | 103.2 | 33.5 | 7.7 | 87.0 | 119.4 | |
| -4 | 21 | 120.0 | 124.7 | 40.4 | 8.8 | 106.3 | 143.1 | |
| -3 | 21 | 130.0 | 144.2 | 48.3 | 10.5 | 122.2 | 166.2 | |
| -2 | 21 | 168.0 | 176.2 | 49.0 | 10.7 | 153.9 | 198.5 | |
| -1 | 20 | 225.0 | 218.6 | 56.2 | 12.6 | 192.3 | 244.9 | |
| 0 | 23 | 191.5 | 200.4 | 49.5 | 10.3 | 179.0 | 221.8 | |
| +1 | 21 | 140.0 | 145.5 | 43.4 | 9.5 | 125.7 | 165.3 | a |
| +2 | 23 | 130.0 | 126.2 | 31.5 | 6.6 | 112.6 | 139.8 | |
| +3 | 23 | 145.0 | 140.8 | 29.8 | 6.2 | 127.9 | 153.7 | |
| +4 | 23 | 140.0 | 152.8 | 47.3 | 9.9 | 132.3 | 173.3 | |
| +5 | 23 | 135.0 | 156.7 | 56.1 | 11.7 | 132.4 | 181.0 | |
| +6 | 21 | 150.0 | 158.5 | 50.4 | 11.0 | 135.5 | 181.5 | |
| +7 | 22 | 152.5 | 159.1 | 47.3 | 10.1 | 138.1 | 180.1 | |
| +8 | 21 | 145.0 | 160.4 | 49.9 | 10.9 | 137.7 | 183.1 | |
| +9 | 20 | 145.0 | 165.5 | 77.6 | 17.3 | 129.2 | 201.8 | |
| +10 | 19 | 140.0 | 151.7 | 57.9 | 13.3 | 123.8 | 179.6 | |
| +11 | 21 | 140.0 | 149.0 | 60.3 | 13.2 | 121.6 | 176.4 | |
| +12 | 19 | 135.0 | 133.3 | 53.7 | 12.3 | 107.4 | 159.2 | |
| +13 | 18 | 115.0 | 116.8 | 42.3 | 10.0 | 95.7 | 137.9 | |
| +14 | 16 | 102.5 | 103.1 | 29.3 | 7.3 | 87.5 | 118.7 | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls | Normal P index |
|---|---|---|
| p <0.05 | a | i |

Table 5.1.43

Large cysts (>20mm normal P index)

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 5 | 65.0 | 72.0 | 17.2 | 7.7 | 50.7 | 93.3 |
| -9 | 5 | 80.0 | 73.0 | 22.8 | 10.2 | 44.7 | 101.3 |
| -8 | 7 | 65.0 | 67.1 | 20.0 | 7.5 | 48.6 | 85.6 |
| -7 | 6 | 85.0 | 79.2 | 12.4 | 5.1 | 66.2 | 92.2 |
| -6 | 7 | 85.0 | 86.4 | 16.8 | 6.3 | 70.9 | 101.9 |
| -5 | 7 | 110.0 | 113.6 | 14.4 | 5.4 | 100.3 | 126.9 |
| -4 | 7 | 115.0 | 119.7 | 36.1 | 13.6 | 86.3 | 153.1 |
| -3 | 7 | 145.0 | 143.7 | 23.7 | 9.0 | 121.8 | 165.6 |
| -2 | 7 | 210.0 | 196.4 | 54.8 | 20.7 | 145.8 | 247.0 |
| -1 | 7 | 210.0 | 208.6 | 35.9 | 13.6 | 175.4 | 241.8 |
| 0 | 7 | 185.0 | 182.6 | 70.5 | 26.7 | 117.4 | 247.8 |
| +1 | 7 | 135.0 | 120.0 | 37.0 | 14.0 | 85.8 | 154.2 |
| +2 | 7 | 100.0 | 104.0 | 18.0 | 6.8 | 87.4 | 120.6 |
| +3 | 7 | 120.0 | 121.1 | 19.8 | 7.5 | 102.8 | 139.4 |
| +4 | 6 | 120.0 | 118.3 | 11.7 | 4.8 | 106.0 | 130.6 |
| +5 | 7 | 125.0 | 134.0 | 33.6 | 12.7 | 103.0 | 165.0 |
| +6 | 7 | 115.0 | 120.0 | 33.3 | 12.6 | 89.2 | 150.8 |
| +7 | 7 | 130.0 | 138.6 | 35.7 | 13.5 | 105.6 | 171.6 |
| +8 | 7 | 130.0 | 133.6 | 33.1 | 12.5 | 103.0 | 164.2 |
| +9 | 6 | 120.0 | 134.2 | 35.6 | 14.5 | 96.9 | 171.5 |
| +10 | 6 | 120.0 | 133.3 | 48.4 | 19.8 | 84.9 | 181.7 |
| +11 | 6 | 110.0 | 124.2 | 43.3 | 17.7 | 78.8 | 169.6 |
| +12 | 7 | 110.0 | 110.7 | 46.3 | 17.5 | 67.9 | 153.5 |
| +13 | 6 | 87.5 | 83.8 | 25.2 | 10.3 | 57.3 | 141.1 |
| +14 | 6 | 77.5 | 80.8 | 31.8 | 13.0 | 47.4 | 114.2 |

No significant differences from controls.
(Wilcoxon Rank Sum Test)

FIGURE 5.1.21

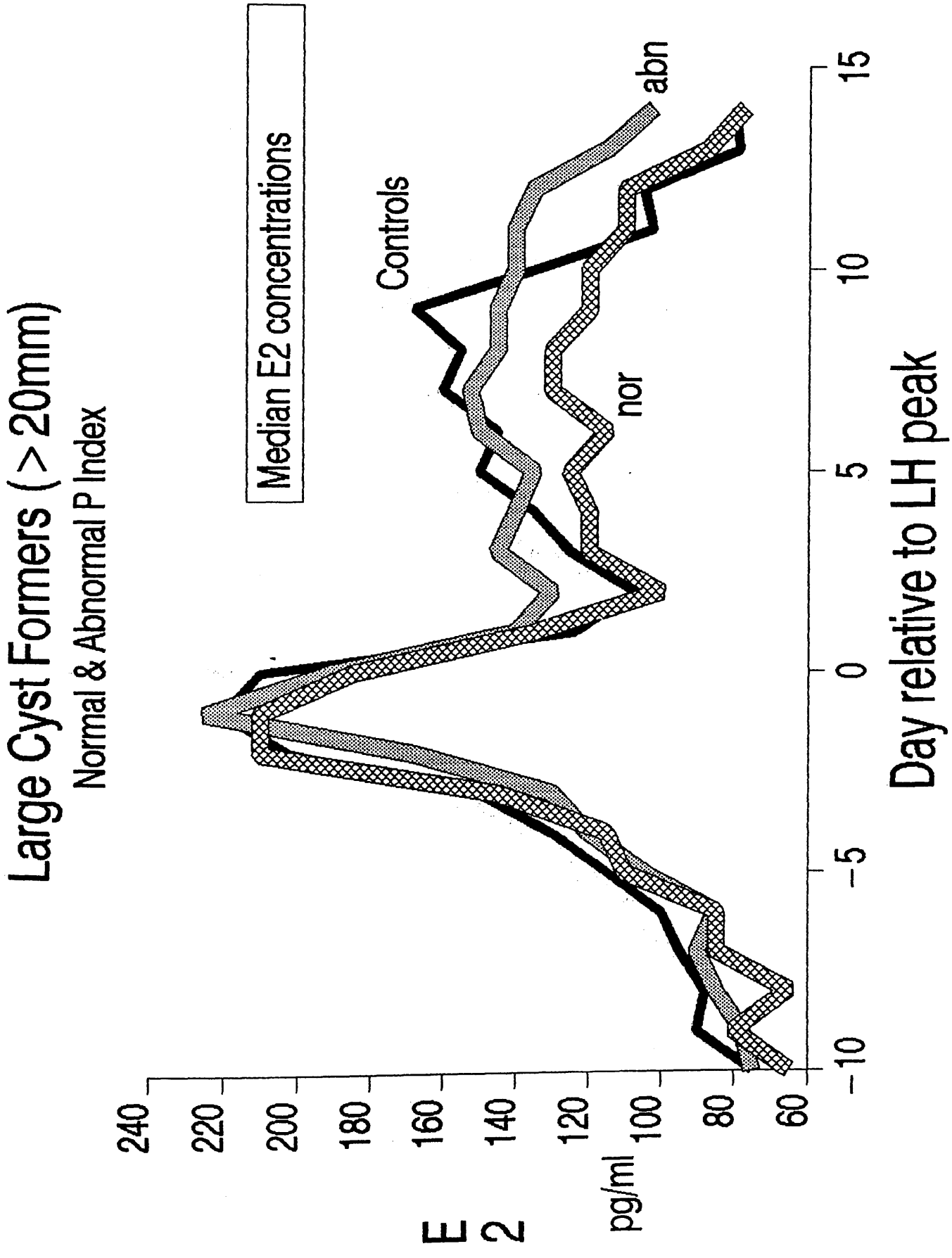

Large Cyst Formers (>20mm)
Normal & Abnormal P Index
Median E2 concentrations
Controls
abn
nor
E 2
pg/ml
240
220
200
180
160
140
120
100
80
60
-10
-5
0
5
10
15
Day relative to LH peak

Table 5.1.44

Large Cysts (>20mm low P index)

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | | |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 13 | 0.9 | 0.9 | 0.5 | 0.2 | 0.6 | 1.2 | | |
| +1 | 20 | 1.3 | 1.3 | 0.7 | 0.2 | 1.0 | 1.6 | c | |
| +2 | 22 | 2.7 | 2.5 | 0.9 | 0.2 | 2.1 | 2.9 | d | i |
| +3 | 23 | 3.6 | 4.1 | 1.7 | 0.4 | 3.3 | 4.9 | d | ii |
| +4 | 23 | 6.2 | 6.0 | 2.9 | 0.6 | 4.7 | 7.3 | d | ii |
| +5 | 23 | 9.2 | 8.9 | 3.7 | 0.8 | 7.3 | 10.5 | d | ii |
| +6 | 21 | 12.8 | 12.6 | 5.5 | 1.2 | 10.1 | 15.1 | d | ii |
| +7 | 22 | 15.5 | 15.3 | 6.6 | 1.4 | 12.4 | 18.2 | a | ii |
| +8 | 22 | 14.4 | 13.8 | 5.7 | 1.2 | 11.3 | 16.3 | b | i |
| +9 | 20 | 13.2 | 13.3 | 6.1 | 1.4 | 10.4 | 16.2 | | ii |
| +10 | 19 | 13.2 | 13.4 | 6.6 | 1.5 | 10.2 | 16.6 | | |
| +11 | 21 | 11.6 | 11.7 | 6.8 | 1.5 | 8.6 | 14.8 | c | |
| +12 | 19 | 8.2 | 8.6 | 5.2 | 1.2 | 6.1 | 11.1 | c | |
| +13 | 18 | 7.3 | 6.3 | 5.4 | 1.3 | 3.6 | 9.0 | b | |
| +14 | 16 | 3.5 | 3.7 | 3.7 | 0.9 | 1.8 | 5.6 | | |
| P index | 23 | 63.0 | 54.4 | 20.0 | 4.2 | 45.7 | 63.1 | d | ii |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls | Normal P index |
|---|---|---|
| p <0.05 | a | |
| p <0.02 | b | |
| p <0.01 | c | i |
| p <0.001 | d | ii |

Table 5.1.45

Large Cysts (>20mm normal P index)

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| 0 | 6 | 1.2 | 1.3 | 0.9 | 0.4 | 0.3 | 2.3 | |
| +1 | 7 | 1.5 | 2.3 | 2.1 | 0.8 | 0.2 | 4.4 | |
| +2 | 7 | 5.4 | 6.2 | 4.8 | 1.8 | 1.7 | 10.7 | |
| +3 | 7 | 8.6 | 9.5 | 5.3 | 2.0 | 4.6 | 14.4 | |
| +4 | 6 | 13.6 | 13.8 | 2.5 | 1.0 | 11.2 | 16.4 | |
| +5 | 7 | 17.6 | 18.7 | 4.5 | 1.7 | 14.5 | 22.9 | |
| +6 | 7 | 22.4 | 22.8 | 4.9 | 1.9 | 18.3 | 27.3 | |
| +7 | 7 | 25.2 | 25.5 | 4.4 | 1.7 | 21.4 | 29.6 | b |
| +8 | 7 | 25.2 | 22.8 | 5.7 | 2.1 | 17.6 | 28.0 | |
| +9 | 6 | 26.7 | 24.7 | 3.3 | 1.3 | 21.3 | 28.1 | b |
| +10 | 6 | 16.7 | 19.1 | 6.6 | 2.7 | 12.2 | 26.0 | a |
| +11 | 6 | 17.1 | 17.2 | 7.5 | 3.1 | 9.3 | 25.1 | c |
| +12 | 7 | 12.2 | 12.1 | 7.6 | 2.9 | 5.1 | 19.1 | b |
| +13 | 6 | 4.9 | 4.1 | 2.3 | 1.0 | 1.6 | 6.6 | |
| +14 | 6 | 1.9 | 2.2 | 1.7 | 0.7 | 0.4 | 4.0 | |
| P index | 7 | 101.0 | 109.9 | 22.4 | 8.5 | 89.1 | 130.7 | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

Controls

| | |
|---|---|
| p <0.05 | a |
| p <0.01 | b |
| p <0.001 | c |

FIGURE 5.1.22

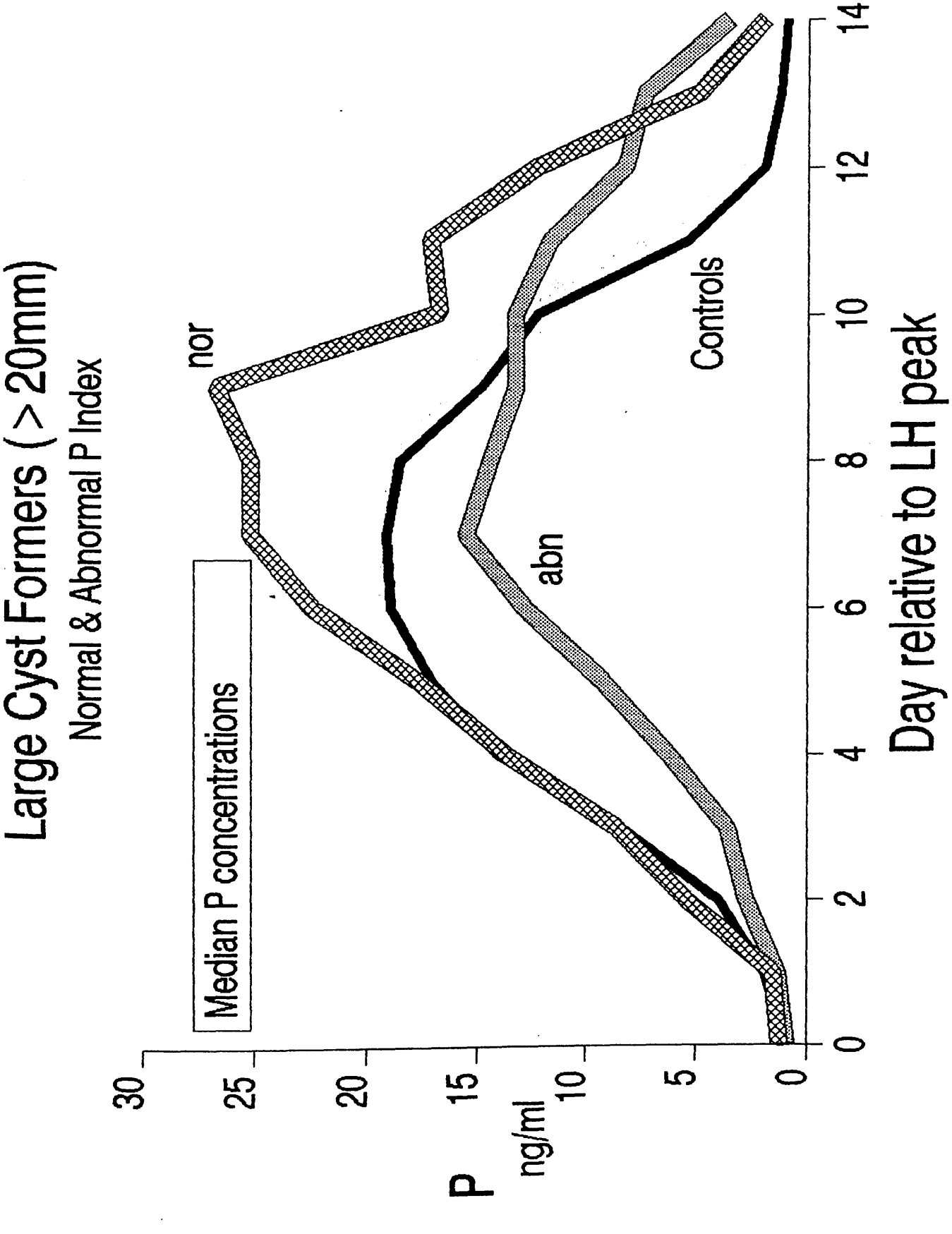

Large Cyst Formers (>20mm)
Normal & Abnormal P Index
Median P concentrations
nor
abn
Controls
P ng/ml
30
25
20
15
10
5
0
0
2
4
6
8
10
12
14
Day relative to LH peak

Table 5.1.46

Large Cysts (>20mm low P index)

Plasma LH concentrations (IU/1)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 14 | 9.9 | 8.8 | 4.2 | 1.1 | 6.4 | 11.2 | |
| -9 | 16 | 8.2 | 8.5 | 5.4 | 1.3 | 5.6 | 11.4 | |
| -8 | 17 | 7.1 | 9.2 | 5.9 | 1.4 | 6.2 | 12.2 | |
| -7 | 18 | 7.6 | 8.4 | 4.4 | 1.0 | 6.2 | 10.6 | |
| -6 | 18 | 9.6 | 9.2 | 4.1 | 1.0 | 7.2 | 11.2 | |
| -5 | 20 | 8.4 | 8.6 | 4.0 | 0.9 | 6.7 | 10.5 | |
| -4 | 21 | 6.9 | 8.2 | 3.8 | 0.8 | 6.5 | 9.9 | |
| -3 | 21 | 9.3 | 10.1 | 6.3 | 1.4 | 7.3 | 12.9 | |
| -2 | 21 | 10.0 | 11.3 | 4.6 | 1.0 | 9.2 | 13.4 | |
| -1 | 20 | 25.0 | 23.5 | 14.0 | 3.1 | 17.0 | 30.0 | |
| 0 | 23 | 70.0 | 63.1 | 17.5 | 3.6 | 55.6 | 70.6 | |
| +1 | 22 | 22.0 | 24.5 | 12.4 | 2.6 | 19.0 | 30.0 | |
| +2 | 23 | 13.0 | 13.2 | 7.4 | 1.5 | 10.0 | 16.4 | |
| +3 | 23 | 15.0 | 15.0 | 6.4 | 1.3 | 12.2 | 17.8 | a |
| +4 | 22 | 12.5 | 14.4 | 8.4 | 1.8 | 10.7 | 18.1 | |
| +5 | 23 | 12.0 | 13.0 | 7.5 | 1.6 | 9.8 | 16.2 | b |
| +6 | 21 | 8.8 | 10.1 | 6.4 | 1.4 | 7.2 | 13.0 | |
| +7 | 23 | 9.5 | 9.7 | 8.4 | 1.3 | 7.1 | 12.3 | |
| +8 | 21 | 5.8 | 7.8 | 7.5 | 1.1 | 5.6 | 10.0 | |
| +9 | 20 | 9.3 | 10.2 | 6.4 | 1.6 | 6.8 | 13.6 | a |
| +10 | 19 | 7.3 | 7.5 | 6.1 | 1.0 | 5.4 | 9.6 | |
| +11 | 21 | 6.0 | 7.2 | 4.8 | 1.1 | 5.0 | 9.4 | |
| +12 | 18 | 7.8 | 8.1 | 4.4 | 1.0 | 5.9 | 10.3 | |
| +13 | 17 | 7.0 | 6.0 | 2.8 | 0.7 | 4.6 | 7.4 | |
| +14 | 14 | 7.2 | 7.5 | 2.6 | 0.7 | 6.0 | 9.0 | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls |
|---|---|
| p <0.05 | a |
| p <0.02 | b |

Table 5.1.47

Large Cysts (>20mm normal P index)

Plasma LH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 4 | 7.0 | 9.5 | 3.8 | 1.9 | 3.5 | 15.5 |
| -9 | 5 | 6.5 | 10.0 | 7.4 | 3.3 | 0.9 | 19.1 |
| -8 | 7 | 7.4 | 8.2 | 4.9 | 1.8 | 3.7 | 12.7 |
| -7 | 6 | 11.0 | 12.7 | 7.1 | 2.9 | 5.3 | 20.1 |
| -6 | 7 | 8.6 | 10.1 | 5.5 | 2.1 | 5.0 | 15.2 |
| -5 | 7 | 9.3 | 9.5 | 4.8 | 1.8 | 5.0 | 14.0 |
| -4 | 6 | 5.7 | 5.7 | 2.5 | 1.0 | 3.1 | 8.3 |
| -3 | 6 | 7.3 | 7.5 | 1.3 | 0.5 | 6.2 | 8.8 |
| -2 | 6 | 8.4 | 8.4 | 4.7 | 1.9 | 3.4 | 13.4 |
| -1 | 6 | 13.5 | 16.3 | 7.4 | 3.0 | 8.5 | 24.1 |
| 0 | 6 | 57.0 | 56.7 | 21.1 | 8.6 | 34.6 | 78.8 |
| +1 | 6 | 13.0 | 23.3 | 22.5 | 9.2 | -0.4 | 47.0 |
| +2 | 6 | 16.0 | 14.6 | 6.4 | 2.6 | 7.8 | 21.4 |
| +3 | 7 | 8.9 | 11.0 | 5.4 | 2.1 | 6.0 | 16.0 |
| +4 | 6 | 9.5 | 15.9 | 17.0 | 6.9 | -1.9 | 33.7 |
| +5 | 7 | 9.2 | 9.1 | 3.9 | 1.5 | 5.5 | 12.7 |
| +6 | 6 | 6.7 | 8.1 | 6.1 | 2.5 | 1.7 | 14.5 |
| +7 | 7 | 4.5 | 7.1 | 5.6 | 2.1 | 1.9 | 12.3 |
| +8 | 5 | 4.2 | 5.3 | 2.5 | 1.1 | 2.2 | 8.6 |
| +9 | 5 | 3.7 | 7.6 | 9.7 | 4.4 | -4.5 | 19.7 |
| +10 | 6 | 4.5 | 7.0 | 7.3 | 2.8 | -0.3 | 14.3 |
| +11 | 5 | 7.9 | 8.9 | 7.1 | 3.2 | 0.1 | 17.7 |
| +12 | 5 | 4.9 | 6.7 | 5.2 | 2.3 | 0.7 | 13.2 |
| +13 | 6 | 8.7 | 8.5 | 2.7 | 1.1 | 5.7 | 11.3 |
| +14 | 5 | 7.2 | 8.0 | 2.7 | 1.2 | 4.7 | 11.3 |

No significant difference from controls.
(Wilcoxon Rank Sum Test)

FIGURE 5.1.23

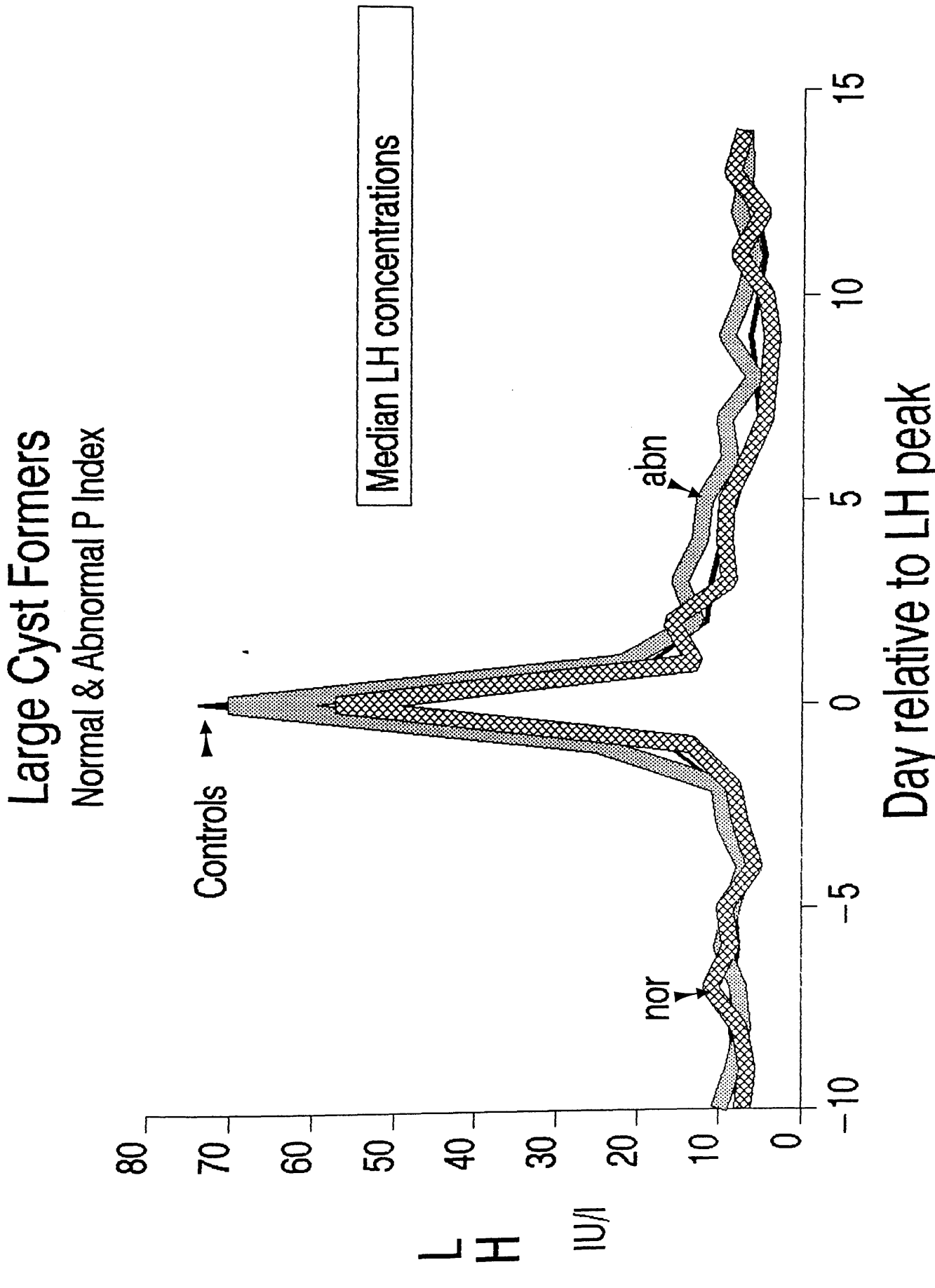

Large Cyst Formers
Normal & Abnormal P Index
Median LH concentrations
Controls
abn
nor
LH IU/l
80
70
60
50
40
30
20
10
0
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.1.48

Large Cysts (>20mm low P index)

Plasma FSH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 14 | 6.6 | 7.3 | 2.2 | 0.6 | 6.0 | 8.6 | b |
| -9 | 16 | 6.3 | 6.5 | 2.0 | 0.5 | 5.5 | 7.5 | |
| -8 | 17 | 6.2 | 6.4 | 2.6 | 0.6 | 5.0 | 7.8 | |
| -7 | 18 | 5.6 | 5.4 | 1.5 | 0.4 | 4.6 | 6.2 | |
| -6 | 18 | 5.2 | 5.5 | 1.9 | 0.4 | 4.6 | 6.4 | |
| -5 | 20 | 5.1 | 4.8 | 1.3 | 0.3 | 4.2 | 5.4 | |
| -4 | 21 | 4.3 | 4.0 | 0.9 | 0.2 | 3.6 | 4.4 | |
| -3 | 21 | 3.9 | 3.8 | 1.2 | 0.3 | 3.2 | 4.4 | |
| -2 | 21 | 4.0 | 3.8 | 1.1 | 0.2 | 3.3 | 4.3 | |
| -1 | 20 | 5.1 | 5.1 | 2.2 | 0.5 | 4.1 | 6.1 | |
| 0 | 23 | 13.0 | 13.7 | 6.2 | 1.3 | 11.0 | 16.4 | |
| +1 | 22 | 7.0 | 7.8 | 4.5 | 1.0 | 5.8 | 9.8 | |
| +2 | 22 | 4.8 | 6.2 | 4.2 | 0.9 | 4.3 | 8.1 | |
| +3 | 23 | 4.3 | 5.2 | 2.8 | 0.6 | 4.0 | 6.4 | |
| +4 | 22 | 4.6 | 5.1 | 3.2 | 0.7 | 3.7 | 6.5 | |
| +5 | 23 | 4.1 | 4.6 | 3.3 | 0.7 | 3.2 | 6.0 | |
| +6 | 21 | 4.0 | 4.1 | 2.7 | 0.6 | 2.9 | 5.3 | a |
| +7 | 23 | 3.5 | 3.9 | 3.2 | 0.7 | 2.5 | 5.3 | a |
| +8 | 21 | 3.4 | 3.7 | 2.7 | 0.6 | 2.5 | 4.9 | a |
| +9 | 20 | 3.2 | 3.9 | 2.9 | 0.7 | 2.5 | 5.3 | c |
| +10 | 19 | 3.2 | 3.6 | 2.9 | 0.7 | 2.2 | 5.0 | a |
| +11 | 21 | 2.9 | 3.2 | 2.6 | 0.6 | 2.0 | 4.4 | |
| +12 | 19 | 2.8 | 3.4 | 2.5 | 0.6 | 2.2 | 4.6 | |
| +13 | 18 | 2.8 | 3.7 | 2.8 | 0.7 | 2.3 | 5.1 | |
| +14 | 14 | 3.7 | 4.8 | 3.1 | 0.8 | 3.0 | 6.6 | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls |
|---|---|
| p <0.05 | a |
| p <0.02 | b |
| p <0.01 | c |

No significant difference from normal P index.

Table 5.1.49

Large Cysts (>20mm normal P index)

Plasma FSH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 4 | 8.0 | 7.5 | 3.7 | 1.8 | 1.7 | 13.3 |
| -9 | 5 | 9.0 | 6.6 | 3.5 | 1.6 | 2.2 | 11.0 |
| -8 | 7 | 5.6 | 7.6 | 5.2 | 2.0 | 2.8 | 12.4 |
| -7 | 6 | 7.1 | 7.5 | 4.5 | 1.8 | 2.8 | 12.2 |
| -6 | 7 | 7.0 | 6.9 | 2.6 | 1.0 | 4.5 | 9.3 |
| -5 | 7 | 6.4 | 5.4 | 1.8 | 0.7 | 3.8 | 7.0 |
| -4 | 7 | 4.5 | 4.6 | 1.4 | 0.5 | 3.3 | 5.9 |
| -3 | 7 | 3.4 | 3.5 | 1.5 | 0.6 | 2.1 | 4.9 |
| -2 | 7 | 3.2 | 3.6 | 1.2 | 0.4 | 2.5 | 4.7 |
| -1 | 7 | 3.8 | 4.7 | 1.9 | 0.7 | 2.9 | 6.5 |
| 0 | 7 | 14.0 | 13.0 | 5.8 | 2.2 | 7.6 | 18.4 |
| +1 | 7 | 7.6 | 8.3 | 4.0 | 1.5 | 4.6 | 12.0 |
| +2 | 6 | 5.7 | 5.5 | 3.1 | 1.3 | 2.3 | 8.7 |
| +3 | 7 | 4.5 | 5.1 | 3.9 | 1.5 | 1.5 | 8.7 |
| +4 | 6 | 3.8 | 4.3 | 3.5 | 1.4 | 0.7 | 7.9 |
| +5 | 7 | 2.4 | 3.5 | 2.6 | 1.0 | 1.1 | 5.9 |
| +6 | 6 | 3.2 | 3.5 | 2.2 | 0.9 | 0.8 | 6.2 |
| +7 | 7 | 3.2 | 2.9 | 1.3 | 0.5 | 1.7 | 4.1 |
| +8 | 7 | 2.7 | 2.6 | 1.1 | 0.4 | 1.5 | 3.7 |
| +9 | 4 | 2.6 | 2.6 | 1.0 | 0.5 | 1.1 | 4.1 |
| +10 | 6 | 2.6 | 3.7 | 3.6 | 1.5 | -0.1 | 7.5 |
| +11 | 6 | 3.1 | 3.2 | 2.0 | 0.8 | 1.1 | 5.3 |
| +12 | 7 | 3.1 | 2.9 | 1.9 | 0.7 | 1.1 | 4.7 |
| +13 | 6 | 4.1 | 3.8 | 2.6 | 1.0 | 1.1 | 6.5 |
| +14 | 5 | 4.3 | 5.2 | 4.0 | 1.8 | 0.3 | 10.1 |

No significant differences from controls.
(Wilcoxon Rank Sum Test)

FIGURE 5.1.24

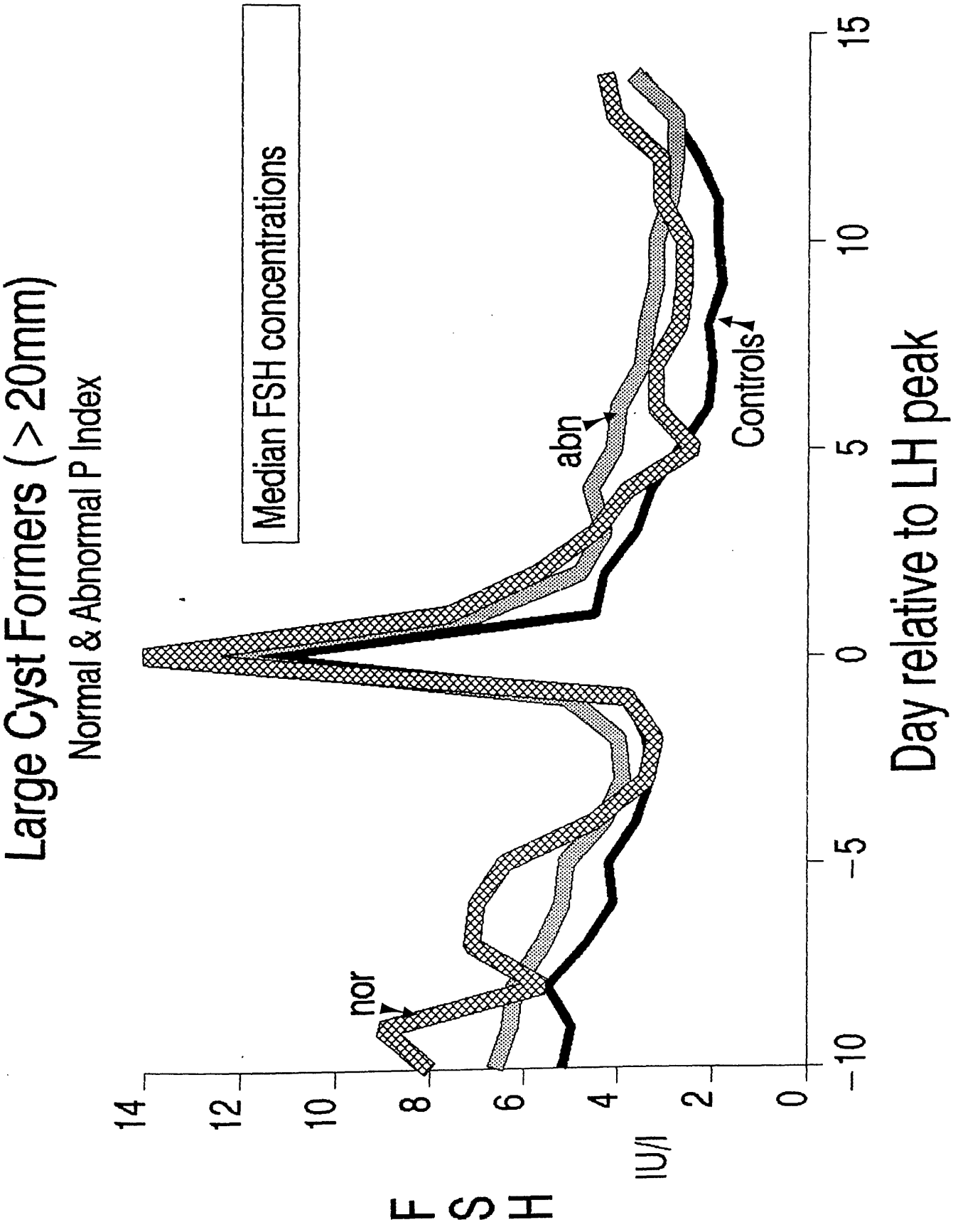

Large Cyst Formers (>20mm)
Normal & Abnormal P Index
Median FSH concentrations
nor
abn
Controls
FSH
IU/l
14
12
10
8
6
4
2
0
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.1.50

Large Cysts (>20mm low P index)

Follicular Diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | | |
|---|---|---|---|---|---|---|---|---|---|
| -5 | 4 | 9.0 | 9.3 | 1.5 | 0.8 | 6.9 | 11.7 | a | i |
| -4 | 7 | 13.0 | 12.9 | 1.4 | 0.6 | 11.4 | 14.4 | | i |
| -3 | 8 | 13.0 | 14.9 | 4.3 | 1.5 | 11.3 | 18.5 | | |
| -2 | 6 | 16.0 | 17.0 | 3.5 | 1.4 | 13.3 | 20.7 | | |
| -1 | 11 | 18.0 | 17.5 | 2.4 | 0.7 | 15.9 | 19.1 | b | i |
| 0 | 13 | 19.0 | 18.9 | 2.7 | 0.7 | 17.3 | 20.5 | | ii |
| +1 | 13 | 20.0 | 21.2 | 6.3 | 1.7 | 17.4 | 25.0 | | |
| +2 | 13 | 25.5 | 24.0 | 4.2 | 1.2 | 21.4 | 26.6 | c | |
| +3 | 16 | 26.0 | 26.6 | 5.5 | 1.4 | 23.6 | 29.6 | c | |
| +4 | 12 | 27.5 | 27.9 | 6.2 | 1.8 | 23.9 | 31.9 | c | |
| +5 | 12 | 27.5 | 28.4 | 6.4 | 1.8 | 24.4 | 32.4 | | |
| +6 | 10 | 28.5 | 30.4 | 8.9 | 2.8 | 24.0 | 36.8 | | |
| +7 | 10 | 29.8 | 29.0 | 6.4 | 2.0 | 24.4 | 33.6 | | |
| +8 | 9 | 30.0 | 30.4 | 9.6 | 3.2 | 23.0 | 37.8 | | |
| Cyst size | 23 | 32.0 | 32.0 | 8.6 | 1.8 | 28.3 | 35.7 | | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

| | Controls | Normal P Index |
|---|---|---|
| p <0.05 | a | i |
| p <0.02 | b | ii |
| p <0.001 | c | |

Table 5.1.51

Large Cysts (>20mm normal P index)

Follicular Diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -5 | 3 | 12.5 | 13.5 | 2.2 | 1.3 | 8.1 | 18.9 | |
| -4 | 4 | 15.0 | 16.3 | 3.2 | 1.6 | 11.2 | 21.4 | |
| -3 | 3 | 13.5 | 14.3 | 1.9 | 1.1 | 9.6 | 19.0 | |
| -2 | 6 | 16.5 | 17.3 | 4.3 | 1.8 | 15.5 | 19.1 | |
| -1 | 2 | 21.8 | 21.8 | 1.8 | 1.3 | 5.9 | 37.7 | |
| 0 | 6 | 21.5 | 22.6 | 2.7 | 1.1 | 19.7 | 25.5 | |
| +1 | 6 | 22.5 | 21.0 | 4.4 | 1.8 | 16.4 | 25.6 | |
| +2 | 4 | 22.0 | 22.4 | 3.1 | 1.6 | 17.4 | 27.4 | a |
| +3 | 5 | 23.0 | 22.8 | 3.2 | 1.4 | 18.8 | 26.8 | b |
| +4 | 2 | 22.5 | 22.5 | 0.7 | 0.5 | 15.1 | 28.9 | b |
| +5 | 6 | 23.0 | 24.2 | 4.5 | 1.9 | 19.4 | 29.0 | |
| +6 | 2 | 25.0 | 25.0 | 7.1 | 5.0 | - | - | |
| +7 | 2 | 25.3 | 25.3 | 3.9 | 2.8 | - | - | |
| +8 | 3 | 26.0 | 28.7 | 7.4 | 4.3 | 10.4 | 47.0 | |
| Cyst size | 7 | 24.5 | 25.2 | 4.9 | 1.8 | 20.8 | 29.6 | |

