Lebanese American University

Physical & Psychological Changes Associated with Controlled Ovarian Hyperstimulation in Women Undergoing Assisted Reproductive Techniques

By

Rana Haddad

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List of Abbreviations

FSH: Follicle Stimulating Hormone

LH: Luteinizing Hormone

HCG: human Chorionic Gonadotropins

PCO: Polycystic Ovarian Syndrome

ART: Assisted Reproductive Technologies

IVF: In Vitro Fertilization

GIFT: Gamete Intra Fallopian Transfer

ICSI: Intra Cytoplasmic Sperm Injection

GnRH: Gonado tropin Releasing Hormone

HMG: Humun Menopausal Gonadotropeis

COH: Controlled Ovarian Hyperstimulation

OHSS: Ovarian Hyperstimulation Syndrome

IM: Intra-Muscular

SC: Sub-Cutaneous

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Haddad building, round
about.Beit Mery
Metn. Lebanon

Phone 00961-3-407302
E-mail: ranarana29@hotmail.com

Curriculum Vitae

Personal Information

- Name: Rana Haddad
- Date of Birth: August,1, 1974
- Place of Birth: Maasser beiteldin
- Citizenship: Lebanese
- Marital status: Single

Education

- Soeurs de Besancon, Baabdath 1977-1989
- Jamhour, 1989-1992
  - -Degree earned: French Baccalaureate II (Serie D)
- Lebanese American University LAU (Jbeil)
  - Degrees earned: - Bachelor of Pharmacy (with Honors) 1992-1998
  - Pharm.D. 1998-1999

Computer Literacy

- Word, Excel, Internet Applications, Power point, SPSS

Languages

- English: write, speak.
- Arabic: write, speak.
- French: write, speak

Pharmacy Clerkship

1996-Pharmacy Zeina (3 months)

1997-Pharmacy Vitale Jal el Dib (3 weeks)

-Pharmadex (industry) Kahale (2 weeks)

-St. George Hospital Pharmacy (5 weeks)

Clinical Experience

1997-98:

- St. George Hospital Clinical rotation (4 months) in the following (internal medicine, laboratory, CCU)
- AUH (4 months) in the following (family medicine, gynecology, ENT, psychiatry)
- Drug Utilization Review (DUR) of Vancomycin versus Teicoplanin with Dr. Marouan Ouwayda (AUH)

1998-99:

- American University Hospital, clinical rotation (7 months) in the following (internal medicine, CCU, ICU, ENT, OB/GYN, family medicine)
- St. George Hospital Clinical rotation (2 months) in the following (psychiatry, CCU)
- Clinical study: Physical and psychological changes associated with the use of Gonadotropins in women undergoing assisted reproductive technologies, at AUH with Dr Jhonny Awwad

Work Experience

1998-99: Pharmacy Zeina Broumana (10 months)

1999 (August) till now: - Medical representative for MENARINI PHARMACEUTICALS – SADCO

Marketing Experience	"Management of the Sales Interview Workshop" Location: Nicosia, Cyprus by CCM/ Tack
Activities	Participant in church activities, reading, swimming, music, walking.

An Abstract of the thesis

Rana Haddad for Pharm D

Title: Physical & Psychological Changes Associated with Controlled Ovarian Hyperstimulation in Women Undergoing Assisted Reproductive Techniques.

The clinical use of assisted reproductive techniques nowadays is intimately dependent on the use of controlled ovarian hyperstimulation. Ovarian hyperstimulation with Gonadotropin Releasing Hormone analogues (GnRHa) suppression of endogenous gonadotropin activity, and with Human Menopausal Gonadotropin (HMG) or FSH monotherapy is commonplace in Vitro Fertilization Programs (IVF).

FSH monotherapy includes purified FSH, highly purified FSH and recombinant FSH. Although the treatment outcome has a significant percentage of success, its process is often a heavy strain on the couples.

The objective of the study is to examine the physical and psychological changes associated with controlled ovarian hyperstimulation in women undergoing assisted reproductive techniques.

A prospective study will be performed at AUH, Assisted Reproductive Technology Unit. The data will be collected from the charts of the patients who presented to the clinic and have been evaluated to receive the treatment for induction of ovulation.

A special questionnaire is designed for the gathering of the data.

Results will be withdrawn and evaluated through a special program SPSS with the assistance of a biostatistician. The patients will be evaluated for the adverse effects

associated with the treatment and for the anxiety accompanied by it. Patients assessment and personal acceptance of the treatment will be also evaluated... The study will give us an idea about the physical and psychological changes that accompany the controlled ovarian hyperstimulation in women undergoing assisted reproductive techniques.

INTRODUCTION

Gonadotropins is a tool in the treatment of infertility both for male and female. Therefore the questions asked must be: Do they work and how efficient are they in achieving a positive result? What are the adverse effects in short and long term?
To make some head and tail of these questions, the following needs to be discussed: History of gonadotropins, the structure of gonadotropins, the indications and the clinical difference comparing the different preparations on the market.

Gonadotropin preparations have been used to promote fertility for over 30 years. The first use of gonadotropins to induce ovulation in hypogonadotropic women was accomplished with human pituitary extract by Gemzell et al , (1958) (1). Later this lead eventually to the first death in 1988 of Creutzfeld Jacobs Disease, and later reports of four other cases (2).
Lunenfeld et al (1962) and Rosemberg et al (1963) reported the first human pregnancy in the early sixties using urinary gonadotropins (2).

