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AN ANALYSIS OF SUBSEQUENT PREGNANCIES IN WOMEN REQUIRING OVULATION INDUCTION

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To My Parents

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ABSTRACT

Numerous studies have been published concerning both the various diseases which cause dysfunctional ovulation, and the pregnancy induction success rates of the medical and surgical therapy for these disorders. However, little work has been done to determine the necessity for ovulation induction in subsequent pregnancies in women with these syndromes. In this study I analyzed 103 patients with dysfunctional ovulation who had conceived once with ovulation inducing agents. Of these, 36 patients were interested in achieving another pregnancy. Twenty-five of these patients (69%) conceived spontaneously the second time ($p<0.1$). Intermittent ovulation or psychogenic factors are hypothesized to explain this significant rate of spontaneous pregnancy.

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1. INTRODUCTION

One of every five American couples are infertile. Of these, between 13 and 50% have ovulatory factors contributing to their infertility.[1-6] Numerous studies have been published concerning both the various diseases causing dysfunctional ovulation, and the medical and surgical therapy for these disorders. These studies have included successs rates in terms of both ovulation induction and pregnancy for each of these treatments. However, little work has been done to determine the necessity of ovulation induction in subsequent pregnancies. In light of the expense and often undesirable side effects of the current pharmacologic therapy for infertility, it is important to be able to advise the infertile couple as to what the probability would be of spontaneously conceiving in future pregnancies, given a history of a particular ovulatory dysfunction.

2. BACKGROUND

DISORDERS CAUSING OVULATORY FAILURE

There are many disorders which cause primary and secondary amenorrhea. These include primary ovarian failure, primary hypothalamic failure, primary pituitary failure, hyperprolactinemia, polycystic ovary disease, luteal deficiency, and hypothalamic feedback disorders.[7] In the following sections, I will address those disorders which are most frequently seen in an infertility practice and are most amenable to treatment. These include polycystic ovary disease, short luteal phase, hyperprolactinemia, and hypothalamic dysfunction.

I. POLYCYSTIC OVARY DISEASE

In 1935, Drs. Irving Stein and Michael Leventhal described a syndrome consisting of amenorrhea, infertility, and hirsutism associated with bilateral polycystic ovaries.[8] They employed pneumoroentgenography to diagnose the abnormal ovaries and initially used intramuscular injections of estrogenic preparations for treatment, with little success. They reported seven cases of patients who became normoovulatory after bilateral ovarian wedge resection, a procedure which entailed removing a portion of the

cystic cortex of the ovaries. Their hypothesis for the etiology of amenorrhea and sterility in patients with this syndrome was based on mechanical considerations; they reasoned that the crowded abnormal cysts prevented normal graafian follicles from migrating to the surface of the ovary preparatory to ovulation.

Since the original work by Stein and Leventhal, there has been much work done on the etiology, diagnosis, and treatment of this disease, which is thought by many to encompass several discrete syndromes. This is illustrated by the work of Goldzieher and Axelrod who analyzed 1097 cases from 187 reports of surgically documented polycystic ovaries.[9] The incidence of clinical symptoms varied widely amongst the reports, however, the mean incidence of the various symptoms were as follows: infertility 74%, hirsutism 69%, amenorrhea 51%, obesity 41%, functional bleeding 29%, dysmenorrhea 23%, corpus luteum at operation 22%, virilization 21%, biphasic basal temperature 15%, cyclic menses 12%. The authors conclude from these statistics that Stein and Leventhal described only a small fraction of the spectrum of polycystic ovary disease (PCOD). This has presented a problem in terms of clinical diagnosis, therefore, endocrinological studies have been turned to as an aid in diagnosis. Yen et al showed abnormal gonadotropin secretion in patients with documented polycystic ovaries.[10] The serum luteinizing hormone (LH) secretory

pattern consisted of erratic fluctuations with a high baseline, instead of the cyclical pulsatile secretion found in normal women. The mean serum follicle stimulating hormone (FSH) concentrations were lower than normal during early follicular phase and comparable to normal during late follicular phase. DeVane et al measured hormone concentrations in 19 PCOD patients and 10 normal women.[11] They found significantly higher concentrations of estrone, testosterone, androstenedione, and LH in the serum of the PCOD patients compared to normals. FSH and estradiol levels, however, were comparable in the two groups.

Since the initial report by Stein and Leventhal, there has been much speculation as to the pathogenesis of the polycystic ovary syndrome. Their mechanical barrier theory, mentioned previously, has been discredited as have the ideas of Miklowski and McCosker who postulated autoimmunity to gonadotropins as the cause of polycystic ovary formation[12] and Reynolds who believed that increased hydrostatic pressure in the ovarian vasculature led to the transudation of fluid into the follicles, causing cyst formation.[13] These theories have been discarded in the face of increasing knowledge of the neuroendocrine interrelationship between the hypothalamus, pituitary and ovaries.

A recent comprehensive consideration of the endocrinology of the menstrual cycle includes a hypothesis of the cause of polycystic ovary disease as follows.[14] Aromatization of thecal

cell androgens to estrogens early in the follicular phase occurs in the granulosa cells. A positive feedback mechanism exists allowing FSH and estrogen together to raise the concentration of FSH receptor. Androgen receptors are also present in the cytoplasm of the granulosa cells. At low androgen concentrations, the androgens enhance their own aromatization to estrogens. At higher concentrations, however, androstenedione is converted to more potent androgens, rather than to estrogens. These androgens, in turn, cannot be converted to estrogens. Simultaneously, the decrease in local estrogens impairs FSH receptor formation so that FSH induction of aromatization is diminished, further decreasing ovarian estrogen production. Follicles, therefore, become atretic instead of developing naturally.

As for the cause of elevated androgen levels in these patients, recent work has demonstrated that in patients with PCOD, there is enhanced bioactivity of LH.[15] Since LH induces androgen synthesis by the theca cells, this may partially explain the elevated androgen levels in these patients. It has also been shown that there is an increased sensitivity to luteinizing hormone releasing hormone (LHRH) in PCOD patients which leads to the increased release of LH found in this syndrome.[16] This may result from chronically elevated circulating estrogen levels caused

by peripheral conversion of androstenedione to estrogen in the adipose tissue of these frequently obese patieents. By direct action on the pituitary, these elevated estrogens can augment pituitary sensitivity to LHRH.[17] Another explanation for the state of androgen excess is that PCOD patients have a decrease in testosterone-binding globulin (TeBG). In normal women 96% of circulating testosterone is bound to TeBG, while in PCOD women only 92% of the hormone is bound. Thus, these patients have not only higher serum testosterone levels, but also a higher percentage of the hormone is available for biological activity.[18]

Treatment of PCOD

Initial reports of successful management of PCOD in terms of promoting cyclic ovulation and fertility were based on surgical treatment. Stein and Leventhal reported a 100% success rate in inducing ovulation in their first series of patients with a 30% pregnancy rate.[8] In a later series reported by Stein and Cohen 90% of the patients became ovulatory and 60% achieved pregnancy.[19] In the review of 1097 cases by Goldzieher and Axelrod, the mean frequency of restoration of regular cycles was 80% and of pregnancy was 63%, tabulated from 187 reports.[9] Judd et al showed that ovarian wedge resection resulted in a significant transient reduction of ovarian androstenedione and a persistent reduction of testosterone secretion.[20] Katz et al reported

that postoperatively the LH:FSH ratio decreased significantly and cyclic gonadotropin activity was noted during the first week. During the second postoperative week there was an estradiol surge followed by LH and FSH peaks. This led to ovulation by the end of the first postoperative month. They also noted an intraoperative fall in plasma estradiol concentration.[21] This may lead to facilitation of FSH secretion which may cause follicular development and consequent ovulation.[12]

With the development of hormonal therapy for dysfunctional ovulation, ovarian wedge resection was relegated to a treatment of last resort. This was especially true in light of the fact that reports of failure due to postoperative complications began to appear in the literaure. For example, Toaff et al reported on seven cases of wedge resection failure.[22] At laparoscopy, all patients exhibited extensive periovarian and peritubal adhesions. In addition, they noted one case of bilateral and two cases of unilateral ovarian atrophy.