Significance (Wilcoxon Rank Sum Test) in comparison with :

Controls

p <0.02 a
p <0.001 b

FIGURE 5.1.25

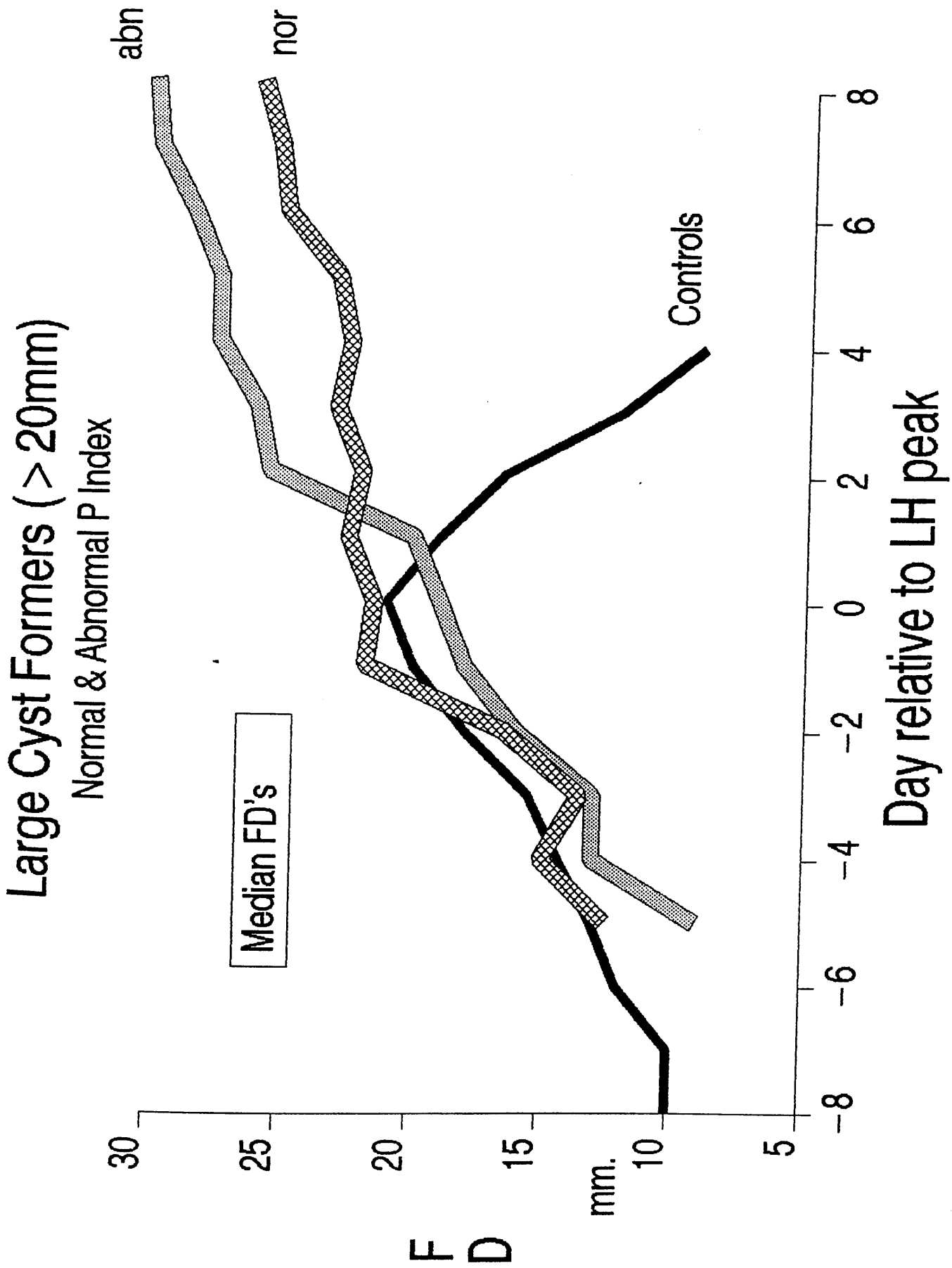

Large Cyst Formers (>20mm)
Normal & Abnormal P Index
abn
nor
Controls
Median FD's
F D
mm.
30
25
20
15
10
5
-8
-6
-4
-2
0
2
4
6
8
Day relative to LH peak

Table 5.2.1

Poor Progesterone Surge

Patient/cycle characteristics

| | Nos | Mean | SD | SEM | Median | Range | |
|---|---|---|---|---|---|---|---|
| AGE (years) | | | | | | | |
| | 51 | 30.0 | 4.0 | 0.6 | 30 | 22-40 | a |
| FOLLICULAR PHASE (Days) | | | | | | | |
| | 51 | 15.2 | 3.7 | 0.5 | 15 | 8-27 | |
| LUTEAL PHASE (Days) | | | | | | | |
| | 51 | 15.1 | 1.7 | 0.3 | 15 | 11-18 | |
| CYCLE LENGTH (Days) | | | | | | | |
| | 51 | 30.4 | 4.3 | 0.6 | 30 | 24-44 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $P < 0.001$

Table 5.2.2

Poor Progesterone Surge

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 37 | 73.0 | 72.3 | 16.3 | 2.7 | 66.8 | 77.8 | |
| -9 | 40 | 75.0 | 75.1 | 18.6 | 2.9 | 69.2 | 81.0 | |
| -8 | 43 | 78.0 | 79.6 | 18.2 | 2.8 | 74.0 | 85.2 | |
| -7 | 45 | 84.0 | 83.6 | 16.9 | 2.5 | 78.5 | 88.7 | |
| -6 | 47 | 90.0 | 92.1 | 19.6 | 2.9 | 86.3 | 97.9 | |
| -5 | 46 | 100.0 | 99.7 | 20.6 | 3.0 | 93.6 | 105.8 | b |
| -4 | 50 | 112.5 | 115.3 | 34.3 | 4.9 | 105.5 | 125.1 | a |
| -3 | 50 | 133.0 | 131.8 | 39.8 | 5.6 | 120.4 | 143.2 | b |
| -2 | 51 | 164.0 | 161.6 | 47.3 | 6.6 | 148.2 | 175.0 | b |
| -1 | 49 | 205.0 | 199.6 | 56.7 | 8.1 | 183.2 | 216.0 | a |
| 0 | 50 | 185.0 | 188.1 | 42.5 | 6.0 | 176.0 | 200.2 | |
| +1 | 50 | 135.0 | 134.1 | 40.5 | 5.7 | 122.5 | 145.7 | |
| +2 | 51 | 110.0 | 111.7 | 42.9 | 6.0 | 99.6 | 123.8 | |
| +3 | 50 | 125.0 | 125.1 | 37.5 | 5.3 | 114.4 | 135.8 | |
| +4 | 51 | 135.0 | 133.5 | 45.9 | 6.4 | 120.5 | 146.5 | |
| +5 | 51 | 140.0 | 141.7 | 50.2 | 7.0 | 127.5 | 155.9 | |
| +6 | 48 | 142.0 | 141.7 | 41.0 | 5.9 | 129.7 | 153.7 | |
| +7 | 49 | 150.0 | 150.4 | 45.3 | 6.5 | 137.3 | 163.5 | |
| +8 | 47 | 155.0 | 156.8 | 56.0 | 8.2 | 140.3 | 173.3 | |
| +9 | 48 | 165.0 | 165.1 | 73.9 | 10.7 | 143.6 | 186.6 | |
| +10 | 46 | 150.0 | 149.4 | 57.5 | 8.5 | 132.3 | 166.5 | |
| +11 | 48 | 150.0 | 152.6 | 75.7 | 10.9 | 130.5 | 174.7 | |
| +12 | 43 | 145.0 | 147.5 | 90.9 | 13.9 | 119.5 | 175.5 | |
| +13 | 38 | 130.0 | 125.7 | 57.6 | 9.3 | 106.8 | 144.6 | |
| +14 | 35 | 102.5 | 105.8 | 41.2 | 7.0 | 91.7 | 119.9 | |

Significance (Wilcoxon Rank Sum Test) in comparison with controls

a = $p < 0.05$
b = $p < 0.01$

FIGURE 5.2.1

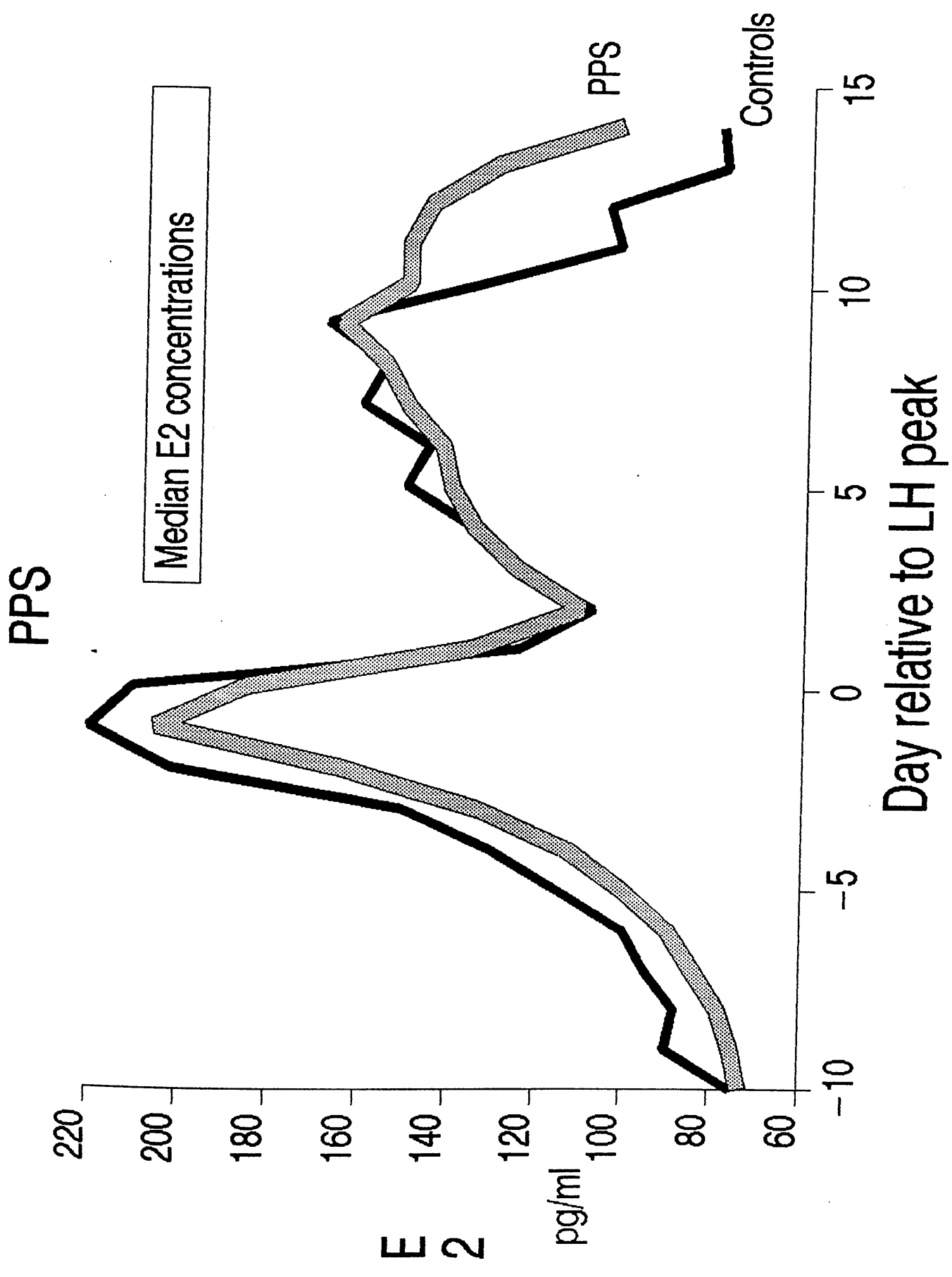

PPS
Median E2 concentrations
PPS
Controls
E 2
pg/ml
220
200
180
160
140
120
100
80
60
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.2.3

Poor Progesterone Surge

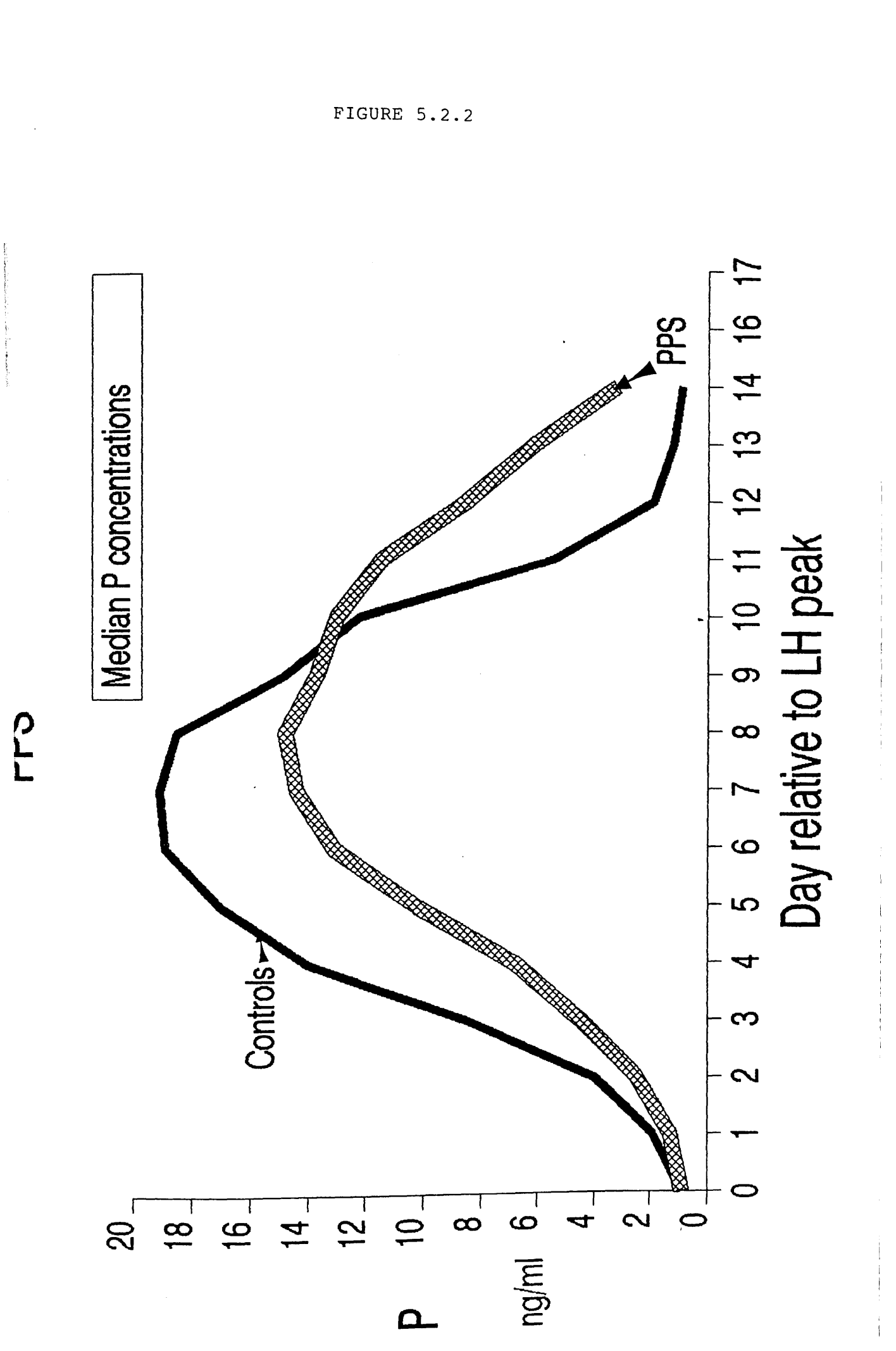
Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| 0 | 27 | 0.9 | 0.8 | 0.4 | 0.1 | 0.6 | 1.0 | |
| +1 | 45 | 1.3 | 1.2 | 0.5 | 0.1 | 1.0 | 1.4 | d |
| +2 | 50 | 2.5 | 2.3 | 0.8 | 0.1 | 2.1 | 2.5 | d |
| +3 | 49 | 4.5 | 4.0 | 1.4 | 0.2 | 3.6 | 4.4 | d |
| +4 | 50 | 6.8 | 6.3 | 2.5 | 0.4 | 5.6 | 7.0 | d |
| +5 | 51 | 10.2 | 9.7 | 3.8 | 0.5 | 8.6 | 10.8 | d |
| +6 | 48 | 13.1 | 12.7 | 5.4 | 0.8 | 11.1 | 14.3 | d |
| +7 | 49 | 14.4 | 14.5 | 6.2 | 0.9 | 12.7 | 16.3 | c |
| +8 | 47 | 14.8 | 14.6 | 6.5 | 0.9 | 12.7 | 16.5 | b |
| +9 | 48 | 13.7 | 13.6 | 6.5 | 0.9 | 11.7 | 15.5 | |
| +10 | 45 | 13.0 | 12.6 | 7.0 | 1.0 | 10.5 | 14.7 | |
| +11 | 48 | 11.4 | 11.0 | 7.8 | 1.1 | 8.7 | 13.3 | b |
| +12 | 43 | 8.5 | 8.5 | 6.2 | 0.9 | 6.6 | 10.4 | c |
| +13 | 38 | 6.1 | 6.2 | 5.7 | 0.9 | 4.3 | 8.1 | a |
| +14 | 35 | 3.2 | 3.4 | 3.4 | 0.6 | 2.2 | 4.6 | |
| P index | 51 | 61.0 | 54.9 | 19.3 | 2.7 | 49.4 | 60.4 | d |

Significance (Wilcoxon Rank Sum Test) in comparison with controls

a = p <0.05
b = p <0.02
c = p <0.01
d = p <0.001

FIGURE 5.2.2


Median P concentrations
Controls
PPS
P
ng/ml
20
18
16
14
12
10
8
6
4
2
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 16 17
Day relative to LH peak

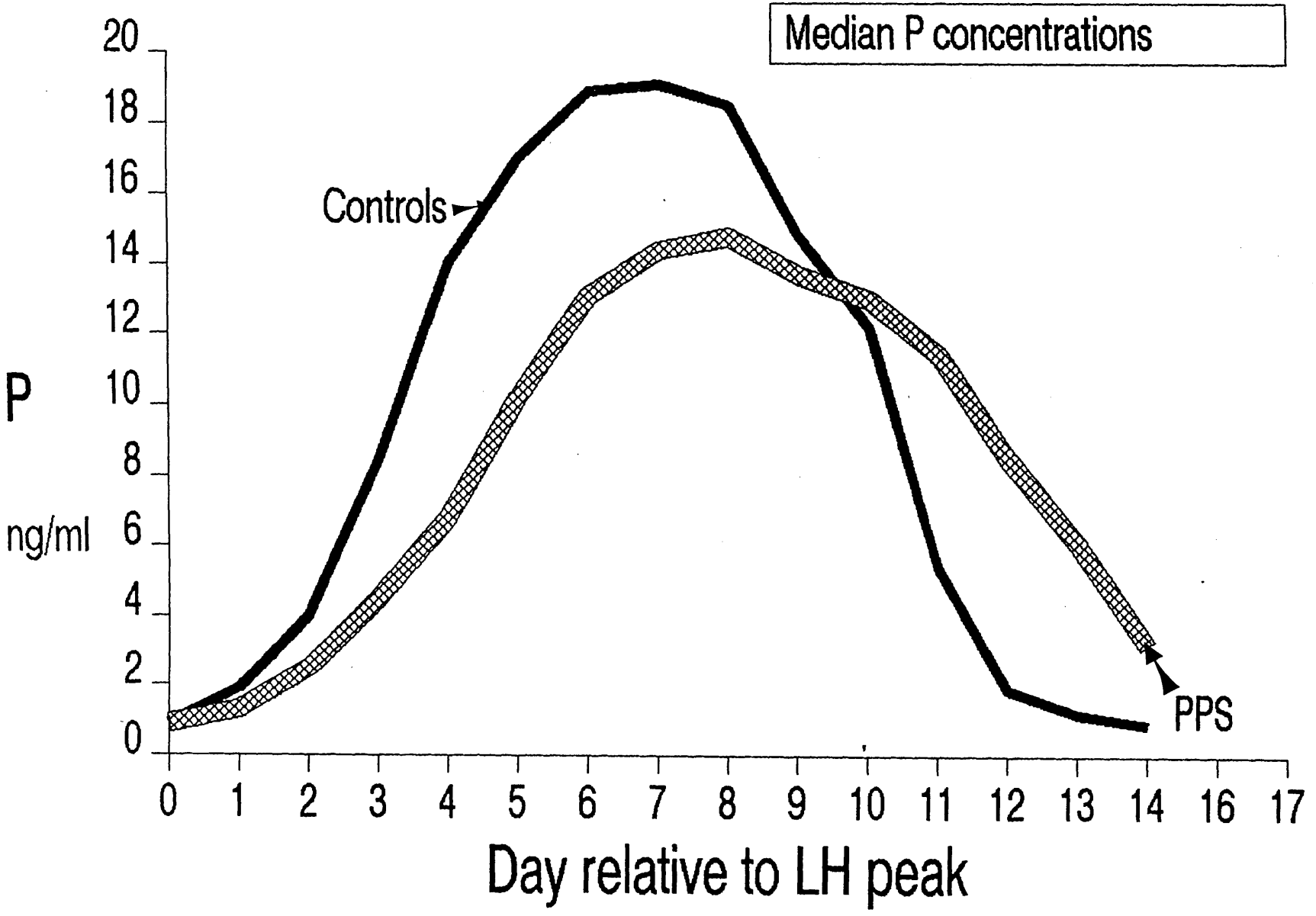

Median P concentrations
Controls
PPS
P
ng/ml
20
18
16
14
12
10
8
6
4
2
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 16 17
Day relative to LH peak

FIGURE 5.2.2

Table 5.2.4

Poor Progesterone Surge

Plasma LH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 36 | 8.8 | 8.9 | 5.0 | 0.8 | 7.2 | 10.6 | |
| -9 | 40 | 8.8 | 8.9 | 6.1 | 1.0 | 7.0 | 10.8 | |
| -8 | 43 | 10.0 | 10.0 | 7.8 | 1.2 | 7.6 | 12.4 | |
| -7 | 44 | 10.3 | 10.3 | 9.3 | 1.4 | 7.5 | 13.1 | |
| -6 | 46 | 9.9 | 10.0 | 7.3 | 1.1 | 7.8 | 12.2 | |
| -5 | 47 | 9.6 | 9.5 | 6.6 | 1.0 | 7.6 | 11.4 | |
| -4 | 50 | 10.1 | 10.0 | 7.1 | 1.0 | 8.0 | 12.0 | |
| -3 | 49 | 11.5 | 11.5 | 9.0 | 1.3 | 8.9 | 14.1 | |
| -2 | 51 | 11.7 | 11.8 | 6.6 | 0.9 | 9.8 | 13.8 | |
| -1 | 49 | 23.0 | 23.0 | 14.9 | 2.1 | 18.7 | 27.3 | |
| 0 | 50 | 60.0 | 58.3 | 23.0 | 3.3 | 51.7 | 64.9 | |
| +1 | 51 | 29.5 | 29.3 | 16.4 | 2.3 | 24.7 | 33.9 | |
| +2 | 51 | 14.5 | 14.9 | 9.2 | 1.3 | 12.3 | 17.5 | |
| +3 | 50 | 12.7 | 13.5 | 7.8 | 1.1 | 11.3 | 15.7 | |
| +4 | 48 | 12.4 | 15.8 | 12.4 | 1.8 | 12.2 | 19.4 | |
| +5 | 51 | 12.9 | 13.5 | 9.5 | 1.3 | 10.2 | 16.8 | a |
| +6 | 48 | 10.8 | 11.5 | 8.9 | 1.3 | 8.9 | 14.1 | |
| +7 | 50 | 10.2 | 10.1 | 7.4 | 1.0 | 8.0 | 12.2 | a |
| +8 | 47 | 9.1 | 9.1 | 6.9 | 1.0 | 7.1 | 11.1 | |
| +9 | 48 | 9.1 | 9.3 | 7.3 | 1.1 | 7.2 | 11.4 | |
| +10 | 44 | 8.7 | 8.5 | 6.7 | 1.0 | 6.5 | 10.5 | |
| +11 | 47 | 7.2 | 7.1 | 5.0 | 0.7 | 5.6 | 8.6 | |
| +12 | 42 | 8.0 | 8.1 | 6.0 | 0.9 | 6.2 | 10.0 | |
| +13 | 36 | 6.9 | 6.9 | 4.5 | 0.7 | 5.4 | 8.4 | |
| +14 | 33 | 7.0 | 7.3 | 5.0 | 0.9 | 5.5 | 9.1 | |

Significance (Wilcoxon Rank Sum Test) in comparison with controls

a = $p < 0.02$

FIGURE 5.2.3

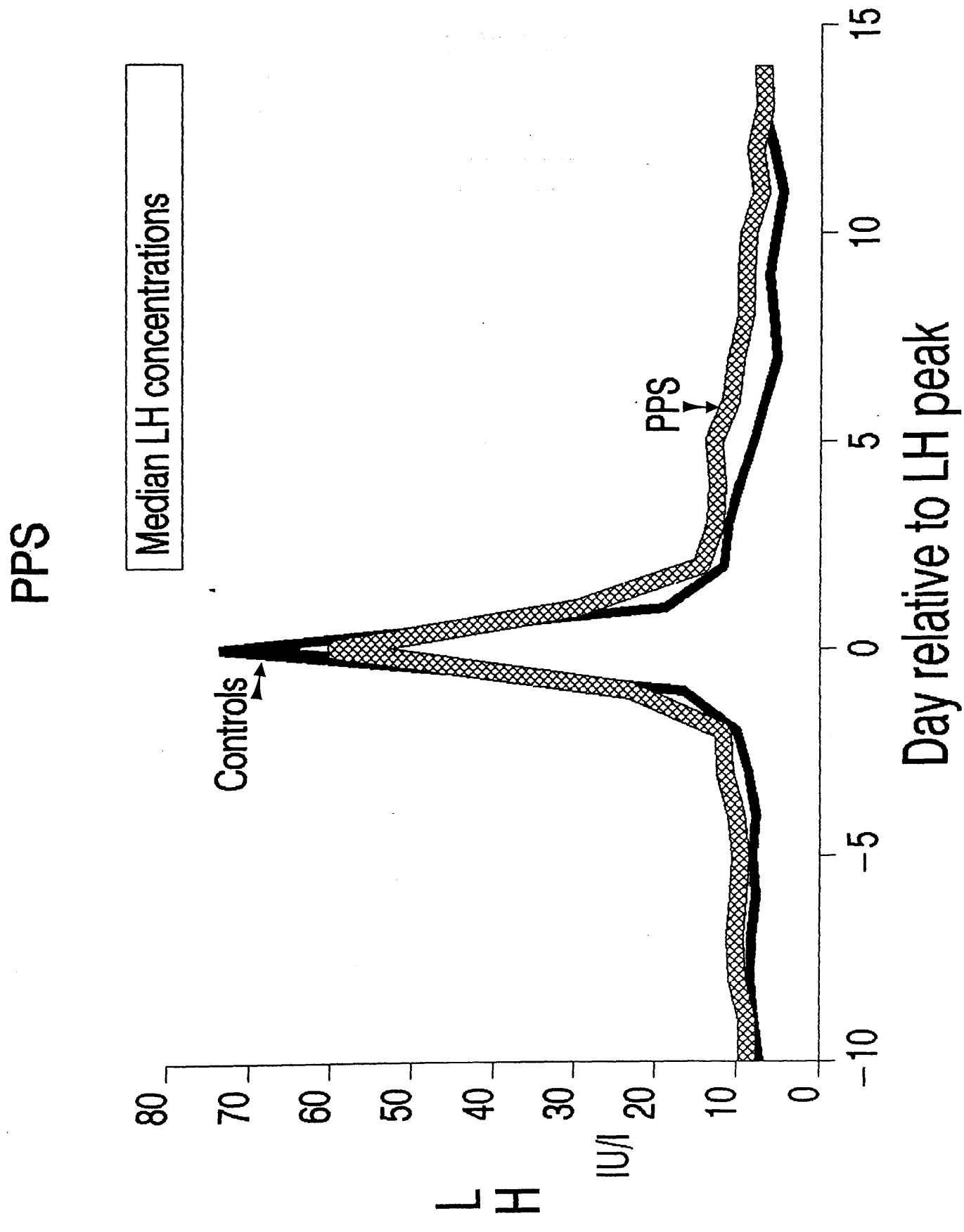

PPS
Median LH concentrations
Controls
PPS
LH IU/l
80
70
60
50
40
30
20
10
0
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.2.5

Poor Progesterone Surge

Plasma FSH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 36 | 6.8 | 6.7 | 2.5 | 0.4 | 6.0 | 7.6 | a |
| -9 | 40 | 6.5 | 6.5 | 2.1 | 0.3 | 5.8 | 7.2 | |
| -8 | 43 | 6.6 | 6.7 | 3.7 | 0.6 | 5.6 | 7.8 | |
| -7 | 44 | 6.3 | 6.3 | 3.4 | 0.5 | 5.3 | 7.3 | |
| -6 | 46 | 6.0 | 6.1 | 3.2 | 0.5 | 5.1 | 7.1 | a |
| -5 | 47 | 5.4 | 5.4 | 2.7 | 0.4 | 4.6 | 6.2 | |
| -4 | 50 | 4.6 | 4.6 | 1.9 | 0.3 | 4.1 | 5.1 | |
| -3 | 49 | 4.4 | 4.4 | 1.8 | 0.3 | 3.9 | 4.9 | a |
| -2 | 51 | 4.5 | 4.5 | 2.1 | 0.3 | 3.9 | 5.1 | |
| -1 | 49 | 6.4 | 6.3 | 4.7 | 0.7 | 4.9 | 7.7 | |
| 0 | 50 | 13.6 | 13.7 | 6.7 | 0.9 | 11.8 | 15.6 | |
| +1 | 51 | 9.6 | 9.4 | 5.0 | 0.7 | 8.0 | 10.8 | |
| +2 | 50 | 6.5 | 6.6 | 4.1 | 0.6 | 5.4 | 7.8 | |
| +3 | 51 | 5.5 | 5.5 | 3.4 | 0.5 | 4.5 | 6.5 | |
| +4 | 48 | 5.4 | 5.4 | 3.6 | 0.5 | 4.3 | 6.5 | a |
| +5 | 51 | 4.8 | 4.9 | 3.1 | 0.4 | 4.0 | 5.8 | b |
| +6 | 48 | 4.5 | 4.4 | 2.6 | 0.4 | 3.6 | 5.2 | c |
| +7 | 50 | 3.9 | 3.9 | 2.5 | 0.3 | 3.2 | 4.6 | c |
| +8 | 47 | 3.6 | 3.6 | 2.3 | 0.3 | 2.9 | 4.3 | c |
| +9 | 48 | 3.8 | 3.7 | 2.7 | 0.4 | 2.9 | 4.5 | c |
| +10 | 44 | 3.8 | 3.8 | 3.1 | 0.5 | 2.8 | 4.8 | b |
| +11 | 47 | 3.3 | 3.3 | 2.6 | 0.4 | 2.5 | 4.1 | |
| +12 | 43 | 3.6 | 3.5 | 2.6 | 0.4 | 2.7 | 4.3 | |
| +13 | 37 | 3.7 | 3.7 | 2.3 | 0.4 | 2.9 | 4.5 | |
| +14 | 33 | 4.0 | 4.1 | 2.6 | 0.7 | 2.7 | 5.5 | |

Significance (Wilcoxon Rank Sum Test) in comparison with controls

a = $p < 0.05$
b = $p < 0.02$
c = $p < 0.01$

FIGURE 5.2.4

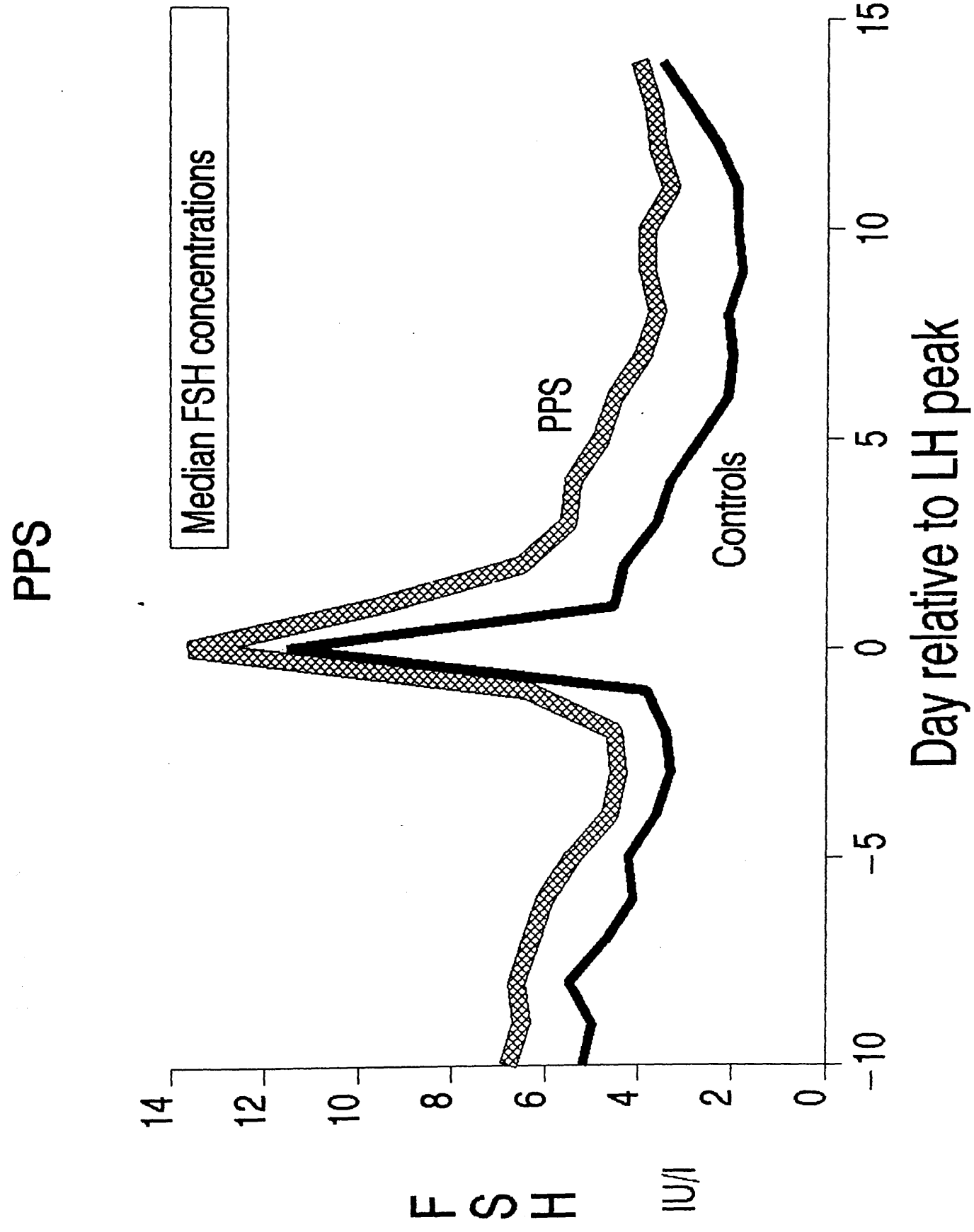

PPS
Median FSH concentrations
PPS
Controls
FSH IU/l
14
12
10
8
6
4
2
0
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.2.6

Poor Progesterone Surge

Follicular Diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -5 | 10 | 11.5 | 11.5 | 2.5 | 0.8 | 9.7 | 13.3 | |
| -4 | 20 | 12.8 | 12.8 | 2.1 | 0.5 | 11.8 | 13.8 | |
| -3 | 19 | 14.5 | 14.5 | 3.1 | 0.7 | 13.0 | 16.0 | |
| -2 | 22 | 16.0 | 16.1 | 3.2 | 0.7 | 14.7 | 17.5 | |
| -1 | 28 | 18.0 | 17.8 | 2.5 | 0.5 | 16.8 | 18.8 | a |
| 0 | 30 | 19.0 | 18.7 | 3.0 | 0.5 | 17.6 | 19.8 | |
| +1 | 21 | 21.0 | 21.5 | 9.2 | 2.0 | 17.2 | 25.6 | |
| +2 | 22 | 22.0 | 21.9 | 8.9 | 1.9 | 18.0 | 25.8 | |
| +3 | 16 | 26.5 | 27.3 | 9.4 | 2.4 | 22.3 | 32.3 | |
| +4 | 22 | 24.0 | 20.6 | 8.1 | 1.7 | 18.0 | 24.2 | |
| +5 | 9 | 28.0 | 28.4 | 7.2 | 2.4 | 22.9 | 33.9 | |
| +6 | 16 | 27.0 | 25.9 | 12.2 | 3.1 | 19.4 | 32.4 | |
| +7 | 11 | 30.0 | 30.6 | 9.1 | 2.7 | 24.5 | 36.7 | |
| +8 | 9 | 34.0 | 33.8 | 13.2 | 4.4 | 23.7 | 43.9 | |

Significance (Wilcoxon Rank Sum Test) in comparison with controls

a = 0.01

FIGURE 5.2.5

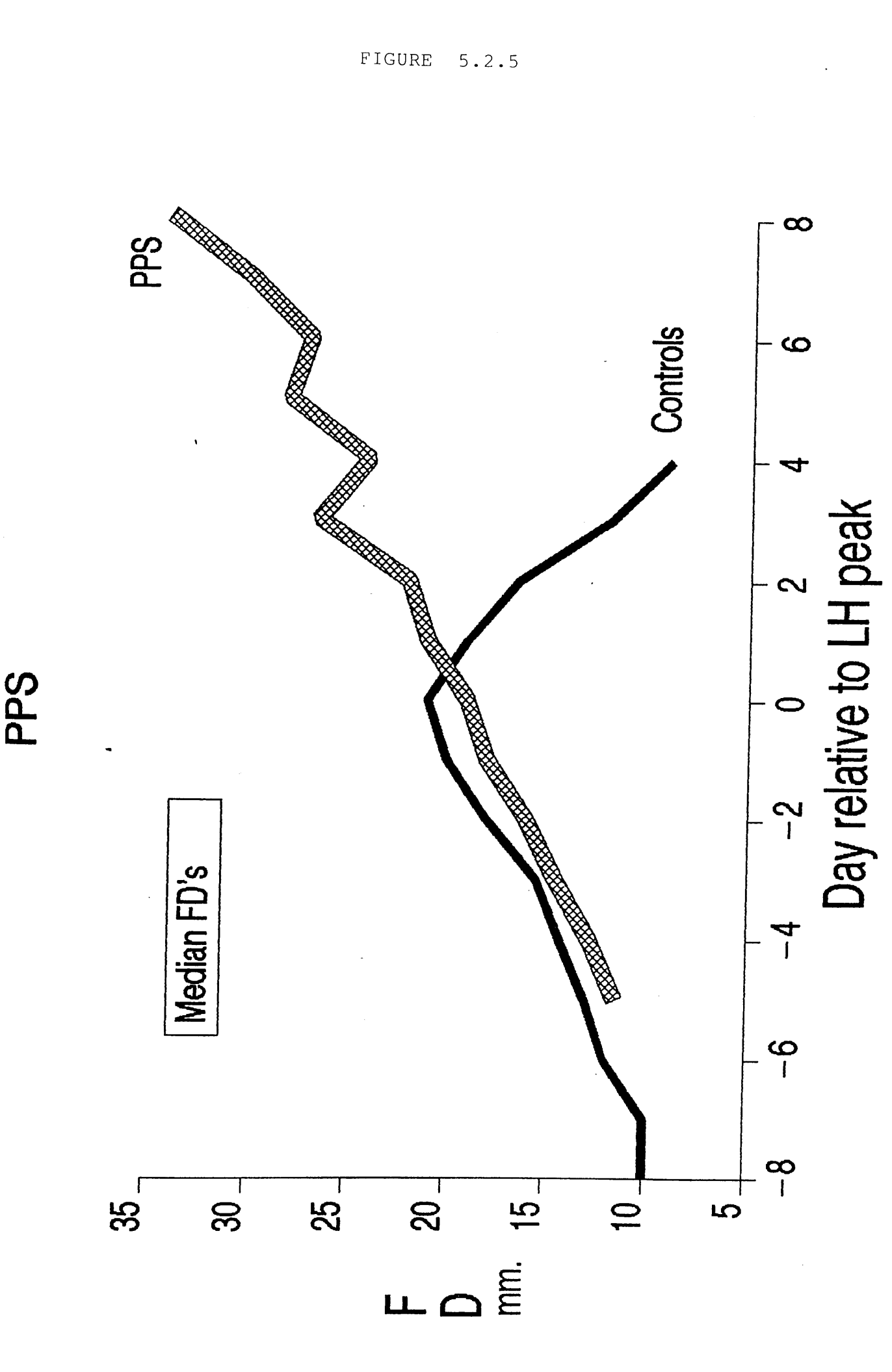

PPS
PPS
Median FD's
Controls
F D mm.
35
30
25
20
15
10
5
-8
-6
-4
-2
0
2
4
6
8
Day relative to LH peak