The follicle stimulating hormone (FSH), the lutealising hormone (LH) and the human chorionic gonadotropins (hCG), all belong to a group of dedimeric glycoproteins with identical alpha-chain but dissimilar beta-chain. The beta-chain is responsible for the difference in biological activity.
Those peptide chains have saccharides attached to them and these carbohydrate chains end with a sialic acid (2).
Gonadotropins (FSH) in serum have several different isoforms, depending on how many sialic acids are attached to the molecule.

In fact gonadotropins (FSH) have a range of isoforms, maybe in the hundreds, from those with most acidic properties with many sialic acid attached, to the less acidic. The different isoforms have different biological activity.

It has been shown, that the more acidic forms have a lesser degree of receptor binding, a longer half-life but a lower in vitro bioactive potency than the less acidic forms.

The isoform composition of serum FSH seems to change at critical times in the life of women, such as peri-puberty, peri-menopause, but also during the menstrual cycle.

Younger women tend to have more basic FSH isoforms than older fertile women.

In preovulatory phase, a higher portion of basic isoforms exist, and in the luteal phase, the more acidic forms are to be found (2).

When we now compare this knowledge to the composition of hFSH isoforms in the preparations available on the market, one may wonder if we have the right isoform composition and variation during the cycle.

As for the indications, gonadotropins are a tool in the treatment of infertility, both for males and females.

Gonadotropins applied in the treatment of male infertility have been reported with variable success, on all other indications than hypopituitary hypogonadal indications.

The classical indication is in the treatment of women with a total anovulation and amenorrhea with hypopituitary hypogonadal women (WHO I) and those with normal or low gonadotropin level in serum, but with regular to irregular menses and with partial anovulation (WHO II). The other group includes many with the polycystic ovarian syndrome (PCO).

Gonadotropins are also used to correct a hostile cervical condition. Another indication is in an unexplained infertile couple situation.

An increasinsly large group of women in the world are treated by ovarian hypestimulation with gonadotropins in connection with insemination and with Assisted Reproductive Technologies (ART)(2).

ART include, In vitro fertilization (IVF), Gamete Intra Fallopian Transfer (GIFT), Zygote Intra Fallopian transfer (ZIFT), Intracytoplasmic sperm injection (ICSI)

Patients with no fallopian tubes or with previous tubal damage and a poor prognosis for effective repair are candidates for In Vitro Fertilization.

A typical protocol for standard IVF is as follows:

1. GnRH agonist downregulation is performed prior to ovulation induction with gonadotropins.
2. Follicular maturation and ovulation are effected with combined hMG or hFSH/ hCG administration.
3. Oocytes retrieval is performed transvaginally, under ultrasonographic guidance.
4. Analgesia for oocyte retrieval is provided on an individualized basis but most commonly involves intravenous sedation or spinal nerve block.
5. Embryo transfer is undertaken 48 hours after oocyte retrieval, when most embryos have reached the four-to six-cell stage. For standard IVF procedures, transfer is accomplished via trancervical cannulation and injection of embryos into the uterine cavity.
6. Luteal phase support is provided until menses or pregnancy is documented. The initial evaluation for pregnancy during IVF cycles consists of quantitative beta-hCG measurement 16 days after embryo transfer

Patients considered appropriate candidates for GIFT and ZIFT must have functional fallopian tubes. As in standard IVF, all regimens typically involve ovarian induction

with HMG or hFSH/hCG after GnRH agonist downregulation. The time at which the techniqes first differ is the time of transfer.

Intra cytoplasmic sperm injection is effective for the treatment of severe male factor infertility and of [previous fertilization failure. ICSI method involves the direct insertion of a single sperm cell into the cytoplasm of a single oocyte(3,4).

The goal of Controlled Ovarian Hyperstimulation with gonadotropins in ART, is to obtain mature oocytes in high numbers and thereby improve the likelihood of obtaining adequate numbers of embryos for subsequent transfer (3).

The addition of GnRH agonists to ovulation induction regimens for ART is now common .The major advantage consists of downregulation of the physiologic hypothalamic- pituitary-ovarian feedback mechanisms and the subsequent effective suppression or spontaneous ovulation. The result should be the elimination of premature follicular luteinization and the cancellation of ART cycles secondary to premature ovulation (spontaneous ovulation prior to oocyte retrieval) (3). Usually, the long protocol GnRHa is used, with treatment beginning in the previous luteal phase.

On the other hand, HCG is structurally similar to and has a longer half-life than LH, its use in gonadotropin stimulation of ovulation is now a standard (3). In general, 10,000 IU of HCG are administered when at least two follicles have reached an average diameter of 18mm (as documented by ultrasound) and estradiol levels are > 600 pg/ml (3).

We note that controlled ovarian hyperstimulation in ART is accompanied by some complications which include: Ovarian hyperstimulation syndrome (OHSS); OHSS is associated with increase in the numbers of follicles, in follicular size and in serum

estradiol levels(3), occurring in 1 to 5 percent of cycles. When severe, it can result in blood clots, kidney damage, ovarian twisting (torsion), and chest and abdominal fluid collections. In severe cases, hospitalization is required for monitoring.

Multiple gestation; Up to 20 percent of pregnancies resulting from gonadotropins are multiple, in contrast to a rate of 1to 2 percent in the general population. While most of the pregnancies are twins, a significant percentage are triplets or higher. High order multiple gestation pregnancy is associated with increased risk of pregnancy loss, premature delivery, infant abnormalities, handicap due to the consequences of very premature delivery, pregnancy induced hypertension, hemorrhage and other significant maternal complications. Ectopic (tubal) pregnancies; ectopic pregnancies occur in 1 to 3 percent of the time in gonadotropin cycles.