The unexpected action of clomiphene citrate (Clomid) in promoting ovulation in anovulatory women was discovered in the early 1960's while testing the compound for contraceptive effectiveness.[23,24] The first report of its efficacy for treating PCOD patients is found in a series of four patients studied by Kistner and Smith.[25] All four of their patients became

ovulatory as a result of this therapy, three of whom achieved pregnancy. Later it was determined that Clomid acts as a competitive inhibitor of estrogen binding to pituitary receptors, thus interrupting negative feedback on FSH secretion.[26] Reports of success rates for Clomid in inducing ovulation in PCOD patients range from 60 to 90% with an approximately 20% pregnancy rate.[24,27,29] By causing an increase in FSH secretion, Clomid induces follicular maturation and a pre-ovulatory FSH and LH peak occurs three to nine days after cessation of therapy leading to ovulation.[30]

In patients who do not respond to Clomid, human menopausal gonadotropins (HMG) is the next therapy of choice. As early as the 1940's animal experiments showed successful induction of ovulation using homologous pituitary extracts. Van Wagenen and Simpson used FSH from rhesus monkey pituitaries mixed with human gonadotropin to induce ovulation in both mature and immature rhesus monkeys.[31] In an early test on 40 women using a partially purified human pituitary preparation of FSH, Gemzell et al found polycystic enlargement of the ovaries and highly elevated urinary estrogen levels.[32] In the PCOD women tested, ovulation was induced within three days of treatment.

It is interesting to note one study of FSH administration in PCOD patients. Keetel et al observed marked ovarian enlargement after therapy as opposed to controls who showed no change in

ovarian size.[33] They concluded from this that FSH administration, followed by bimanual pelvic examination, was a good clinical test for the presence of polycystic ovaries.

The dose of human gonadotropins has been standardized recently; the most commonly used preparation in Pergonal, an ampule of which consists of 75 IU FSH and 75 IU of LH purified from the urine of postmenopausal women. Human chorionic gonadotropin (HCG) has biological properties which are similar to LH. It is obtained from the urine of pregnant women and is used in conjunction with Pergonal to induce ovulation of the mature follicle.

Van de Wiele et al reported a series of 35 patients with dysfunctional ovulation treated with the combined regimen of Pergonal and HCG.[34] Ten of these patients had PCOD, three were status post failed wedge resections. All of these patients ovulated while receiving this therapy. Thompson and Hansen published a computer tabulation of results of Pergonal therapy of 1,286 patients from 100 investigators.[35] Of these patients, 212 had proven or probable polycystic ovary disease. Sixty-two percent of the cycles, representing 76% of patients ovulated with various combinations of menotropins and/or clomiphene, with a pregnancy rate of only 26%. Of these pregnancies, 39% resulted in abortion, and 17% yielded multiple gestations. There was a 1.1% incidence of hyperstimulation syndrome. This was comparable with the incidence of hyperstimulation in other patient categories, which does

not support earlier reports that PCOD patients are more prone to hyperstimulation than other patients with dysfunctional ovulation. A more recent report of combination HMG-HCG treatment for PCOD yielded higher ovulation, pregnancy, and complication rates.[36] Of 41 women treated, there was a 97.4% rate of ovulatory cycles (number of patients represented by this unreported), a 65.9% pregnancy rate, a 36.3% multiple gestation rate, a 24.1% abortion rate, and an 11.7% rate of ovarian hyperstimulation. It was concluced that while the pregnancy rate was the same as in women with anovulation for other reasons, the incidence of spontaneous abortion and hyperstimulation was higher.

In light of the high incidence of undesirable complications of this therapy, recent trials have sought to modify the HMG-HCG treatment in an attempt to prevent these side effects. Kamrava et al tried using low-dose FSH alone to induce ovulation in two PCOD patients.[37] Both patients became pregnant, with one aborting at 10 weeks. The authors reasoned that with the already high LH levels in PCOD patients, the addition of exogenous LH might be the causal factor in hyperstimulation and multiple pregnancy. The efficacy of FSH alone in reducing complications while inducing ovulation requires further study.

Corticosteroids and oral contraceptives are other medical treatments for PCOD. Since they do not enhance fertility, but are sometimes useful for the relief from other symptoms of PCOD, they will not be considered further here.

II. INADEQUATE LUTEAL PHASE

The corpus luteum is the main source of luteal phase progesterone.[14] McNatty delineated three conditions which must be fulfilled in order for a follicle to become a functioning corpus luteum.[38] These include: (1) sufficient granulosa cells in the follicle prior to ovulation (2) the granulosa cells must be able to produce enough progesterone (3) both the granulosa and theca cells must have sufficient LH receptors to be responsive to that hormone. The importance of the evaluation of the luteal phase in infertility was first described by Jones in 1949.[39] In her population of infertility patients in whom anatomic factors had been ruled out, 14% of the cycles studied exhibited inadequate luteal phase on the basis of basal body temperature charts, while 50% showed luteal defects when endometrial biopsies were used for diagnosis. Jones advocated elimination of excessive alcohol intake and smoking, and adequate rest and dietary protein in addition to 60 milligrams of pregneninolone daily as therapy for this disorder.

Later reports have given a range of 3 to 10% incidence of short luteal phase in infertile women.[40,41] Since Jones' initial publication, there have been many attempts to explain the pathophysiology of this entity and also much controversy over the optimal means of diagnosis. Strott et al noted that after the

midcycle LH surge in these patients, lower than normal amounts of progesterone were secreted leading to endometrial sloughing only six to eight days later.[42] They hypothesized that the short luteal phase was due to deficient preovulatory FSH levels leading to inadequate luteinization. DiZerega and Hodgen point out that numbers of progesterone and estradiol receptors in the endometrium vary during the menstrual cycle depending on the circulating steroid levels.[43] They cite animal studies which indicate that for implantation to occur, a certain level of steroid receptors must be present in the endometrium. This could explain why a a deficiency in progesterone would not permit nidation. In addition, there is evidence that probably for the same reason, defective corpora lutea are unable to respond to HCG, which normally allows maternal recognition of pregnancy.[43]

In addition to the importance of the accumulation of sufficient LH receptors during the follicular phase to ensure luteinization and normal functioning of the corpus luteum, it is necessary that low-density-lipoproteins (LDL) be available as a source of cholesterol for progesterone synthesis.[14] After ovulation, a vascularization of the granulosa occurs. This allows LDL to reach the luteinized granulosa to be used in progesterone synthesis. Another corpus luteum function is continued tonic LH secretion after the LH surge.

It is apparent then, that both adequate folliculogenesis and maintenance of the corpus luteum after ovulation are necessary for normal endometrial implantation to occur.