Table 5.3.1

High LH

Patient/cycle characteristics

| | Nos | Mean | SD | SEM | Median | Range | |
|---|---|---|---|---|---|---|---|
| AGE (Years) | | | | | | | |
| | 20 | 28.6 | 4.7 | 1.0 | 28 | 22-37 | |
| FOLLICULAR PHASE (Days) | | | | | | | |
| | 20 | 17.7 | 5.3 | 1.2 | 15.5 | 12-30 | a |
| LUTEAL PHASE (Days) | | | | | | | |
| | 20 | 15.2 | 1.8 | 0.4 | 15.5 | 9-17 | |
| CYCLE LENGTH (Days) | | | | | | | |
| | 20 | 32.8 | 5.7 | 1.3 | 31 | 26-44 | a |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.01$

Table 5.3.2

High LH

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 15 | 85.0 | 78.3 | 16.9 | 4.4 | 68.9 | 87.7 | |
| -9 | 16 | 80.0 | 78.4 | 17.3 | 4.3 | 69.2 | 87.6 | |
| -8 | 18 | 80.0 | 79.2 | 12.3 | 2.9 | 73.1 | 85.3 | |
| -7 | 17 | 82.5 | 83.2 | 16.4 | 4.0 | 74.8 | 91.6 | |
| -6 | 17 | 95.0 | 91.4 | 18.0 | 4.4 | 82.1 | 100.7 | |
| -5 | 18 | 97.5 | 99.9 | 19.1 | 4.5 | 90.4 | 109.4 | |
| -4 | 19 | 102.5 | 111.5 | 36.7 | 8.4 | 93.8 | 129.2 | a |
| -3 | 18 | 129.0 | 130.1 | 36.3 | 8.6 | 112.0 | 148.2 | c |
| -2 | 19 | 155.0 | 159.5 | 57.6 | 13.2 | 131.7 | 187.3 | b |
| -1 | 19 | 210.0 | 192.4 | 53.1 | 12.2 | 166.8 | 218.0 | a |
| 0 | 20 | 192.5 | 183.2 | 38.6 | 8.6 | 165.1 | 201.3 | |
| +1 | 19 | 125.0 | 129.5 | 42.3 | 9.7 | 109.1 | 149.9 | |
| +2 | 20 | 103.0 | 113.5 | 30.2 | 6.8 | 99.4 | 127.6 | |
| +3 | 20 | 130.0 | 125.4 | 27.1 | 6.1 | 112.7 | 138.1 | |
| +4 | 20 | 135.0 | 137.8 | 41.5 | 9.3 | 118.4 | 157.2 | |
| +5 | 20 | 135.0 | 134.6 | 35.3 | 7.9 | 118.1 | 151.1 | |
| +6 | 20 | 150.0 | 143.0 | 39.2 | 8.8 | 124.7 | 161.3 | |
| +7 | 19 | 150.0 | 153.0 | 46.5 | 10.7 | 130.6 | 175.4 | |
| +8 | 17 | 152.5 | 160.2 | 42.3 | 10.3 | 138.5 | 181.9 | |
| +9 | 17 | 160.0 | 168.8 | 72.2 | 17.5 | 131.7 | 205.9 | |
| +10 | 16 | 167.5 | 165.1 | 51.4 | 12.9 | 152.3 | 178.0 | |
| +11 | 16 | 152.5 | 157.1 | 45.6 | 11.4 | 132.8 | 181.4 | |
| +12 | 16 | 130.0 | 137.5 | 47.7 | 11.9 | 112.1 | 162.9 | |
| +13 | 15 | 130.0 | 121.0 | 42.1 | 10.9 | 97.7 | 144.3 | |
| +14 | 13 | 95.0 | 102.5 | 34.9 | 9.7 | 81.4 | 123.6 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.05$
b = $p < 0.02$
c = $p < 0.01$

FIGURE 5.3.1

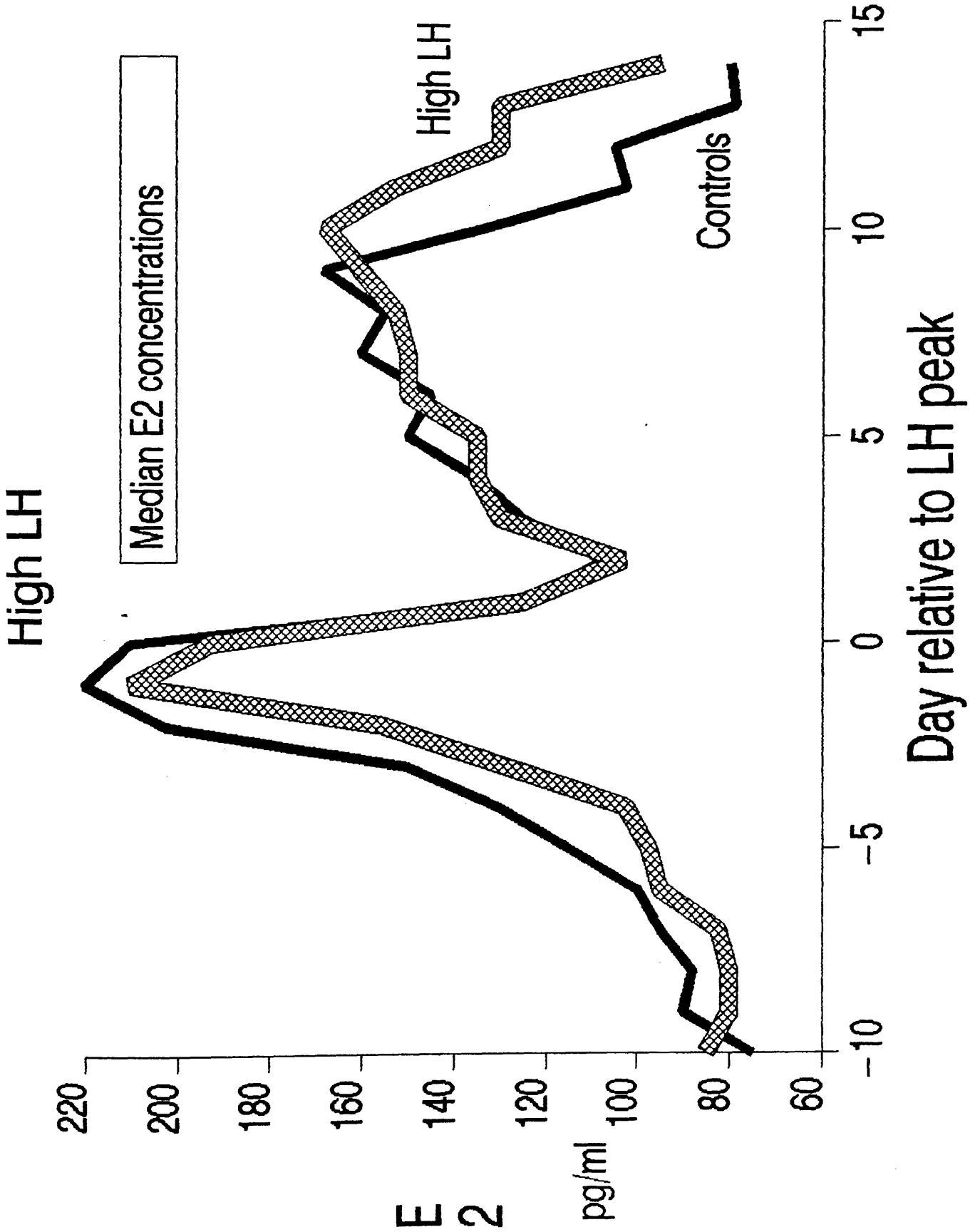

High LH
Median E2 concentrations
High LH
Controls
E 2
pg/ml
220
200
180
160
140
120
100
80
60
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.3.3

High LH

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| 0 | 16 | 0.9 | 1.2 | 0.8 | 0.2 | 0.8 | 1.6 | |
| +1 | 20 | 1.4 | 1.9 | 1.6 | 0.4 | 1.2 | 2.6 | |
| +2 | 19 | 3.3 | 4.0 | 3.7 | 0.8 | 2.2 | 5.8 | |
| +3 | 20 | 6.0 | 6.8 | 5.0 | 1.1 | 4.5 | 9.1 | |
| +4 | 20 | 8.6 | 9.3 | 5.0 | 1.1 | 7.0 | 11.6 | a |
| +5 | 20 | 13.1 | 14.2 | 6.6 | 1.5 | 11.1 | 17.3 | |
| +6 | 20 | 17.8 | 16.9 | 6.4 | 1.4 | 13.9 | 19.9 | |
| +7 | 19 | 16.4 | 16.9 | 7.0 | 1.6 | 13.5 | 20.3 | |
| +8 | 17 | 17.3 | 17.3 | 5.8 | 1.4 | 14.3 | 20.3 | |
| +9 | 17 | 19.0 | 18.0 | 6.4 | 1.6 | 14.7 | 21.3 | |
| +10 | 15 | 17.6 | 18.7 | 4.9 | 1.3 | 16.0 | 21.4 | a |
| +11 | 16 | 15.8 | 15.3 | 6.4 | 1.6 | 11.9 | 18.7 | b |
| +12 | 16 | 10.4 | 11.2 | 5.6 | 1.4 | 8.2 | 14.2 | b |
| +13 | 15 | 5.4 | 7.0 | 5.2 | 1.3 | 4.1 | 9.9 | a |
| +14 | 13 | 3.1 | 3.9 | 3.7 | 1.0 | 1.7 | 6.1 | |
| P index | 20 | 71.5 | 80.4 | 36.3 | 8.1 | 63.4 | 97.4 | a |

Significance (Wilcoxon Rank Sum Test) in comparison with controls

a = $p < 0.01$
b = $p < 0.001$

FIGURE 5.3.2

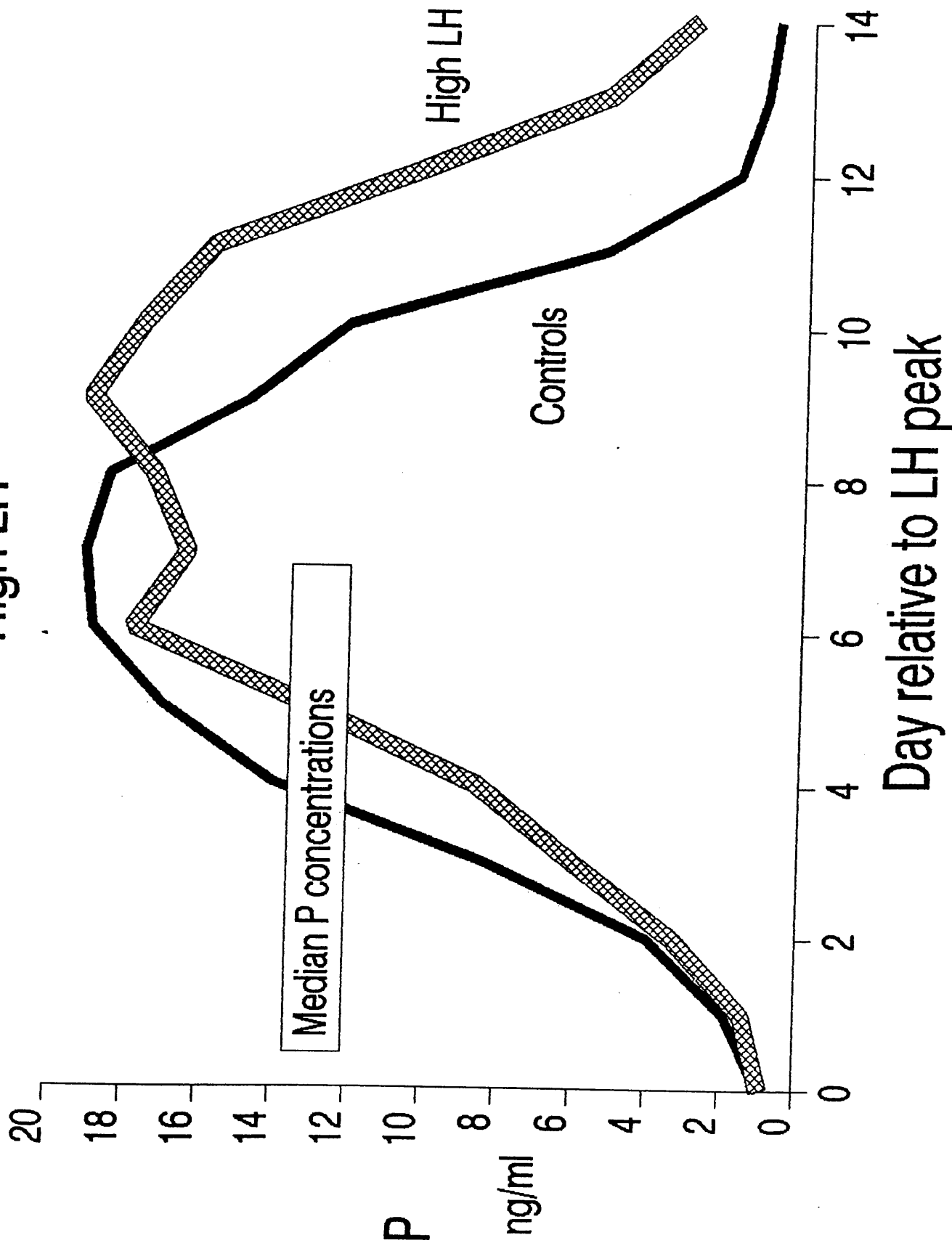

High LH
High LH
Controls
Median P concentrations
P
ng/ml
20
18
16
14
12
10
8
6
4
2
0
0
2
4
6
8
10
12
14
Day relative to LH peak

Table 5.3.4

High LH

Plasma LH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 15 | 14.0 | 14.2 | 6.4 | 1.7 | 10.7 | 17.7 | b |
| -9 | 16 | 16.0 | 16.2 | 6.9 | 1.7 | 12.5 | 19.9 | b |
| -8 | 18 | 17.0 | 19.4 | 7.4 | 1.7 | 15.7 | 23.1 | b |
| -7 | 17 | 18.0 | 20.4 | 11.3 | 2.7 | 14.6 | 26.2 | b |
| -6 | 17 | 17.0 | 18.9 | 8.2 | 2.0 | 14.7 | 23.1 | b |
| -5 | 18 | 17.0 | 17.6 | 6.4 | 1.5 | 14.4 | 20.8 | b |
| -4 | 18 | 17.2 | 16.9 | 7.3 | 1.8 | 13.2 | 20.6 | b |
| -3 | 17 | 17.0 | 19.5 | 10.4 | 2.5 | 14.2 | 24.8 | b |
| -2 | 18 | 19.0 | 19.4 | 7.3 | 1.7 | 15.8 | 23.0 | b |
| -1 | 18 | 35.0 | 36.8 | 16.1 | 3.8 | 28.8 | 44.8 | b |
| 0 | 19 | 75.0 | 64.6 | 17.8 | 4.1 | 56.0 | 73.2 | |
| +1 | 19 | 32.5 | 36.0 | 18.7 | 4.3 | 27.0 | 45.0 | |
| +2 | 19 | 21.0 | 22.3 | 13.4 | 3.1 | 15.8 | 28.8 | b |
| +3 | 20 | 21.5 | 21.0 | 10.3 | 2.3 | 16.2 | 25.8 | b |
| +4 | 20 | 24.0 | 24.2 | 15.5 | 3.5 | 16.9 | 31.5 | b |
| +5 | 20 | 20.5 | 20.7 | 10.8 | 2.4 | 15.6 | 25.8 | b |
| +6 | 19 | 15.0 | 18.0 | 10.9 | 2.5 | 12.7 | 23.3 | b |
| +7 | 19 | 14.9 | 15.5 | 6.8 | 1.6 | 12.2 | 18.8 | b |
| +8 | 15 | 15.0 | 15.4 | 7.3 | 1.9 | 11.4 | 19.4 | b |
| +9 | 16 | 14.0 | 13.9 | 7.1 | 1.8 | 10.1 | 17.7 | b |
| +10 | 15 | 8.3 | 11.1 | 7.1 | 1.8 | 7.2 | 15.0 | a |
| +11 | 15 | 8.4 | 11.6 | 6.8 | 1.8 | 7.8 | 15.4 | b |
| +12 | 14 | 8.1 | 10.3 | 7.3 | 2.0 | 6.1 | 14.5 | |
| +13 | 14 | 8.1 | 9.4 | 5.8 | 1.6 | 6.1 | 12.7 | |
| +14 | 11 | 12.0 | 11.7 | 6.4 | 1.9 | 7.4 | 16.0 | |

Significance (Wilcoxon Rank Sum Test) in comparison with controls

a = $p < 0.01$
b = $p < 0.001$

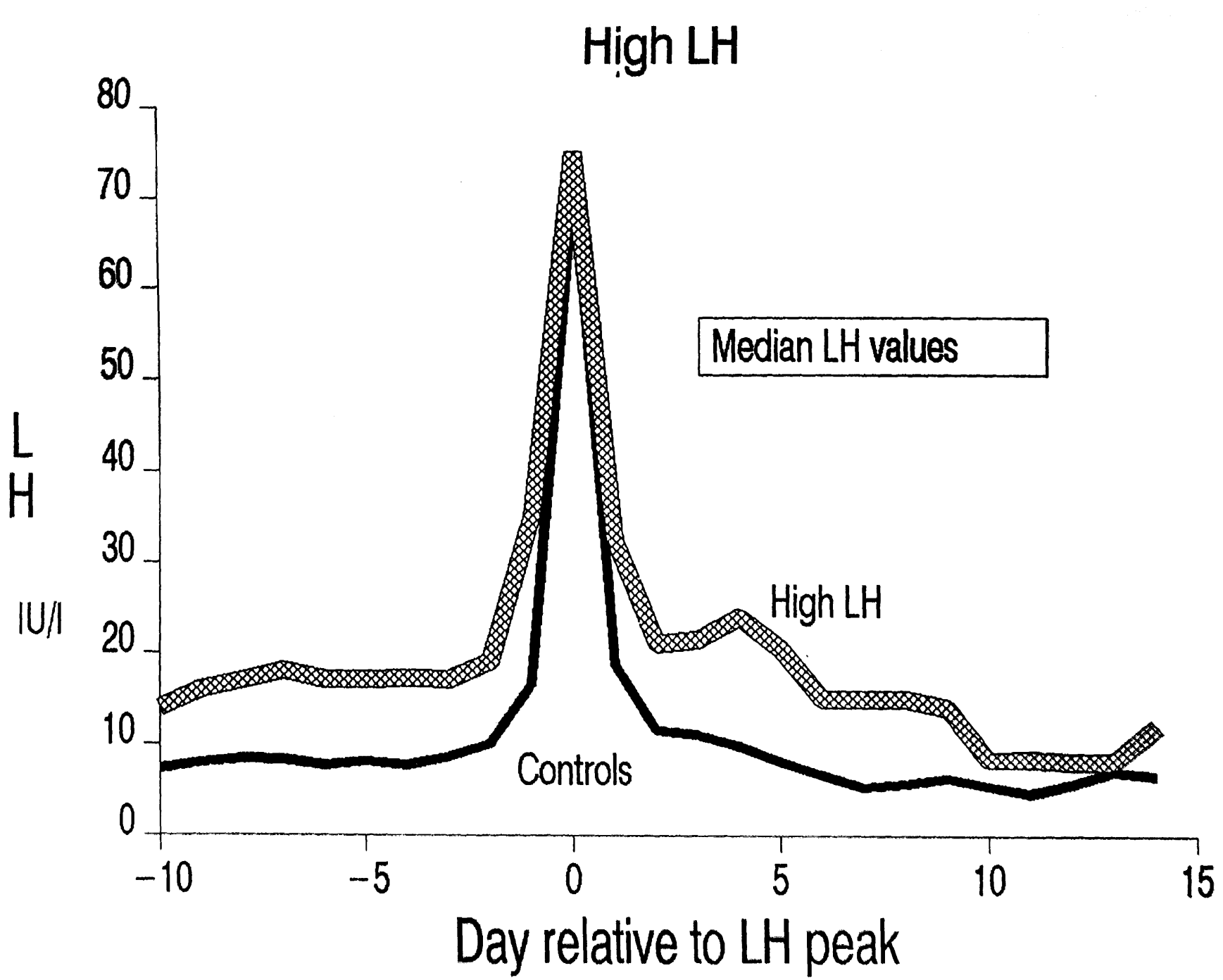

High LH
80
70
60
50
40
30
20
10
0
L
H
IU/l
Median LH values
High LH
Controls
−10
−5
0
5
10
15
Day relative to LH peak

FIGURE 5.3.3

Table 5.3.5

High LH

Plasma FSH concentrations (IU/1)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 15 | 6.0 | 6.6 | 2.3 | 0.6 | 5.3 | 7.9 | |
| -9 | 16 | 6.8 | 7.1 | 2.9 | 0.7 | 5.6 | 8.6 | |
| -8 | 18 | 6.4 | 7.0 | 3.5 | 0.8 | 5.3 | 8.7 | |
| -7 | 17 | 5.4 | 6.4 | 2.7 | 0.7 | 5.0 | 7.8 | |
| -6 | 17 | 5.5 | 6.0 | 2.0 | 0.5 | 5.0 | 7.0 | |
| -5 | 18 | 5.3 | 5.5 | 2.0 | 0.5 | 4.5 | 6.5 | |
| -4 | 19 | 4.5 | 4.8 | 1.6 | 0.4 | 4.0 | 5.6 | |
| -3 | 18 | 3.8 | 4.3 | 1.6 | 0.4 | 3.5 | 5.1 | |
| -2 | 19 | 3.6 | 4.2 | 1.8 | 0.4 | 3.3 | 5.1 | |
| -1 | 19 | 5.5 | 5.5 | 2.4 | 0.6 | 4.3 | 6.7 | |
| 0 | 20 | 9.9 | 10.8 | 4.5 | 1.0 | 8.7 | 12.9 | |
| +1 | 20 | 6.1 | 7.0 | 3.9 | 0.9 | 5.2 | 8.8 | |
| +2 | 18 | 4.1 | 4.7 | 2.2 | 0.5 | 3.6 | 5.8 | |
| +3 | 20 | 4.0 | 4.3 | 2.0 | 0.4 | 3.4 | 5.2 | |
| +4 | 20 | 4.0 | 4.2 | 1.8 | 0.4 | 3.4 | 5.0 | |
| +5 | 20 | 3.6 | 3.9 | 1.9 | 0.4 | 3.0 | 4.8 | |
| +6 | 19 | 3.1 | 3.9 | 2.2 | 0.5 | 2.8 | 5.0 | |
| +7 | 19 | 2.7 | 3.4 | 2.0 | 0.5 | 2.4 | 4.4 | |
| +8 | 17 | 2.6 | 3.2 | 1.8 | 0.4 | 2.3 | 4.1 | |
| +9 | 15 | 2.9 | 3.0 | 1.7 | 0.4 | 2.1 | 3.9 | a |
| +10 | 15 | 2.6 | 3.3 | 2.6 | 0.7 | 1.9 | 4.7 | |
| +11 | 16 | 2.7 | 2.9 | 1.8 | 0.5 | 1.9 | 3.9 | |
| +12 | 16 | 2.5 | 3.4 | 3.2 | 1.7 | 1.7 | 5.1 | |
| +13 | 15 | 2.8 | 2.9 | 1.6 | 0.4 | 2.0 | 3.8 | |
| +14 | 11 | 3.1 | 3.2 | 1.3 | 0.4 | 2.3 | 4.1 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.05$

FIGURE 5.3.4

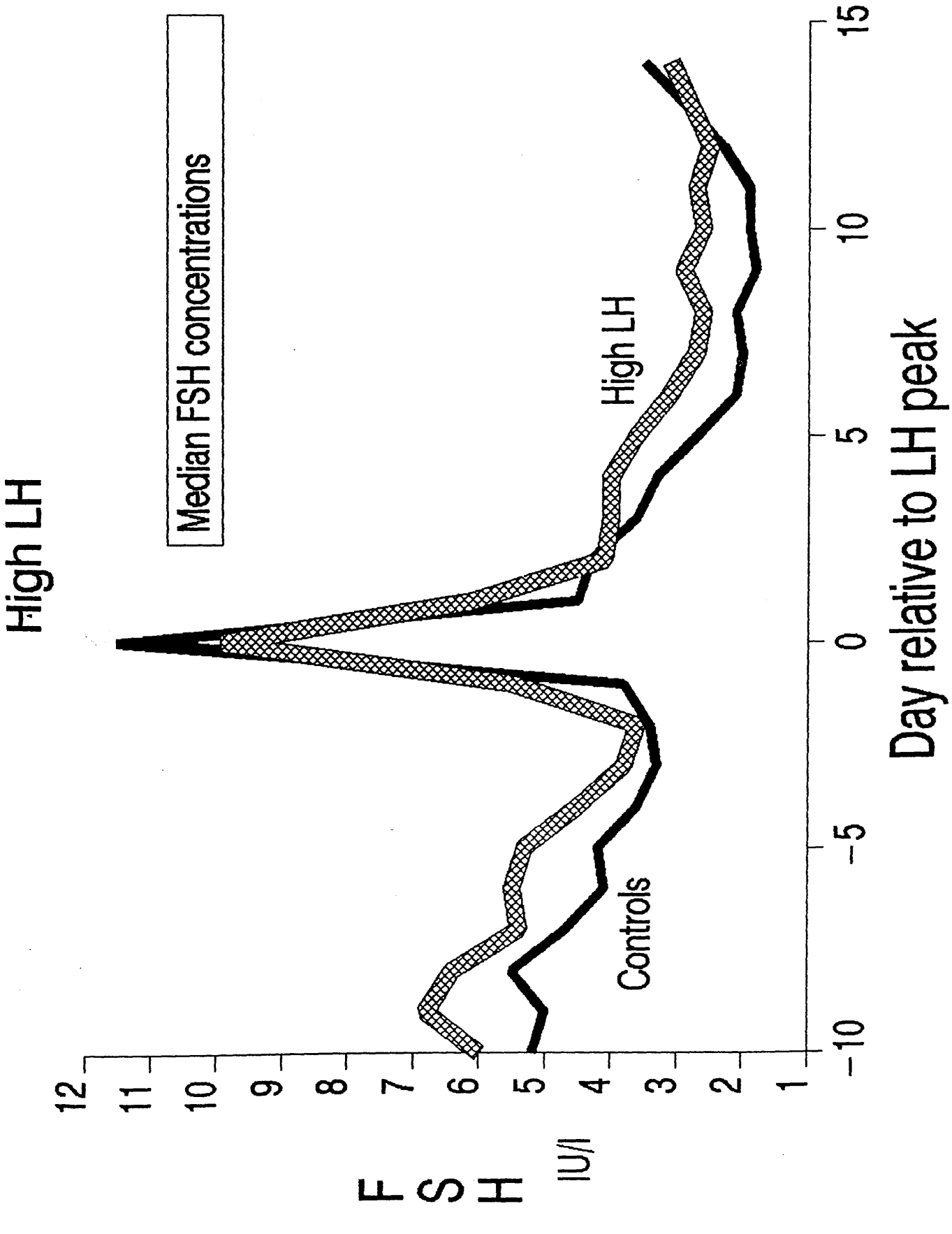

High LH
Median FSH concentrations
High LH
Controls
FSH IU/l
12
11
10
9
8
7
6
5
4
3
2
1
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.3.6

High LH

Follicular Diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -5 | 3 | 16.0 | 15.7 | 3.0 | 1.7 | 7.2 | 23.2 | |
| -4 | 6 | 15.5 | 15.6 | 2.9 | 1.2 | 12.6 | 18.6 | |
| -3 | 7 | 15.0 | 15.2 | 4.1 | 1.5 | 11.4 | 19.0 | |
| -2 | 8 | 16.0 | 15.0 | 3.7 | 1.3 | 11.9 | 18.1 | a |
| -1 | 12 | 17.0 | 17.2 | 3.9 | 1.1 | 14.7 | 19.7 | b |
| 0 | 11 | 21.0 | 21.6 | 2.8 | 0.9 | 19.6 | 23.6 | |
| +1 | 10 | 20.0 | 21.0 | 7.4 | 2.3 | 15.7 | 26.3 | |
| +2 | 6 | 19.5 | 20.1 | 5.5 | 2.2 | 14.3 | 25.9 | |
| +3 | 5 | 26.0 | 23.8 | 10.1 | 4.5 | 11.3 | 36.3 | |
| +4 | 8 | 20.0 | 21.6 | 10.0 | 3.5 | 13.2 | 30.0 | |
| +5 | 3 | 21.0 | 23.3 | 4.9 | 2.8 | 11.1 | 35.5 | |
| +6 | 4 | 22.0 | 25.3 | 15.1 | 7.6 | 1.3 | 49.3 | |
| +7 | 3 | 28.0 | 28.3 | 6.5 | 3.8 | 12.2 | 44.4 | |
| +8 | 4 | 33.5 | 36.0 | 13.3 | 6.7 | 14.8 | 57.2 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.05$
b = $p < 0.02$

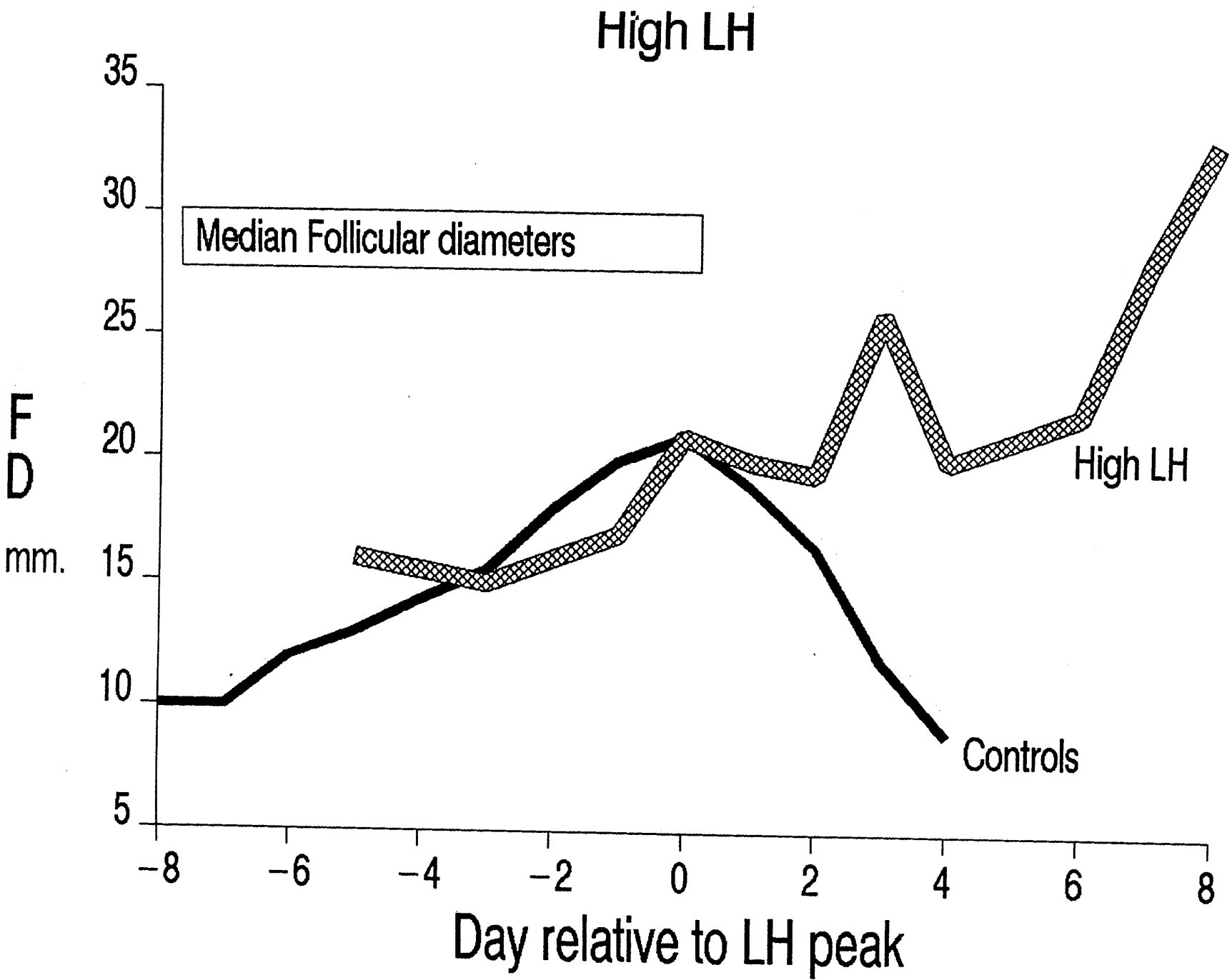

High LH
Median Follicular diameters
F
D
mm.
35
30
25
20
15
10
5
High LH
Controls
−8
−6
−4
−2
0
2
4
6
8
Day relative to LH peak

FIGURE 5.3.5

Table 5.4.1

Poor Follicular Maturation

Patient/cycle characteristics

| | Nos | Mean | SD | SEM | Median | Range | |
|---|---|---|---|---|---|---|---|
| AGE (Years) | | | | | | | |
| | 16 | 29.2 | 2.3 | 0.6 | 29 | 25-32 | b |
| FOLLICULAR PHASE (Days) | | | | | | | |
| | 16 | 17.0 | 3.9 | 1.0 | 15.5 | 10-27 | c |
| LUTEAL PHASE (Days) | | | | | | | |
| | 16 | 15.7 | 1.0 | 0.3 | 16 | 14-17 | a |
| CYCLE LENGTH (Days) | | | | | | | |
| | 16 | 31.2 | 4.5 | 1.1 | 31 | 25-44 | |

Significance (Wilcoxon Rank Sum Test) in comparison with controls

a = $p < 0.05$
b = $p < 0.02$
c = $p < 0.01$

Table 5.4.2

Poor Follicular Development (<17mm Day 0)

Patient/cycle characteristics

| | Nos | Mean | SD | SEM | Median | Range | |
|---|---|---|---|---|---|---|---|
| AGE (Years) | | | | | | | |
| | 12 | 32.5 | 4.7 | 1.4 | 31.5 | 26-41 | a |
| FOLLICULAR PHASE (Days) | | | | | | | |
| | 12 | 13.2 | 2.9 | 0.8 | 13 | 8-19 | |
| LUTEAL PHASE (Days) | | | | | | | |
| | 12 | 15.4 | 1.4 | 0.4 | 16 | 13-17 | |
| CYCLE LENGTH (Days) | | | | | | | |
| | 12 | 29.4 | 3.1 | 0.9 | 29.5 | 25-36 | |

Significance (Wilcoxon Rank Sum Test) in comparison with controls

a = $p < 0.001$

Table 5.4.3

Poor Follicular Maturation

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 14 | 60.0 | 63.2 | 15.4 | 4.1 | 54.3 | 72.1 | b |
| -9 | 15 | 65.0 | 63.2 | 14.1 | 3.6 | 55.4 | 71.0 | d |
| -8 | 15 | 65.0 | 62.9 | 12.3 | 3.2 | 56.1 | 69.7 | d |
| -7 | 14 | 65.0 | 69.6 | 11.5 | 3.1 | 63.0 | 76.2 | d |
| -6 | 15 | 70.0 | 75.9 | 13.7 | 3.5 | 68.3 | 83.5 | d |
| -5 | 14 | 82.5 | 82.5 | 13.0 | 3.5 | 75.0 | 90.0 | d |
| -4 | 15 | 80.0 | 82.1 | 13.7 | 3.5 | 74.5 | 89.7 | d |
| -3 | 16 | 105.0 | 101.4 | 14.2 | 3.6 | 93.9 | 108.9 | d |
| -2 | 16 | 127.5 | 121.6 | 23.3 | 5.8 | 109.2 | 134.0 | d |
| -1 | 16 | 147.5 | 147.4 | 26.0 | 6.5 | 133.6 | 161.2 | d |
| 0 | 16 | 165.0 | 158.8 | 30.7 | 7.7 | 142.5 | 175.1 | c |
| +1 | 15 | 115.0 | 120.5 | 31.3 | 8.1 | 103.2 | 137.8 | |
| +2 | 16 | 76.5 | 84.6 | 26.9 | 6.7 | 70.3 | 98.9 | c |
| +3 | 16 | 95.0 | 99.9 | 34.6 | 8.7 | 81.5 | 118.3 | a |
| +4 | 16 | 110.0 | 107.2 | 33.3 | 8.3 | 89.5 | 124.9 | b |
| +5 | 16 | 107.5 | 111.9 | 35.7 | 8.9 | 93.0 | 131.0 | c |
| +6 | 16 | 112.5 | 115.8 | 29.4 | 7.4 | 100.1 | 131.5 | c |
| +7 | 15 | 125.0 | 124.2 | 25.6 | 6.6 | 110.0 | 138.4 | c |
| +8 | 14 | 120.0 | 123.4 | 34.1 | 9.1 | 103.7 | 143.1 | c |
| +9 | 13 | 125.0 | 131.9 | 32.9 | 9.1 | 112.0 | 151.8 | a |
| +10 | 13 | 125.0 | 134.1 | 36.9 | 10.2 | 111.8 | 156.4 | |
| +11 | 13 | 140.0 | 142.7 | 30.5 | 8.5 | 124.3 | 161.1 | |
| +12 | 13 | 110.0 | 121.4 | 50.9 | 14.1 | 90.6 | 152.2 | |
| +13 | 12 | 92.5 | 106.9 | 50.9 | 14.7 | 74.6 | 139.2 | |
| +14 | 12 | 80.0 | 87.5 | 37.0 | 10.7 | 64.0 | 111.0 | |