Birth defects; The rate of birth defects after gonadotropin cycles is no higher than in the general population at 2 to 3 percent, furthermore, these children are developmentally no different than their peers. Adnexal torsion or ovarian twisting; less than 1 percent of the time, the stimulated ovary can twist on itself, cutting off its own blood supply. Ovarian cancer; controversial data exist that associate ovulation stimulation drugs like gonadotropins to the risk of future ovarian cancer (6).

Currently available gonadotropin preparations are either extracted from urine of postmenopansal urine or made available through recombinant techniques.

Human menopausal gonadotropins, hMGα(Pergonal, Humegon), contain equal parts of hFSH and LH, and about 5%of bioactive gonadotropins, and the contents of LH and hFSH may following the international pharmacopea vary from 80 to 125% of the stated amount on each ampoule available for treatment. So, large clinically expressed variation in potency is a possibility, due to the large batch to batch variation in bioactive hFSH and LH (2).

Due to the increasing concern of the negative effect of an elevated level of LH in serum in IVF patients expressed in premature luteinisation, less oocyte quality, lower fertilization rate and increased percentage of spontaneous abortions (2), and the fact that a small amount of circulating LH is sufficient to produce enough substrate for the estradiol production (7,8), preparations with less amount of LH were produced.

So purified hFSH, (Metrodin, Fostimon) a urine base gonadotropin, which contains about 5% of LH activity was marketed.

HMG and the purified hFSH, have low specific activity (100 to 150 IU FSH/ mg of protein). They are not pure because >95% of the protein content consists of non specific co-purified urinary proteins (8).

Co- purified proteins could be a source of adverse immune reactions (9), and they may be unattractive to patients because they must be administered IM(10).

The pure hFSH preparation was followed by the highly purified FSH preparation (Metrodin-HP), which is still a urine based preparation but contains nearly none protein contaminants and less than 1 % LH (2).

Nowadays, gonadotropins can be produced independently of the collection of the collection of postmenopausal urine. Recombinant human FSH preparation is available, produced by genetically engineered mammalian cells (Puregon) (11).

This preparation is pure with absolutely no LH activity. Due to this, their will be a batch consistency (2).

Recombinant FSH and highly purified FSH are much more well defined with > 95 % of the total protein content being FSH, and with specific activity exceeding 9.000 IU/mg of protein (12). Thus, unknown proteins in recombinant FSH and in highly purified FSH are usually absent and SC administration by the patient is a possible and attractive option (12).

In fact immediate and delayed type reactions including local reactions and hypersensitivity, were seen with HMG preparations, but avoided with recombinant FSH and highly purified FSH (9). Furthermore, crude urinary HMG/FSH preparations from different manufactures modulate parameters of immune function in vitro, they have different in vitro immunological effects, reflecting a different profile of contaminants (9).

Other adverse effects of gonadotropins could be associated with elevated estrogen levels and these include: headache, abdominal pressure and pain, gastrointestinal effects, and probably irritability anxiety and depressed mood (5).

Abdominal pain and headache were significantly reported higher with urinary purified FSH in a study comparing adverse effects and complications of recombinant hFSH versus urinary purified hFSH(13).

On the other hand, during the past ten years several studies concerning the psychological aspects of infertility have been published. When psychological effects were assessed three months before IVF, their was no difference between infertile women and normative sample with respect to anxiety and depression (14), the same results were obtained when evaluating anxiety and psychological factors before IVF (15).

Other studies compared the stress & distress of infertile couples versusαthe general population (16,17) or gender differences in emotional reactions to infertility among couples, seeking IVF and ICSI treatment (18). Some studies related the stress of infertile couples to the medical interventions (19,20).

Moreover, positive correlation was found between stress and treatment cost (21) and number of infertility tests and treatments were significant predictors of fertility problem stress for both women and men (21)

Patient assessment of the treatment, including patient satisfaction, quality of life and pessimism about the treatment were also studied. During the treatment patient were found to have an increased hope, they were more close to their partner, they were optimistic (22,23).

As for the willingness to take the treatment, patients were willing to accept it in the pursuit of a successful pregnancy even when they were aware of the potential link between fertility drugs and ovarian cancer (24).

Therefore, the more important questions remain: Does treatment play a role in the genesis of anxiety or of any other psychological disorders? Do different FSH products have different adverse effects profile?

Based upon this, we thought to evaluate the Psychological as well as the Physical changes associated with Controlled Ovarian Hyperstimulation in women undergoing Assisted Reproductive Technologies.

The purpose of this study is to maximize patient tolerance and acceptability of the treatment and to consider the patient's different needs.

MATERIALS & METHODS

Study design:

This is a cohort study of women undergoing treatment for infertility problems at one specialty clinic, at the American University Hospital of Beirut.

The study was held from the first of March 1999 till mid of June 1999.

The main objective is to evaluate the association between infertility medications and the physical and psychological changes experienced by the patients.

Criteria:

Criteria for acceptance into the study include:

Pre-menopausal women;

Infertile woman, defined as women desiring a pregnancy and having failed to conceive after one or more year of unprotected intercourse;

Infertility attributed to either tubal disease, ovarian factor endometriosis, male factor or unexplained;

Women able to ovulate either spontaneously or with fertility drugs;

Exhaustion of other attempts to restore fertility,

Women with good physical health, not previously diagnosed with a chronic disease;

Women with good mental health, with no previous history of psychiatric diagnosis or treatment or present consumption of mood altering drugs;

Women undergoing assisted reproductive technologies at various stages of infertility treatment, including women who had never taken fertility enhancing medications and women who had taken one or more cycles of fertility enhancing medications.