There have been various methods proposed for diagnosing this condition. In Jones' original article, she advocated premenstrual endometrial biopsy as the diagnostic test of choice.[39] Almost 30 years later, she still recommended this method of diagnosis.[40] If the biopsy is out of phase by two or more days, another biopsy should be obtained in a later cycle to confirm the findings. The biopsy is dated according to the histologic criteria of Noyes et al.[44] Soules et al agree that the method of choice for diagnosis of luteal phase defects is endometrial biopsy and advocates using the menstrual period following the biopsy as the reference point.[45] Other studies also favor endometrial biopsies as a diagnostic technique.[46,47]

Serum progesterone determinations have also been used for diagnosis. Israel and colleagues determined that progresterone values of 3 ng/ml or greater obtained between 11 and four days prior to the onset of menstruation could be used as presumptive evidence of ovulation.[48] The advantage of this method over endometrial biopsy is the ease and minimal discomfort of performing a venipuncture as opposed to the pain involved with a biopsy. Other investigators also believed that a single, well-timed serum

progesterone assay is more accurate than a single endometrial biopsy for evaluation of luteal function.[49] Abraham et al, however, challenged the accuracy of a single progesteone determination and recommended a more complicated scheme for determining adequate luteal function based on three progesterone measurements.[50] They calculated that from 4 to 11 days before menstruation, three separate progesterone determinations taken from the same cycle would total 15 ng/ml or greater if the cycle was normal. If the sum of the three progesterone levels equaled less than this amount, then this indicated abnormal luteal function. The disadvantage of this technique is its relative inconvenience in that three venipunctures at different times during one week are required.

A third method of diagnosing luteal problems is using basal body temperature graphs. Jones criticized this approach, stating that some women have a poor thermogenic response to progesterone which would give a false positive indication of a luteal defect.[40] In addition she notes the usual problems of temperature curves due to patient inconsistencies in methodology.

Today most clinicians employ the endometrial biopsy to diagnose abnormal cycles. It should be performed two days before the expected onset of menses because at that time the endometrium reflects stimulation by progesterone for almost the entire life span of the corpus luteum.[51]

Treatment of Inadequate Luteal Phase

There have been many pharmacological treatments described for short luteal phase. In light of the low serum progesterone levels present in this condition, progesterone replacement is often efficacious. A 50 to 70% pregnancy rate has been reported with progesterone therapy.[52,54] Moszkowski and associates reported successful correction of the luteal defect using various forms of progesterone replacement including oral, sublingual, intramuscular, and suppository treatment.[55] These results were later confirmed.[56] Of these routes of administration, it has been shown that synthetic oral progestagens may suppress endogenous production of progesterone by the corpus luteum.[57] Therefore, this form of progesterone replacement should not be employed to treat women with short luteal phase.

As mentioned before, levels of serum FSH indirectly influence the status of the corpus luteum by its effect on the developing follicle, while LH is necessary to prolong luteal function. For this reason clomiphene, an anti-estrogen, has been recommended to treat short luteal phase since it causes an increase in serum gonadotropins.[58-60] Echt et al reported a 21% pregnancy rate using this drug.[61] Another series of 26 patients only had an 11% pregnancy rate.[62] The authors of this report went on to treat those patients who had failed Clomid therapy with progesterone

suppositories. Many of these patients successfully conceived. Therefore, they concluded that Clomid is not the drug of choice for treating short luteal phase. Another argument against the use of Clomid for short luteal phase is that Clomid itself has been shown by some to cause luteal phase defects[63,64] This controversy has not been resolved.

In order to directly increase levels of circulating gonadotropins, human menopausal gonadotropin may be administered. This treatment for inadequate luteal phase was first described by Shapiro in 1972.[65] He reported on a patient who did not respond to combination Clomid and HCG therapy, but did become pregnant using Pergonal and HCG. Jayle and Palmer quoted two reports from the French literature where HMG and HCG, and HMG alone were used to treat luteal insufficiency.[58] In the former, by Palmer and Kamoun, 32% of the patients became pregnant. Sixty-three of the births were normal; five percent of the pregnancies were ectopic, and 29% resulted in spontaneous abortions. Using the HMG alone Jayle et al achieved a 50% pregnancy rate, using higher doses of HMG than Palmer and Kamoun. In a recent report patients who had failed high dose Clomid or Clomid plus HCG were treated with sequential HMG and HCG.[66] Of those patients with poor corpus luteum function, 50% became pregnant with this treatment. Of these pregnancies, 13% ended in spontaneous abortions, and five

percent resulted in multiple gestation. Interestingly, this group presented evidence that while the monthly probability of pregnancy was only nine percent for the first three months of treatment, it increased to 90% for the second three months of treatment. This may indicate that the ovaries have to be primed for a few months before they can respond.[66]

Another therapy for this type of ovulatory dysfunction which is sometimes effective is bromocriptine. The indications for use of this medication will be discussed in the following section.

III. HYPERPROLACTINEMIA

The amenorrhea-galactorrhea syndrome was described as early as 2,000 years ago by Hippocrates: "If a woman who is not with child, nor has brought forth, have milk, her menses are obstructed."[67] However, it was not until recent years, with the advent of hormonal assay techniques, that this syndrome has begun to be understood. In 1932 there was two case reports in The Lancet describing spontaneous lactation associated with an enlarged sella turcica.[68] The authors related evidence which indicated that the anterior pituitary influences mammary activity and postulated the existence of a "mammary hormone". Twenty years

later Forbes et al presented 15 women with amenorrhea and galactorrhea associated with low urinary FSH.[69] On skull x-ray, seven had evidence of a pituitary tumor; three of these had documented chromophobe adenomas on biopsy. The authors proposed that all of the patients had overproduction of prolactin by the pituitary, whether or not a tumor was present. Similar cases were reported by Argonz and Del Castillo.[70] Over the years there was much controversy concerning whether or not prolactin existed as a unique hormone. Human growth hormone itself possesses strong intrinsic lactogenic properties, and, therefore, detection of the small amounts of prolactin present in human pituitary extracts was difficult.[71]

A breakthrough came in 1970 when a sensitive bioassay for prolactin was published.[72] This assay was based on the ability of prolactin to cause differentiation and milk secretion of mouse breast tissue in vitro. By means of this assay, prolactin was for the first time shown to be immunologically distinct from growth hormone. Using this method, Forsyth et al detected prolactin in the plasma of patients with galactorrhea, both with and without pituitary tumors.[73] Shortly thereafter, a radioimmunoassay was developed for prolactin.[74] This radioimmunoassay used I^{131} labelled monkey prolactin and antibodies to monkey or human prolactin. Radioimmunoassay is today the definitive method for measurement of prolactin in human serum.

Treatment of Hyperprolactinemia

Radiation or surgical treatment of pituitary tumors was usually successful in curing the amenorrhea-galactorrhea syndrome in patients where tumors were found to be present. However, the treatment of "idiopathic" galactorrhea up until this time was based on oral contraceptives and estrogen, although it was recognized that estrogen could stimulate prolactin secretion.[75] In fact, it had been noted that exogenous estrogen could itself cause galactorrhea.[76] Selected cases of amenorrhea-galactorrhea responded to sequential treatment with clomiphene citrate and HCG[77], but this was not uniformly successful. The first definitive treatment for this syndrome was L-dopa, which was routinely used for patients with Parkinson's disease. On the basis of the fact that increased hypothalamic concentrations of dopamine were shown to inhibit prolactin secretion in animals,[78] Turkington tried using L-dopa, the precursor of dopamine, to treat amenorrhea-galactorrheic patients.[79] Forty percent of the patients became normoprolactinemic with L-dopa therapy. An additional 35% of the patients became clinically asymptomatic, although their prolactin levels did not completely normalize with treatment. Similarly promising results were also obtained by Zarate et al.[80] Simultaneously as this reseach on L-dopa was proceeding, a new drug

also was showing promise of effectively treating this disorder. In 1971 Lutterbeck et al described successful treatment of galactorrhea using the ergot alkaloid, 2-Br-alpha-ergocryptine,[81] which had previously been shown to interfere with pituitary prolactin production in animals. Other reports confirmed the effectiveness of this drug in resolving galactorrhea and inducing ovulatory cycles.[82,84] Bromocriptine is superior to L-dopa for treating this condition because frequent administration of L-dopa is necessary due to its short duration of action.