Significance (Wilcoxon Rank Sum Test) in comparison with controls

a = $p < 0.05$
b = $p < 0.02$
c = $p < 0.01$
d = $p < 0.001$

FIGURE 5.4.1

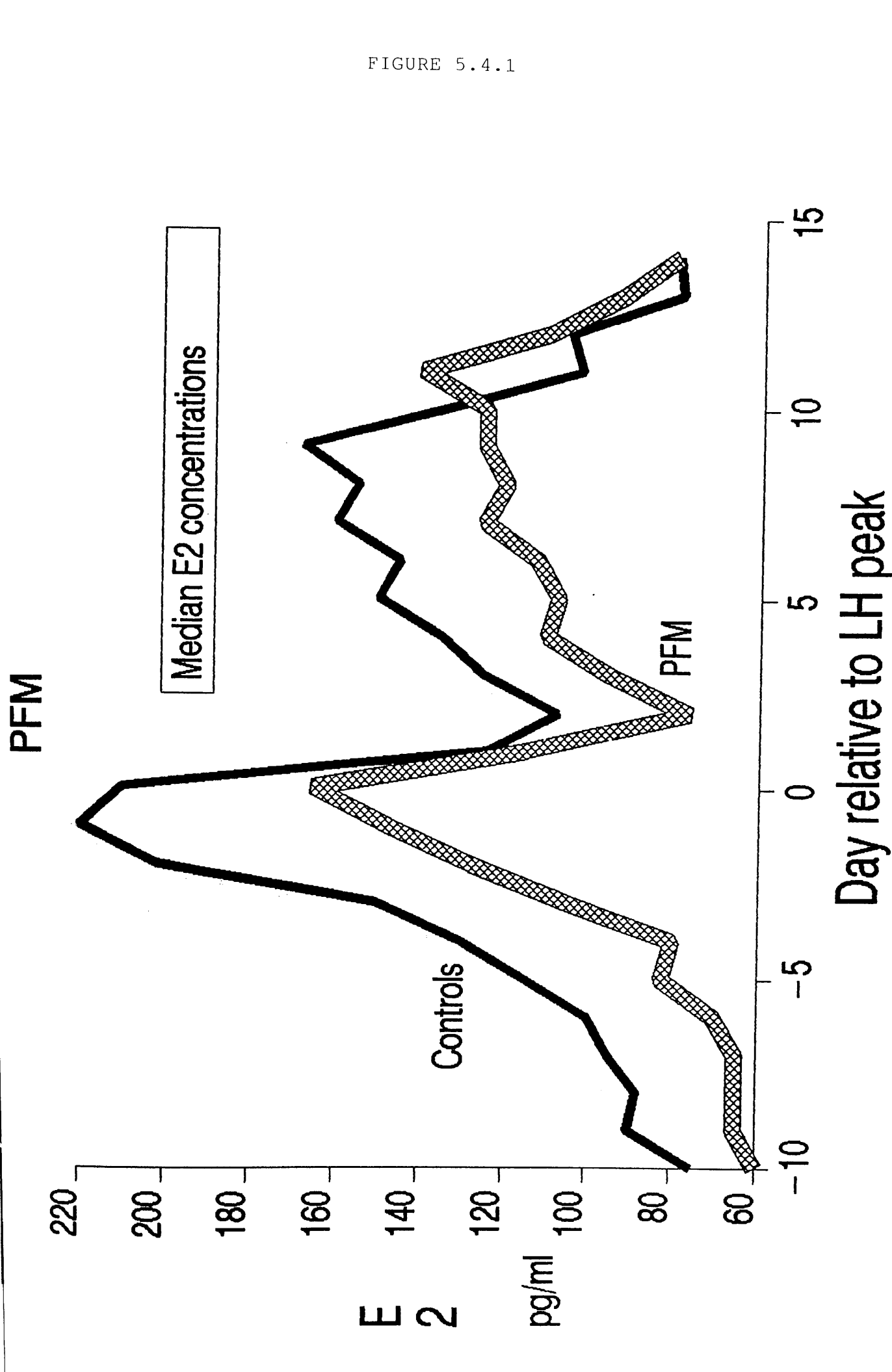

PFM
Median E2 concentrations
Controls
PFM
E 2
pg/ml
220
200
180
160
140
120
100
80
60
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.4.4

Poor Follicular Development (<17mm Day 0)

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 9 | 70.0 | 72.2 | 13.5 | 10.4 | 48.3 | 96.1 | |
| -9 | 9 | 70.0 | 73.1 | 26.1 | 8.7 | 53.0 | 93.2 | |
| -8 | 9 | 75.0 | 74.8 | 14.0 | 4.7 | 64.0 | 85.6 | |
| -7 | 11 | 85.0 | 84.2 | 18.5 | 5.6 | 71.8 | 96.6 | |
| -6 | 11 | 80.0 | 83.3 | 17.6 | 5.3 | 71.5 | 95.1 | a |
| -5 | 11 | 95.0 | 98.7 | 22.1 | 6.7 | 83.9 | 113.5 | |
| -4 | 11 | 110.0 | 124.1 | 48.5 | 14.6 | 91.5 | 156.7 | |
| -3 | 12 | 137.5 | 151.4 | 55.8 | 16.1 | 115.9 | 186.9 | |
| -2 | 12 | 166.5 | 177.4 | 57.4 | 16.6 | 140.9 | 213.9 | |
| -1 | 11 | 200.0 | 221.3 | 59.0 | 17.8 | 181.7 | 260.9 | |
| 0 | 12 | 195.0 | 184.9 | 35.4 | 10.2 | 162.4 | 207.4 | |
| +1 | 12 | 107.5 | 108.2 | 34.2 | 9.9 | 86.5 | 129.9 | |
| +2 | 12 | 91.5 | 87.6 | 18.9 | 5.5 | 75.6 | 99.6 | a |
| +3 | 12 | 102.5 | 103.9 | 15.2 | 4.4 | 94.2 | 113.6 | |
| +4 | 12 | 120.0 | 124.3 | 26.4 | 7.6 | 107.5 | 141.1 | |
| +5 | 11 | 110.0 | 116.9 | 17.9 | 5.4 | 104.9 | 128.9 | b |
| +6 | 11 | 115.0 | 117.1 | 27.6 | 8.3 | 98.6 | 135.6 | c |
| +7 | 12 | 122.5 | 121.3 | 29.8 | 8.6 | 102.3 | 140.2 | c |
| +8 | 12 | 122.5 | 118.7 | 37.7 | 10.9 | 94.7 | 142.7 | c |
| +9 | 12 | 137.5 | 128.8 | 37.0 | 10.7 | 105.3 | 152.3 | a |
| +10 | 12 | 130.0 | 131.8 | 37.4 | 10.8 | 108.0 | 155.6 | |
| +11 | 12 | 134.0 | 125.5 | 39.8 | 11.5 | 100.2 | 150.8 | |
| +12 | 11 | 110.0 | 120.4 | 58.4 | 17.6 | 81.2 | 159.6 | |
| +13 | 11 | 95.0 | 116.7 | 52.5 | 15.8 | 81.4 | 152.0 | |
| +14 | 10 | 85.0 | 84.9 | 33.3 | 10.5 | 61.1 | 108.7 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.05$
b = $p < 0.02$
c = $p < 0.01$

FIGURE 5.4.2

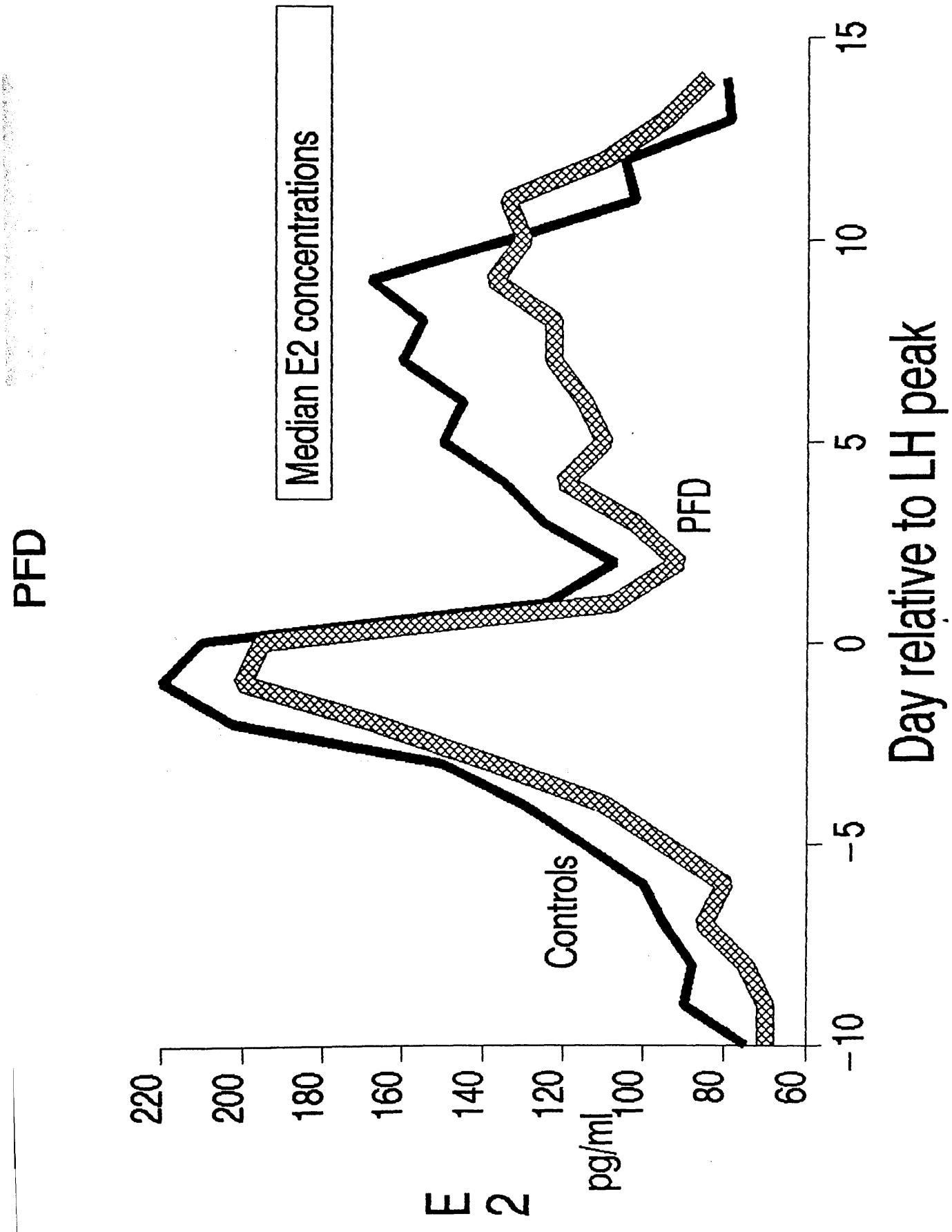

PFD
Median E2 concentrations
Controls
PFD
E 2
pg/ml
220
200
180
160
140
120
100
80
60
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.4.5

Poor Follicular Maturation

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| 0 | 10 | 0.8 | 0.9 | 0.6 | 0.2 | 0.5 | 1.4 | |
| +1 | 15 | 1.0 | 1.2 | 0.8 | 0.2 | 0.8 | 1.6 | b |
| +2 | 15 | 2.3 | 2.5 | 0.9 | 0.2 | 2.0 | 3.0 | c |
| +3 | 16 | 4.6 | 5.2 | 2.0 | 0.5 | 4.1 | 6.3 | b |
| +4 | 16 | 7.2 | 8.1 | 3.2 | 0.8 | 6.4 | 9.8 | c |
| +5 | 16 | 12.5 | 13.0 | 6.1 | 1.5 | 9.8 | 16.2 | a |
| +6 | 16 | 16.5 | 16.1 | 6.4 | 1.6 | 12.7 | 19.5 | |
| +7 | 15 | 17.2 | 17.8 | 7.3 | 1.9 | 13.8 | 21.8 | |
| +8 | 14 | 17.0 | 17.7 | 6.6 | 1.8 | 13.9 | 21.5 | |
| +9 | 13 | 16.4 | 15.6 | 4.0 | 1.1 | 13.2 | 18.0 | |
| +10 | 12 | 18.2 | 17.7 | 5.3 | 1.5 | 14.4 | 21.0 | a |
| +11 | 13 | 16.0 | 17.1 | 7.2 | 2.0 | 12.7 | 21.5 | c |
| +12 | 13 | 12.2 | 12.4 | 6.7 | 1.9 | 8.4 | 16.4 | c |
| +13 | 12 | 7.0 | 8.7 | 6.8 | 2.0 | 4.4 | 13.0 | b |
| +14 | 12 | 3.5 | 4.2 | 3.4 | 1.0 | 2.0 | 6.4 | |
| P index | 16 | 67.0 | 70.4 | 24.9 | 6.2 | 57.1 | 83.7 | c |

Significance (Wilcoxon rank sum test) in comparison with controls

a = <0.02
b = <0.01
c = <0.001

FIGURE 5.4.3

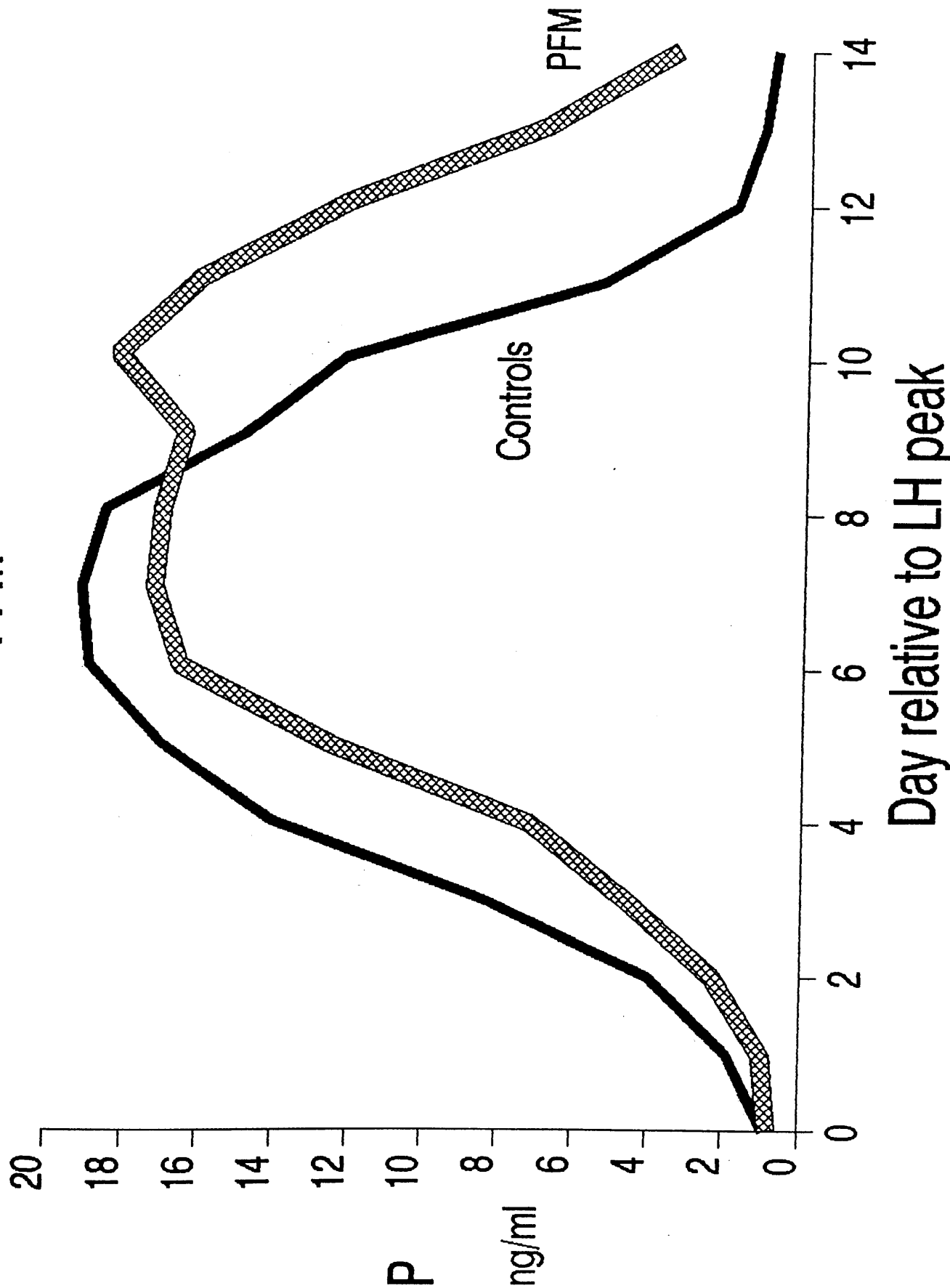

PFM
PFM
Controls
P
ng/ml
20
18
16
14
12
10
8
6
4
2
0
0
2
4
6
8
10
12
14
Day relative to LH peak

Table 5.4.6

Poor Follicular Development (<17mm Day 0)

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| 0 | 10 | 1.0 | 1.1 | 0.7 | 0.2 | 0.6 | 1.6 | |
| +1 | 11 | 1.7 | 2.1 | 2.0 | 0.6 | 0.8 | 3.4 | |
| +2 | 12 | 3.2 | 4.2 | 3.6 | 1.0 | 1.9 | 6.5 | |
| +3 | 12 | 5.7 | 7.1 | 5.2 | 1.5 | 3.8 | 10.4 | |
| +4 | 12 | 10.6 | 11.3 | 6.7 | 1.9 | 7.0 | 15.6 | |
| +5 | 11 | 14.4 | 14.1 | 4.7 | 1.4 | 10.9 | 17.3 | |
| +6 | 11 | 16.4 | 17.1 | 7.0 | 2.1 | 12.4 | 21.8 | |
| +7 | 12 | 20.3 | 18.7 | 7.9 | 2.3 | 13.7 | 23.7 | |
| +8 | 12 | 19.6 | 18.7 | 7.2 | 2.1 | 14.1 | 23.3 | |
| +9 | 11 | 16.4 | 16.2 | 6.4 | 1.9 | 11.9 | 20.5 | |
| +10 | 11 | 16.8 | 17.5 | 7.8 | 2.4 | 12.2 | 22.8 | a |
| +11 | 11 | 12.8 | 14.9 | 7.3 | 2.2 | 10.0 | 19.8 | c |
| +12 | 11 | 9.6 | 11.5 | 7.6 | 2.3 | 6.4 | 16.6 | b |
| +13 | 11 | 6.6 | 7.8 | 6.3 | 1.9 | 3.6 | 12.0 | b |
| +14 | 8 | 4.3 | 4.8 | 2.2 | 1.0 | 2.4 | 7.2 | b |
| P index | 12 | 85.0 | 85.7 | 37.0 | 10.7 | 62.0 | 109.2 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = p <0.05
b = p <0.01
c = p <0.001

FIGURE 5.4.4

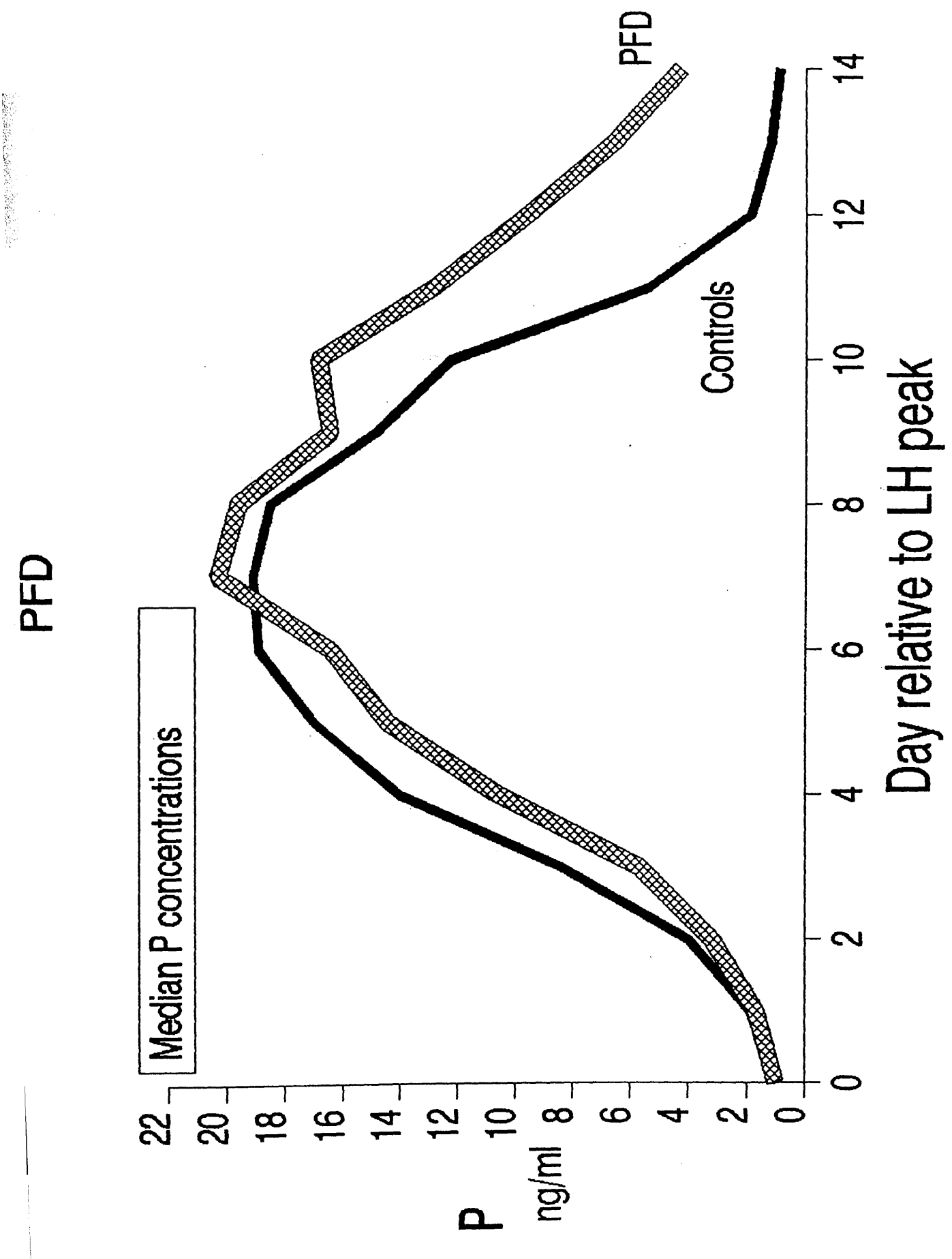

PFD
Median P concentrations
P ng/ml
22
20
18
16
14
12
10
8
6
4
2
0
0
2
4
6
8
10
12
14
Day relative to LH peak
PFD
Controls

Table 5.4.7

Poor Follicular Maturation

Plasma FSH concentrations (IU/1)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 14 | 6.5 | 6.7 | 2.1 | 0.6 | 5.5 | 7.9 | |
| -9 | 15 | 6.1 | 6.3 | 1.9 | 0.5 | 5.2 | 7.4 | |
| -8 | 15 | 6.1 | 6.2 | 2.2 | 0.6 | 5.0 | 7.4 | |
| -7 | 14 | 5.5 | 5.9 | 2.1 | 0.6 | 4.7 | 7.1 | |
| -6 | 15 | 5.2 | 5.6 | 2.0 | 0.5 | 4.5 | 6.7 | |
| -5 | 14 | 4.7 | 5.1 | 2.4 | 0.6 | 3.7 | 6.5 | |
| -4 | 15 | 4.4 | 4.5 | 1.9 | 0.5 | 3.4 | 5.6 | |
| -3 | 16 | 4.3 | 4.4 | 1.8 | 0.5 | 3.4 | 5.4 | |
| -2 | 16 | 3.6 | 4.1 | 1.8 | 0.5 | 3.1 | 5.1 | |
| -1 | 16 | 4.1 | 4.9 | 2.3 | 0.6 | 3.7 | 6.1 | |
| 0 | 16 | 12.0 | 13.0 | 6.8 | 1.7 | 9.4 | 16.6 | |
| +1 | 16 | 8.6 | 9.7 | 5.3 | 1.3 | 6.9 | 12.5 | |
| +2 | 15 | 5.0 | 5.8 | 2.8 | 0.7 | 4.2 | 7.4 | |
| +3 | 16 | 4.8 | 5.1 | 2.2 | 0.6 | 3.9 | 6.3 | |
| +4 | 16 | 4.7 | 4.8 | 1.6 | 0.4 | 3.9 | 5.7 | |
| +5 | 16 | 4.3 | 4.4 | 1.8 | 0.4 | 3.5 | 5.3 | a |
| +6 | 16 | 3.7 | 4.1 | 2.2 | 0.5 | 3.0 | 5.2 | b |
| +7 | 15 | 3.7 | 3.8 | 1.8 | 0.5 | 2.8 | 4.8 | c |
| +8 | 14 | 2.8 | 2.9 | 1.6 | 0.4 | 2.0 | 3.8 | |
| +9 | 13 | 2.9 | 2.9 | 1.6 | 0.5 | 1.9 | 3.9 | a |
| +10 | 13 | 2.6 | 2.8 | 1.4 | 0.4 | 1.9 | 3.7 | |
| +11 | 13 | 2.7 | 2.9 | 1.6 | 0.4 | 2.0 | 3.8 | |
| +12 | 13 | 2.8 | 2.8 | 1.3 | 0.4 | 2.0 | 3.6 | |
| +13 | 12 | 2.8 | 3.2 | 1.7 | 0.5 | 2.1 | 4.3 | |
| +14 | 10 | 3.5 | 3.3 | 1.4 | 0.4 | 2.3 | 4.3 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.05$
b = $p < 0.02$
c = $p < 0.001$

FIGURE 5.4.5

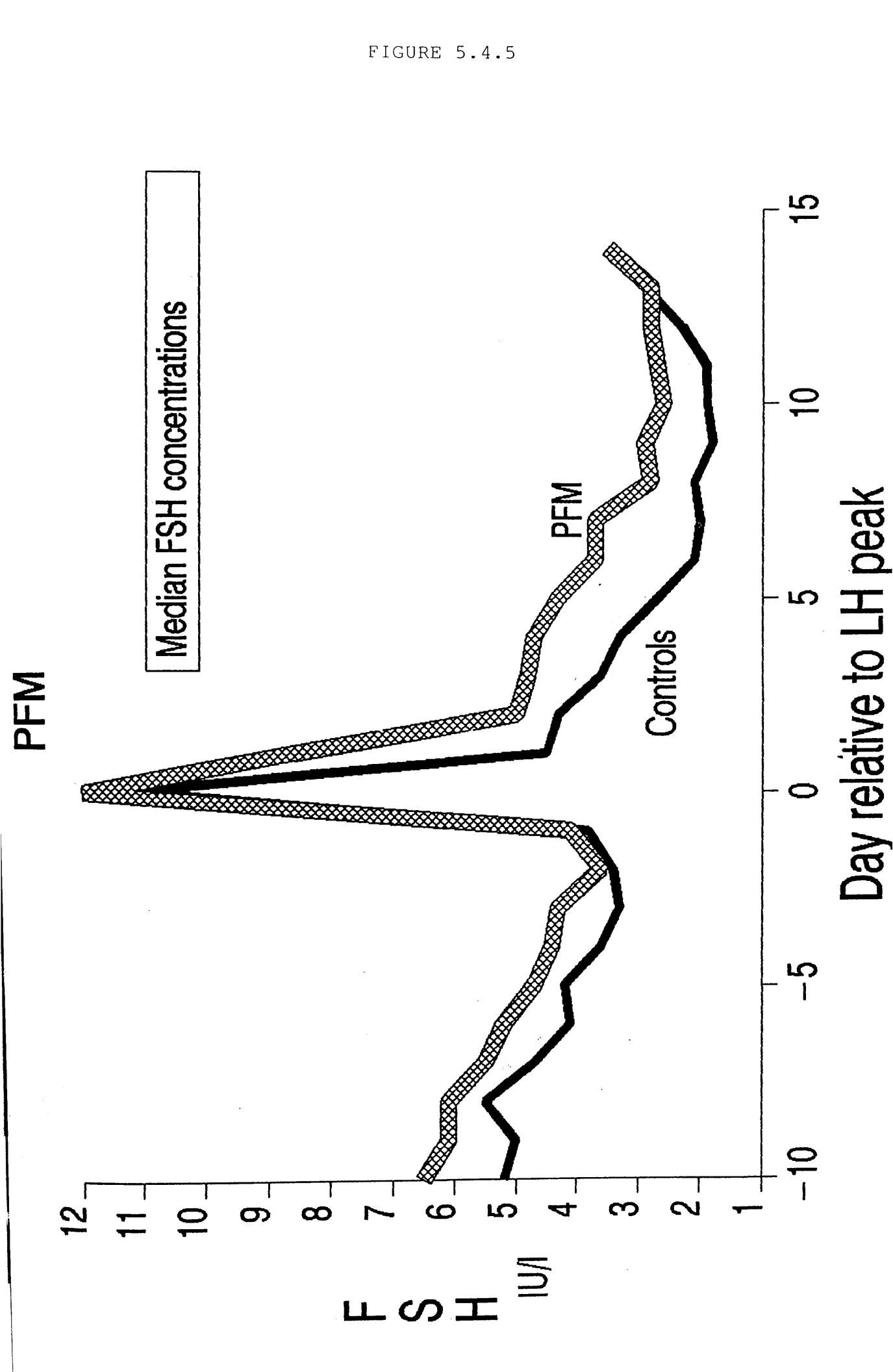

PFM
Median FSH concentrations
PFM
Controls
FSH IU/l
12
11
10
9
8
7
6
5
4
3
2
1
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.4.8

Poor Follicular Development (<17mm Day 0)

Plasma FSH concentrations (IU/1)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 9 | 6.7 | 6.6 | 3.2 | 1.1 | 4.2 | 9.0 | |
| -9 | 9 | 6.4 | 6.5 | 2.1 | 0.7 | 4.9 | 8.1 | |
| -8 | 9 | 6.1 | 6.4 | 2.9 | 0.9 | 4.2 | 8.6 | |
| -7 | 11 | 5.7 | 5.9 | 2.5 | 0.8 | 4.2 | 7.6 | |
| -6 | 11 | 6.5 | 6.4 | 2.4 | 0.7 | 4.8 | 8.0 | a |
| -5 | 11 | 6.9 | 6.6 | 3.5 | 1.1 | 4.2 | 9.0 | a |
| -4 | 11 | 4.7 | 5.9 | 4.4 | 1.3 | 3.0 | 8.8 | |
| -3 | 12 | 4.7 | 5.2 | 2.9 | 0.8 | 3.4 | 7.0 | a |
| -2 | 12 | 4.4 | 4.7 | 2.0 | 0.6 | 3.4 | 6.0 | |
| -1 | 11 | 5.2 | 6.8 | 3.8 | 1.1 | 4.3 | 9.3 | |
| 0 | 12 | 15.0 | 15.6 | 6.7 | 1.9 | 11.2 | 19.8 | b |
| +1 | 12 | 10.5 | 11.1 | 5.5 | 1.6 | 7.6 | 14.6 | a |
| +2 | 12 | 7.2 | 8.1 | 4.9 | 1.4 | 5.0 | 11.2 | a |
| +3 | 12 | 5.9 | 7.2 | 4.8 | 1.4 | 4.1 | 10.3 | a |
| +4 | 12 | 4.8 | 6.4 | 4.4 | 1.3 | 3.6 | 9.2 | b |
| +5 | 11 | 4.4 | 5.9 | 4.7 | 1.4 | 2.8 | 9.0 | b |
| +6 | 11 | 3.7 | 4.6 | 3.7 | 1.1 | 2.1 | 7.1 | a |
| +7 | 12 | 3.4 | 4.3 | 3.9 | 1.1 | 1.8 | 6.8 | a |
| +8 | 12 | 2.7 | 3.6 | 3.5 | 1.0 | 1.4 | 5.8 | |
| +9 | 12 | 3.0 | 3.5 | 3.1 | 0.9 | 1.5 | 5.5 | |
| +10 | 12 | 3.0 | 3.6 | 3.2 | 0.9 | 1.6 | 5.6 | a |
| +11 | 12 | 3.0 | 3.6 | 3.5 | 1.0 | 1.4 | 5.8 | |
| +12 | 12 | 3.2 | 3.6 | 3.0 | 0.9 | 1.7 | 5.5 | |
| +13 | 10 | 3.3 | 4.2 | 3.3 | 1.0 | 1.9 | 6.5 | |
| +14 | 10 | 3.1 | 5.0 | 4.5 | 1.4 | 1.8 | 8.2 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.05$
b = $p < 0.02$

FIGURE 5.4.6

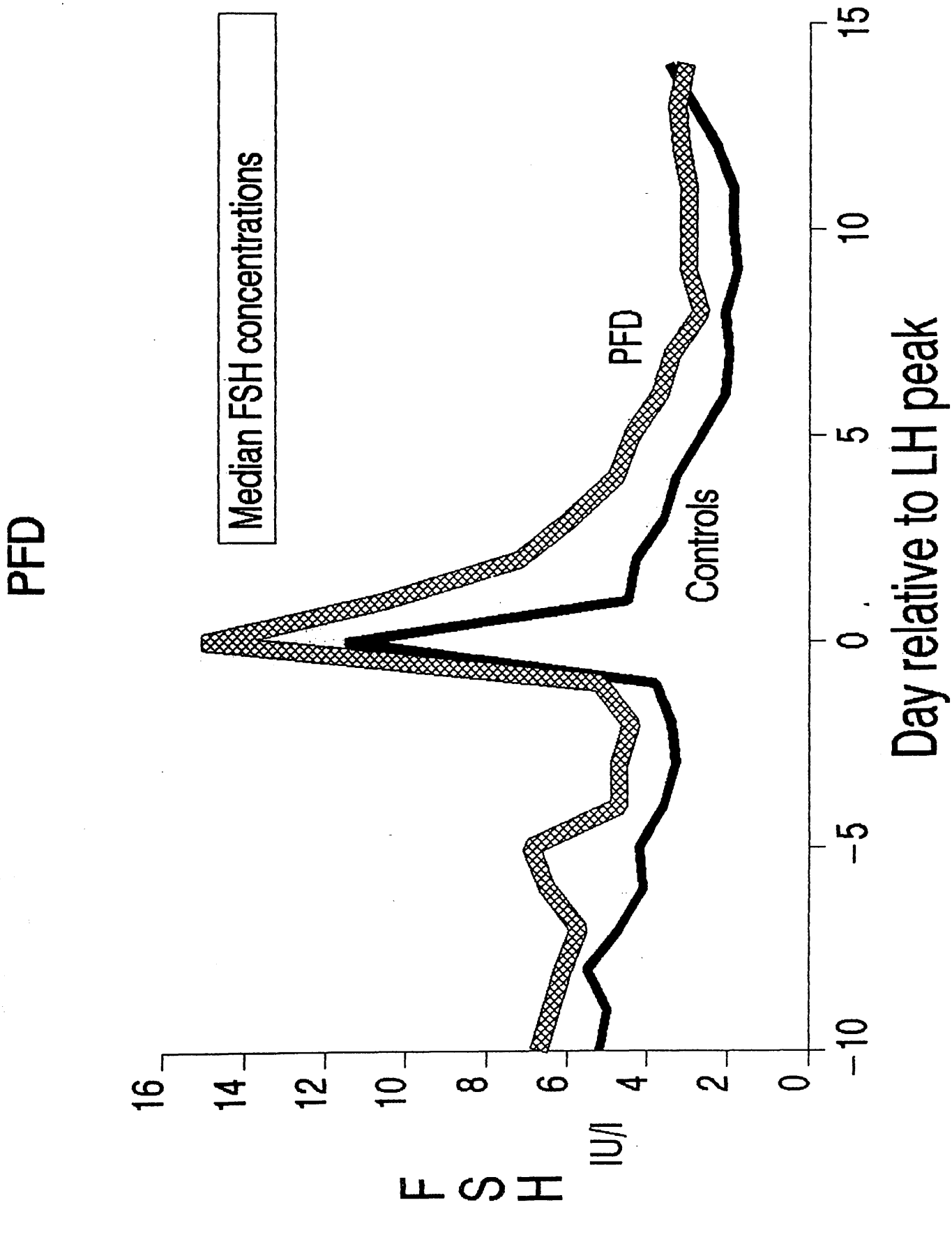

PFD
Median FSH concentrations
PFD
Controls
FSH IU/l
16
14
12
10
8
6
4
2
0
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.4.9

Poor Follicular Maturation

Plasma LH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 14 | 9.0 | 8.5 | 4.2 | 1.1 | 6.1 | 10.9 | |
| -9 | 15 | 8.0 | 9.4 | 4.9 | 1.3 | 6.7 | 12.1 | |
| -8 | 15 | 8.1 | 10.4 | 5.0 | 1.3 | 7.6 | 13.2 | |
| -7 | 14 | 9.6 | 11.3 | 6.4 | 1.7 | 7.6 | 15.0 | |
| -6 | 15 | 9.2 | 11.1 | 7.5 | 1.9 | 6.9 | 15.3 | |
| -5 | 15 | 8.0 | 9.8 | 5.1 | 1.3 | 7.0 | 12.6 | |
| -4 | 15 | 11.0 | 11.2 | 5.5 | 1.4 | 8.2 | 14.2 | b |
| -3 | 15 | 9.8 | 10.6 | 5.2 | 1.3 | 7.7 | 13.5 | |
| -2 | 16 | 10.5 | 11.7 | 4.9 | 1.2 | 9.1 | 14.3 | |
| -1 | 16 | 17.0 | 19.4 | 9.8 | 2.5 | 14.2 | 24.6 | |
| 0 | 16 | 70.0 | 62.5 | 17.0 | 4.3 | 53.4 | 71.6 | |
| +1 | 16 | 39.0 | 38.7 | 17.9 | 4.5 | 29.2 | 48.2 | a |
| +2 | 16 | 12.0 | 17.8 | 12.8 | 3.2 | 11.0 | 24.6 | |
| +3 | 16 | 11.0 | 14.0 | 8.8 | 2.2 | 9.3 | 18.7 | |
| +4 | 16 | 11.5 | 17.1 | 14.6 | 3.7 | 9.3 | 24.9 | |
| +5 | 16 | 9.7 | 14.6 | 11.1 | 2.8 | 10.7 | 20.5 | |
| +6 | 16 | 9.1 | 13.1 | 11.0 | 2.8 | 7.2 | 19.0 | |
| +7 | 15 | 8.2 | 11.0 | 6.9 | 1.8 | 7.2 | 14.8 | |
| +8 | 14 | 5.9 | 8.2 | 6.6 | 1.8 | 4.4 | 12.0 | |
| +9 | 13 | 6.2 | 8.6 | 7.4 | 2.1 | 4.1 | 13.1 | |
| +10 | 13 | 6.1 | 6.8 | 3.7 | 1.0 | 4.6 | 9.0 | |
| +11 | 13 | 6.1 | 8.2 | 6.0 | 1.7 | 4.6 | 11.8 | |
| +12 | 13 | 5.5 | 7.3 | 3.9 | 1.1 | 5.0 | 9.6 | |
| +13 | 12 | 5.8 | 7.5 | 5.6 | 1.6 | 3.9 | 11.1 | |
| +14 | 10 | 5.7 | 7.7 | 4.8 | 1.5 | 4.3 | 11.1 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.05$
b = $p < 0.01$

FIGURE 5.4.7

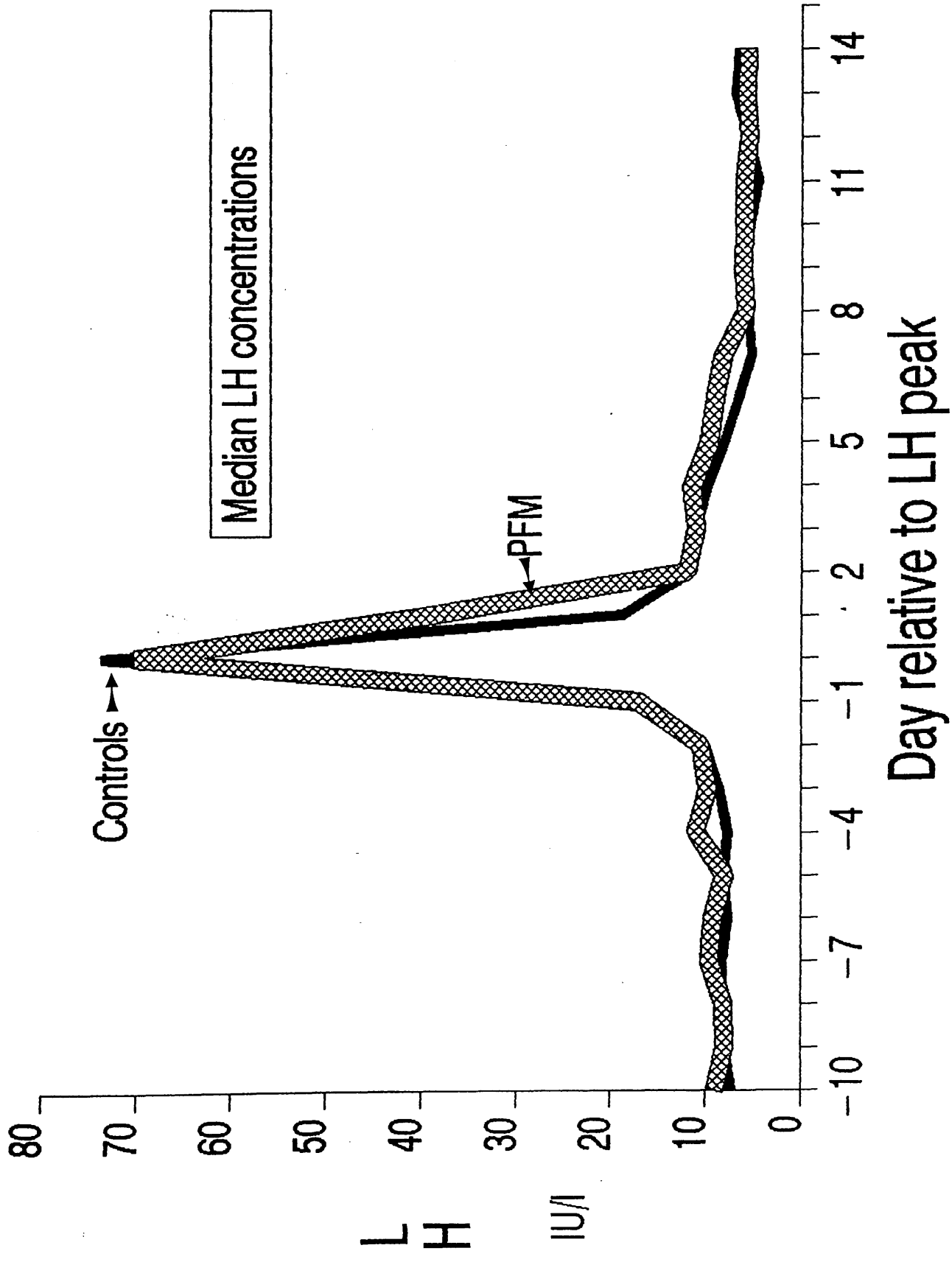

PFM
Median LH concentrations
Controls
PFM
LH IU/l
80
70
60
50
40
30
20
10
0
−10
−7
−4
−1
2
5
8
11
14
Day relative to LH peak