Sample:

Data were collected from 40 patients undergoing 57 cycles of treatment.

Data was collected prospectively for 40 cycles and retrospective for 17 cycles.

Patients were previously diagnosed for their cause of infertility and were assessed for the type of Assisted Reproductive Technology they need.

All patients and their spouses underwent a complete infertility work-up, that included a hysterosalpingogram, a semen analysis, determination of day 3 gonadotropin levels.

All patients were sacnned 7-9 days after starting stimulation and also within 24 hours of hCG administration.

Oocytes retrieval was scheduled for 36 hours after hCG administration.

None of the patients or of the cycles was excluded from the study due to the occurrence of a complication, or due to incomplete data set or absence of cooperation.

Study drugs:

Commercially available urinary hFSH was used as a lyophilized powder in vials containing 75 IU of hFSH bioactivity. Purified FSH (Metrodin® ,Fostimon®) and highly purified hFSH (Metrodin® HP,)were used.

Recombinant hFSH (Puregon®) was used as lyophilized powder in vials containing 50IU of hFSH bioactivity.

The commercially available GnRH agonist (Decapeptyl®) was used as ampoules containing 0.1 mg of peptide in 1 ml of solution.

Human CG (Pregnyl ®) was used as lyophilized powder in vials containing 5000 IU of hCG bioactivity.

All patients were treated with long GnRH suppression protocol, or, 0.05 mg SC per day from mid luteal phase of a spontaneous cycle until the day of hCG, for inducing

pituitary gonadotrope cell desensitization, to control endogenous secretion of LH during the superovulation treatment.

For controlled ovarian hyperstimulation, follicular stimulation was effected with urinary or recombinant hFSH, IM or SC. Luteinization was stimulated by administration of one dose of hCG , 5000 or 10000 IU, IM, when appropriate follicular growth was identified.

Measures:

Beck anxiety inventory (3):

This is a 21item scale, which assesses the severity of anxiety, and it is widely used both in clinical populations to assess severity and in normal populations to detect anxiety. Individuals are asked to report on their symptoms for the previous 7 days.

Adverse effects of GnRHa treatment (4):

Twenty-seven items assess the occurrence and severity of GnRHa adverse effects. Each item is rated from 0 to 3 according to its presence or severity.

Adverse effects of hFSH treatment (4):

Twenty- four items assess the occurrence of FSH adverse effects. Each item is rated from 0 to 3 according to its presence or severity. These adverse effects do not reflect complications from the infertility medications, they are just symptoms or physical changes experienced by the patient during the course of treatment.

Convenience with the mode of administration of hFSH products:

Three items were used to assess the convenience with the mode of administration. Each item is rated from 0 to 3 according to its presence or severity.

Patient assessment of the treatment (9):

Seven items were included to describe the patient perceptions and feelings about the period of treatment, independently if the treatment terminated without success. Each item is rated from 0 to 3 according to its presence or severity In addition, the patient assessment of the treatment is not related to the specific treatment given.

Personal acceptance of the treatment (27):

The final step is reserved to evaluate the patient's willingness to take, repeat or even continue the treatment including the procedure itself.

Demographic information together with information from the medical notes (medical charts and physician's notes) were recorded, the later included: cause of infertility, duration of infertility, infertility medications used, dose or total number of ampoules given, duration of the treatment, type of assisted reproductive technology used.

Procedure:

Demographic and medical information were recorded from the patient medical chart. Beck anxiety inventory, adverse effects of the GnRHa treatment, adverse effects of hFSH treatment, convenience with the mode of administration of hFSH products, patient assessment of the treatment and personal acceptance of the treatment were all included in a structured questionnaire designed for the study.

The questionnaire was filled by the patient and the physician during the clinical visits. Adverse effects of GnRHa treatment were assessed before beginning the hFSH treatment.

Human FSH adverse effects and convenience with the mode of administration were recorded before the administration of hCG .

Patient assessment of the treatment and the willingness to repeat it were included at the end of the questionnaire and were filled at any time during the course of the treatment, before the oocytes retrieval.

Beck anxiety inventory was assessed at three different intervals of stimulation, before the GnRHa administration, before the hFSH administration and at the end of the hFSH treatment.

Statistical Analysis:

Data were analyzed through the Statistical Program for Social Studies (SPSS).

Means (±SD) values for age, duration of infertility, days of stimulation and ampoules of gonadotropins used were calculated. Diagnosis, type of assisted reproductive technology, adverse effects of GnRHa, patient assessment of the treatment, and willingness to repeat it also were determined.

A two-way analysis of variance (ANOVA) was used to compare means of Beck anxiety scores, means of duration of hFSH treatment and total dose used.

Student *t*-test was used to compare Beck anxiety scores among the different hFSH products.

Chi-square tests were used for categorical variables to determine statistical significance i.e. to compare adverse effects and patient assessment of the treatment with the different hFSH products, to compare patient convenience with IM versus SC administration.

Statistical significance was tested at alpha level of 0.05.

RESULTS

Data was analyzed on the 40 female patients undergoing 57 cycles of treatment. Twenty seven patients underwent one cycle of treatment and the remaining took 2 cycles. Data was collected prospectively for 40 cycles and retrospectively for17 cycles.