In order to understand the mechanism of action of bromocriptine (Parlodel), it is necessary to understand the pathophysiology of the amenorrhea-galactorrhea syndrome. Although still not completely elucidated, there is data to support hypothalamic, pituitary, and ovarian mechanisms. Prolactin differs from other pituitary hormones in that it is tonically controlled by an inhibitory, rather than stimulatory, factor from the hypothalamus. Dopamine, the precursor to norepinephrine, inhibits prolactin release from the pituitary. It is possible, therefore, that prolactin may be the so-called prolactin inhibitory factor (PIF), or at least be a part of it.[85] In addition, dopamine inhibits GnRH release. The following chain of events was proposed by Wutke et al.[86] Hyperprolactinemia positively feeds back on hypothalamic dopamine causing increased inhibition of GnRH release. The

dopamine receptor may gradually become desensitized due to the continuously high dopamine turnover. Consequently, dopamine may become less and less effective in inhibiting GnRH release leading to acyclicity of LH and FSH release. This leads to anovulation and amenorrhea.[12] Bromocriptine, as a dopamine agonist, would then be effective in restoring LH levels to normal leading to cyclic ovulatory cycles. The etiology of pituitary adenoma formation may be due to dysfunction in dopamine sensitivity to prolactin feedback.[87] This would lead to hypersecretion of prolactin by the pituitary, eventually causing hyperplasia of the pituitary lactotrophs, or prolactin secreting cells.

At the ovarian level, FSH induces specific prolactin receptors on granulosa cells in the rat.[14] Prolactin is always present in follicular fluid and it causes interruption of FSH induced aromatization of androgen to estrogen in that animal.[14] This evidence suggests that hyperprolactinemic women may be anovulatory on the basis of events at the ovarian level.

It has been shown that hyperprolactinemia can cause luteal phase defects. This has been illustrated in the case of amenorrheic lactating mothers where hyperprolactinemia causes luteal insufficiency and subsequent impaired progesterone secretion.[88] If hyperprolactinemia disrupts the cyclic patterns of LH and FSH release, this could explain its effects on the corpus luteum. As

mentioned in the previous section, both normal folliculogenesis under control by FSH, and normal luteal maintenance by LH are necessary for normal luteal lifespan. Corenblum and colleagues suggest that short luteal phase may be an early manifestation of future development of the amenorrhea-galactorrhea syndrome and, therefore, hyperprolactinemia should be looked for and treated if present.[89] The relationship of hyperprolactinemia and luteal phase deficiencies, and the beneficial effect of bromocriptine in correcting the luteal phase under these circumstances was later reported by others.[90-92]

IV. HYPOTHALAMIC DYSFUNCTION

Hypothalamic amenorrhea, often implicated in women with secondary amenorrhea, is a catch-all diagnosis which includes cases with no obvious organic cause for amenorrhea, and also those cases where psychogenic factors may be implicated. Tolis and Naftolin use the following criteria to diagnose hypothalamic amenorrhea: (1) Normal to low basal serum gonadotropin levels; (2) Adequate reserves of pituitary gonadotropins; (3) No evidence of pituitary tumor.[93] Two categories of hypothalamic

amenorrhea which have received much attention in the literature are psychological amenorrhea, and athlete/weight loss amenorrhea.

Hypothalamic amenorrhea was first described by Klinefelter et al in 1943.[94] They showed that emotionally disturbed women with ovarian dysfunction had normal FSH levels but extremely low estrogen levels. The authors therefore hypothesized that there was failure of the hypothalamic-pituitary release of LH which prevented estrogen secretion by the ovaries. In 1944 Whitacre and Barrera reported a 14.8% incidence of amenorrhea amongst women interned in Manila during World War II.[95] They hypothesized that the "war amenorrhea" was due to psychic shock, fear, and worry and that this affected the autonomic nervous system which in turn led to suppression of ovarian function.

Various authors have found evidence for different endocrinologic profiles of patients in this category. For example, Rakoff divided 38 patients into six hormonal patterns.[96] They noted that the most common pattern in women with both acute and chronic psychological dysfunction was simple hypogonadotropism, followed by the group with primary ovarian inhibition characterized by high FSH and low estrogens in the case of the acute group, and a persistent estrus pattern in the case of the chronic group. Matsumato et al studied 54 women with psychogenic or environmental

amenorrhea and found most of them to have low total gonadotropin levels, low serum LH, high 17-OH- corticosteroids, and high 17-ketosteroids.[97] They explained this by citing the "shift phenomenon" hypothesized by Seyle in 1952.[98] This theory proposes that amenorrhea develops because during emergency the hypothalamus stimulates the pituitary to release more ACTH at the expense of gonadotropin. Thus, these patients have high urinary 17-OH-corticosteroids and low gonadotropin and estrogen levels.

Rothman et al reported six patients with no organic cause for their infertility who were treated by supportive psychotherapy for 4 to 12 months.[99] The sessions exposed feelings of self-criticism on the part of the patients in that they felt that their infertility was a punishment for earlier wrong doings or bad thoughts. All six women became pregnant and had normal deliveries following the psychotherapy. The authors suggest using psychotherapy as an approach to the infertile woman with no organic etiology of her infertility.

Similarly, Lachelin and Yen studied a series of 11 normogonadotropic patients with amenorrhea and apparent psychological disturbances.[100] These patients all had normal age of menarche and development of secondary sexual characteristics. Their basal levels of pituitary and ovarian hormones were within the range found in the early follicular phase of normal women. Their

psychological disturbances included some depression, and they resumed normal cyclic menstrual function following counseling. Based on the cure effected by counseling in these patients, the authors postulated that these patients have acyclicity of gonadotropin release due to suprahypothalamic dysfunction. This might be related to disorders of the metabolism of central catecholamines which are associated both with psychological depression and also with the regulation of hypothalamic and thus pituitary gonadotropin secretion. The ovaries of these patients are sensitive to gonadotropin stimulation and undergo follicular activity. However, the acyclic gonadotropin release which is present leads to inability of the follicles to mature.

A subdivision of the group of patients with psychological aspects to their infertility, are those women with anorexia nervosa. Anorexia nervosa is a disorder characterized by extreme voluntary weight loss associated with abnormal ideation regarding food and body image. Many endocrinological studies have been performed on these patients to try and elucidate the mechanism of their amenorrhea. Knuth et al found amenorrhea due to loss of weight in 39 of 170 consecutive patients presenting with amenorrhea.[101] Twenty-four of these patients had anorexia nervosa; in the remaining 15 patients it was not clear whether their weight loss was due to this disorder. Endocrine studies revealed

decreased estrogen production, low serum LH levels, and a failure to ovulate with the administration of clomiphene in all patients. Thirty-six percent of the patients resumed ovulatory menstrual cycles after gaining a mean of 3.6 kg. The authors concluded that a significant loss of weight rather than falling below an absolute minimum weight for height is the critical factor causing ovulatory dysfunction in these patients. Vigersky et al studied endocrine function in 19 patients with simple weight loss and secondary amenorrhea and compared the results to patients with anorexia nervosa.[102] They found abnormal thermoregulatory function in these patients which correlated with their percentage below ideal body weight. In addition, partial diabetes insipidus was found in 27% of these patients. They also had delayed peak plasma LH and thyrotropin levels after administration of exogenous LHRH and TRH, respectively. These findings were similar to those found in the patients with anorexia nervosa but to a lesser degree. In light of the abnormal thermoregulation and partial diabetes insipidus exhibited by these patients, hypothalamic dysfunction as a result of weight loss was postulated as the etiology. This may be due to the ability of the adipose tissue of the breast, abdomen, omentum, and fatty marrow of the long bones to aromatize androgens to estrogens.[103]