Table 5.4.10

Poor Follicular Development (<17mm Day 0)

Plasma LH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 9 | 9.0 | 7.8 | 3.1 | 1.0 | 5.4 | 10.2 |
| -9 | 9 | 6.4 | 6.9 | 3.7 | 1.2 | 4.1 | 9.7 |
| -8 | 9 | 6.9 | 7.2 | 3.2 | 1.1 | 4.7 | 9.7 |
| -7 | 11 | 7.8 | 7.8 | 3.3 | 1.0 | 5.6 | 10.0 |
| -6 | 11 | 7.9 | 9.2 | 3.5 | 1.1 | 6.8 | 11.6 |
| -5 | 11 | 8.0 | 9.7 | 5.0 | 1.5 | 6.3 | 13.1 |
| -4 | 11 | 6.6 | 7.8 | 3.4 | 1.0 | 5.5 | 10.1 |
| -3 | 12 | 9.1 | 9.2 | 3.2 | 0.9 | 7.2 | 11.2 |
| -2 | 12 | 11.0 | 12.6 | 6.7 | 1.9 | 8.3 | 16.9 |
| -1 | 11 | 15.0 | 22.2 | 13.6 | 4.1 | 13.1 | 31.3 |
| 0 | 12 | 66.5 | 60.0 | 16.8 | 4.8 | 49.3 | 70.7 |
| +1 | 12 | 27.5 | 26.4 | 13.1 | 3.8 | 16.1 | 34.7 |
| +2 | 12 | 12.0 | 13.3 | 4.2 | 1.2 | 12.6 | 16.0 |
| +3 | 12 | 10.5 | 10.9 | 3.1 | 0.9 | 9.0 | 13.0 |
| +4 | 12 | 10.5 | 10.7 | 4.7 | 1.4 | 7.7 | 13.7 |
| +5 | 11 | 8.3 | 8.3 | 2.7 | 0.8 | 6.5 | 10.1 |
| +6 | 11 | 7.5 | 7.4 | 2.7 | 0.8 | 5.6 | 9.2 |
| +7 | 12 | 7.3 | 7.0 | 3.0 | 0.9 | 5.1 | 8.9 |
| +8 | 12 | 6.4 | 6.6 | 3.5 | 1.0 | 4.4 | 8.8 |
| +9 | 12 | 6.5 | 6.3 | 2.1 | 0.6 | 5.0 | 7.6 |
| +10 | 12 | 4.9 | 5.0 | 2.7 | 0.8 | 3.3 | 6.7 |
| +11 | 12 | 4.2 | 5.3 | 4.1 | 1.2 | 2.7 | 7.9 |
| +12 | 11 | 5.2 | 7.0 | 3.8 | 1.1 | 4.4 | 9.6 |
| +13 | 10 | 6.2 | 6.9 | 3.1 | 1.0 | 4.7 | 9.1 |
| +14 | 10 | 6.0 | 6.5 | 3.3 | 1.0 | 4.1 | 8.9 |

No significant differences in comparison with controls
(Wilcoxon rank sum test)

FIGURE 5.4.8

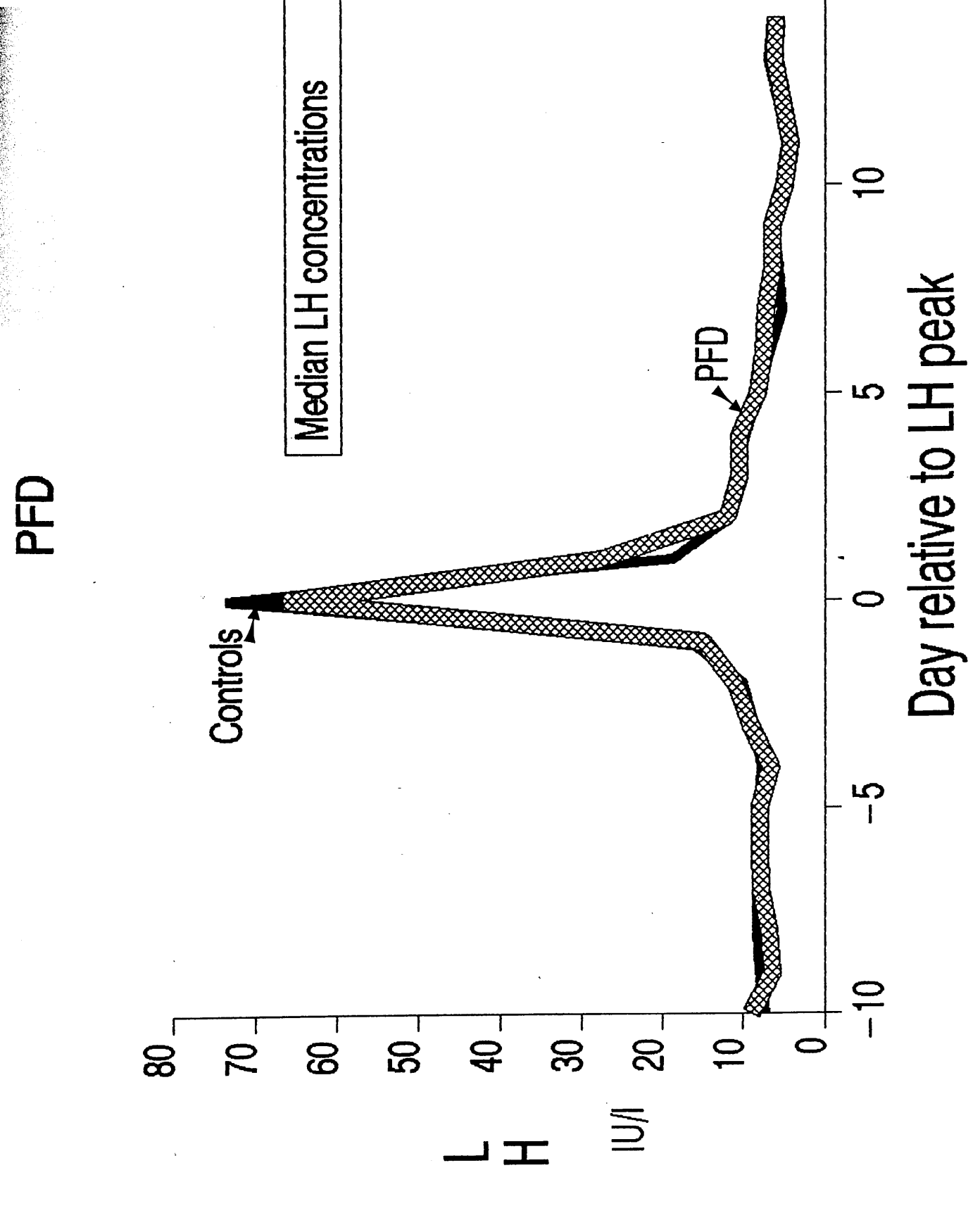

PFD
Median LH concentrations
Controls
PFD
LH IU/l
80
70
60
50
40
30
20
10
0
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.4.11

Poor Follicular Maturation

Follicular Diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -5 | 3 | 12.0 | 12.3 | 1.5 | 0.9 | 8.5 | 16.1 | |
| -4 | 3 | 12.0 | 12.0 | 4.0 | 2.3 | 2.1 | 21.9 | |
| -3 | 5 | 16.5 | 16.7 | 4.6 | 2.0 | 11.1 | 22.3 | |
| -2 | 5 | 14.0 | 12.7 | 2.9 | 1.3 | 9.1 | 16.3 | b |
| -1 | 8 | 16.8 | 16.5 | 3.2 | 1.1 | 13.9 | 19.1 | b |
| 0 | 7 | 16.0 | 16.7 | 3.6 | 1.4 | 13.4 | 20.0 | a |
| +1 | 8 | 17.5 | 20.0 | 8.6 | 3.0 | 12.8 | 27.2 | |
| +2 | 5 | 17.0 | 16.2 | 3.2 | 1.4 | 12.2 | 20.2 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.05$
b = $p < 0.01$

FIGURE 5.4.9

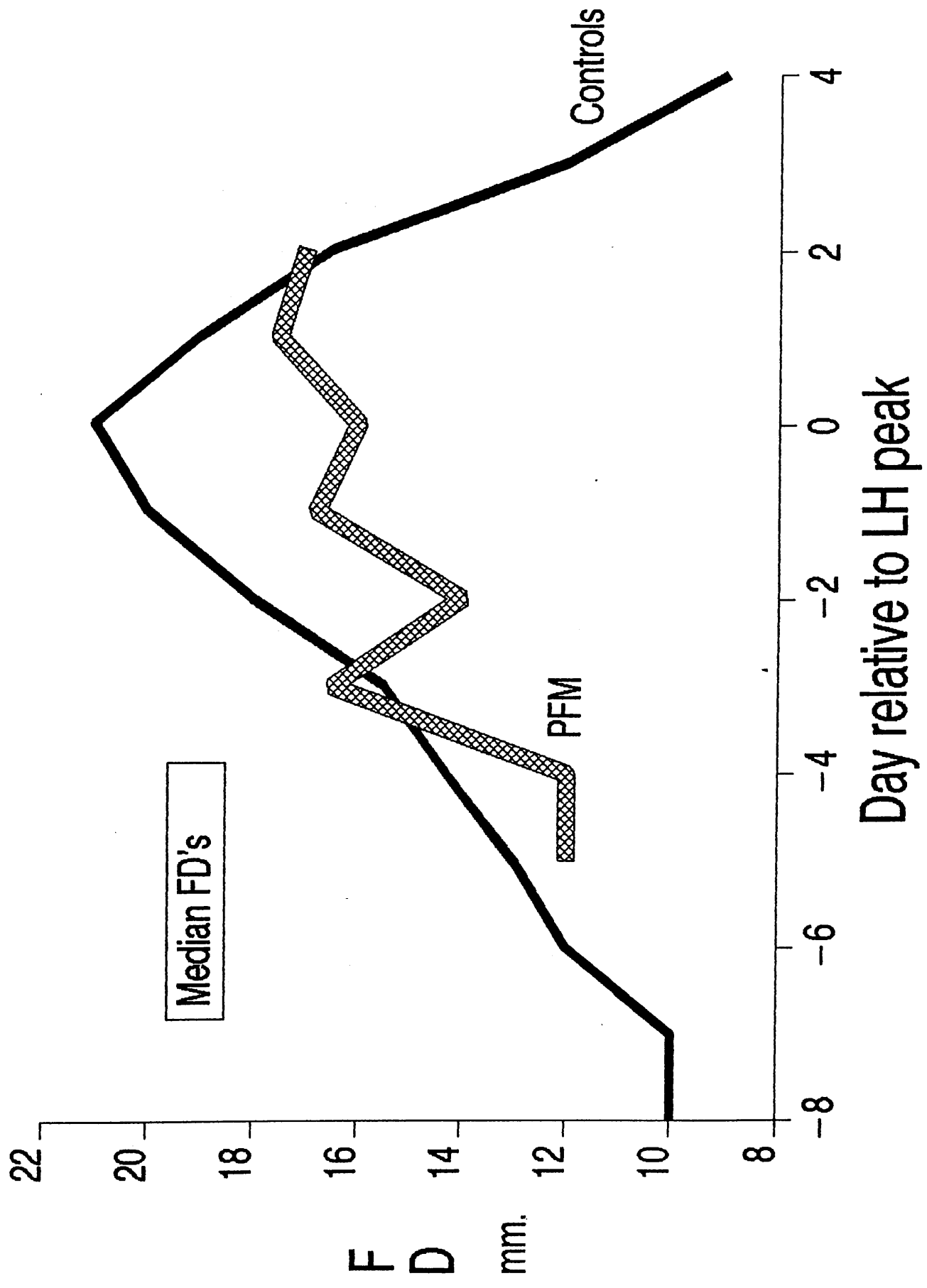

PFM
Median FD's
Controls
PFM
FD mm.
22
20
18
16
14
12
10
8
-8
-6
-4
-2
0
2
4
Day relative to LH peak

Table 5.4.12

Poor Follicular Development (<17mm Day 0)

Follicular diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -4 | 3 | 12.0 | 11.3 | 3.1 | 1.8 | 3.6 | 19.0 | |
| -3 | 5 | 15.0 | 14.4 | 2.0 | 0.9 | 12.0 | 16.8 | |
| -2 | 4 | 14.8 | 15.5 | 3.0 | 1.5 | 10.8 | 20.2 | |
| -1 | 2 | 18.0 | 18.0 | 2.8 | 2.0 | - | - | |
| 0 | 12 | 15.0 | 14.3 | 2.1 | 0.6 | 13.0 | 15.6 | a |
| +1 | 8 | 14.5 | 14.9 | 3.5 | 1.2 | 12.0 | 17.8 | |
| +2 | 2 | 14.5 | 14.5 | 3.5 | 2.5 | - | - | |
| +3 | 5 | 16.5 | 15.4 | 4.6 | 2.0 | 9.7 | 21.1 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = p <0.001

FIGURE 5.4.10

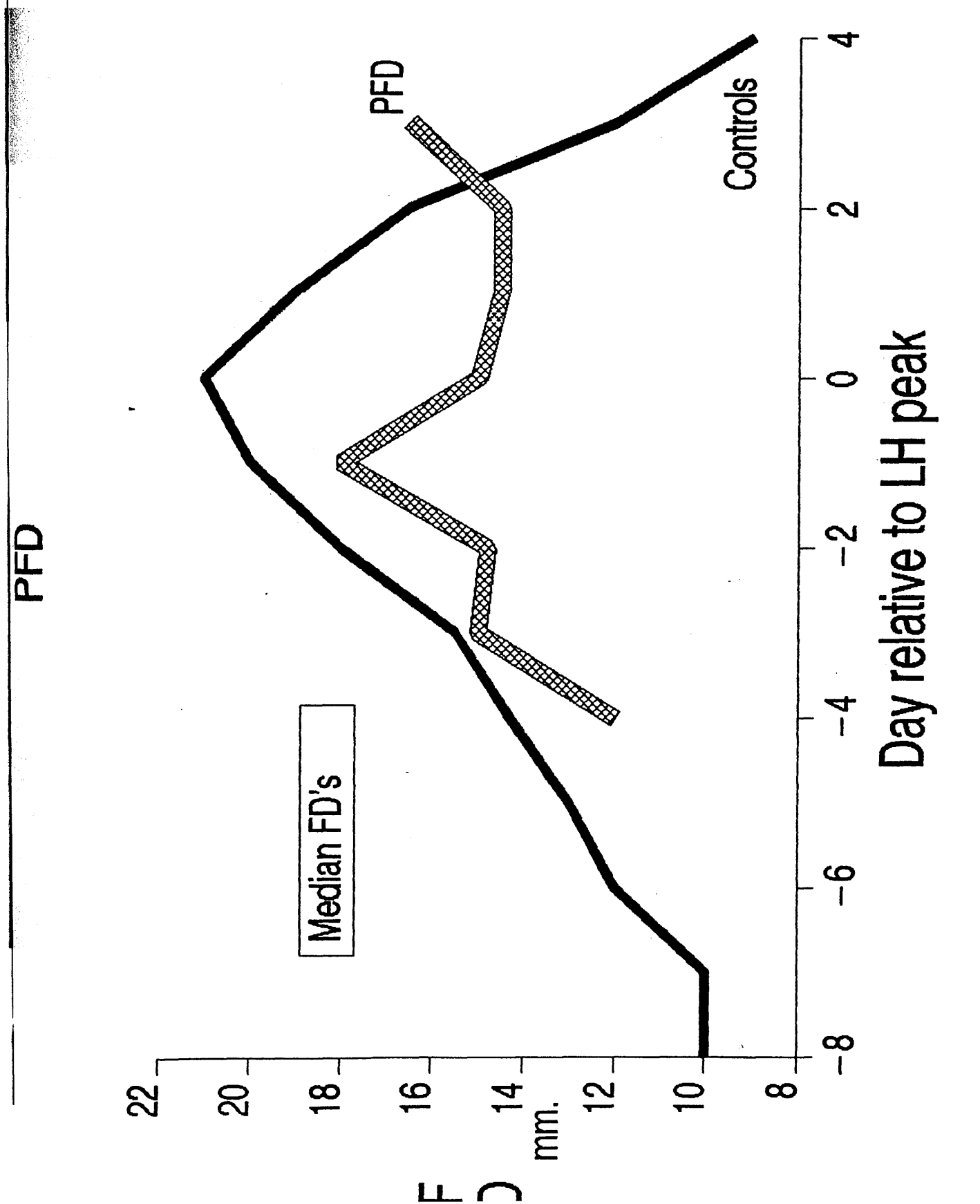

PFD
Median FD's
PFD
Controls
22
20
18
16
14
12
10
8
mm.
-8
-6
-4
-2
0
2
4
Day relative to LH peak

Table 5.5.1

Short Luteal Phase

Patient/cycle characteristics

| | Nos | Mean | SD | SEM | Median | Range | |
|---|---|---|---|---|---|---|---|
| AGE (Years) | | | | | | | |
| | 6 | 33.0 | 3.5 | 1.4 | 33 | 28-37 | b |
| FOLLICULAR PHASE (Days) | | | | | | | |
| | 6 | 14.5 | 2.9 | 1.2 | 13.5 | 11-18 | |
| LUTEAL PHASE (Days) | | | | | | | |
| | 6 | 10.5 | 0.8 | 0.3 | 11 | 9-11 | b |
| CYCLE LENGTH (Days) | | | | | | | |
| | 6 | 25.0 | 2.2 | 0.9 | 24.5 | 22-28 | a |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.01$
b = $p < 0.001$

Table 5.5.2

Short Luteal Phase

Plasma E2 concentrations (pg/ml)

| Day | Nos | Mean | SD | SEM | Median | Range |
|---|---|---|---|---|---|---|
| -10 | 3 | 81.7 | 20.2 | 11.7 | 85.0 | 60-100 |
| -9 | 4 | 85.8 | 28.0 | 14.0 | 86.5 | 55-115 |
| -8 | 4 | 70.0 | 14.7 | 7.4 | 70.0 | 55-85 |
| -7 | 4 | 84.5 | 19.8 | 9.9 | 85.0 | 65-103 |
| -6 | 6 | 110.5 | 19.7 | 8.1 | 115.0 | 80-130 |
| -5 | 6 | 120.0 | 26.1 | 10.6 | 115.0 | 90-155 |
| -4 | 6 | 148.0 | 40.7 | 16.6 | 130.0 | 110-200 |
| -3 | 6 | 158.3 | 54.9 | 22.4 | 147.5 | 115-235 |
| -2 | 6 | 217.2 | 65.3 | 26.7 | 222.5 | 130-308 |
| -1 | 5 | 264.6 | 51.2 | 22.9 | 283.0 | 210-330 |
| 0 | 6 | 206.7 | 72.1 | 29.4 | 192.5 | 130-340 |
| +1 | 6 | 140.8 | 39.4 | 16.1 | 142.5 | 100-210 |
| +2 | 6 | 115.0 | 30.7 | 12.5 | 110.0 | 90-175 |
| +3 | 6 | 143.3 | 40.6 | 16.6 | 137.5 | 105-215 |
| +4 | 6 | 159.2 | 44.3 | 18.1 | 150.0 | 115-245 |
| +5 | 6 | 163.0 | 58.7 | 24.0 | 142.5 | 125-280 |
| +6 | 6 | 163.3 | 60.3 | 24.6 | 142.5 | 130-285 |
| +7 | 6 | 163.8 | 49.6 | 20.3 | 156.5 | 120-250 |
| +8 | 6 | 154.7 | 40.7 | 16.6 | 147.5 | 110-230 |
| +9 | 6 | 136.7 | 54.5 | 22.2 | 125.0 | 90-235 |
| +10 | 5 | 107.0 | 42.7 | 19.1 | 110.0 | 65-170 |
| +11 | 4 | 98.8 | 68.4 | 34.2 | 70.0 | 55-200 |

No significant differences in comparison with controls (Wilcoxon rank sum test)

FIGURE 5.5.1

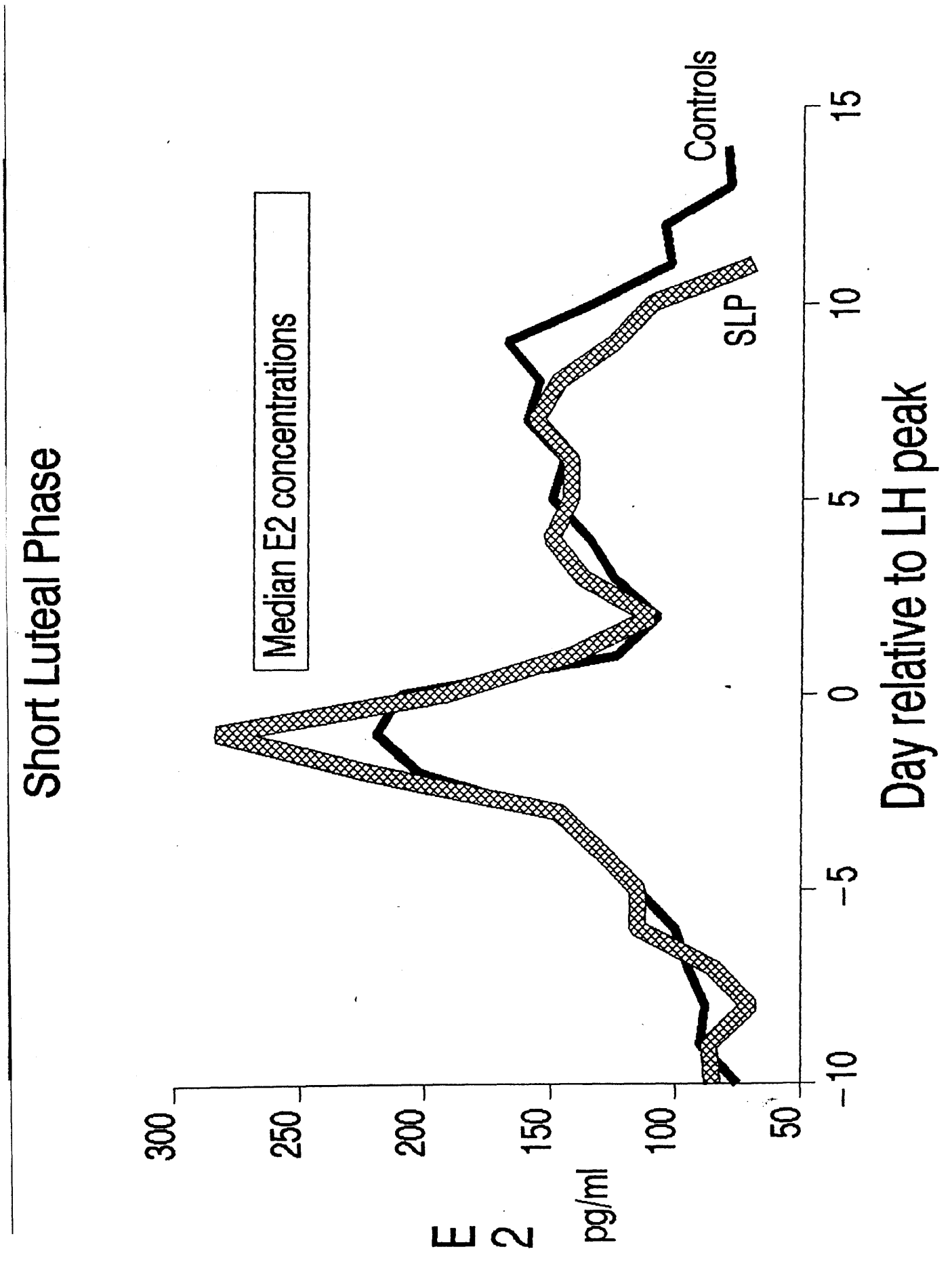

Short Luteal Phase
Median E2 concentrations
Controls
SLP
E 2
pg/ml
300
250
200
150
100
50
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.5.3

Short Luteal Phase

Plasma P concentrations (ng/ml)

| Day | Nos | Mean | SD | SEM | Median | Range | |
|---|---|---|---|---|---|---|---|
| 0 | 5 | 1.3 | 0.6 | 0.2 | 1.3 | 0.7- 1.8 | |
| +1 | 5 | 2.7 | 1.5 | 0.7 | 3.2 | 0.9- 4.2 | |
| +2 | 6 | 4.9 | 3.3 | 1.4 | 5.1 | 0.7- 9.0 | |
| +3 | 6 | 8.3 | 5.8 | 2.4 | 6.7 | 5.2-18.6 | |
| +4 | 6 | 11.9 | 6.8 | 2.8 | 11.6 | 3.4-23.4 | |
| +5 | 6 | 14.8 | 6.5 | 2.6 | 13.6 | 7.5-26.6 | |
| +6 | 6 | 13.3 | 7.5 | 3.1 | 10.7 | 5.9-23.0 | a |
| +7 | 6 | 10.8 | 2.8 | 1.1 | 11.4 | 7.4-13.4 | c |
| +8 | 6 | 9.6 | 5.5 | 2.2 | 7.5 | 5.2-20.4 | b |
| +9 | 6 | 5.2 | 2.6 | 1.1 | 5.2 | 2.4- 9.4 | c |
| +10 | 5 | 1.9 | 1.9 | 0.9 | 1.7 | 0.5- 5.0 | b |
| +11 | 3 | 0.9 | 0.6 | 0.4 | 0.5 | 0.5- 1.6 | a |
| P Index | 6 | 79.8 | 41.2 | 16.8 | 77.5 | 30.0-151.0 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.05$
b = $p < 0.01$
c = $p < 0.001$

FIGURE 5.5.2

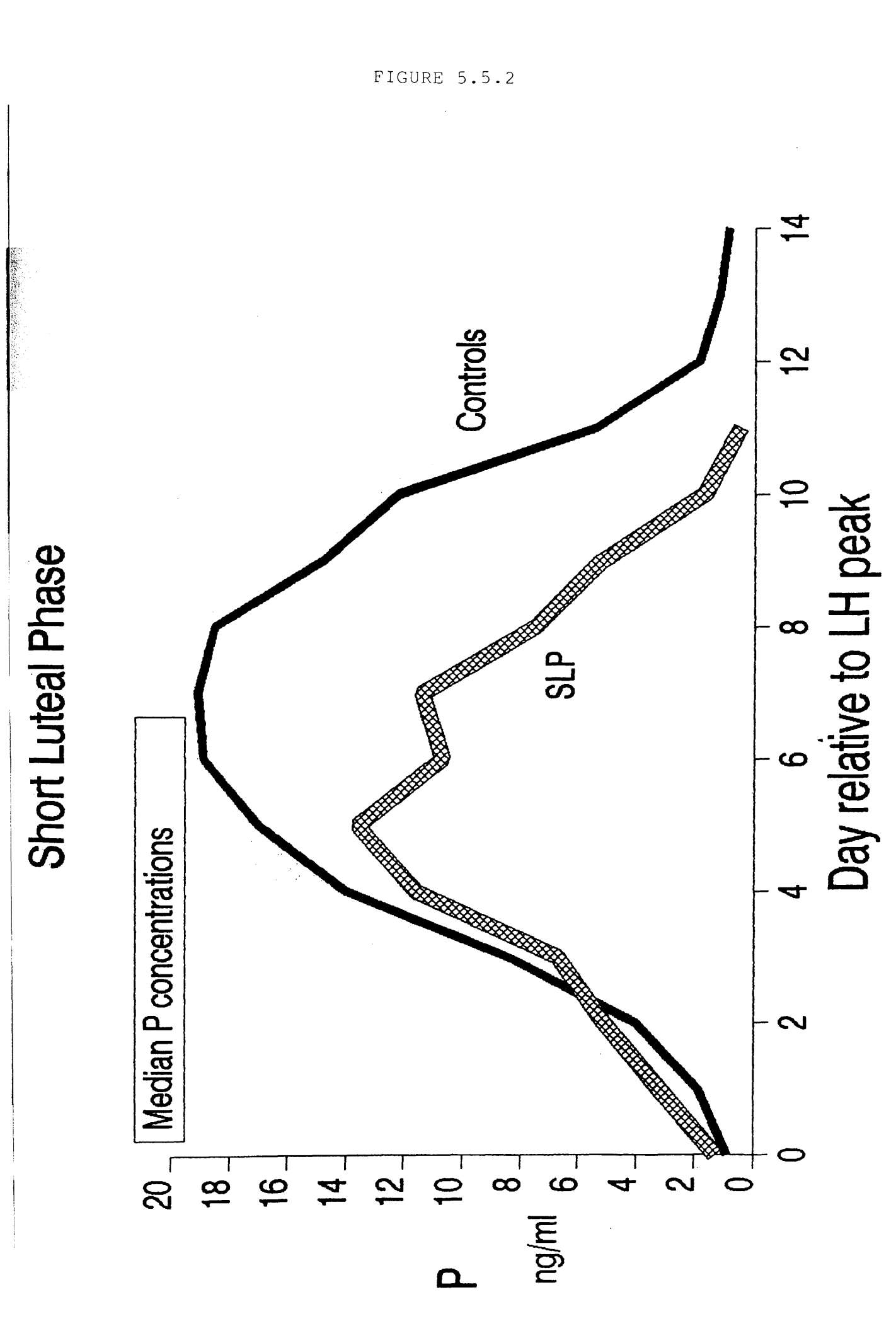

Short Luteal Phase
Median P concentrations
Controls
SLP
P
ng/ml
20
18
16
14
12
10
8
6
4
2
0
0
2
4
6
8
10
12
14
Day relative to LH peak

Table 5.5.4

Short Luteal Phase

Plasma LH concentrations (IU/l)

| Day | Nos | Mean | SD | SEM | Median | Range |
|---|---|---|---|---|---|---|
| -10 | 3 | 10.3 | 7.7 | 4.4 | 7.5 | 4.5-19.0 |
| -9 | 4 | 9.3 | 7.7 | 3.9 | 7.1 | 3.0-20.0 |
| -8 | 4 | 8.1 | 6.1 | 3.0 | 4.2 | 4.1-17.0 |
| -7 | 4 | 9.6 | 7.8 | 3.9 | 6.5 | 4.3-21.0 |
| -6 | 6 | 7.2 | 7.3 | 3.0 | 4.4 | 2.8-22.0 |
| -5 | 6 | 6.6 | 5.2 | 2.1 | 4.9 | 1.7-16.0 |
| -4 | 6 | 6.3 | 3.9 | 1.6 | 5.0 | 3.8-14.0 |
| -3 | 5 | 6.7 | 3.8 | 1.7 | 6.3 | 2.8-13.0 |
| -2 | 6 | 7.5 | 2.3 | 0.9 | 6.6 | 6.1-12.0 |
| -1 | 6 | 16.7 | 10.6 | 4.3 | 15.0 | 5.0-33.0 |
| 0 | 5 | 51.6 | 25.4 | 11.4 | 45.0 | 20.0-80.0 |
| +1 | 6 | 26.1 | 18.4 | 7.5 | 22.0 | 8.7-60.0 |
| +2 | 6 | 11.5 | 7.8 | 3.2 | 8.6 | 5.9-27.0 |
| +3 | 6 | 10.0 | 8.6 | 3.5 | 7.7 | 3.9-27.0 |
| +4 | 5 | 9.8 | 7.0 | 3.1 | 6.5 | 4.1-21.0 |
| +5 | 6 | 13.5 | 8.4 | 3.4 | 13.2 | 4.6-23.0 |
| +6 | 6 | 8.2 | 5.7 | 2.3 | 8.7 | 2.3-17.0 |
| +7 | 6 | 9.1 | 8.0 | 3.3 | 5.7 | 2.2-24.0 |
| +8 | 6 | 6.6 | 5.9 | 2.4 | 4.9 | 0.9-16.0 |
| +9 | 6 | 5.3 | 6.1 | 2.5 | 2.9 | 0.9-17.0 |
| +10 | 5 | 2.9 | 1.5 | 0.7 | 3.0 | 0.9- 4.4 |
| +11 | 4 | 4.6 | 0.5 | 0.3 | 4.7 | 4.0- 5.1 |

No significant differences in comparison with controls (Wilcoxon rank sum test)

FIGURE 5.5.3

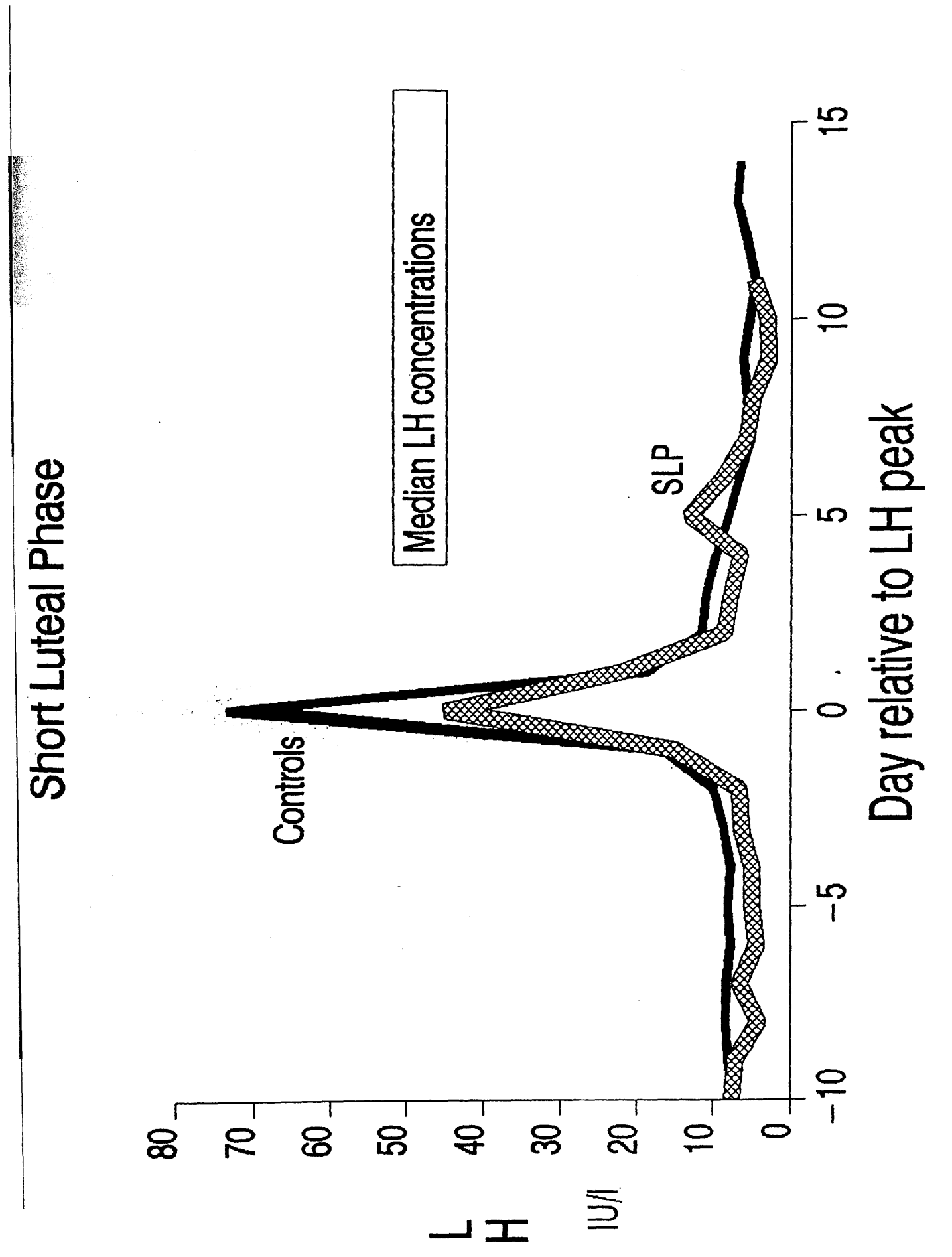

Short Luteal Phase
Median LH concentrations
Controls
SLP
LH IU/l
80
70
60
50
40
30
20
10
0
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.5.5

Short Luteal Phase

Plasma FSH concentrations (IU/1)

| Day | Nos | Mean | SD | SEM | Median | Range |
|---|---|---|---|---|---|---|
| -10 | 3 | 11.2 | 7.7 | 4.4 | 7.5 | 6.0-20.0 |
| -9 | 4 | 7.4 | 5.1 | 2.5 | 5.0 | 4.7-15.0 |
| -8 | 4 | 6.8 | 3.5 | 1.8 | 5.6 | 4.1-12.0 |
| -7 | 4 | 6.6 | 2.9 | 1.5 | 5.4 | 4.8-11.0 |
| -6 | 6 | 6.0 | 2.7 | 1.1 | 4.5 | 4.0-10.0 |
| -5 | 6 | 5.2 | 3.6 | 1.5 | 3.3 | 3.0-12.0 |
| -4 | 6 | 4.9 | 3.2 | 1.3 | 3.8 | 2.0-11.0 |
| -3 | 5 | 3.3 | 1.1 | 0.4 | 3.2 | 1.8- 4.5 |
| -2 | 6 | 4.1 | 1.8 | 0.7 | 4.2 | 1.6- 7.0 |
| -1 | 6 | 5.9 | 4.0 | 1.6 | 4.0 | 2.0-11.0 |
| 0 | 5 | 12.4 | 6.7 | 3.0 | 10.0 | 6.4-21.0 |
| +1 | 6 | 9.1 | 3.1 | 1.3 | 9.1 | 5.6-13.0 |
| +2 | 6 | 5.9 | 2.7 | 1.1 | 5.6 | 3.0- 9.4 |
| +3 | 6 | 4.7 | 1.6 | 0.7 | 4.8 | 2.8- 6.4 |
| +4 | 5 | 4.2 | 2.2 | 1.0 | 3.9 | 1.8- 7.4 |
| +5 | 6 | 3.1 | 1.0 | 0.4 | 2.9 | 1.8- 4.7 |
| +6 | 6 | 2.7 | 1.4 | 0.6 | 2.4 | 1.0- 5.1 |
| +7 | 6 | 2.5 | 1.5 | 0.6 | 2.2 | 0.4- 4.6 |
| +8 | 6 | 2.5 | 1.6 | 0.7 | 1.9 | 0.8- 4.9 |
| +9 | 6 | 1.9 | 0.8 | 0.3 | 1.7 | 0.8- 3.1 |
| +10 | 5 | 1.7 | 0.7 | 0.3 | 2.0 | 0.6- 2.0 |
| +11 | 4 | 2.6 | 1.5 | 0.7 | 2.5 | 1.0- 4.6 |

No significant differences in comparison with controls
(Wilcoxon rank sum test)