Subjects characteristics:

The characteristics of the patient population are described in table 1.

Table 1: Patients Characteristics

	Total	Mean (SD)	Median	Min	Max
Age (years)	39	31.62(5.[illegible])	32.00	20	43
Duration of infertility (years)	33	4.97(3.74)	4.00	0.83	15

Cause of infertility	**Number (%)**
Primary	31(77.5)
Secondary	7 (17.5)
Primary and secondary	1 (2.5)
Primary infertility	
Male factor	20(50.0)
Endometriosis + male factor	3 (7.5)
Endometriosis	2 (5.0)
Idiopathic	2 (5.0)
Tubal factor	1 (2.5)

Ovarian factor	2 (5.0)
Endometriosis +unexplained	1 (2.5)
Tubal factor +male factor	1 (2.5)
Secondary infertility	
Male factor	4 (10.0)
Endometriosis + male factor	2 (5.0)
Uterine factor	1 (2.5)
Poor ovarian reserve	1 (2.5)
Previous pregnancies	
0	32 (80.0)
1	6 (15.0)
3	1 (2.5)

The mean (± SD) patient age was 31.6 (± 5.9) years, the mean ± SD patient duration of infertility was 4.9 (± 3.7) years.

Eighty percent of the subjects had no children (primary infertility), 15.0% had one child, and 2.5% had 3 children.

The percentages on the cause of infertility were: male factor, 60%, female factor, 20%, both male factor and female factor, 12.5% and idiopathic, 5%.

Controlled ovarian hyperstimulation characteristics:

Controlled ovarian hyperstimulation characteristics are described in table 2.

Table 2: Controlled Ovarian Hyperstimulation Characteristics

Dose of Hcg	Number (%)
5000 IU	11 (21.2)
10000 IU	41 (78.8)
Type of hFSH	
Urinary purified hFSH	27 (47.4)
Urinary highly purified hFSH	11 (19.3)
Recombinant hFSH	19 (33.3)
Mode of administration of hFSH	
IM	27 (47.5)
SC	30 (52.6)
Assisted Reproductive Technology	
IVF	11 (20.8)
ICSI	40 (75.5)
IVF + ICSI	2 (3.8)

Days of stimulation	Total	Mean(SD)	Median	Min	Max.	F	*P*
Urinary Purified hFSH	24	8.08 (0.88)	8.00	7	10	0.429	0.654
Urinary Highly P. hFSH	9	8.33 (1.00)	8.00	7	10		
Recombinant hFSH	19	8.00 (0.94)	8.00	6	10		
All hFSH	52	8.21(0.91)	8.00	6	10		
Total # of ampoules							
Urinary Purified hFSH	24	37.79 (10.47)	35.0000	21	60	1.157	0.323
Urinary Highly P.hFSH	9	33.33 (10.80)	32.0000	23	54		
Recombinant hFSH	19	34.10 (6.89)	34.0000	24	52		
All hFSH	52	35.67(9.41)	34.0000	21	60		
Total dose (IU)							
Urinary Purified hFSH	24	2835(785.66)	2812	1575	4500	15.57	.000*
Urinary Highly P.hFSH	9	2500(810.38)	2888	1725	4050		
Recombinant hFSH	19	1705(79.09)	1900	1200	2600		
All hFSH	52	2364(832.09)	2850	4500	4500		

*Significant at $p < 0.05$

As for the type of hFSH, 47.4% of the patients took urinary purified hFSH, 19.3% took urinary highly purified hFSH and 33.3% took recombinant hFSH.

Mean days of stimulation was 8.21 (± 0.91) days for all hFSH products and there was no significant difference between the average days of stimulation of the three groups.

Means for the total number of ampoules consumed were 37.8 (± 10.5) for urinary purified hFSH, 33.33 (± 10.8) for urinary highly purified hFSH and 34.1 (± 6.9) for recombinant hFSH. However significant difference between groups was not reported.

Means (± SD) for Intenational Units of hFSH received were as follow: 2835 (± 786) IU 2500(±811) IU, 1706 (±80IU), for urinary purified, urinary highly purified and recombinant hFSH respectively. Significant statistical difference was found when comparing means IU of urinary purified and recombinant groups (p=0.000) and when comparing means IU of urinary highly purified and recombinant groups (p= 0.005).

Human FSH was administered IM for 47.5% of the cases and SC for the remaining ones.

Concerning the dosage of Human chorionic gonadotropin, 10000 IU were given for 78.8% of the subjects and 5000 IU for 21.2%.

ICSI was used in 75.5% of the cycles, IVF in 20.8% and IVF together with ICSI in 3.8%.

Adverse effects of GnRH agonist:

Percentages and severity of the GnRH agonist adverse effects are described in table 3, and are as follow:

Table 3: Adverse effects of GnRH agonist

Symptoms	Not at all Number (%)	Mild Number (%)	Moderate Number (%)	Severe Number (%)
Acne	54 (94.7)	2 (3.5)	1 (1.8)	–
Bone pain	52 (91.2)	5 (8.8)	–	–
Chest pain	55 (96.5)	1 (1.8)	1 (1.8)	–
Decreased libido	57 (100)	–	–	–
Dizziness	46 (80.7)	8 (14)	3 (5.3)	–