It has been shown that there are estrogen receptors present in dopaminergic neurons of the hypothalamus. Estrogen feedback effects may, therefore, modulate inhibition of GnRH release by dopamine.[14] Therefore, in the presence of low circulating estrogen, this hypothalamic function would be modified. This hypothesis is consistent with the study by Wentz, whose results indicated that amount of body fat was more crucial in determining menstrual function than absolute body weight or amount of weight loss.[104]

There have been numerous reports in the literature concerning amenorrhea in athletes. In contrast to weight loss patients, Schwartz et al found elevated LH levels in runners with amenorrhea.[105] They also demonstrated that compared to runners with normal cycles, amenorrheic runners had a higher incidence of prior menstrual irregularity, weighed less, had a lower percentage of body fat, and were faster runners. Studies by Baker et al contradicted the hormonal results of Schwartz in that they found LH and also prolactin levels to be lower in the amenorrheic group compared to normals.[106] They found secondary amenorrhea had the highest incidence in younger, nulliparous runners with late onset of menarche. Frisch and colleagues showed that runners and swimmers who had begun training prior to puberty had delayed onset of menarche and all athletes had an increased in-

cidence of oligomenorrhea and amenorrhea with training.[103] They hypothesized that a raised lean/fat ratio might explain the menstrual dysfunction in athletes since in women athletes, proportionally more body weight is represented by muscle rather than adipose tissue. They also noted that the stress of training might lead to increased output of adrenal corticosteroids and catecholamines, which would influence the hypothalamic-pituitary control of gonadotropin secretion. As can be seen from these and other reports,[107,108] there is not yet a consensus as to the mechanism involved in causing anovulatory cycles in women undergoing various forms of stress. However, it is clear that hypothalamic dysfunction in some way may be implicated.

Treatment of Hypothalamic Dysfunction

All of the pharmacological compounds previously mentioned in reference to other disorders have been used to treat hypothalamic anovulation. In the clomiphene study by Garcia et al, 75 patients had either psychogenic, weight loss, or idiopathic amenorrhea or oligomenorrhea.[62] Of these patients, 50% of the psychogenic amenorrhea patients, 60% of the weight loss patients, and 50% of the idiopathic oligomenorrhea patients ovulated with clomiphene. Gysler et al reported a higher incidence of ovulation, 77%, in the patients with hypothalamic-pituitary dysfunction treated with Clomid.[27] This difference between the two studies may have been due to population or drug administration difference.

Human menopausal gonadotropin has also been used to treat hypothalamic dysfuntion. In the series published by Spadoni et al, 12 patients had anovulation or oligoovulation of unknown etiology.[109] Of these, all had ovulation successfully induced with HMG.

Bromocriptine has also been shown to be effective in treating this disorder. This was reported by Tolis and Naftolin in three patients[93] and Seppala et al in nine of 18 normoprolactinemic patients.[110] The former group postulated a central action of the drug on catecholamine receptors as the mechanism of its action. More recently, Koike et al published results of therapy using combination bromocriptine-clomiphene therapy in normoprolactinemic patients who did not respond to clomiphene alone.[111] Sixty-one percent of their paients became ovulatory with this treatment. Treatment caused a decrease in serum prolactin levels, and a gradual increase in serum LH levels followed by an LH surge.

From the results of these studies, it may be concluded that clomiphene is the first line drug of choice for hypothalamic amenorrhea. If this fails, other drugs or drug combinations should be tried. In addition, psychotherapy may be helpful in selected patients.

3. METHODS

The records of 675 patients seen at the Yale Infertility Clinic over a period of six years were reviewed. These patients represented all the patients who had presented with primary or secondary infertility seen by one physician (A.D.) from 1976 to 1982, excluding those with no follow-up visits. Also excluded were those patients whose infertility was due to previous tubal ligation and those patients in whom habitual abortion was the principal reason for seeking medical assistance.

The work-up of each patient in the study involved the currently accepted routine evaluation of the infertility patient. It included basal body temperature profiles, serum progesterone determination, and endometrial biopsy as evaluators of ovulatory activity or inadequate luteal phase. Each patient submitted for analysis a semen specimen from her partner that was judged normal if it had greater than 20 million sperm per high-power field, greater than 60% motile forms, and greater than 60% normal morphology. Tubal function and anatomy were assessed using hysterosalpingography with water soluble or oil soluble dye as well as laparoscopy performed under general anesthesia. Postcoital cevical mucus analysis was considered normal if greater than 10 sperm per high-power field were visualized.

In specific patients ancillary testing was done to further document the diagnosis. Patients with pituitary adenomas and hyperprolactinemia had visual field examinations, CAT scan, and thyroid function studies. Patients with hypothalamic amenorrhea had gonadotropin assays. Those with PCOD had total and free testosterone evaluations. All patients with ovulatory difficulty had thyroid function studies and prolactin and gonadotropin levels measured to rule out specific pathology.

After analyzing the diagnoses and treatments the patients had received in the process of evaluation of their infertility, those patients whose chief diagnosis consisted of some type of ovulatory dysfunction were considered. If the patient never conceived while being treated at the infertility clinic, she was excluded from the study population. The study population thus consisted of those women with primary or secondary infertility due to some disorder of ovulation who had become pregnant at least once while being treated with an ovulation-inducing agent. The circumstances of their subsequent pregnancies were then analyzed as to whether or not medical therapy was necessary to conceive. Letters containing questionnaires (see Fig. 1, Appendix) were sent to all patients for whom follow-up was unknown, including those where it was not known whether even one conception had occurred. Results were analyzed using the Chi-square test.

4. RESULTS

One-hundred-thirty-two letters were sent to patients who were lost to follow-up from the infertility clinic. Of these, 83 patients responded (63%), 16 letters were undeliverable, and 33 letters were not returned; presumably these patients chose not to answer the questionnaire. The results from these questionnaires were combined with the data gleaned from patients' charts to yield the following results (see Fig. 2, Appendix). Of 675 patients presenting to the Yale Infertility Clinic, 227 (34%) were found to have ovulatory dysfunction as the principal cause for their infertility. The remaining 449 patients had male, anatomical, or immunological factors as their presumed reasons for infertility. Of the 227 patients with the diagnosis of an ovulatory abnormality, 102 (45%) achieved pregnancy with medical therapy. These 102 were then studied in detail concerning attempts at subsequent pregnancies. Thirty-six patients were known to be interested in conceiving again. Eleven of these patients (31%) conceived spontaneously without additional treatment ($p<0.1$) following the birth of their first child. Twenty-five patients were unable to achieve a second pregnancy without medication. Thirteen of these patients did become pregnant with medical treatment and 12 are in the process of being treated with ovulatory agents but have not yet become pregnant. Of the remaining

58 of the original 102 patients who conceived at least once, 10 are in the midst of their first pregnancy, 17 are not interested in having another child at this time, and the follow-up is unknown for 31 patients, including patients who did not return the questionnaire and those who only partially completed the questionnaire which was sent to them.