FIGURE 5.5.4

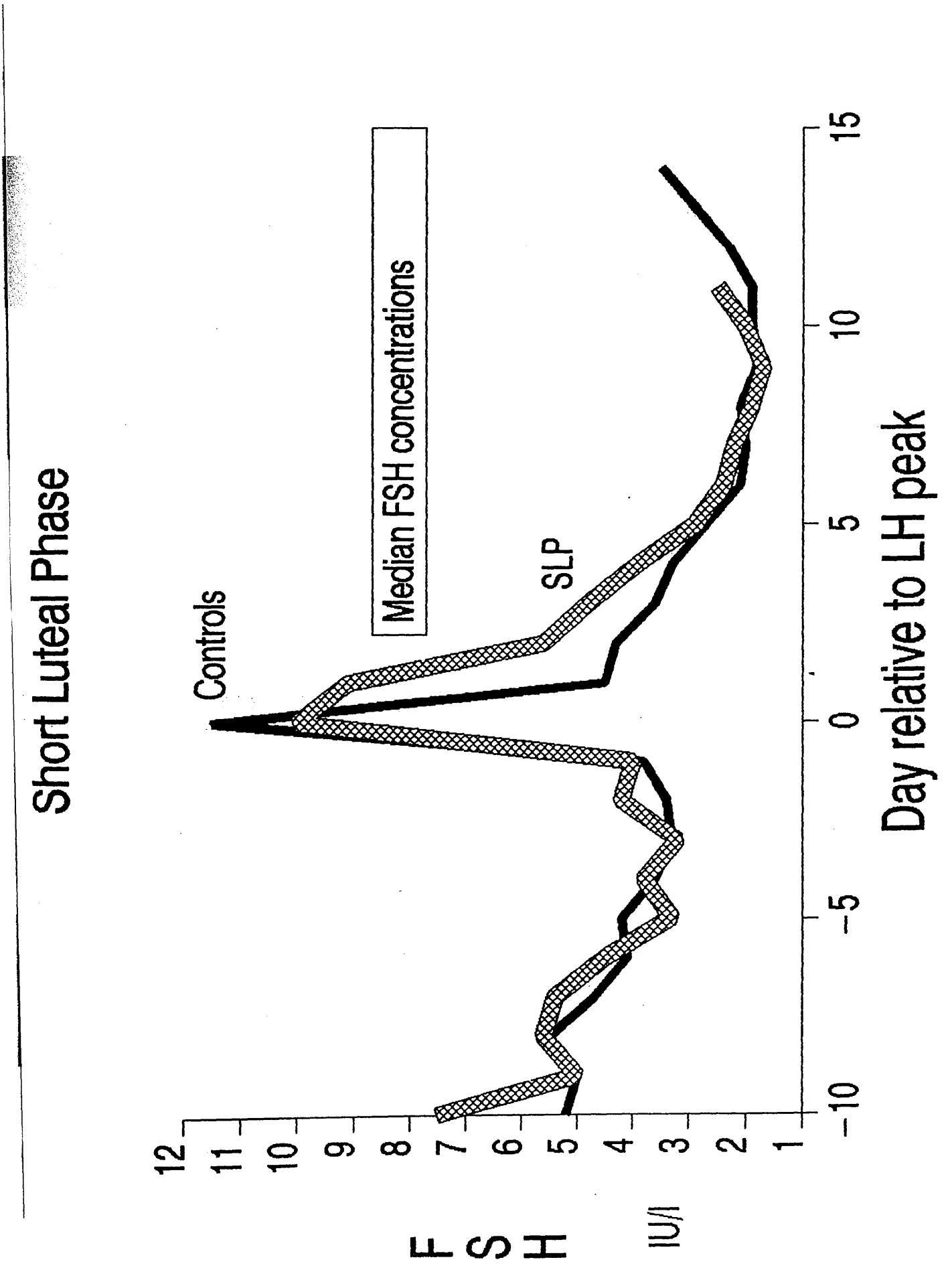

Short Luteal Phase
Median FSH concentrations
Controls
SLP
FSH IU/l
12
11
10
9
8
7
6
5
4
3
2
1
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.5.6

Short Luteal Phase

Follicular Diameters (mm)

| Day | Nos | Mean | SD | SEM | Median | Range |
|---|---|---|---|---|---|---|
| -4 | 4 | 15.6 | 4.3 | 2.2 | 15.0 | 12.0-20.5 |
| -3 | 3 | 16.8 | 2.6 | 1.5 | 17.5 | 14.0-19.0 |
| -2 | 2 | 19.5 | 0.7 | 0.5 | 19.5 | 19.0-20.0 |
| -1 | 4 | 20.8 | 2.2 | 1.1 | 20.0 | 19.0-24.0 |
| 0 | 5 | 22.2 | 1.9 | 0.9 | 22.0 | 20.0-25.0 |
| +1 | 4 | 18.8 | 3.0 | 1.5 | 19.0 | 15.0-22.0 |

No significant differences in comparison with controls (Wilcoxon rank sum test)

FIGURE 5.5.5

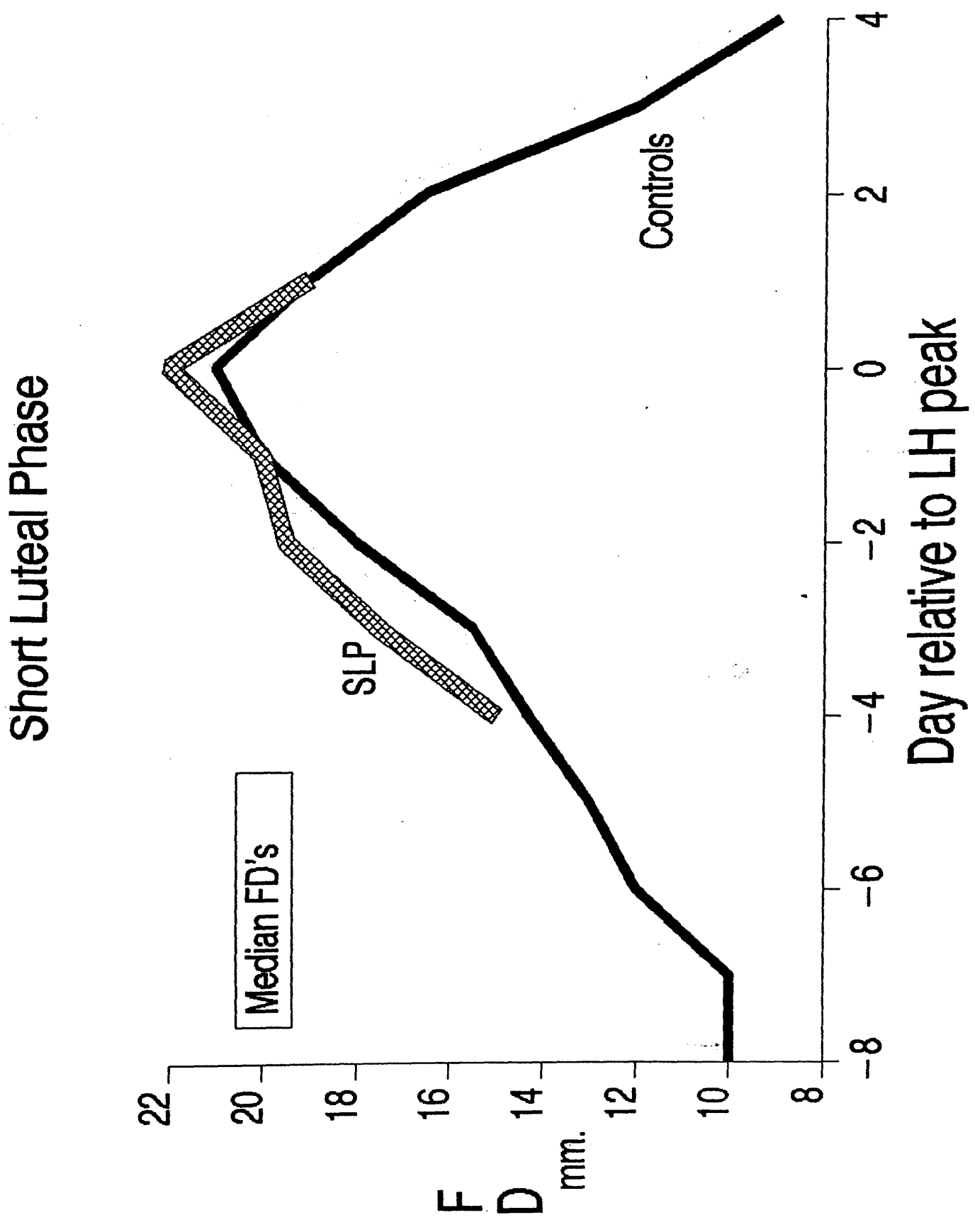

Short Luteal Phase
Median FD's
SLP
Controls
FD mm.
22
20
18
16
14
12
10
8
-8
-6
-4
-2
0
2
4
Day relative to LH peak

Table 5.5.7

Long Follicular Phase (20 days +)

Patient/cycle characteristics

| | Nos | Mean | SD | SEM | Median | Range | |
|---|---|---|---|---|---|---|---|
| AGE (Years) | | | | | | | |
| | 9 | 27.1 | 3.9 | 1.3 | 27 | 22-34 | |
| FOLLICULAR PHASE (Days) | | | | | | | |
| | 9 | 24.8 | 3.7 | 1.2 | 25 | 20-30 | a |
| LUTEAL PHASE (Days) | | | | | | | |
| | 9 | 14.8 | 1.7 | 0.6 | 15 | 12-17 | |
| CYCLE LENGTH (Days) | | | | | | | |
| | 9 | 39.7 | 4.7 | 1.6 | 41 | 33-44 | a |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.001$

Table 5.5.8

Long Follicular Phase (20 days +)

Plasma E2 concentrations (pg/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 8 | 82.5 | 81.9 | 19.1 | 6.7 | 66.0 | 97.8 | |
| -9 | 8 | 85.0 | 80.0 | 22.0 | 7.8 | 61.6 | 98.4 | |
| -8 | 8 | 80.0 | 84.4 | 21.8 | 7.7 | 66.2 | 102.6 | |
| -7 | 7 | 80.0 | 85.0 | 16.3 | 6.2 | 69.9 | 100.1 | |
| -6 | 8 | 102.5 | 103.8 | 22.3 | 7.9 | 85.1 | 122.5 | |
| -5 | 9 | 100.0 | 120.0 | 50.7 | 16.9 | 81.0 | 159.0 | |
| -4 | 8 | 130.0 | 123.8 | 31.7 | 11.2 | 97.3 | 150.3 | |
| -3 | 8 | 147.5 | 150.0 | 45.6 | 16.1 | 111.9 | 188.1 | |
| -2 | 8 | 175.0 | 188.1 | 78.0 | 27.6 | 122.9 | 253.3 | |
| -1 | 7 | 215.0 | 208.6 | 61.6 | 23.3 | 151.7 | 265.5 | |
| 0 | 8 | 220.0 | 202.5 | 61.8 | 21.8 | 150.9 | 254.1 | |
| +1 | 9 | 120.0 | 136.1 | 58.5 | 19.5 | 91.1 | 181.1 | |
| +2 | 9 | 110.0 | 112.8 | 36.8 | 12.3 | 84.6 | 141.0 | |
| +3 | 9 | 120.0 | 119.4 | 31.2 | 10.4 | 95.4 | 143.4 | |
| +4 | 9 | 130.0 | 123.9 | 39.1 | 13.0 | 93.8 | 154.0 | |
| +5 | 8 | 142.5 | 137.5 | 40.2 | 14.2 | 103.9 | 171.1 | |
| +6 | 7 | 150.0 | 143.6 | 55.5 | 21.0 | 92.3 | 194.9 | |
| +7 | 9 | 135.0 | 139.4 | 44.0 | 14.7 | 105.6 | 173.2 | |
| +8 | 8 | 147.5 | 144.4 | 60.1 | 21.3 | 94.1 | 194.7 | |
| +9 | 9 | 150.0 | 155.6 | 72.7 | 24.2 | 98.3 | 212.9 | |
| +10 | 7 | 160.0 | 150.7 | 41.5 | 15.7 | 112.3 | 189.1 | |
| +11 | 9 | 160.0 | 141.1 | 78.9 | 26.3 | 80.5 | 201.7 | |
| +12 | 8 | 165.0 | 155.0 | 60.7 | 21.5 | 104.2 | 205.8 | a |
| +13 | 6 | 120.0 | 135.8 | 69.4 | 28.3 | 63.0 | 208.6 | |
| +14 | 5 | 60.0 | 83.0 | 56.0 | 25.0 | 13.5 | 152.5 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.05$

FIGURE 5.5.6

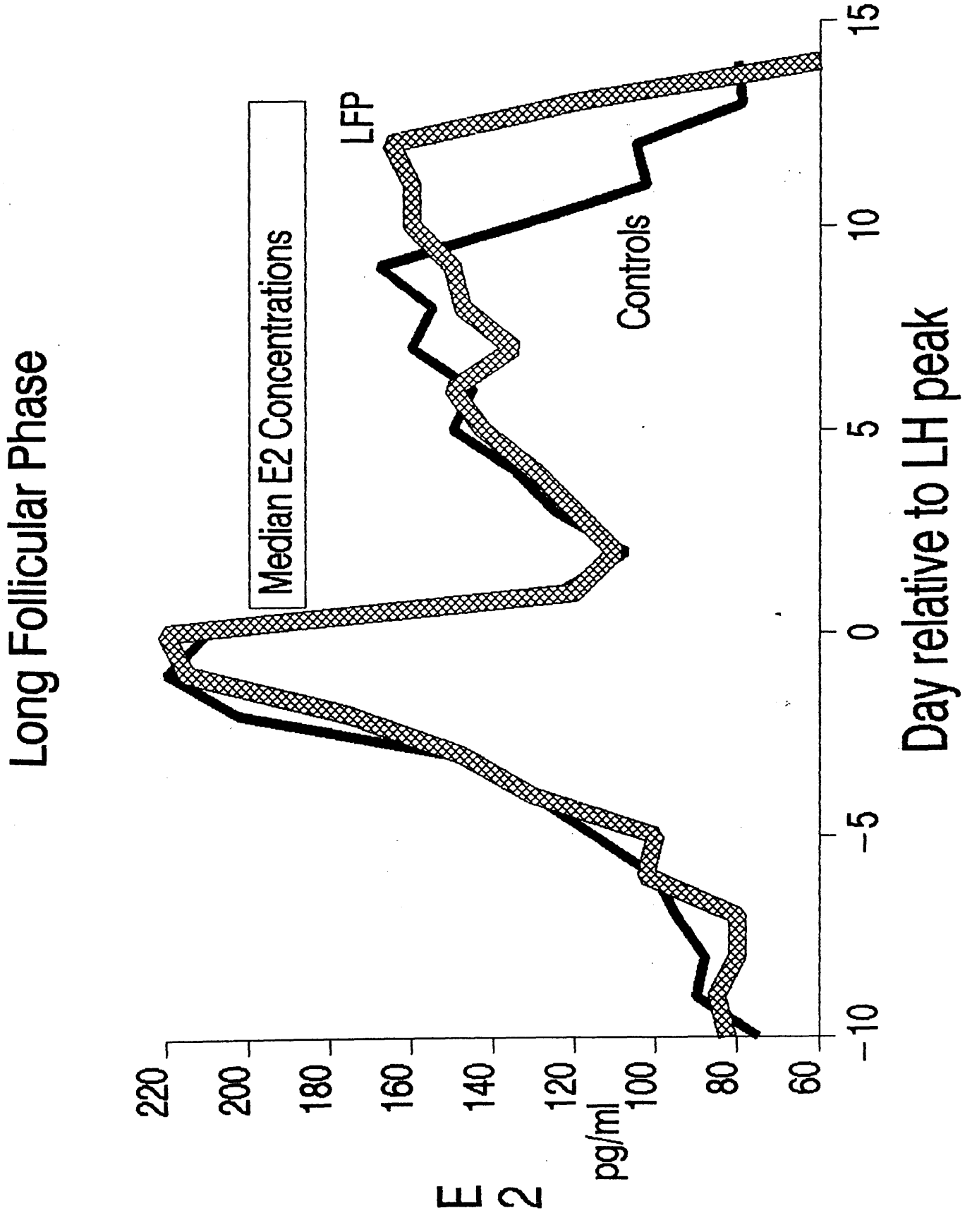

Long Follicular Phase
Median E2 Concentrations
LFP
Controls
E 2
pg/ml
220
200
180
160
140
120
100
80
60
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.5.9

Long Follicular Phase (20 days +)

Plasma P concentrations (ng/ml)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| 0 | 8 | 0.9 | 1.1 | 0.7 | 0.3 | 0.5 | 1.7 | |
| +1 | 9 | 1.7 | 2.2 | 2.2 | 0.7 | 0.5 | 3.9 | |
| +2 | 9 | 2.3 | 4.1 | 4.2 | 1.4 | 0.9 | 7.3 | |
| +3 | 9 | 6.1 | 7.8 | 6.2 | 2.1 | 3.0 | 12.6 | |
| +4 | 9 | 9.6 | 11.2 | 7.0 | 2.3 | 5.8 | 16.6 | |
| +5 | 7 | 13.5 | 14.6 | 7.2 | 2.7 | 8.0 | 21.2 | |
| +6 | 6 | 14.4 | 15.8 | 6.4 | 2.6 | 9.1 | 22.5 | |
| +7 | 9 | 15.2 | 16.8 | 9.4 | 3.1 | 9.6 | 24.0 | |
| +8 | 7 | 16.8 | 16.6 | 5.3 | 2.0 | 11.7 | 21.5 | |
| +9 | 8 | 18.0 | 16.6 | 8.5 | 3.0 | 9.5 | 23.7 | |
| +10 | 5 | 18.8 | 17.8 | 8.7 | 3.9 | 7.0 | 28.6 | |
| +11 | 8 | 13.1 | 14.2 | 7.9 | 2.8 | 7.6 | 20.8 | b |
| +12 | 8 | 9.3 | 10.1 | 4.6 | 1.6 | 6.2 | 14.0 | b |
| +13 | 6 | 6.4 | 7.9 | 6.3 | 2.6 | 1.2 | 14.6 | a |
| +14 | 3 | 1.8 | 1.9 | 1.8 | 1.0 | - | - | |
| P index | 9 | 73.0 | 83.9 | 44.5 | 14.8 | 49.7 | 118.1 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.02$
b = $p < 0.01$

FIGURE 5.5.7

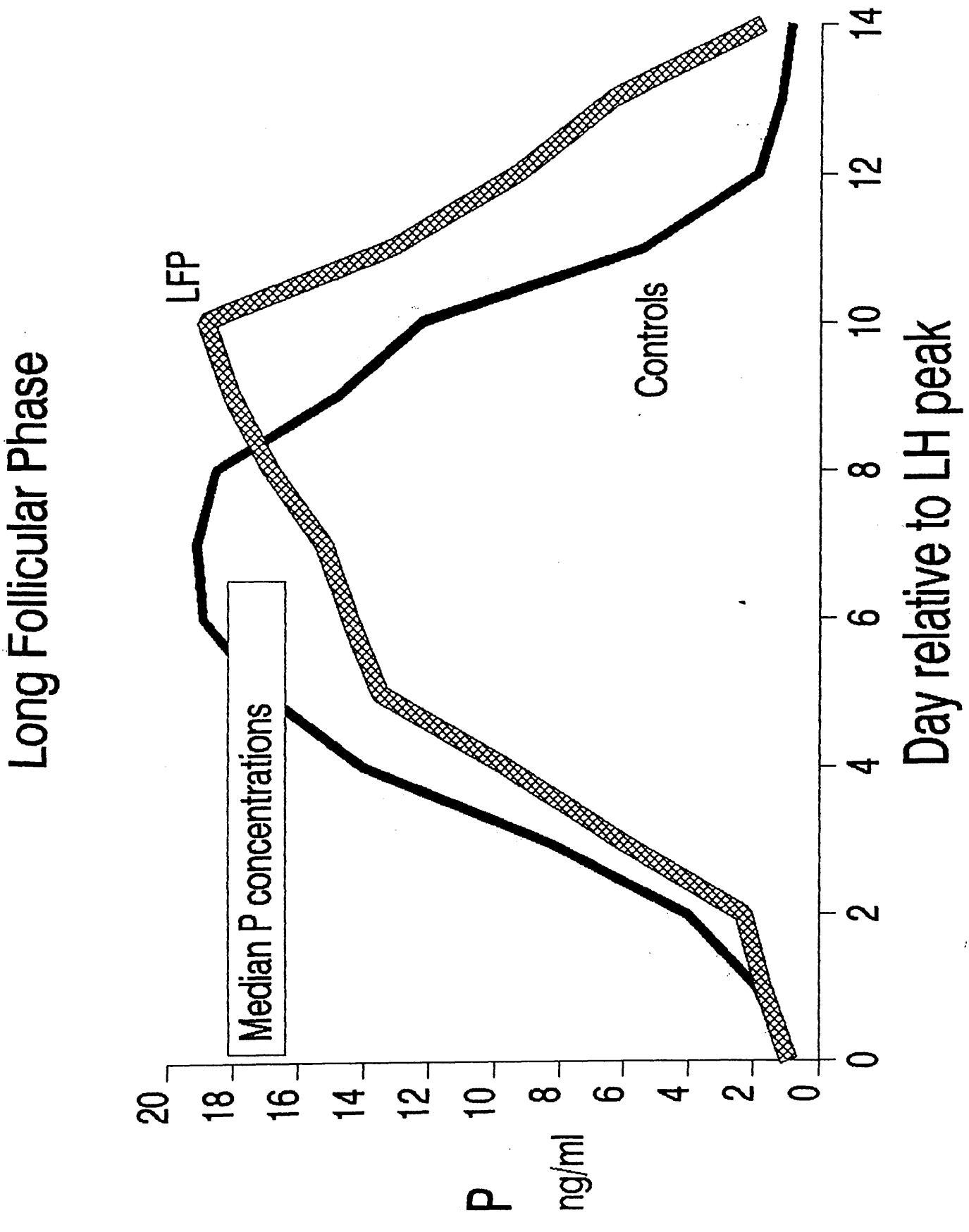

Long Follicular Phase
LFP
Controls
Median P concentrations
P
ng/ml
20
18
16
14
12
10
8
6
4
2
0
0
2
4
6
8
10
12
14
Day relative to LH peak

Table 5.5.10

Long Follicular Phase (20 days +)

Plasma LH concentrations (IU/l)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high | |
|---|---|---|---|---|---|---|---|---|
| -10 | 8 | 12.0 | 9.8 | 6.7 | 2.4 | 4.2 | 15.4 | |
| -9 | 7 | 14.0 | 13.1 | 5.8 | 2.2 | 7.7 | 18.5 | b |
| -8 | 8 | 18.7 | 15.2 | 7.9 | 2.8 | 8.6 | 21.8 | b |
| -7 | 7 | 14.0 | 14.4 | 4.4 | 1.7 | 10.3 | 18.5 | c |
| -6 | 8 | 10.9 | 13.3 | 6.3 | 2.2 | 8.0 | 18.6 | b |
| -5 | 9 | 13.0 | 12.3 | 5.3 | 1.8 | 8.2 | 16.4 | b |
| -4 | 9 | 11.0 | 12.2 | 4.7 | 1.6 | 8.6 | 15.8 | c |
| -3 | 9 | 12.0 | 11.8 | 4.3 | 1.4 | 8.5 | 15.1 | |
| -2 | 9 | 15.0 | 15.9 | 8.6 | 2.9 | 9.3 | 22.5 | a |
| -1 | 8 | 28.5 | 28.6 | 10.8 | 3.8 | 19.6 | 37.6 | a |
| 0 | 9 | 75.0 | 61.3 | 23.0 | 7.7 | 43.6 | 79.0 | |
| +1 | 9 | 13.0 | 28.0 | 28.8 | 9.6 | 5.9 | 50.1 | |
| +2 | 9 | 12.4 | 11.6 | 6.2 | 2.1 | 6.8 | 16.4 | |
| +3 | 9 | 12.0 | 11.1 | 4.7 | 1.6 | 7.5 | 14.7 | |
| +4 | 9 | 7.5 | 8.8 | 4.5 | 1.5 | 5.4 | 12.2 | |
| +5 | 8 | 10.0 | 10.9 | 7.3 | 2.6 | 4.8 | 17.0 | |
| +6 | 7 | 8.6 | 9.8 | 6.6 | 2.5 | 4.0 | 15.6 | |
| +7 | 9 | 7.1 | 7.8 | 5.8 | 1.9 | 3.3 | 12.3 | |
| +8 | 8 | 7.9 | 9.0 | 7.1 | 2.5 | 3.1 | 14.9 | |
| +9 | 8 | 4.7 | 6.9 | 7.2 | 2.5 | 0.9 | 12.9 | |
| +10 | 7 | 9.7 | 10.0 | 6.9 | 2.6 | 3.7 | 16.3 | |
| +11 | 8 | 5.8 | 7.1 | 4.1 | 1.5 | 3.6 | 10.6 | |
| +12 | 7 | 4.7 | 6.5 | 4.3 | 1.6 | 2.5 | 10.5 | |
| +13 | 5 | 7.1 | 6.6 | 2.3 | 1.1 | 3.7 | 9.5 | |
| +14 | 5 | 4.5 | 6.6 | 4.1 | 1.8 | 1.5 | 11.7 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.02$
b = $p < 0.01$
c = $p < 0.001$

FIGURE 5.5.8

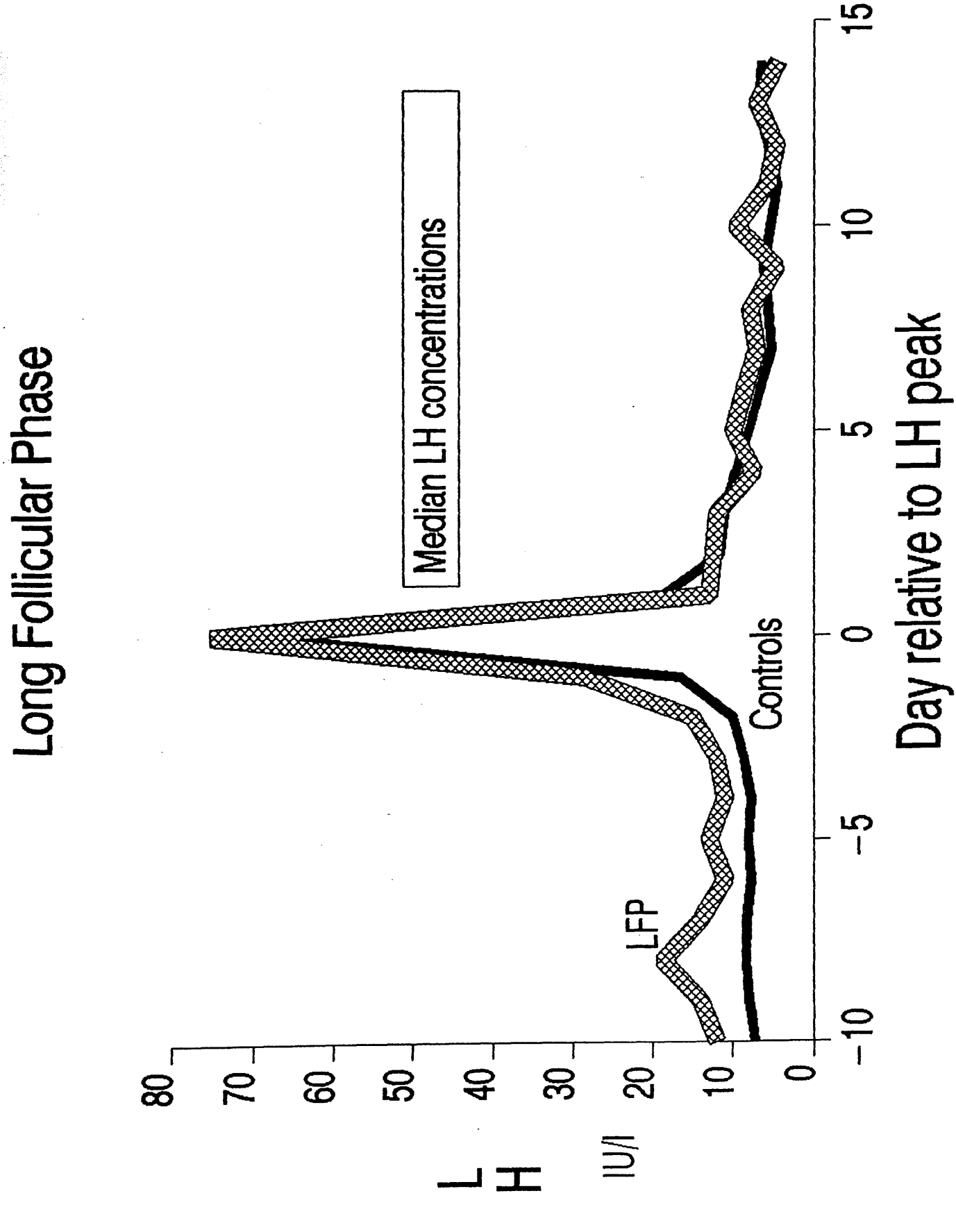

Long Follicular Phase
Median LH concentrations
LFP
Controls
LH IU/l
80
70
60
50
40
30
20
10
0
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.5.11

Long Follicular Phase (20 days +)

Plasma FSH concentrations (IU/1)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -10 | 8 | 5.3 | 5.3 | 1.9 | 0.7 | 3.7 | 6.9 |
| -9 | 8 | 4.7 | 5.5 | 2.3 | 0.8 | 3.6 | 7.4 |
| -8 | 8 | 4.1 | 5.2 | 2.6 | 0.9 | 3.0 | 7.4 |
| -7 | 7 | 4.6 | 4.7 | 1.1 | 0.4 | 3.7 | 5.7 |
| -6 | 8 | 3.9 | 4.2 | 1.2 | 0.4 | 3.2 | 5.2 |
| -5 | 9 | 3.6 | 3.9 | 1.1 | 0.4 | 3.1 | 4.7 |
| -4 | 9 | 3.8 | 3.7 | 0.8 | 0.3 | 3.1 | 4.3 |
| -3 | 8 | 3.2 | 3.2 | 1.1 | 0.4 | 2.3 | 4.1 |
| -2 | 9 | 3.2 | 3.2 | 1.2 | 0.4 | 2.3 | 4.1 |
| -1 | 8 | 4.1 | 4.3 | 1.2 | 0.4 | 3.3 | 5.3 |
| 0 | 9 | 8.3 | 9.2 | 3.8 | 1.3 | 6.3 | 12.1 |
| +1 | 9 | 5.0 | 6.2 | 4.9 | 1.6 | 2.4 | 10.0 |
| +2 | 9 | 3.1 | 3.6 | 1.9 | 0.6 | 2.1 | 5.1 |
| +3 | 9 | 2.7 | 2.9 | 1.0 | 0.3 | 2.1 | 3.7 |
| +4 | 9 | 2.3 | 2.7 | 1.1 | 0.4 | 1.9 | 3.5 |
| +5 | 8 | 2.6 | 2.6 | 1.0 | 0.3 | 1.8 | 3.4 |
| +6 | 7 | 2.5 | 2.7 | 1.4 | 0.5 | 1.4 | 4.0 |
| +7 | 9 | 1.7 | 2.1 | 1.0 | 0.3 | 1.3 | 2.9 |
| +8 | 8 | 1.6 | 2.0 | 1.4 | 0.5 | 0.9 | 3.1 |
| +9 | 9 | 1.2 | 1.8 | 1.0 | 0.3 | 1.1 | 2.5 |
| +10 | 7 | 2.2 | 2.3 | 1.4 | 0.5 | 1.1 | 3.5 |
| +11 | 9 | 1.2 | 1.5 | 0.7 | 0.2 | 0.9 | 2.1 |
| +12 | 9 | 1.6 | 1.6 | 0.8 | 0.3 | 1.0 | 2.2 |
| +13 | 6 | 1.7 | 1.8 | 1.1 | 0.4 | 0.6 | 3.0 |
| +14 | 5 | 2.3 | 2.5 | 1.2 | 0.5 | 0.6 | 4.4 |

No significant differences in comparison with controls
(Wilcoxon rank sum test)

FIGURE 5.5.9

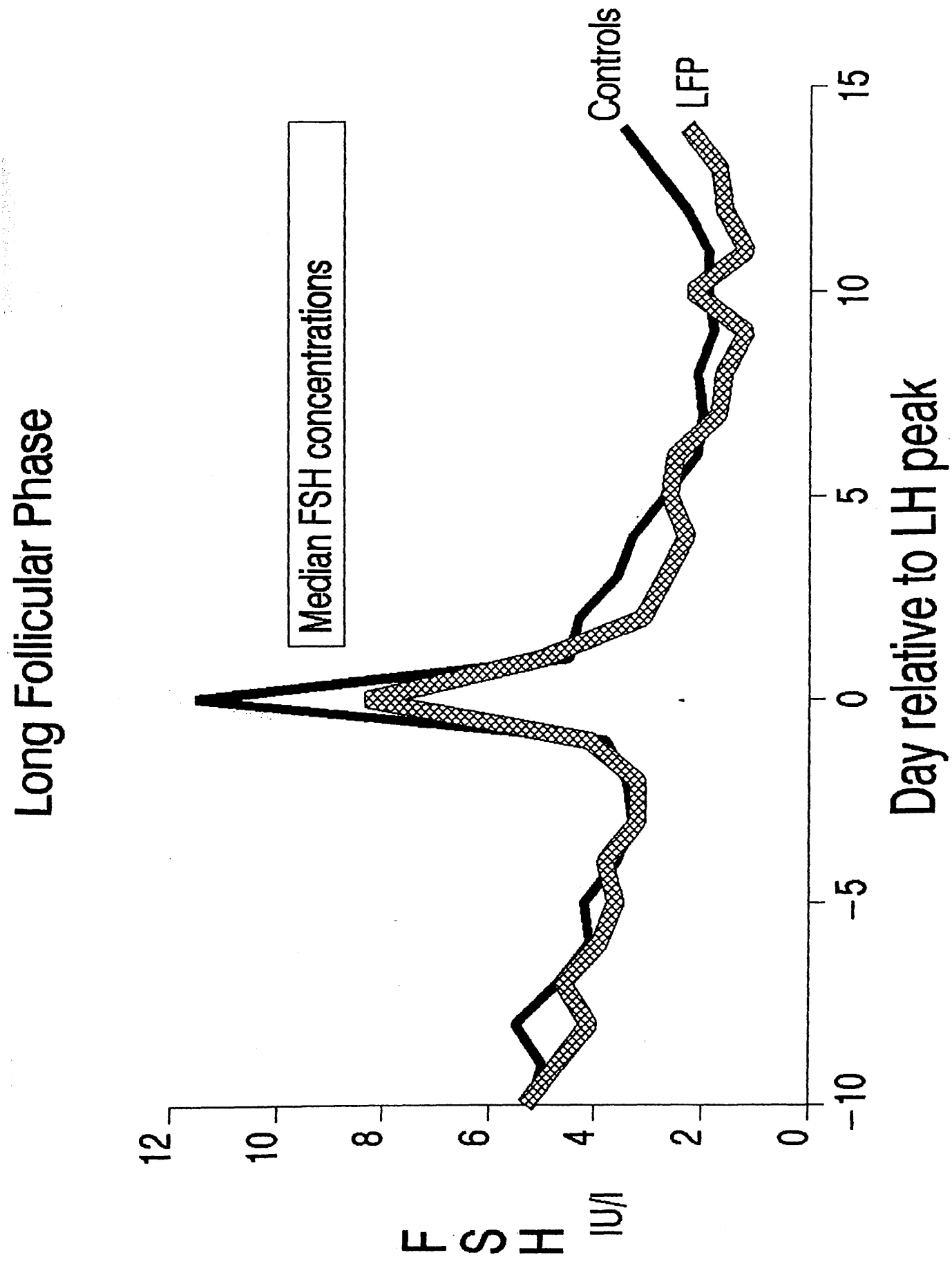

Long Follicular Phase
Median FSH concentrations
Controls
LFP
FSH IU/l
12
10
8
6
4
2
0
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.5.12

Long Follicular Phase (20 days +)

Follicular Diameters (mm)

| Day | Nos | Median | Mean | SD | SEM | 95% low | 95% high |
|---|---|---|---|---|---|---|---|
| -5 | 3 | 13.0 | 12.3 | 4.0 | 2.3 | 2.4 | 22.2 |
| -4 | 2 | 13.8 | 13.8 | 3.2 | 2.3 | - | - |
| -3 | 3 | 14.5 | 13.8 | 1.6 | 0.9 | 9.8 | 17.8 |
| -2 | 7 | 16.0 | 16.6 | 3.2 | 1.2 | 13.6 | 19.6 |
| -1 | 4 | 18.5 | 19.8 | 1.9 | 0.9 | 16.8 | 22.8 |
| 0 | 5 | 21.0 | 20.5 | 3.9 | 1.7 | 15.8 | 25.2 |
| +1 | 4 | 20.0 | 20.0 | 1.6 | 0.8 | 17.4 | 22.6 |

No significant differences in comparison with controls
(Wilcoxon rank sum test)

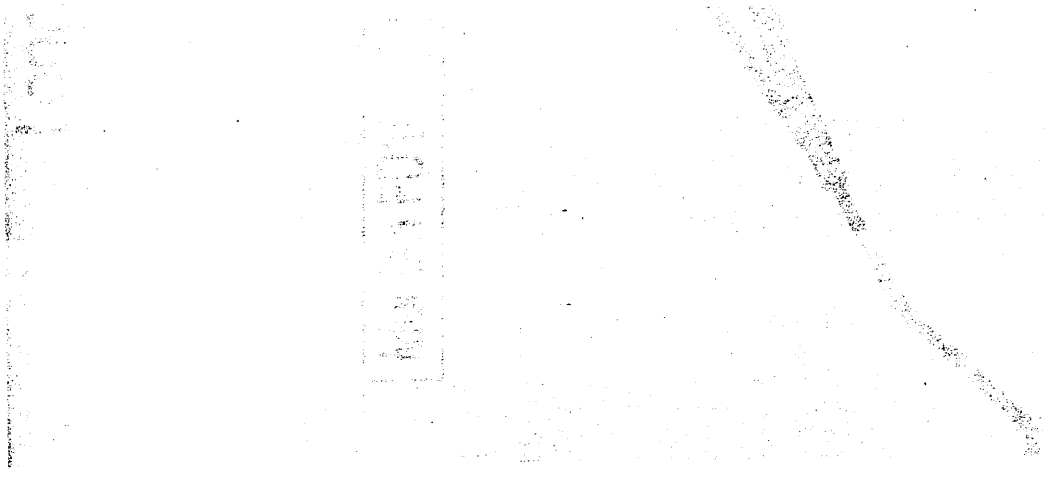


FIGURE 5.5.10

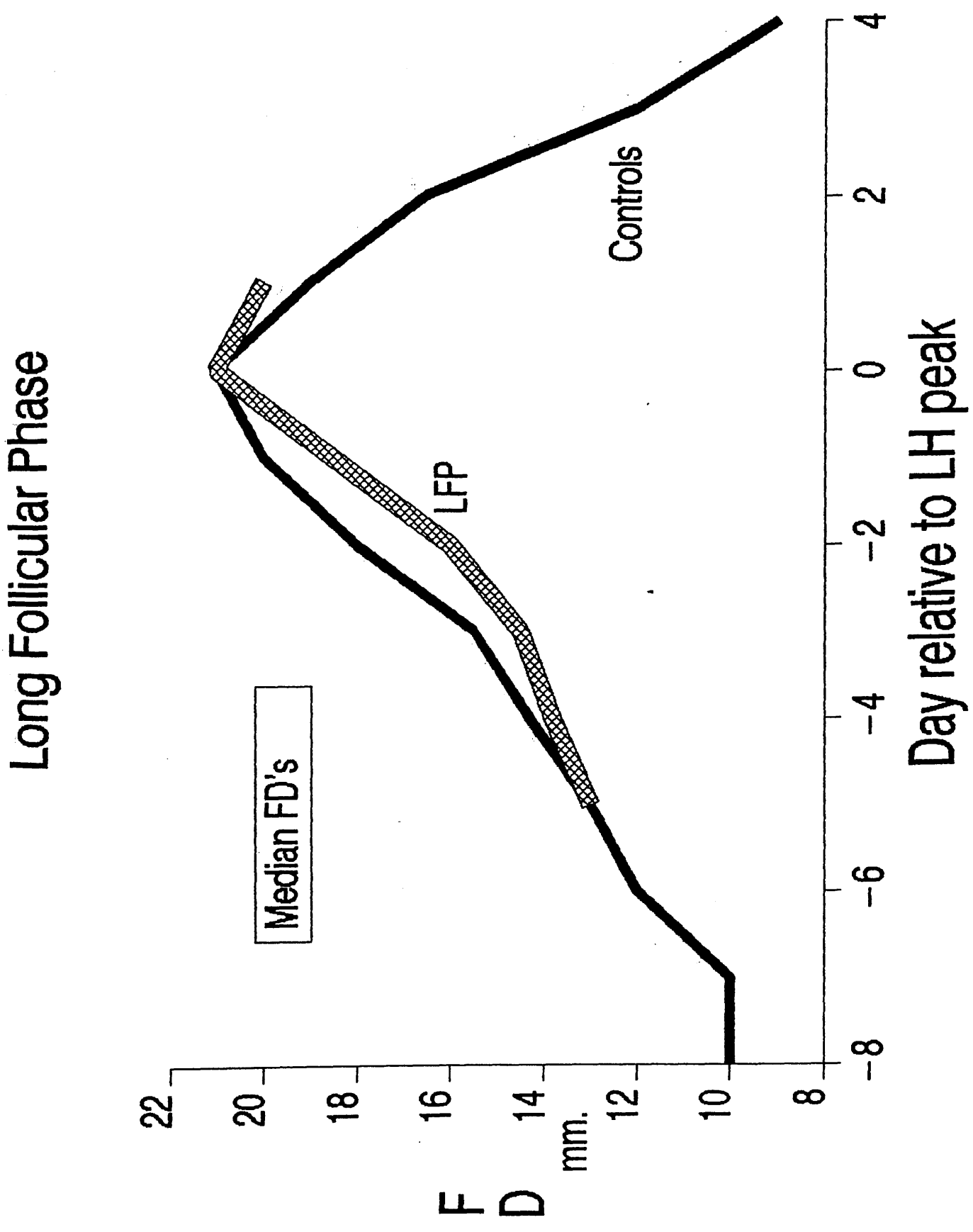

Long Follicular Phase
Median FD's
LFP
Controls
FD mm.
22
20
18
16
14
12
10
8
-8
-6
-4
-2
0
2
4
Day relative to LH peak