Symptoms	Not at all Number (%)	Mild Number (%)	Moderate Number (%)	Severe Number (%)
Edema	56 (98.2)	1 (1.8)	–	–
Emotional labile	27 (47.4)	17 (29.8)	10 (17.5)	3 (5.3)
Headache	39 (68.4)	11 (19.3)	2 (3.5)	5 (8.8)
Hirsutism	57 (100)	–	–	–
Hot flushes	38 (66.7)	11 (19.3)	6 (10.5)	2 (3.5)
Injection site reactions	36 (63.2)	11 (19.3)	5 (8.8)	5 (8.8)
Insomnia	46 (980.7)	5 (89.5)	2 (93.0)	4 (7.0)
Malaise	41 (71.9)	12 (21.1)	4 (7.0)	–
Myalgia	45 (78.9)	10 (17.5)	2 (3.5)	–
Nasal irritation	57 (1000	–	–	–
Nausea	43 (75.4)	10 (17.5)	1 (1.8)	3 (5.3)
Pruritis	55 (96.5)	1 91.8)	1 (1.8)	–
Rash	54 (94.7)	1 (1.8)	1 (1.8)	1 (1.8)
Reduced breast size	52 (91.2)	5 (8.8)	–	–
Seborrhea	55 (96.5)	2 (3.5)	–	–
Shortness of breath	43 (75.4)	11 (19.3)	2 (3.5)	1 (1.8)
Sleep disturbances	44 (77.2)	6 (10.5)	2 (3.5)	5 (8.8)
Urinary symptoms	47 (82.5)	6 (10.5)	2 (3.5)	2 (3.5)
Urticaria	55 (96.5)	1 (1.8)	1 (1.8)	–
Vaginal bleeding	57 (100)	–	–	–
Vaginal discharge	50 (87.5)	4 (7.0)	2 (3.5)	1 (1.8)
Vagina dryness	49 (86.0)	4 (7.0)	4 (7.0)	–

Emotional labile, 54.6%; injection site reactions, 36.8%; hot flushes, 33.3%, headache 31.6%; malaise, 28.1%; shortness of breath, 24.6%; nausea, 24.6%; sleep disturbances, 22.8%; myalgia, 21.15; dizziness, 19.3%; insomnia, 19.3%; urinary symptoms, 17.5%; vaginal dryness, 14.0%; vaginal discharge, 12.3%. Other adverse effects were reported in less then 10%.

Severe headache, injection site reactions and sleep disturbances were each reported in 8.8%. Severe insomnia was detected in 7.0% of the cases and severe nausea and emotional lability was seen in 5.3%. Other severe adverse effects were reported in1.8%.

Adverse effects of hFSH:

Adverse effects of hFSH therapy are detailed in tables 4, 5 and 6.

Table 4: Adverse effects of hFSH

Symptoms	Not at all Number (%)	Mild Number (%)	Moderate Number (%)	Severe Number (%)
Nausea	39 (68.4)	12 (21.1)	3 (5.3)	3 (5.3)
Vomiting	53 (93.0)	3 (5.3)	1 (1.8)	–
Diarrhea	55 (96.5)	1 (1.8)	1 (1.8)	–
Abdominal cramps	41 (71.3)	9 (15.8)	3 (5.3)	4 (7.0)
Abdominal pain	41 (71.9)	7 (12.3)	3 (5.3)	6 (10.5)
Abdominal pressure	34 (59.6)	12 (21.1)	7 (12.3)	4 (7.0)
Local soreness	40 (70.2)	7 (12.3)	5 (8.8)	5 (8.8)
Local redness	54 (94.7)	2 (3.5)	–	1 (1.8)
Local swelling	49 (86.0)	5 (8.8)	1 (1.8)	2 (3.5)

Symptoms	Not at all Number (%)	Mild Number (%)	Moderate Number (%)	Severe Number (%)
Local pain	19 (33.3)	19 (33.3)	6 (10.5)	13 (22.8)
Febrile reactions	53 (93.0)	4 (7.0)	–	–
Chills	50 (87.7)	6 (10.5)	–	1 (1.8)
Musculosceletal aches	41 (71.9)	9 (15.8)	5 (8.8)	2 (3.5)
Joints pain	42 (73.7)	8 (14.0)	4 (7.0)	3 (5.3)
Malaise	40 (70.2)	8 (14.0)	8 (14.0)	1 (1.8)
Headache	35 (61.4)	10 (17.5)	5 (8.8)	7 (12.3)
Hot flushes	56 (98.2)	–	–	1 (1.8)
Fatigue	31 (54.4)	11 (19.3)	12 (21.1)	3 (5.3)
Breast tenderness	42 (73.7)	6 (10.5)	5 (8.8)	4 (7.0)
Dry skin	53 (93.0)	4 (7.0)	–	–
Body rash	45 (78.9)	7 (12.3)	2 (3.5)	3 (5.3)
Hair loss	55 (96.5)	2 (3.5)	–	–
Irritability	30 (52.6)	15 (26.3)	4 (7.0)	8 (14.0)
Depressed mood	36 (63.2)	14 (24.6)	2 (3.5)	5 (8.8)

Table 5: Adverse effects of hFSH: urinary purified, urinary highly purified & recombinant

***: Significant at $p < 0.05$**

Symptoms	Urinary purified hFSH Number (%)	Urinary highly purified hFSH Number (%)	Recombinant hFSH Number (%)	Total Number (%)	X″	P
Nausea	8 (29.6)	4 (36.4)	6 (31.6)	18 (31.6)	0.164	0.921
Vomiting	1 (3.7)	1 (9.1)	2 (10.5)	4 (7.0)	0.885	0.642
Diarrhea	1 (3.7)	–	1 (5.3)	2 (3.5)	0.576	0.750