The 11 patients who spontaneously became pregnant compose a varied picture (see Fig. 3, Appendix). Their ages at presentation range from 27 to 33 years old, with a mean and median age both equal to 30. Eight (73%) suffered from primary infertility; the remaining three had been pregnant before. Six patients (55%) were considered to have hypothalamic oligoovulation or anovulation because no other explanation for their ovulatory dysfunction could be determined. Five of these six patients conceived while taking Clomid; one required Pergonal and HCG. Of the remaining five patients, three had polycystic ovary disease, one had hyperprolactinemia, and one had luteal phase deficiency.

The distribution of the 25 patients who did not conceive spontaneously differed from the group that did (see Fig. 4, Appendix). Their ages at presentation ranged from 24 to 37 with a mean and median age equal to thirty years old. The incidence of primary versus secondary infertility in this group was almost equal; 13 patients with primary, and 12 patients with secondary

infertility. Short luteal phase was diagnosed in 12 patients (48%) and hypothalamic anovulation was the diagnosis in 10 (40%). Three patients had PCOD, and no patients had hyperprolactinemia. Fifteen patients (60%) conceived the first time using Clomid, while the other 14 patients were divided amongst various therapies.

5. DISCUSSION

Pregnancy was used as the endpoint in this study, rather than ovulation, as pregnancy is the only absolute indication of treatment success and consequent normal ovulation. Thirty-four percent of patients with infertility were found to have ovulatory problems as the main explanation for their infertility. This is a somewhat lower percentage than that reported by others. Cox found a prevalence of 43% ovulatory failure in his population,[5] while Thomas and Forrest found a 50% rate in theirs.[6] The lower percentage of patients in this category found in the present study could be explained by the fact that the Yale Infertility Clinic is known for its innovative microsurgical techniques and therefore many patients with tubal problems are referred to Yale for treatment. This may result in a skewed patient population. The pregnancy rate in this population, 45%, was also somewhat

lower than previous series which vary from 56 to 93% in anovulatory populations.[5,6,112,113] One explanation for this lower success rate in the present study is that of the 227 patients where ovulatory dysfunction was diagnosed as the major contributing factor to infertility, 57 patients (25%) had other relative contributory problems. These included six patients who had partially obstructed fallopian tubes on hysterosalpingogram, three patients with uterine factors, seven patients whose partners had a sperm count in the intermediate range of 20 to 40 million/cc or sperm with decreased motility, eight patients with endometriosis, 28 patients with possible cervical mucus hostility problems, and five patients with two of these problems in addition to ovulatory dysfunction. These patients were not excluded from the study population as none of these findings absolutely preclude fertility, and, in fact, several of the patients who did conceive were in this category.

There is no consistent pattern which differentiates those women who were able to conceive spontaneously the second time from those who again required medication. Their mean and median age at presentation was 30 years in both groups. In both groups hypothalamic anovulation comprised a high proportion of the patients, and in the group that spontaneously conceived it was the diagnosis in the majority of the patients. Contrary to what one

might expect, there were more patients with primary infertility who were able to spontaneously conceive the second time, than with secondary infertility.

With no obvious distinction between those patients who were able to conceive spontaneously and those who were not, we must try to explain what might possibly have enabled some patients to become pregnant without ovarian stimulation, where such stimulation had been required previously.

This phenomenon has been previously reported by others. In 1972 a British study found that of 40 patients who became pregnant after treatment, 12 (30%) became pregnant again within two years without further treatement.[114] A report from Australia studied 100 women who had been previously treated with clomiphene or gonadotropins for anovulatory infertility.[115] Sixty-nine of these women became pregnant during this treatment. Of these 69 women 210 (30%) achieved a second pregnancy after spontaneous ovulation. Also, five patients who had not previously achieved pregnancy with treatment, spontaneously conceived during the follow-up period. A group from the same institution published another series of patients a year later.[116] Of 136 patients who had previously withdrawn from ovulatory treatment or who had an induced-ovulation pregnancy, 80 (59%) exhibited improved menstrual patterns. Forty-six of these patients spontaneously

became pregnant again within one year (34%). These results are not directly comparable with the other studies cited because the population being considered differs. Another study which used the same population as the one just cited, i.e, women who had previous ovulatory stimulation either with or without conception, found a 16% spontaneous pregnancy rate.[5]

There are several possible explanations for the occurrence of spontaneous pregnancy in women where treatment was previously required: (1) Patients were not adequately evaluated initially and therapy was commenced when not indicated; (2) Ovarian stimulation medication has a long term effect; (3) Pregnancy induces long term changes in the hypothalamic-pituitary-ovarian axis; (4) Changes in the patient's emotional attitudes, either consciously or subconsciously, as a result of being pregnant or for other reasons influences the hypothalamic-pituitary-ovarian axis.

It is unlikely that the first of these explanations holds true in this study. All patients had been infertile for at least one year with adequate coital activity prior to initiation of evaluation. Basal body temperature charts, luteal phase endometrial biopsies, and serum progesterone measurements were used to compliment each other to make the correct diagnosis in each patient along with hormonal studies when applicable. However, it is possible that undocumented sporadic ovulations can lead to

fertilization and implantation. This is known to occur in the case of PCOD. In as series of 39 patients with PCOD reported by Goldzieher and Green, a corpus luteum was found at surgery in four patients, a biphasic temperature curve was seen in one patient, three patients had dysmenorrhea, and five had borne children previously.[117] These findings were interpreted as evidence of ovulation in these patients with proven polycystic ovaries. Similarly, in patients with hypothalamic anovulation, intermittent ovulation might occur. For example, a study of the menstrual patterns of ballet dancers showed that menstrual regularity improved during periods of injury and vacation.[108] Presumably the decreased level of stress at these times influenced the hypothalamic-pituitary axis to promote normal ovulatory function.

It is possible that the spontaneous conceptions might be due to a long term effect of the stimulatory medications used. Spontaneous pregnancy has been documented in the case of gonadotropin therapy. Thompson and Taymor reported that of 38 anovulatory patients who became pregnant following HMG induction of ovulation, eight (21%) subsequently conceived spontaneously without additional therapy.[118] Seven of these eight women had PCOD. In a more recent report, 24% of patients who had an HMG/HCG induced pregnancy, subsequently conceived spontaneously.[119] The same

long term influence on ovulatory function has not been demonstrated as convincingly in the case of clomiphene. Garcia et al reported that of 131 patients with disorders of ovulation who did not become pregnant after clomiphene therapy, 23 achieved pregnancy from a spontaneous ovulation following cessation of clomiphene therapy.[62] In this case the variable of pregnancy is not present, however, it is not clear whether the spontaneous pregnancies were a direct result of the clomiphene therapy. There has been little research on possible long term effects of clomiphene.

A recent in vitro study using pituitary cell cultures showed that the effect of bromocriptine in lowering prolactin secretion is sustained after removal of the drug.[120] However, this has only rarely been shown to be the case in vivo. In an early trial of bromocriptine, Del Pozo et al found that hyperprolactinemia and galactorrhea tended to recur when therapy was withheld.[84] Seppala et al also reported that with most of their patients who responded to bromocriptine administation, the effect did not persist after the drug was discontinued.[110] However, menses appeared spontaneously after treatment in four of their patients, and another two patients had "fairly" regular cycles for a year following discontinuation of therapy. Several studies of the effect of bromocriptine on pituitary prolactinomas have documented dramatic rises in prolactin levels[116,117] and also increase in the size of tumors[117] after discontinuation of the drug.