Table 5.5.13

Short Follicular Phase (10 days or less)

Patient/cycle characteristics

| | Nos | Mean | SD | SEM | Median | Range | |
|---|---|---|---|---|---|---|---|
| AGE (Years) | | | | | | | |
| | 6 | 32.3 | 4.8 | 1.9 | 32 | 26-38 | a |
| FOLLICULAR PHASE (Days) | | | | | | | |
| | 6 | 8.0 | 1.8 | 0.7 | 8 | 6-10 | b |
| LUTEAL PHASE (Days) | | | | | | | |
| | 6 | 15.3 | 2.0 | 0.8 | 16 | 12-17 | |
| CYCLE LENGTH (Days) | | | | | | | |
| | 6 | 23.3 | 3.3 | 1.4 | 23.5 | 18-27 | b |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.01$
b = $p < 0.001$

Table 5.5.14

Short Follicular Phase (10 days or less)

Plasma E2 concentrations (pg/ml)

| Da | Nos | Mean | SD | SEM | Median | Range |
|---|---|---|---|---|---|---|
| -9 | 2 | 86.5 | 44.5 | 31.5 | 86.5 | 55-118 |
| -8 | 2 | 65.0 | 21.2 | 15.0 | 65.0 | 50- 80 |
| -7 | 3 | 85.0 | 20.0 | 11.5 | 85.0 | 65-105 |
| -6 | 3 | 84.3 | 12.5 | 7.2 | 90.0 | 70-93 |
| -5 | 4 | 91.3 | 21.7 | 10.9 | 97.5 | 60-110 |
| -4 | 5 | 149.0 | 64.8 | 29.0 | 145.0 | 70-250 |
| -3 | 6 | 183.8 | 69.3 | 28.3 | 175.0 | 105-308 |
| -2 | 6 | 224.7 | 69.8 | 28.5 | 245.0 | 135-325 |
| -1 | 6 | 227.7 | 53.7 | 21.9 | 209.0 | 160-313 |
| 0 | 6 | 184.7 | 44.8 | 18.3 | 186.5 | 130-245 |
| 1 | 6 | 109.7 | 33.5 | 13.7 | 100.0 | 80-175 |
| +2 | 6 | 96.3 | 29.8 | 12.2 | 87.0 | 65-140 |
| +3 | 6 | 113.0 | 33.3 | 13.6 | 112.0 | 75-150 |
| +4 | 6 | 109.7 | 27.3 | 11.1 | 112.0 | 80-155 |
| +5 | 5 | 124.6 | 27.2 | 12.2 | 110.0 | 105-170 |
| +6 | 6 | 116.2 | 30.3 | 12.4 | 133.0 | 84-160 |
| +7 | 5 | 137.0 | 13.5 | 6.0 | 135.0 | 120-155 |
| +8 | 6 | 137.7 | 36.8 | 15.0 | 127.5 | 98-195 |
| +9 | 6 | 141.3 | 33.0 | 13.5 | 141.5 | 95-195 |
| +10 | 6 | 122.2 | 19.8 | 8.1 | 120.0 | 100-150 |
| +11 | 6 | 127.2 | 19.5 | 8.0 | 131.5 | 100-155 |
| +12 | 6 | 118.8 | 19.5 | 8.0 | 111.5 | 100-150 |
| +13 | 6 | 117.7 | 41.4 | 16.9 | 121.5 | 60-160 |
| +14 | 5 | 87.6 | 31.0 | 13.9 | 93.0 | 50-135 |

No significant differences in comparison with controls

FIGURE 5.5.11

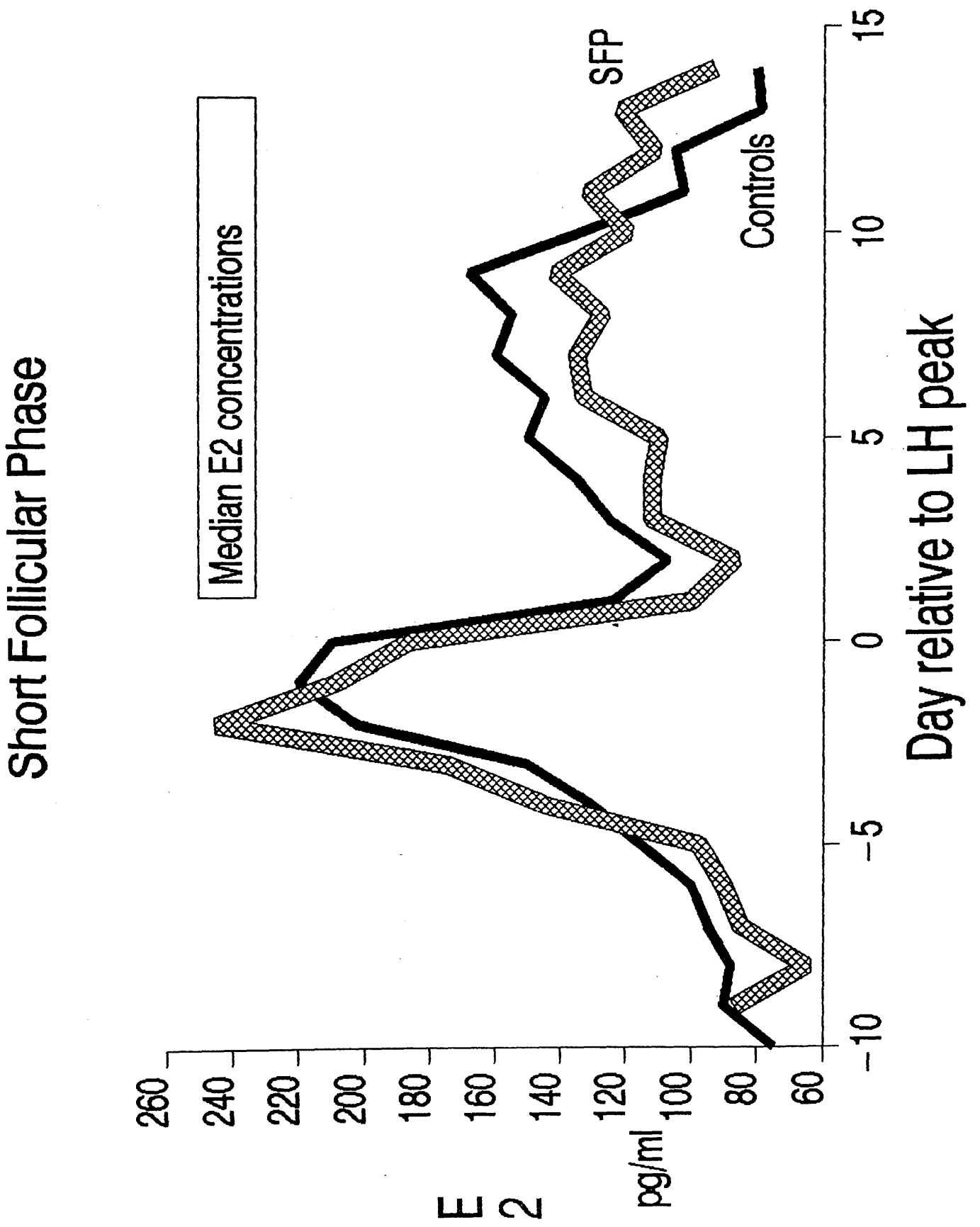

Short Follicular Phase
Median E2 concentrations
SFP
Controls
E 2
pg/ml
260
240
220
200
180
160
140
120
100
80
60
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.5.15

Short Follicular Phase (10 days or less)

Plasma P concentrations (ng/ml)

| Day | Nos | Mean | SD | SEM | Median | Range | |
|---|---|---|---|---|---|---|---|
| 0 | 5 | 0.9 | 0.2 | 0.1 | 1.0 | 0.5- 1.0 | |
| +1 | 6 | 1.4 | 0.6 | 0.2 | 1.5 | 0.5- 2.0 | |
| +2 | 6 | 3.3 | 1.0 | 0.4 | 3.6 | 2.0- 4.4 | |
| +3 | 6 | 5.8 | 2.6 | 1.1 | 5.2 | 3.1- 9.4 | |
| +4 | 6 | 8.8 | 3.9 | 1.6 | 8.9 | 3.5-13.7 | a |
| +5 | 5 | 13.7 | 8.4 | 3.7 | 12.6 | 3.4-26.8 | |
| +6 | 6 | 19.1 | 9.0 | 3.7 | 19.9 | 3.6-28.0 | |
| +7 | 5 | 16.2 | 7.4 | 3.3 | 18.4 | 3.3-22.4 | |
| +8 | 6 | 17.4 | 8.1 | 3.3 | 18.4 | 3.5-26.8 | |
| +9 | 6 | 15.9 | 6.3 | 2.6 | 18.4 | 4.9-21.0 | |
| +10 | 6 | 13.8 | 8.1 | 3.3 | 17.2 | 2.7-20.8 | |
| +11 | 6 | 13.5 | 8.0 | 3.3 | 13.4 | 3.0-22.8 | b |
| +12 | 6 | 8.7 | 6.1 | 2.5 | 8.9 | 0.7-16.0 | |
| +13 | 5 | 7.9 | 4.9 | 2.2 | 8.6 | 1.0-14.0 | b |
| +14 | 5 | 3.4 | 2.1 | 1.5 | 3.6 | 0.5- 6.3 | |
| P index | 6 | 76.5 | 31.9 | 13.0 | 79.0 | 25-120 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.05$
b = $p < 0.01$

FIGURE 5.5.12

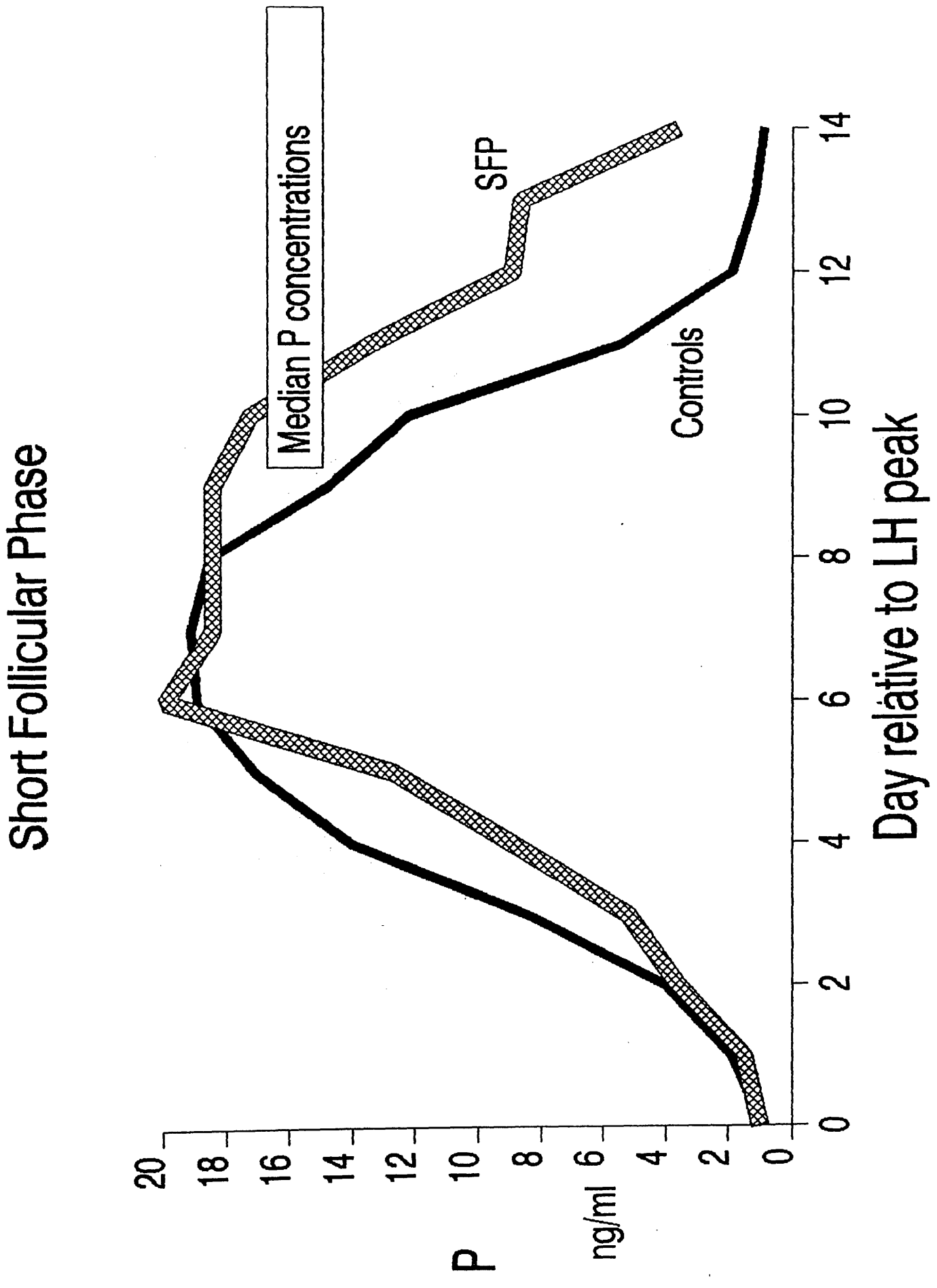

Short Follicular Phase
Median P concentrations
SFP
Controls
P
ng/ml
20
18
16
14
12
10
8
6
4
2
0
0
2
4
6
8
10
12
14
Day relative to LH peak

Table 5.5.16

Short Follicular Phase (10 days or less)

Plasma LH concentrations (IU/l)

| Day | Nos | Mean | SD | SEM | Median | Range | |
|---|---|---|---|---|---|---|---|
| -9 | 2 | 4.8 | 4.5 | 3.2 | 4.8 | 1.6- 8.0 | |
| -8 | 2 | 4.7 | 5.4 | 3.8 | 4.7 | 0.9- 8.5 | |
| -7 | 3 | 4.6 | 2.5 | 1.4 | 4.0 | 2.4- 7.3 | a |
| -6 | 3 | 5.9 | 4.1 | 2.3 | 5.8 | 1.9-10.0 | |
| -5 | 4 | 7.9 | 4.5 | 2.3 | 6.8 | 3.9-14.0 | |
| -4 | 5 | 4.7 | 2.8 | 1.2 | 4.7 | 1.0- 8.4 | a |
| -3 | 6 | 5.1 | 3.7 | 1.5 | 3.8 | 0.9-11.0 | a |
| -2 | 6 | 7.3 | 3.3 | 1.4 | 8.3 | 1.7-11.0 | |
| -1 | 6 | 13.5 | 6.5 | 2.7 | 15.5 | 3.0-20.0 | |
| 0 | 6 | 39.1 | 17.1 | 7.0 | 37.8 | 20.0-68.0 | b |
| +1 | 6 | 16.5 | 12.5 | 5.1 | 11.5 | 3.6-34.0 | |
| +2 | 6 | 8.3 | 4.6 | 1.9 | 8.8 | 3.2-13.0 | |
| +3 | 6 | 8.3 | 5.5 | 2.2 | 9.3 | 1.8-13.0 | |
| +4 | 6 | 7.6 | 3.5 | 1.4 | 8.3 | 2.7-11.0 | |
| +5 | 5 | 8.5 | 5.5 | 2.5 | 9.8 | 1.4-16.0 | |
| +6 | 6 | 8.1 | 6.4 | 2.6 | 6.4 | 2.2-20.0 | |
| +7 | 5 | 9.2 | 11.0 | 4.9 | 5.6 | 1.2-28.0 | |
| +8 | 6 | 7.5 | 3.1 | 1.3 | 7.8 | 3.7-11.0 | |
| +9 | 6 | 5.3 | 2.2 | 0.9 | 5.1 | 2.9- 9.0 | |
| +10 | 6 | 5.2 | 3.7 | 1.5 | 4.3 | 1.6-10.0 | |
| +11 | 6 | 4.7 | 3.5 | 1.4 | 3.8 | 0.9- 9.9 | |
| +12 | 6 | 4.9 | 4.4 | 1.8 | 3.9 | 0.9-12.0 | |
| +13 | 5 | 6.3 | 4.5 | 2.0 | 7.1 | 0.9-11.0 | |
| +14 | 5 | 5.3 | 4.8 | 2.1 | 4.8 | 0.9-12.0 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.05$
b = $p < 0.001$

FIGURE 5.5.13

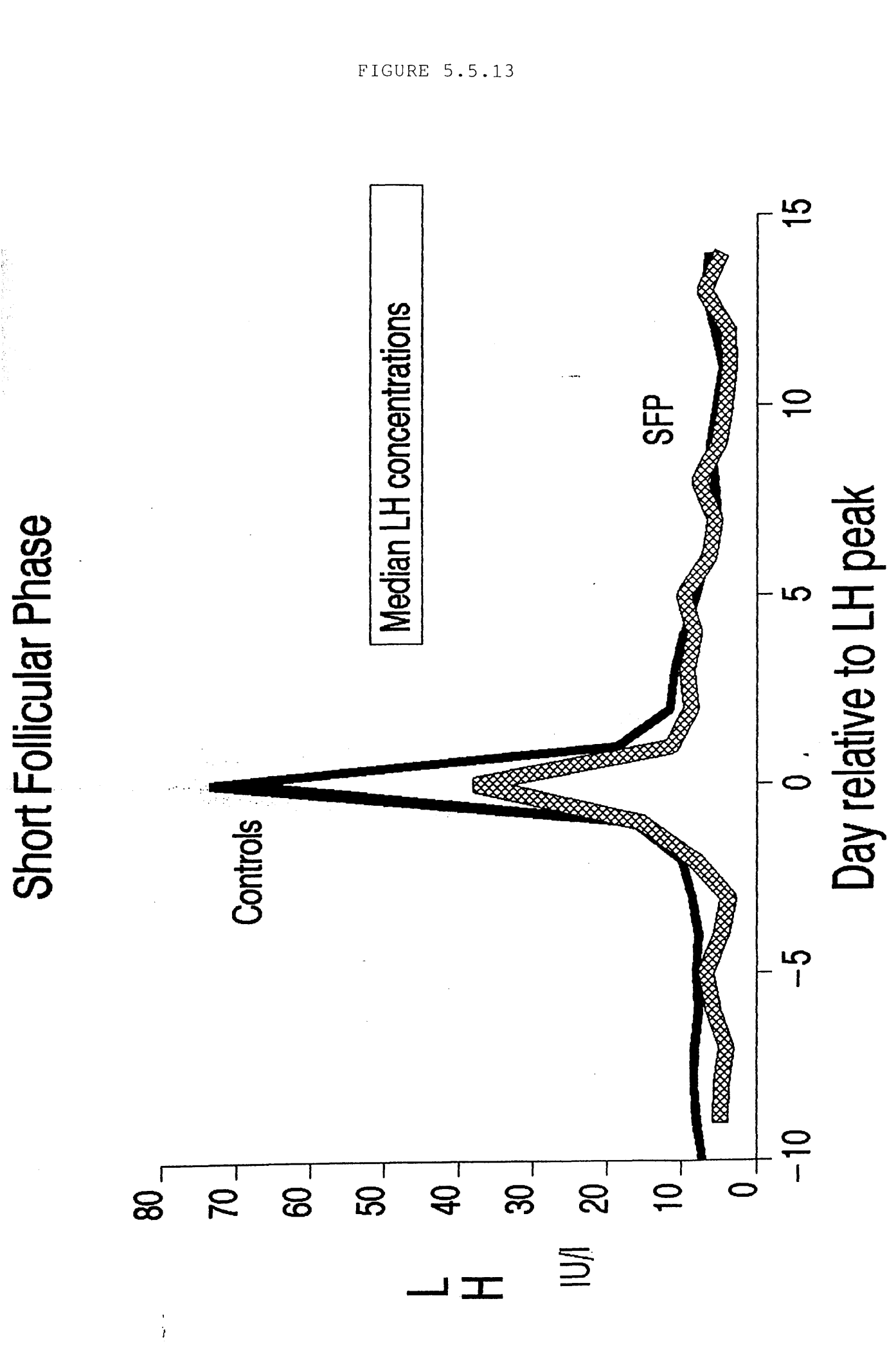

Short Follicular Phase
Median LH concentrations
Controls
SFP
LH IU/l
80
70
60
50
40
30
20
10
0
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.5.17

Short Follicular Phase (10 days or less)

Plasma FSH concentrations (IU/l)

| Day | Nos | Mean | SD | SEM | Median | Range | |
|---|---|---|---|---|---|---|---|
| -9 | 2 | 4.5 | 1.6 | 1.1 | 4.5 | 3.4- 5.6 | |
| -8 | 2 | 4.5 | 0.4 | 0.3 | 4.5 | 4.2- 4.7 | |
| -7 | 3 | 4.9 | 0.7 | 0.4 | 4.5 | 4.4- 5.7 | |
| -6 | 3 | 5.6 | 2.1 | 1.2 | 5.0 | 3.8- 7.9 | |
| -5 | 4 | 6.0 | 2.2 | 1.1 | 6.0 | 4.0- 7.9 | |
| -4 | 5 | 5.0 | 1.6 | 0.7 | 4.6 | 3.2- 7.4 | |
| -3 | 6 | 4.2 | 1.4 | 0.6 | 3.6 | 2.9- 6.5 | |
| -2 | 6 | 4.6 | 1.5 | 0.6 | 4.2 | 2.9- 6.8 | |
| -1 | 6 | 6.6 | 2.4 | 1.0 | 6.6 | 3.4- 9.9 | |
| 0 | 6 | 12.8 | 2.7 | 0.9 | 13.0 | 10.0-17.0 | |
| +1 | 6 | 10.9 | 3.3 | 1.3 | 10.3 | 6.6-16.0 | |
| +2 | 6 | 9.6 | 4.9 | 2.0 | 10.3 | 2.4-15.0 | c |
| +3 | 6 | 8.7 | 5.5 | 2.2 | 8.3 | 2.8-16.0 | b |
| +4 | 6 | 9.2 | 5.2 | 2.1 | 9.0 | 3.4-16.0 | d |
| +5 | 5 | 8.5 | 6.3 | 2.8 | 7.2 | 3.0-18.0 | b |
| +6 | 6 | 5.8 | 4.4 | 1.8 | 6.6 | 3.4-14.0 | b |
| +7 | 5 | 6.9 | 5.2 | 2.3 | 5.3 | 3.6-16.0 | d |
| +8 | 6 | 5.8 | 4.4 | 1.8 | 4.0 | 2.6-14.0 | d |
| +9 | 6 | 4.8 | 4.1 | 1.7 | 3.3 | 1.8-13.0 | c |
| +10 | 6 | 5.0 | 4.0 | 1.6 | 4.1 | 2.4-13.0 | c |
| +11 | 6 | 4.6 | 4.2 | 1.7 | 3.2 | 2.0-13.0 | a |
| +12 | 6 | 4.8 | 3.6 | 1.5 | 3.4 | 2.8-12.0 | |
| +13 | 5 | 5.8 | 3.6 | 1.6 | 4.9 | 2.8-12.0 | |
| +14 | 5 | 6.5 | 3.8 | 1.7 | 6.8 | 2.7-12.0 | |

Significance (Wilcoxon rank sum test) in comparison with controls

a = $p < 0.05$
b = $p < 0.02$
c = $p < 0.01$
d = $p < 0.001$

FIGURE 5.5.14

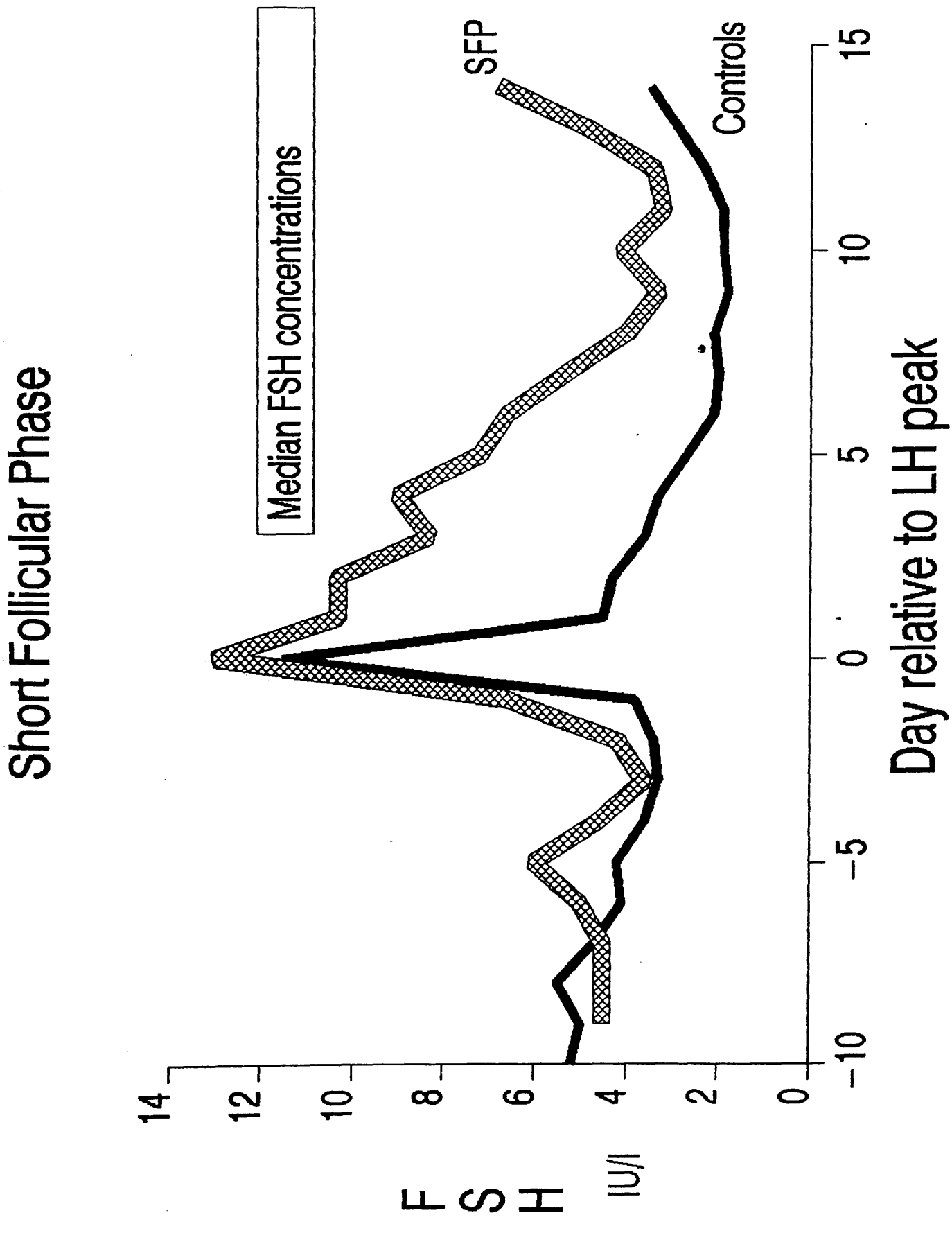

Short Follicular Phase
Median FSH concentrations
SFP
Controls
FSH IU/l
14
12
10
8
6
4
2
0
−10
−5
0
5
10
15
Day relative to LH peak

Table 5.5.18

Short Follicular Phase (10 days or less)

Follicular Diameters (mm)

| Day | Nos | Mean | SD | SEM | Median | Range |
|---|---|---|---|---|---|---|
| -2 | 2 | 13.8 | 1.1 | 0.8 | 13.8 | 13.0-14.5 |
| -1 | 3 | 18.8 | 2.6 | 1.5 | 19.5 | 16.0-21.0 |
| 0 | 4 | 19.3 | 3.0 | 1.5 | 19.0 | 16.0-23.0 |
| +1 | 3 | 18.5 | 0.5 | 0.3 | 18.5 | 18.0-19.0 |
| +2 | 2 | 14.5 | 3.5 | 2.5 | 14.5 | 12.0-17.0 |

No significant differences in comparison with controls
(Wilcoxon rank sum test)

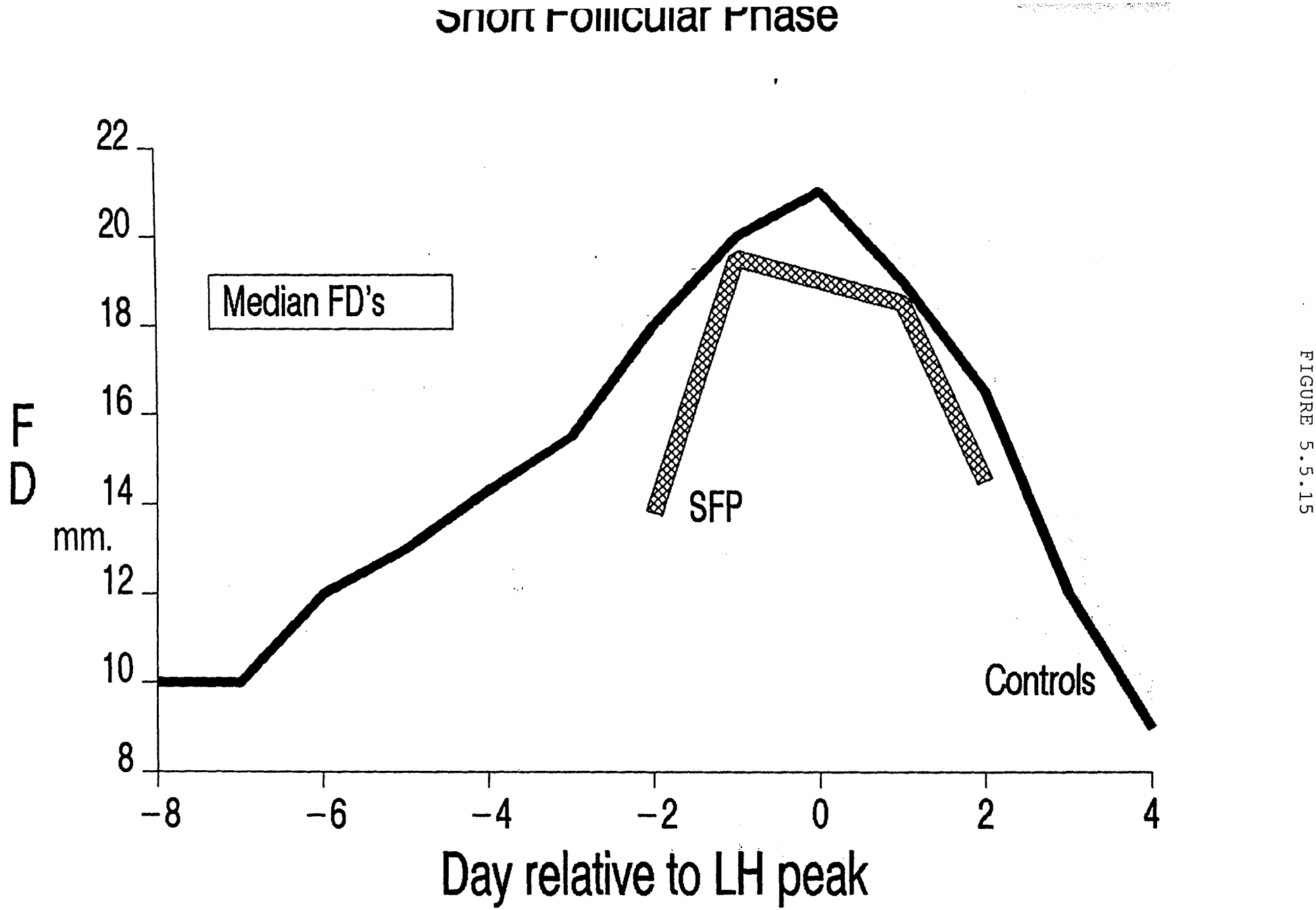

Short Follicular Phase
22
20
18
16
14
12
10
8
F
D
mm.
Median FD's
SFP
Controls
−8
−6
−4
−2
0
2
4
Day relative to LH peak

FIGURE 5.5.15

Table 6.1

Paired Cycle Data

Patient Characteristics

| | Nos | Mean | SD | Median | Range |
|---|---|---|---|---|---|
| AGE (Years) | | | | | |
| | 26 | 30.4 | 4.4 | 30.5 | 21-39 |
| DURATION INFERTILITY (Years) | | | | | |
| | 26 | 4.8 | 1.7 | 4.0 | 3-10 |
| INTERVAL BETWEEN CYCLES (Months) | | | | | |
| | 26 | 3.6 | 2.4 | 3.0 | 1-9 |

Table 6.2

Paired Cycle Data

Cycle Characteristics

| | 1 | | | 2 | | |
|---|---|---|---|---|---|---|
| | Foll | Lut | Tot | Foll | Lut | Tot |
| Nos | 23 | 21 | 24 | 23 | 21 | 24 |
| Mean | 14.0 | 15.1 | 29.0 | 14.0 | 14.1 | 28.1 |
| SD | 4.1 | 1.8 | 4.8 | 3.1 | 1.8 | 4.3 |
| Med | 13.0 | 15.0 | 28.0 | 14.0 | 14.0 | 28.0 |
| Ran | 8-29 | 10-19 | 22-43 | 9-22 | 10-17 | 18-37 |

No significant differences between cycles
(Paired Student's t-test, Wilcoxon Rank Sum Test)

Table 6.3

Paired Cycle Data

Biochemical Indices

| | 1 | | 2 | |
|---|---|---|---|---|
| | E2 Index | P Index | E2 Index | P Index |
| Nos | 23 | 23 | 23 | 23 |
| Mean | 195.3 | 74.6 | 192.7 | 87.8 |
| SD | 37.1 | 24.0 | 41.1 | 30.9 |
| Med | 200.0 | 70.0 | 188.0 | 90.0 |
| Range | 128-284 | 32-150 | 133-277 | 30-162 |

No significant difference between cycles
(Paired Student's t-test, Wilcoxon rank sum test)

Table 6.4

Paired Cycle Data

Biochemical Profiles

| | | Cycle 2 | | |
|---|---|---|---|---|
| | | Normal | Abnormal | Total |
| Cycle 1 | Normal | 1 | 0 | 1 |
| | Abnormal | 11 | 14 | 25 |
| | Total | 12 | 14 | 26 |

Table 6.5

Paired Cycle Data

Biochemical Abnormalities

| | 1 | 2 |
|---|---|---|
| PPS | 17 | 10 |
| PPS-N | 14 | 6 |
| PPS-S | 3 | 4 |
| PFM | 7 | 4 |
| High LH | 5 | 3 |
| Anovulation | 3 | 2 |
| SLP | 1 | 0 |
| SFP | 0 | 1 |
| LFP | 1 | 1 |
| High PRL | 1 | 0 |
| E2 plateau | 1 | 0 |

Table 6.6

Paired Cycle Data

Patients with biochemical abnormalities in both cycles

| | | 1 | 2 |
|---|---|---|---|
| 1. | | (PFM<br>(PPS-N<br>(High LH | (PFM<br>(High LH |
| 2. | * | (PFM<br>(PPS-N<br>(High LH | (PFM<br>(PPS-N<br>(High LH |
| 3. | | High PRL | PPS-N |
| 4. | | PPS-N | PPS-S |
| 5. | * | PPS-S | PPP-S |
| 6. | * | PPS-N | PPS-N |
| 7. | * | PFM | PFM |
| 8. | | Anovulation | Short follic. |
| 9. | * | (PFM<br>(High LH<br>(Anovulation | (PFM<br>(High LH<br>(Anovulation |
| 10. | * | Anovulation | Anovulation |
| 11. | | (PFM<br>(PPS-S | PPS-S |
| 12. | * | PPS-N | PPS-N |
| 13. | * | PPS-N | PPS-N |
| 14. | * | PPS-S | PPS-S |

* : - Patients where abnormality in second cycle was the same as that which occurred in the first.

Table 6.7

Paired Cycle Data

Biochemical Abnormalities : Recurrence Rates

| Abnormality | No in 1 | Total Abn 2 | Same Abn 2 | % Chance same |
|---|---|---|---|---|
| PPS | 17 | 9 (52.9%) | 8 | 88.9 |
| PFM | 7 | 5 (71.4%) | 4 | 80.0 |
| High LH | 5 | 3 (60.0%) | 3 | 100.0 |
| Anovulation | 3 | 2 (66.7%) | 2 | 100.0 |

Table 6.8

Paired Cycle Data

Ultrasonic Profiles

| | | CYCLE 2 | | |
|---|---|---|---|---|
| | | Normal | Abnormal | Total |
| CYCLE 1 | Normal | 6 | 3 | 9 |
| | Abnormal | 9 | 8 | 17 |
| | Total | 15 | 11 | 26 |

Table 6.9

Paired Cycle Data

Ultrasonic Abnormalities

| | Cycle 1 | Cycle 2 |
|---|---|---|
| Luteal cysts | 10 | 6 |
| PFD | 3 | 2 |
| Anovulation | 3 | 2 |
| Twin ovulation | 0 | 1 |
| Non-funct. foll. | 1 | 0 |

Table 6.10

Paired Cycle Data

Patients with ultrasonic abnormalities in both cycles

| | | 1 | 2 |
|---|---|---|---|
| 1. | * | Luteal cyst | Luteal cyst |
| 2. | | Luteal cyst | PFD |
| 3. | * | Luteal cyst | Luteal cyst |
| 4. | | Luteal cyst | Twin ovulation |
| 5. | * | PFD | PFD |
| 6. | * | Anovulation | Anovulation |
| 7. | * | Anovulation | Anovulation |
| 8. | * | Luteal cyst | Luteal cyst |

Table 6.11

Paired Cycle Data

Ultrasonic Abnormalities : Recurrence Rates

| Abnormality | No in 1 | Total Abn 2 | Same Abn 2 | % same |
|---|---|---|---|---|
| Luteal cyst | 10 | 5 (50.0%) | 3 | 60.0 |
| Poor foll. dev. | 3 | 1 (33.3%) | 1 | 100.0 |
| Anovulation | 3 | 2 (66.7%) | 2 | 100.0 |

Table 6.12

Paired Cycle Data

Ultrasonic and Biochemical Abnormalities Combined

| | U/S | Biochemistry |
|---|---|---|
| Cycle 1 | 17 | 25 |
| Cycle 2 | 11 | 14 |

Chi-square significant only for biochemistry
(Chi-square = 10.3, $p < 0.001$)

Table 6.13

Paired Cycle Data

16 patients with abnormalities in both cycles :

| | |
|---|---|
| U/S in both | 1 |
| Biochemistry in both | 7 |
| Combined abnormalities in both | 7 |
| Biochemistry in 1, U/S in 2 | 1 |
| Total | 16 |

Table 6.14

Paired Cycle Data

Maximum follicular diameter (Day 0)

| | 1 | 2 |
|---|---|---|
| Nos. | 10 | 10 |
| Mean | 21.2 | 20.9 |
| SD | 3.3 | 1.8 |
| Median | 21.5 | 21.3 |
| Range | 16-26.5 | 17-22.5 |

Correlation 1 & 2 : Pearson's correlation co-efficient $r = 0.45$
$p = 0.19$

Paired Student's t-test : No significant difference between 1 & 2

$t = 0.32$
$p = 0.76$

Table 6.15

Paired Cycle Data

Side of follicular development

| | | |
|---|---|---|
| Right / Right | 11 | (42.3%) |
| Left / Left | 5 | (19.2%) |
| Right / Left | 4 | (15.4%) |
| Left / Right | 6 | (23.1%) |

No significant difference (Chi-square = 5.95, p = 0.11)

Table 7.1

Peritoneal Fluid Study

CYCLE ANALYSIS

| | | ULTRASOUND | |
|---|---|---|---|
| | | Normal | Abnormal |
| BIOCHEMISTRY | Normal | 16(72.7%) | 4(18.2%) |
| | Abnormal | 1 (4.5%) | 1 (4.5%) |

Table 7.2

Peritoneal Fluid Study

ABNORMAL CYCLES

| ULTRASOUND | BIOCHEMISTRY | DAY OF LAP. |
|---|---|---|
| Small luteal cyst (16mm) | Normal | +12 |
| Contralateral cyst (21mm) | Normal | +5 |
| Poor follicular development | PPS-S | +2 |
| Poor follicular development | Normal | +6 |
| Large ovulatory FD (30mm) | Normal | +5 |
| Normal | PPS-N | +8 |

Poor Follicular Development - Pre-ovulatory follicle <99.9% confidence limit of normal mean.