Symptoms	Urinary purified hFSH Number (%)	Urinary highly purified hFSH Number (%)	Recombinant hFSH Number (%)	Total Number (%)	X″	P
Abdominal cramps	7 (25.9)	4 (36.4)	5 (26.3)	16 (28.1)	1.613	0.446
Abdominal pain	9 (33.3)	3 (27.3)	4 (21.1)	16 (28.1)	0.837	0.658
Abdominal pressure	13 (48.1)	4 (36.4)	6 (31.6)	23 (40.3)	1.362	0.506
Local soreness	8 (29.6)	4 (36.4)	5 (26.3)	17 (29.8)	0.337	0.845
Local redness	2 (7.4)	–	1 (5.3)	3 (5.3)	2.423	0.298
Local swelling	2 (7.4)	2 (18.2)	4 (21.1)	8 (14.0)	1.915	0.384
Local pain	19 (70.4)	5 (45.5)	14 (73.7)	38 (66.7)	2.815	0.245
Febrile reactions	2 (7.2)	1 (9.1)	1 (5.3)	4 (7.01)	0.465	0.792
Chills	6 (22.2)	–	1 (5.3)	7 (12.3)	4.886	0.087
Musculoscelet al aches	8 (29.6)	2 (18.2)	6 (31.6)	16 (28.1)	0.681	0.711
Joints pain	8 (29.6)	2 (18.2)	5 (26.3)	15 (26.3)	0.860	0.650
Malaise	8 (29.6)	4 (36.4)	5 (26.3)	17 (29.8)	0.337	0.845
Headache	12 (44.0)	2 (18.2)	8 (42.1)	22 (38.6)	0.528	0.768
Hot flushes	–	1 (9.1)	–	1 (1.8)	4.256	0.119
Fatigue	15 (55.5)	3 (27.3)	8 (42.1)	26 (45.6)	2.662	0.264
Breast tenderness	10 (37.0)	3 (27.3)	2 (10.5)	15 (26.3)	4.049	0.132
Dry skin	3 (11.1)	–	1 (5.3)	4 (7.0)	0.168	0.919
Body rash	10 (37.0)	1 (9.1)	1 (5.3)	12 (21.1)	7.948	0.019*
Hair loss	1 (3.7)	1 (9.1)	–	2 (3.5)	1.706	0.426
Irritability	13 (48.1)	8 (72.3)	6 (31.6)	27 (47.4)	4.744	0.093
Depressed mood	11 (40.7)	5 (45.5)	5 (26.3)	21(36.84)	1.432	0.489
Total	27	11	19	57 (100)		

Table 6: Adverse effects of hFSH: urinary purified versus recombinant

Symptoms	Urinary purified Hfsh Number (%)	Recombinant hFSH Number (%)	Total Number (%)	X″	*P*
Nausea	8 (29.6)	6 (31.6)	14 (30.4)	0.020	0.887
Vomiting	1 (3.7)	2 (10.5)	3 (6.5)	0.852	0.642
Diarrhea	1 (3.7)	1 (5.3)	2 (4.3)	0.065	0.796
Abdominal cramps	7 (25.9)	5 (26.3)	12 (26.1)	0.001	0.976
Abdominal pain	9 (33.3)	4 (21.1)	13 (28.3)	0.830	0.362
Abdominal pressure	13 (48.1)	7 (31.6)	19 (41.3)	1.263	0.261
Local soreness	8 (29.6)	5 (26.3)	13 (28.3)	0.060	0.806
Local redness	2 (7.4)	1 (5.3)	3 (6.5)	0.084	0.772
Local swelling	2 (7.4)	4 (21.1)	6 (13.0)	1.831	0.176
Local pain	19 (70.4)	14 (73.7)	33 (71.7)	0.060	0.806
Febrile reactions	2 (7.2)	1 (5.3)	3 (6.5)	0.084	0.772
Chills	6 (22.2)	1 (5.3)	7 (15.2)	2.486	0.115
Musculosceletal aches	8 (29.6)	6 (31.6)	14 (30.4)	0.020	0.887
Joints pain	8 (29.6)	5 (26.3)	13 (28.3)	0.806	0.806
Malaise	8 (29.6)	5 (26.3)	13 (28.3)	0.060	0.806
Headache	12 (44.0)	8 (42.1)	20 (43.5)	0.025	0.875
Fatigue	15 (55.5)	8 (42.1)	23 (50.0)	0.807	0.369
Breast tenderness	10 (37.0)	2 (10.5)	12 (26.1)	4.065	0.044*
Dry skin	3 (11.1)	1 (5.3)	4 (8.7)	0.480	0.488
Body rash	10 (37.0)	1 (5.3)	11 (23.9)	6.188	0.013*

Symptoms	Urinary purified Hfsh Number (%)	Recombinant hFSH Number (%)	Total Number (%)	X"	P
Hair loss	1 (3.7)	_	1 (2.2)	0.719	0.426
Irritability	13 (48.1)	6 (31.6)	19 (33.3)	1.263	0.093
Depressed mood	11 (40.7)	5 (26.3)	16 (34.8)	1.023	0.489
Total	27	19	46		

*: Significant at $p< 0.05$

Percentages for the adverse effects of hFSH products were as follow: local soreness,70.2%; local pain, 66.7%; irritability, 47.4%; fatigue, 45.6%; abdominal pressure, 40.4%; headache, 38.6%; depressed mood, 36.8%; abdominal cramps, 28.7%; abdominal pain, 28.7%; malaise, 28.2%; musculosceletal aches, 28.1%; joints pain, 26.3%; breast tenderness, 26.3%; body rash, 21.1%; local swelling, 14.0%; chills, 12.3%. Other adverse effects were reported in less than 10%.