The preceeding data illustrates that except in the case of gonadotropin therapy, there is no indication that ovarian stimulatory medication has long term effects. In the present study, seven patients who conceived spontaneously for their second pregnancies had been treated with clomiphene, one with bromocriptine, one with clomiphene and bromocriptine, and only two with gonadotropins.

It is conceivable that pregnancy itself has a long term therapeutic effect on the hypothalamic-pituitary-ovarian axis. This would be difficult to prove. However, since oral contraceptives induce a state of "pseudopregnancy", they may be used as a model to study the effects of pregnancy.[121] For several years it was believed that oral contraceptives could lead to amenorrhea after they were discontinued.[122-124] A hypothalamic mechanism was implicated to explain this. However, more recently it has been suggested that the syndrome of "post-pill amenorrhea" does not exist as such. Tolis et al found no difference in historical or biochemical characteristics between women with secondary amenorrhea who had discontinued oral contraceptive therapy and those who had never taken oral contraceptives.[125] Jacobs et al compared patients who developed amenorrhea after discontinuing oral

contraceptive therapy with other patients with secondary amenorrhea.[126] The two groups of patients had similar characteristics; both groups had similar percentages of patients with primary ovarian failure, hyperprolactinemia, recent weight loss, and psychological disorders to explain their amenorrhea. In addition, almost half of the post-oral contraceptive amenorrhea patients had had episodes of amenorrhea previously. The authors concluded from this data that oral contraceptive use does not cause subsequent amenorrhea. Friedman and Goldfien also found that there was no significant difference between patients with post-oral contraceptive amenorrhea and other patients with secondary amenorrhea.[127] Halbert and Christian reported a high incidence of prior menstrual dysfunction in these women.[128] The latter two groups also noted a high incidence of galactorrhea amongst post-pill amenorrheic patients; nine of 21 patients presented by Friedman and Goldfien,[127] and 10 of 35 patients of Halbert and Christian.[128] Although the explanation for this finding is not known, it is possible that the symptoms of a developing pituitary adenoma are masked during oral contraceptive therapy, only becoming apparent when the hormonal therapy is discontinued. A similar mechanism might be involved in the so-called Chiari-Frommel syndrome, or postpartum amenorrhea-galactorrhea.

The preceeding discussion illustrates that the current evidence does not support the idea that exogenous hormonal therapy, and by inference, the similar hormonal milieau present during pregnancy, has direct effects on the hypothalamic-pituitary axis.

Lastly, changes in a woman's emotional or mental status might cause a change in ovulatory patterns via central mechanisms. This association has been noted by numerous authors (see p. 22-29), however it is difficult to prove as the elucidation of central neuroendocrine pathways which interrelate thought and emotion with reproductive physiology is only in its infancy.

The study presented in this paper was retrospective in design. Ideally, a random double-blind study would yield the most unbiased analysis of this patient population. While the withholding of treatment in this case would not be life-threatening, due to the sensitive nature of the disorders involved and the finite time period of reproductive life, it would not be ethical to withhold treatment from any patient where it might be potentially beneficial. In this study a significant number of women with diagnosed ovulatory dysfunction were able to conceive spontaneously after a successfully induced pregnancy. The 31% success rate agreed with that found in previous studies.[114,115] The pathophysiologic mechanism which might explain this finding is not known, however, it most likely involves either intermittent

spontaneous ovulations found in certain anovulatory syndromes, or psychologic or emotional changes influencing the hypothalamic-pituitary system via suprahypothalamic pathways. There is little evidence supporting a long term effect on the hypothalamic-pituitary-ovarian axis by either medications or pregnancy.

APPENDIX

Figure 1

QUESTIONNAIRE

Yale University

SCHOOL OF MEDICINE
333 Cedar Street
P.O. Box 3333
New Haven, Connecticut 06510
Department of Obstetrics and Gynecology

Dear Ms.

We are doing a study designed to help answer the question of whether certain drugs are effective in helping women with problems of ovulation to conceive, and whether these drugs are necessary each time conception is desired. As a present or past patient of the Yale Infertility Clinic, we would appreciate it if you would take a few minutes to answer the following questions. Not all of these questions may be applicable to you. In some cases we may already have this information in your clinic file, but please answer whichever questions you think apply to you anyway. Answers to these questions will be strictly confidential, and will not become a part of your permanent clinic or hospital files.

1. Were you found to have problems with ovulation: e.g. abnormal basal body temperature charts, short luteal phase, polycystic ovaries, etc., during evaluation for infertility?

Yes_____ No_____

Specify diagnosis:_____

_____

_____

2. Did you take any medications, either prescribed by the Yale Infertility Clinic or subsequent physicians you may have seen, for this problem?

Yes_____ No_____

Specify which:

Clomid_____ HCG_____

Cortisone_____ Pergonal_____

Progesterone Suppositories_____ Parlodel_____

Other (e.g. Surgery)_____

Combination of_____

_____

3. Did you become pregnant as a result of taking this medication?

Yes_____ No_____

If yes, which of the listed medications were you taking when you conceived, if any?

_____

4. If you became pregnant, what was the outcome of that pregnancy?

Full term delivery_____

Premature delivery_____

Miscarriage (at how many weeks?_)_____

Ectopic (tubal) pregnancy_____

Abortion_____

Other_____

5. If you are no longer a patient at the Yale Infertility Clinic, whether or not you became pregnant while under their care, please summarize below your attempts at having a child since that time.

a) Saw or currently seeing another physician who treated me with_____

_____

_____

and I did, did not, become pregnant.

b) Adopted a child and I am, am not, still actively pursuing a pregnancy.

c) Still have no children and I am, am not, actively pursuing pregnancy and/or adoption.