PPS-S - Subnormal progesterone profile throughout the luteal phase.

PPS-N - Subnormal progesterone profile in the early luteal phase (Days +2 - +6). Values normal thereafter.

Table 7.3

Peritoneal Fluid Study

Day of Laparoscopy

| GROUP | LAPAROSCOPY DAY | NUMBER OF PATIENTS |
|---|---|---|
| Punctum | +2 | 2 |
| | +4 | 2 |
| | +5 | 3 |
| | +6 | 1 |
| | +7 | 5 |
| | +8 | 2 |
| | +12 | 1 |
| Equivocal punctum | +3 | 1 |
| | +12 | 2 |
| LUF | +5 | 1 |
| | +6 | 1 |
| | +9 | 1 |

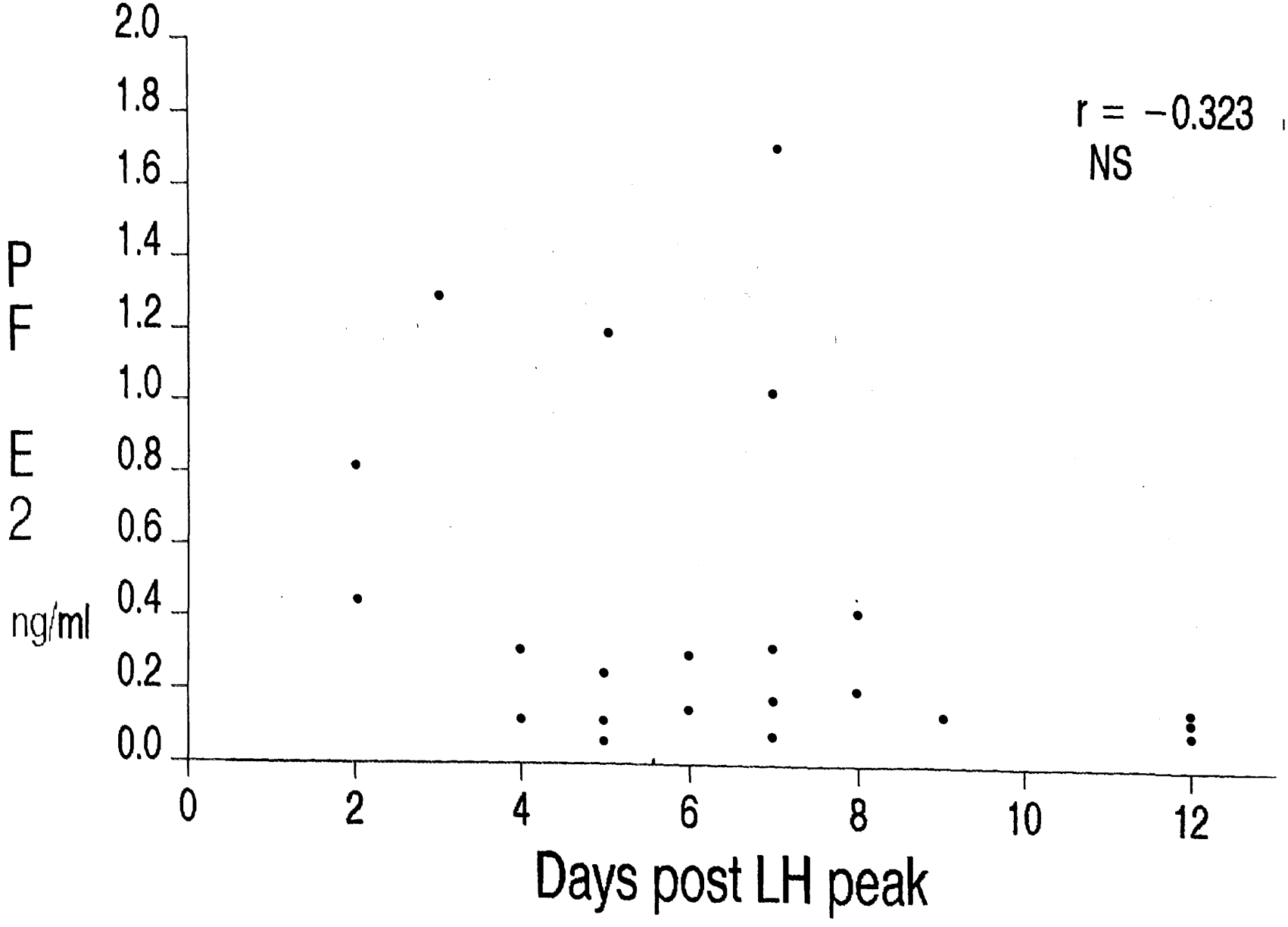
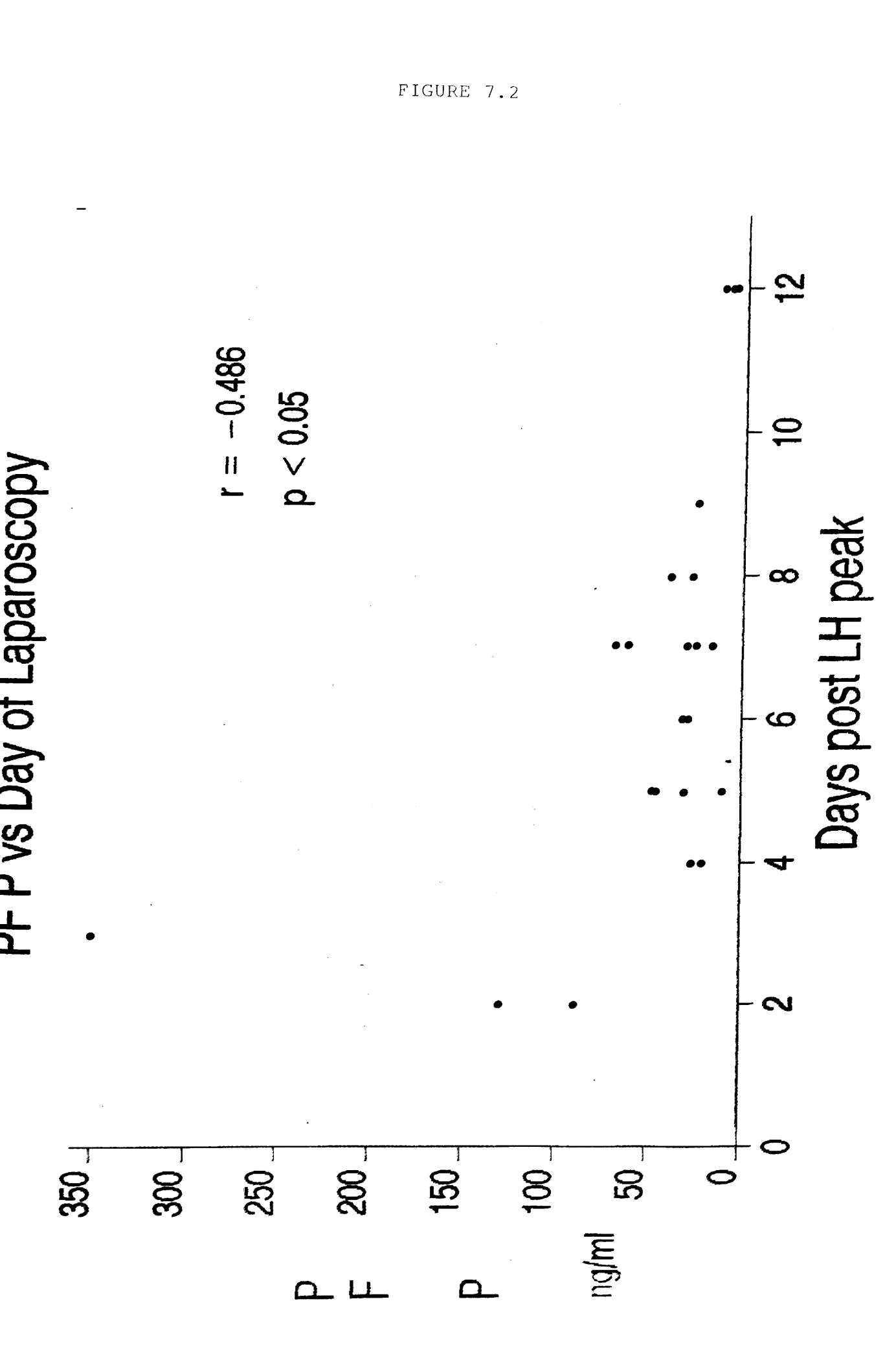

PF E2 vs Day of Laparoscopy
r = −0.323
NS
PF E2 ng/ml
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
Days post LH peak

FIGURE 7.1

A

FIGURE 7.2


PF P vs Day of Laparoscopy
r = −0.486
p < 0.05
PF P ng/ml
350
300
250
200
150
100
50
0
0
2
4
6
8
10
12
Days post LH peak

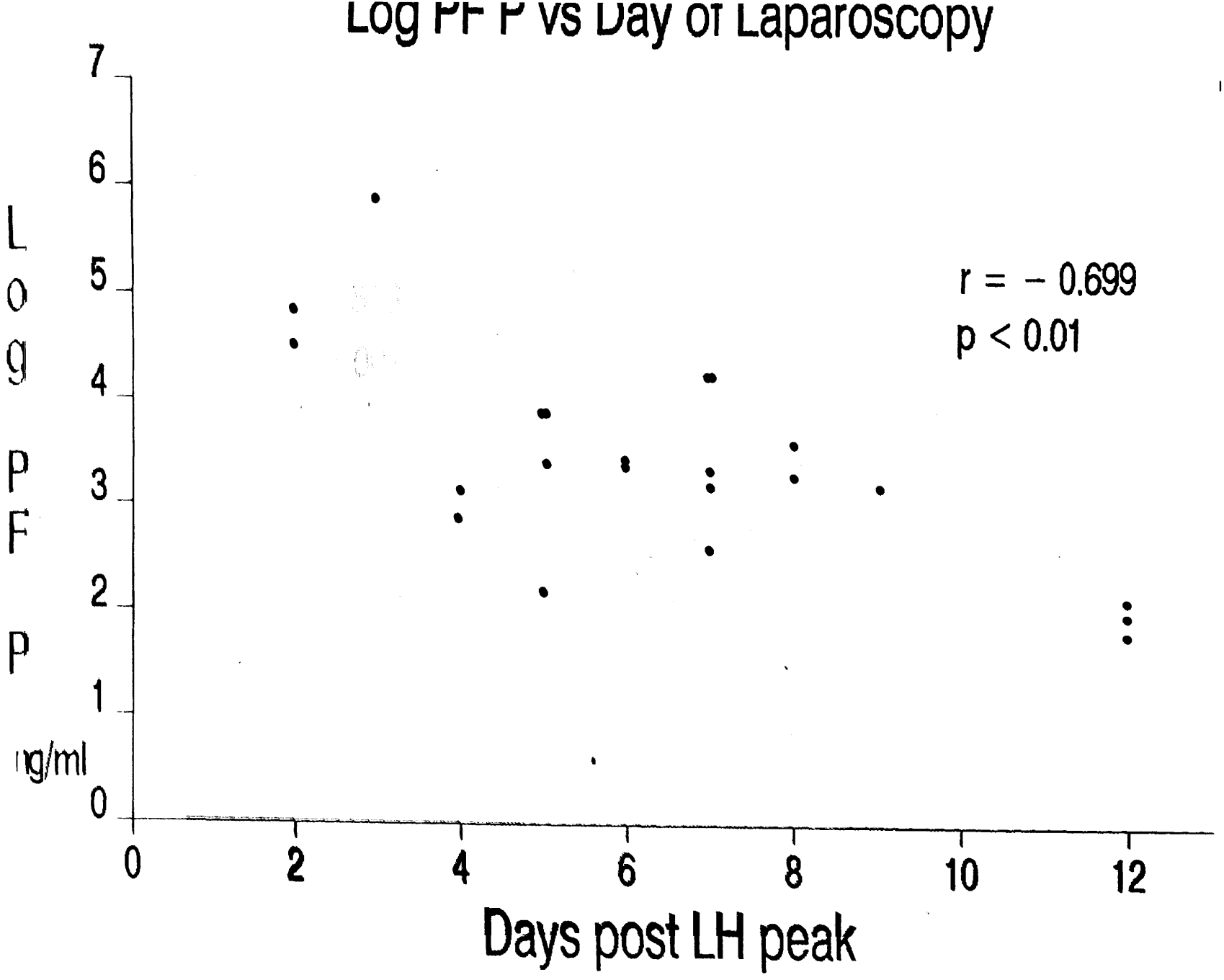
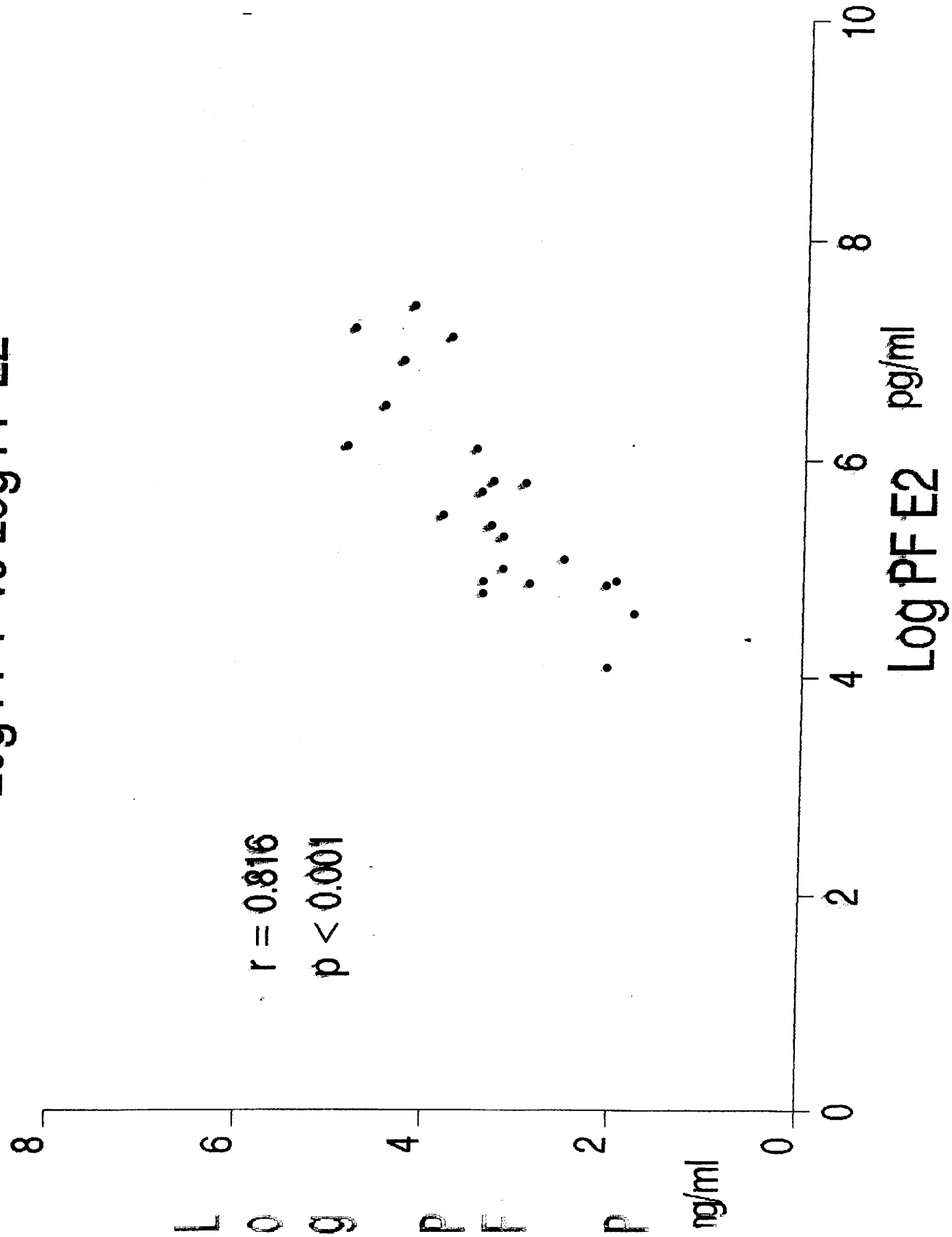

Log PF P vs Day of Laparoscopy
Log PF P ng/ml
7
6
5
4
3
2
1
0
r = − 0.699
p < 0.01
0
2
4
6
8
10
12
Days post LH peak

FIGURE 7.3

FIGURE 7.4


Log PF P vs Log PF E2
r = 0.816
p < 0.001
Log PF P ng/ml
Log PF E2 pg/ml
0
2
4
6
8
10

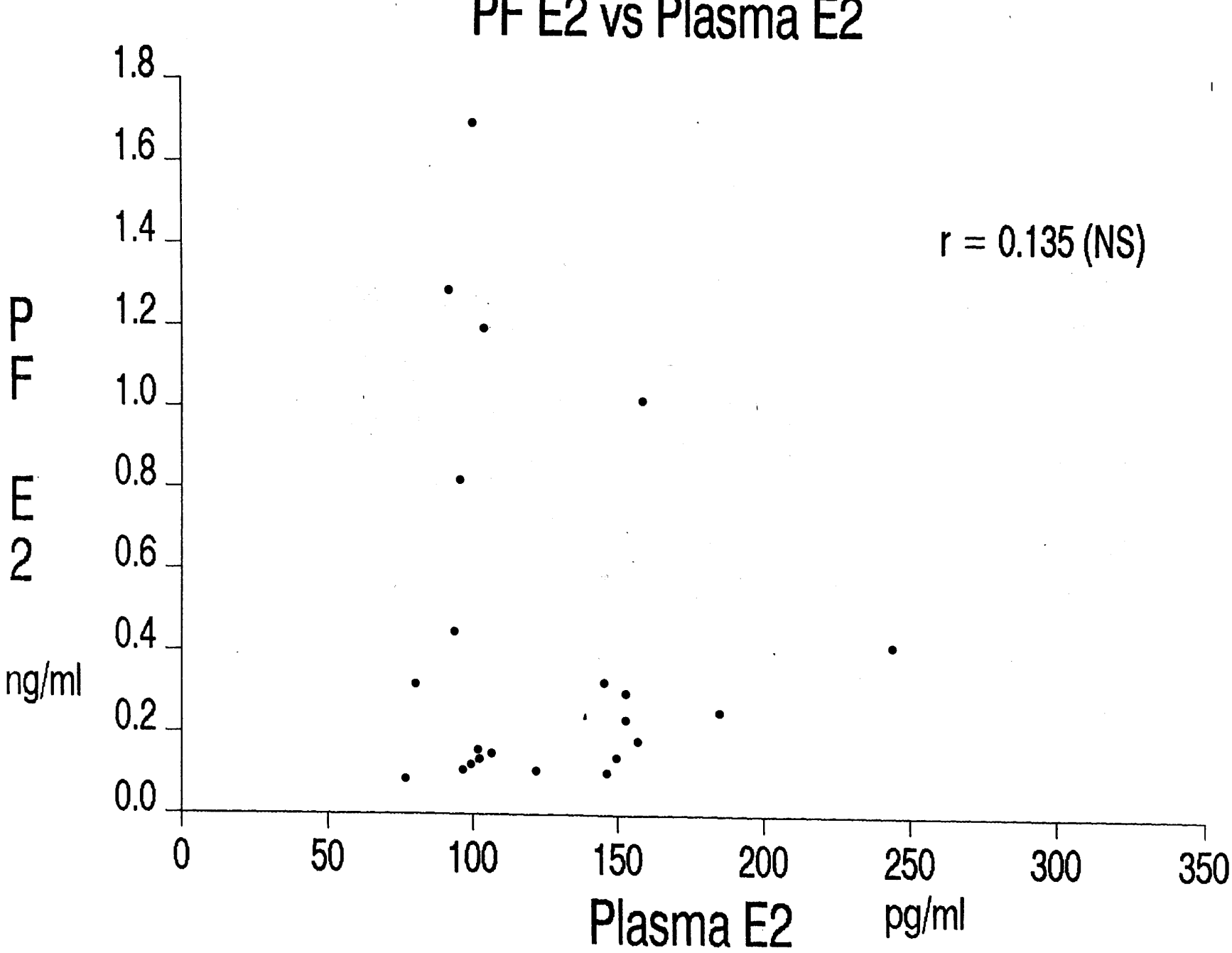

PF E2 vs Plasma E2
r = 0.135 (NS)
PF E2 ng/ml
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
300
350
Plasma E2 pg/ml

FIGURE 7.5

FIGURE 7.6

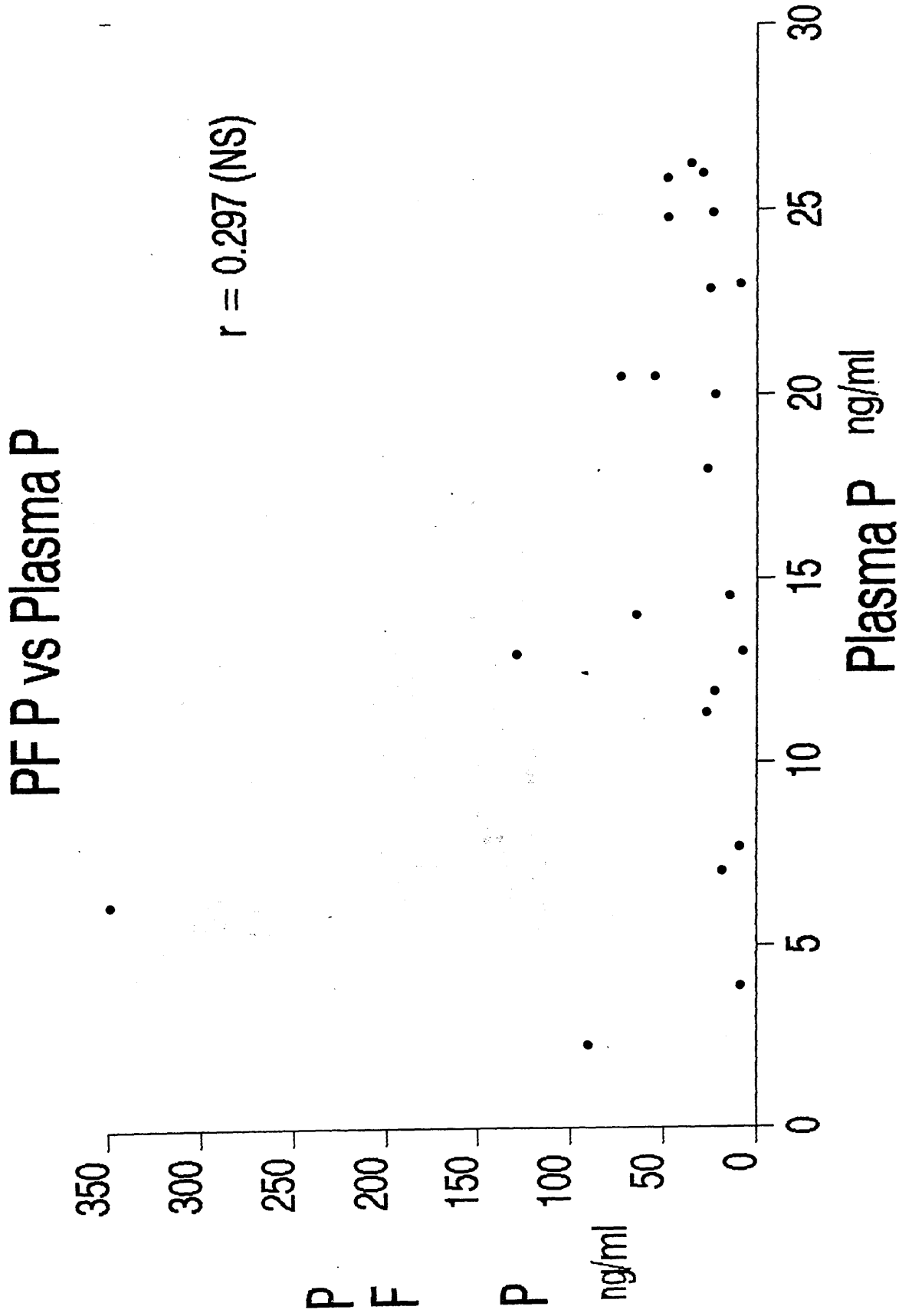

PF P vs Plasma P
r = 0.297 (NS)
PF P ng/ml
Plasma P ng/ml
350
300
250
200
150
100
50
0
0
5
10
15
20
25
30

FIGURE 7.7

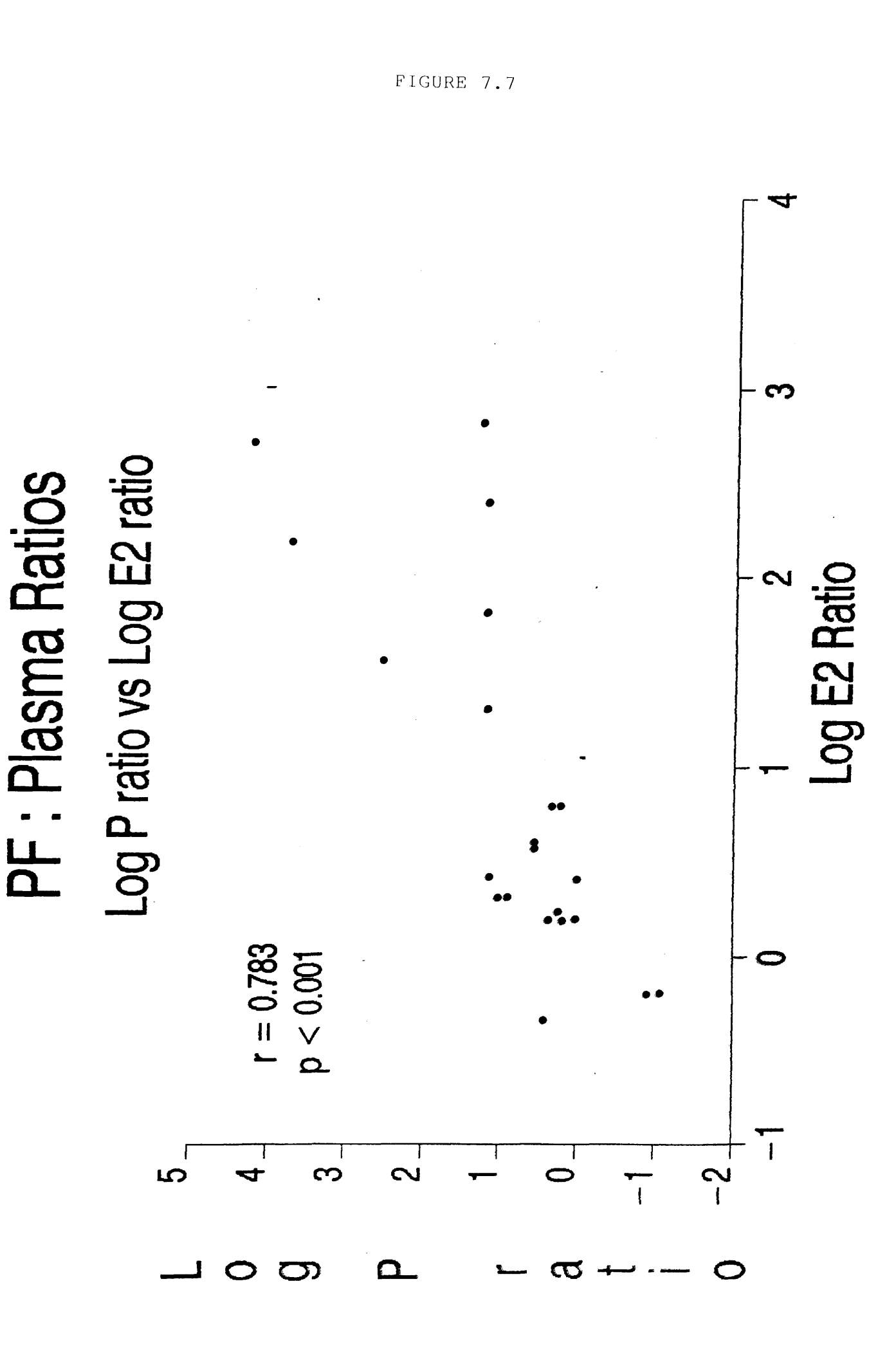

PF : Plasma Ratios
Log P ratio vs Log E2 ratio
r = 0.783
p < 0.001
Log P ratio
Log E2 Ratio
5
4
3
2
1
0
−1
−2
−1
0
1
2
3
4

FIGURE 7.8

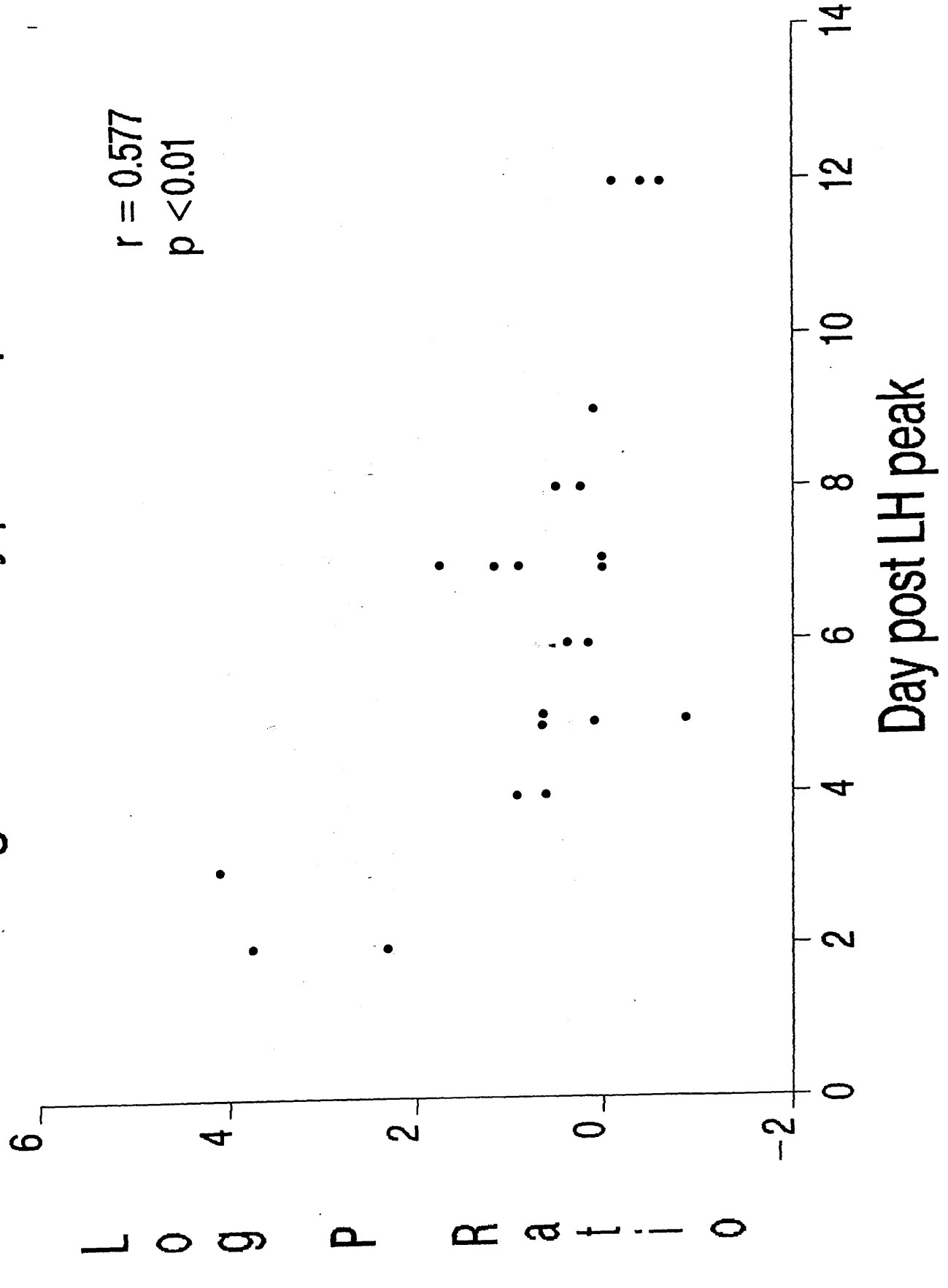

Log P ratio vs Day post LH peak
r = 0.577
p < 0.01
Log P Ratio
6
4
2
0
−2
0
2
4
6
8
10
12
14
Day post LH peak

FIGURE 7.9

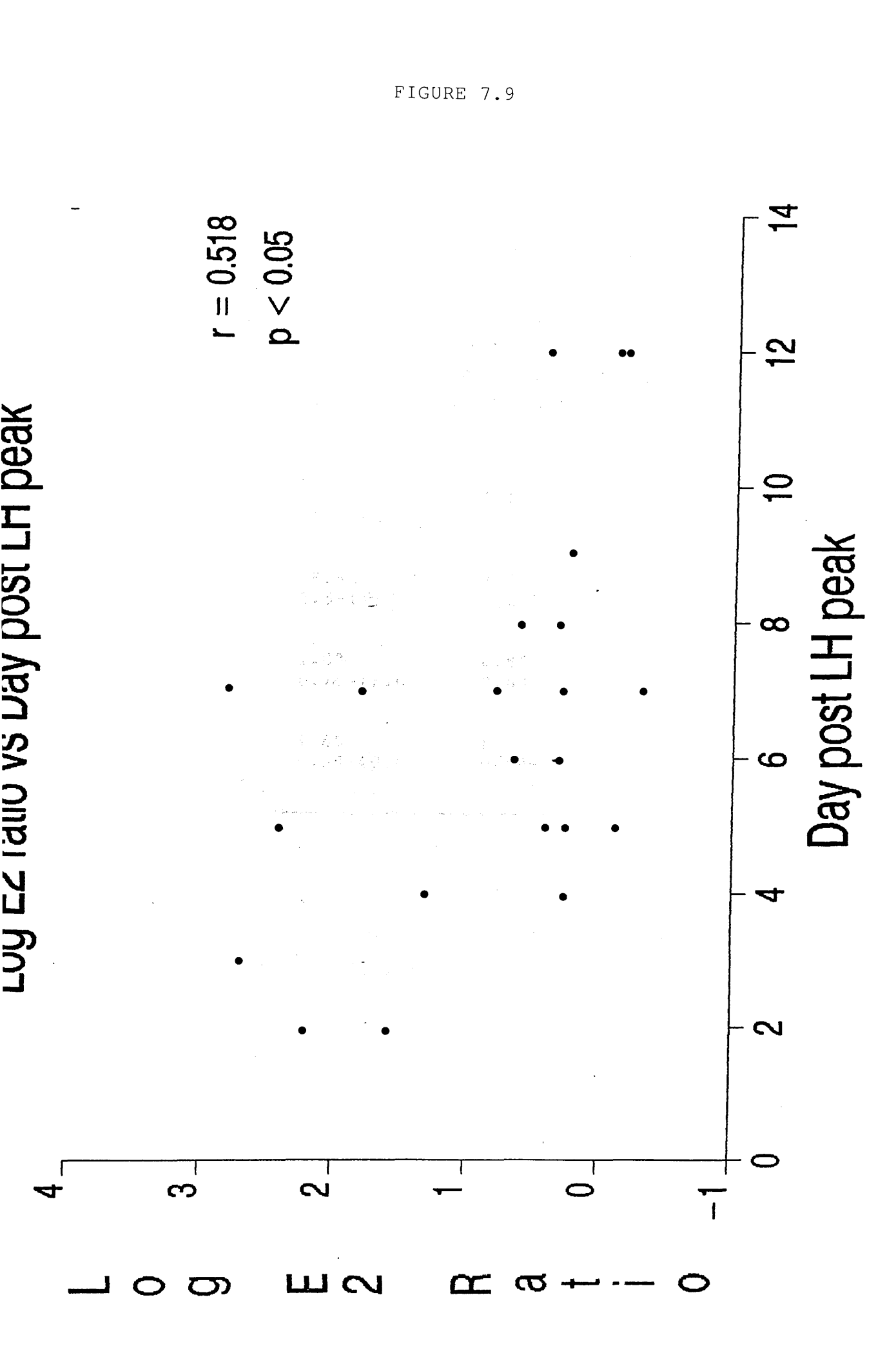

Log E2 Ratio vs Day post LH peak
r = 0.518
p < 0.05
Log E2 Ratio
Day post LH peak
4
3
2
1
0
−1
0
2
4
6
8
10
12
14

Table 7.4

Peritoneal Fluid Study

STEROID LEVELS (pg/ml) IN CL SUB-GROUPS

| | | PUNCTUM | EQUIVOCAL | LUF |
|---|---|---|---|---|
| No. of patients | | 16 | 3 | 3 |
| PF E2 | | | | |
| | median | 307.5 | 130 | 140 |
| | range | 70-1700 | 100-1300 | 125-145 |
| PF P | | | | |
| | median | 28.9 | 7.5 | 30.0 |
| | range | 8.5-131.0 | 6.0-350.0 | 23.8-30.4 |
| E2 ratio | | | | |
| | median | 1.83 | 0.87 | 1.28 |
| | range | 0.75-17.0 | 0.83-14.4 | 1.26-1.23 |
| P ratio | | | | |
| | median | 1.85 | 1.58 | 1.19 |
| | range | 0.39-40.0 | 0.58-58.3 | 1.15-1.48 |

Table 7.5

Peritoneal Fluid Study

STEROID LEVELS (pg/ml) & ENDOMETRIOSIS

| | | NO ENDOMETRIOSIS | ENDOMETRIOSIS |
|---|---|---|---|
| Number of patients | | 12 | 10 |
| PF E2 | | | |
| | Median | 370 | 206.5 |
| | Range | 100-1700 | 70-820 |
| PF P | | | |
| | Median | 33.0 | 25.8 |
| | Range | 6.0-350.0 | 8.5-89.5 |
| E2 ratio | | | |
| | Median | 1.99 | 1.43 |
| | Range | 0.75-17.0 | 0.87-8.81 |
| P ratio | | | |
| | Median | 2.16 | 1.39 |
| | Range | 0.58-58.3 | 0.39-40.7 |

Table 7.6

Peritoneal Fluid Study

PATIENTS WHO CONCEIVED SUBSEQUENTLY

| Patient | Pregs. | Punctum | Endometr. | U/S | Biochemistry |
|---|---|---|---|---|---|
| 1 | 1 | Yes | No | Normal | Normal |
| 2 | 1 | LUF | No | Normal | Normal |
| 3 | 1 | Yes | No | Normal | Normal |
| 4 | 2 | Yes | Yes | Normal | Normal |
| 5 | 1 | Yes | Yes | Normal | PPS-N |
| 6 | 2 | Equiv | No | Normal | Normal |

Table 7.7

Peritoneal Fluid Study

STEROID CONCENTRATIONS IN PATIENT WITH GREATEST CYCLE ABNORMALITY

| | E2 (pg/ml) | P (ng/ml) |
|---|---|---|
| Plasma | 95 | 2.2 |
| Peritoneal fluid | 820 | 90 |
| Corpus luteum | 7800 | 1000 |
| 1cm cyst | 2100 | 20.5 |