d) Have decided that I am no longer interested in having a child because

_____

_____

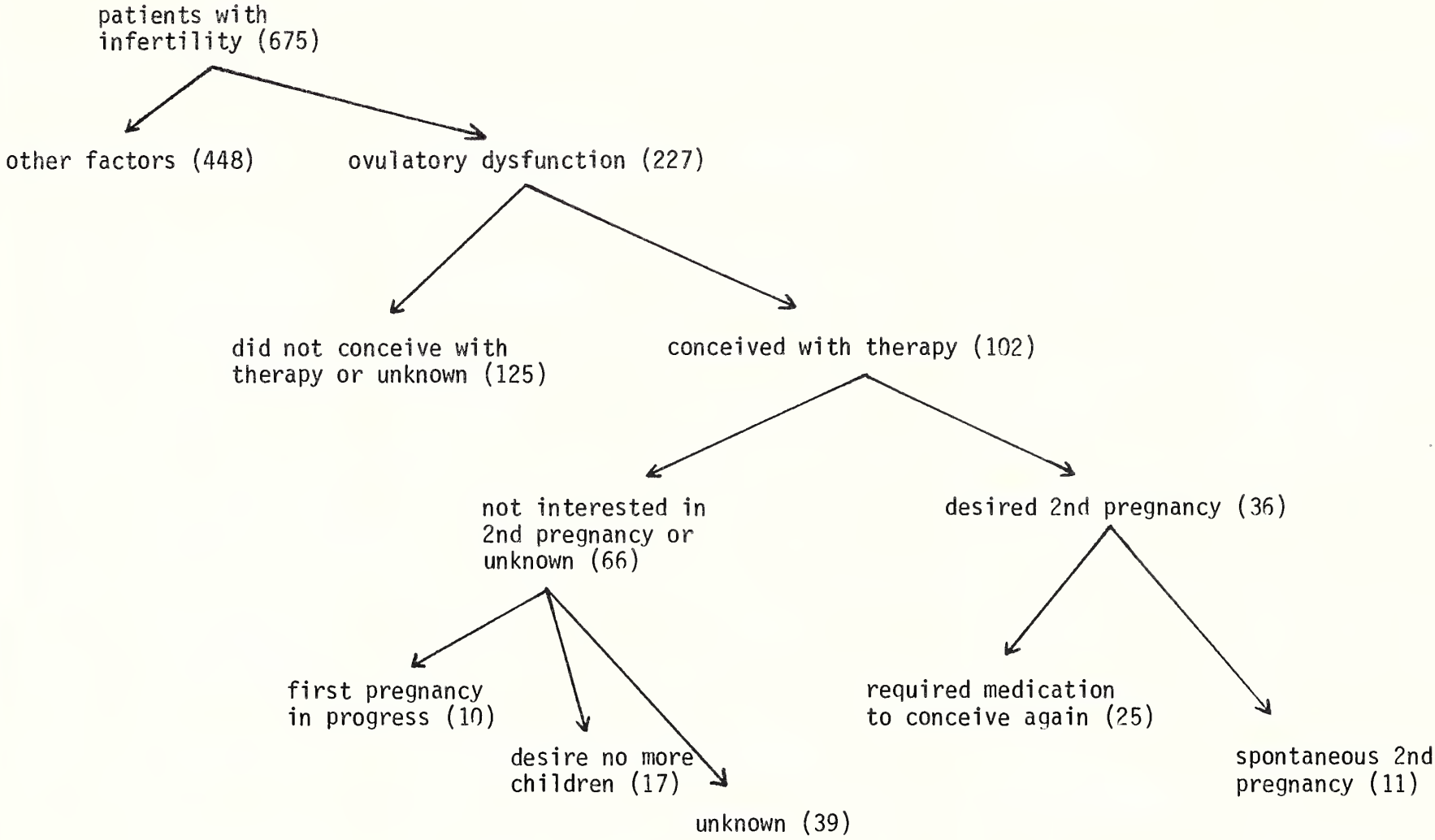
e) Other_____

_____

6. In the space below, please add any other comments you think may be helpful for this study.

Figure 2

DISTRIBUTION OF PATIENTS WITH OVULATORY DYSFUNCTION*



* Numbers in parenthesis = number of patients.

Figure 3

PATIENTS WITH SPONTANEOUS PREGNANCIES FOLLOWING A MEDICATION INDUCED PREGNANCY

PT.	AGE	DIAGNOSIS	1st PREGNANCY(S) - TREATMENT DURING CYCLE WHEN CONCEPTION OCCURRED	OUTCOME OF 1st PREGNANCY	OUTCOME OF SUBSEQUENT SPONTANEOUS PREGNANCY(S)	COMMENT
JB	29	1° infertility luteal phase deficiency	2 pregnancies with Clomid	1st-SAb 2nd-full term	full term	
ED	33	2° infertility PCOD	Clomid Parlodel	full term	pregnancy in progress	had bilat. ov. wedge resection prior to presenting
DF	29	1° infertility pituitary adenoma hyperprolactinemia	Parlodel	full term	pregnancy in progress	
JG	28	2° infertility hypothalamic dysfunction	Clomid	ectopic	ectopic	s/p tubal surgery
NH	31	1° infertility PCOD	2 pregnancies with Pergonal and HCG	1st-SAb 2nd-full term	1st-SAb 2nd-pregnancy with progress	
LH	29	1° infertility PCOD	3 pregnancies with Clomid	1st-full term 2nd-full term 3rd-SAb	1st-TAb 2nd-full term	had bilat. ov. wedge resection

JO	31	1^{o} infertility hypothalamic dysfunction	Clomid	full term	1^{st}-intrauterine demise 2^{nd}-full term	
LS	27	1^{o} infertility hypothalamic dysfunction	Clomid	full term	full term	s/p removal of endometriosis
JS	31	1^{o} infertility hypothalamic dysfunction	Clomid	full term	pregnancy in progress	
KT	30	2^{o} infertility hypothalamic dysfunction	1^{st} and 3^{rd} pregnancies with Clomid	1^{st}-full term 3^{rd}-full term	2^{nd} pregnancy-full term	has been normoov. since stopping lactation after 3^{rd} birth
PT	29	1^{o} infertility hypothalamic dysfunction	Pergonal HCG	full term	full term	

Figure 4

PATIENTS REQUIRING MEDICATION
FOR SUBSEQUENT PREGNANCIES

PT.	AGE	DIAGNOSIS	1st PREGNANCY(S) TREATMENT DURING CYCLE WHEN CONCEPTION OCCURRED	OUTCOME OF 1st PREGNANCY	CIRCUMSTANCES OF SUBSEQUENT PREGNANCY(S)	COMMENT
SB	31	2° infertility hypothalamic dysfunction	Clomid Parlodel	full term	Clomid Parlodel SAb	
JB	26	1° infertility hypothalamic dysfunction	Clomid	full term	Clomid full term	
CB	24	1° infertility PCOD	Clomid	SAb	1st-Clomid 2nd-Clomid full term	
JC	27	2° infertility hypothalamic dysfunction	Pergonal HCG	full term	Pergonal HCG not yet successful	
DC	28	2° infertility luteal phase deficiency	Parlodel	SAb	1st-Parlodel ectopic 2nd-Parlodel full term	
AD	29	1° infertility luteal phase deficiency	Clomid	SAb	1st-Clomid full term 2nd-Not yet successful	
JD	31	2° infertility hypothalamic dysfunction	Clomid	SAb	1st-Clomid, HCG, Parlodel SAb	

JD	29	1^{o} infertility luteal phase deficiency	Clomid	full term	Clomid not yet successful	
LE	29	1^{o} infertility luteal phase deficiency	Clomid	SAb	Clomid full term	
MF	28	2^{o} infertility luteal phase deficiency..	Clomid	ectopic	Clomid ectopic	s/p tubal surgery
EG	37	1^{o} infertility hypothalamic dysfunction	Clomid	full term	Clomid not yet successful	
MG	29	1^{o} infertility hypothalamic dysfunction	Clomid HCG	full term	Clomid full term	
CH	30	2^{o} infertility luteal phase deficiency	Clomid	ectopic	Clomid ectopic	s/p LSO
SK	27	1^{o} infertility hypothalamic dysfunction	Clomid	full term	Clomid full term	
SK	30	2^{o} infertility lutal phase deficiency	Clomid	SAb	Clomid full term	metroplasty for septate uterus
MK	38	2^{o} infertility hypothalamic dysfunction	Clomid	full term	Clomid Parlodel not yet successful	

MK	33	2^{o} infertility PCOD	Clomid	full term	Pergonal HCG full term - twins	
JL	33	1^{o} infertility PCOD	Clomid	full term	Clomid Parlodel Not yet successful	s/p wedge resection prior to presentation
CL	34	1^{o} infertility luteal phase deficiency	Clomid	hydatidiform mole	Clomid full term	
GM	33	2^{o} infertility luteal phase deficiency	Pergonal	SAb	Pergonal Pregnancy in progress	
SM	32	1^{o} infertility hypothalamic dysfunction	Clomid	full term	Pergonal Not yet successful	
AM	33	1^{o} infertility luteal phase deficiency	Clomid	full term	Not yet successful	
MP	30	1^{o} infertility luteal phase deficiency	Progesterone suppositories	full term	Clomid Parlodel Not yet successful	Also has endometriosis - Rx'd with Danazol
SP	34	2^{o} infertility luteal phase deficiency	Clomid	full term	Clomid Parlodel full term	
TS	34	2^{o} infertility luteal phase deficiency	Clomid	full term	Clomid Parlodel Not yet successful	recently had tubal surgery

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