Severe local pain was detected in 22.8%, severe irritability in 14.0%, severe headache in 12.3%, severe abdominal pain in 10.5% of the patients, severe local soreness and severe depressed mood each in 8.8%, severe abdominal cramps and severe breast tenderness each in 7.0%. Severe nausea, musculoske letal aches, joints pain and body rash were each seen in 5.3%. Other severe adverse effects were reported in1.8%

When comparing the different hFSH products, significant difference was found between them with respect to body rash (p=0.019). In fact body rash was reported in 10 patients taking urinary purified hFSH but only in 1 of patient taking urinary highly purified hFSH and in 1 patient taking recombinant hFSH

Chills were seen in 6 patients on urinary purified hFSH, were absent in the sample of patients taking urinary highly purified hFSH, and occurred for 1 of patient taking

recombinant hFSH. Hot flushes were seen in 1 patient taking urinary highly purified hFSH. Breast tenderness was reported in 10 patients on urinary purified hFSH and in 3 patients taking urinary highly purified hFSH and only in 2 patients taking recombinant hFSH. Irritability occurred in 13 patient on urinary purified hFSH, in 8 patients taking urinary highly purified hFSH and in 6 patients taking recombinant hFSH. These differences were not statistically significant.

When comparing urinary purified hFSH and recombinant hFSH, significant differences in percentages were reported for breast tenderness, (p=0.044) and for body rash, (p=0.013).

Checking for the number of ampoules consumed, revealed that it is not a significant confounding variable.

Mode of administration:

Characteristics of this part are given in tables 7and 8.

Table 7: Mode of administration of hFSH

Mode of Administration	Not at all Number (%)	Mild Number (%)	Moderate Number (%)	Severe Number (%)
Inconvenience	35 (61.4)	17 (29.8)	4 (7.0)	1 (1.8)
Dependence	35 (61.4)	16 (28.1)	5 (8.8)	1 (1.8)
Stress	29 (50.9)	15 (26.3)	5 (8.8)	8 (14.0)

Table 8: Mode of administration of hFSH: IM versus SC

Mode of Administration	IM Number (%)	SC Number (%)	Total Number (%)	X^2	*p*
Inconvenience	15 (55.6)	7 (23.3)	22 (38.6)	6.226	0.013*
Dependence	15 (55.6)	7 (23.3)	22 (38.6)	6.226	0.013*
Stress	13 (48.1)	15 (50.0)	28 (49.1)	0.019	0.889
Total	27	30	57		

*: Significant at $p < 0.05$

Inconvenience and dependence related to the administration of the hFSH medications were each reported in 38.6% of the patients, whereas stress accompanied by the injections was reported in 49.1%.

Moreover, severe inconvenience and dependence related to the hFSH injections were each reported in 1.8% and severe stress was seen in 14.0%. When comparing IM versus SC administration, significant difference was found with respect to inconvenience and dependence with the mode of administration (p=0.013). Of the patients taking IM injections, 55.6% were reported to experience inconvenience and dependence with the mode of administration versus 23.3% only of the patients doing SC injections.

Anxiety test scores:

Details are given in tables 9,10 and 11 .

Table 9: Anxiety test score:

Anxiety test scores	total	Mean (SD)	Min.	Max.	F	*P*
Test 1	57	1.1579 (2.1280)	.00	9.00	14.572	.000*
Test 2	57	4.7193 (5.273)	.00	21.00		
Test 3	57	5.8070 (6.0870)	.00	23.00		

*: Significant at $p < 0.05$

Table10: Anxiety test scores and hFSH products: urinary purified urinary highly purified and recombinant

Anxiety test scores	total	Mean (SD)	Min.	Max.	F	*P*
Urinary Purified hFSH	27	5.4815 (6.0977)	-2	21	0.613	0.545
Urinary Highly P. hFSH	11	4.000 (5.2154)	-3	15		
Recombinant hFSH	19	3.8421 (5.3602)	-1	15		

Table11: Anxiety test scores and hFSH products: urinary purified versus Recombinant

Anxiety test scores	total	Mean (SD)	Min.	Max.	T	*P*
Urinary Purified hFSH	27	5.4815 (6.0977)	-2	21	1.068	0.291
Recombinant hFSH	19	3.8421 (5.3602)	-1	15		

Means for the Beck anxiety test scores were as follows: baseline test, 1.6 ± 2.1; before hFSH administration (test2), 4.7 ± 5.2; after hFSH administration (test 3), 5.8 ± 6.1. Significant difference was found between the three different means (p=0.000). When analyzing the data with the Least Significance Difference Test, significant difference was found between test 1 and test 2 (p=0.000), test1 and test 3 (p=0.000) but not between test 2 and test3. No difference was reported between the anxiety test score difference and the different hFSH available.

Age, duration and cause of infertility were checked as confounding variables, and they were not significant.

Patient assessment of the treatment:

Patients assessment of the treatment are described in tables12, 13 and 14.

Table 12: Patient assessment of the treatment

Patient assessment of the treatment	Not at all Number (%)	Mild Number (%)	Moderate Number (%)	Severe Number (%)
Negative experience	31 (54.4)	15 (26.3)	11 (19.3)	–
Severe psychological strain	30 (52.6)	12 (21.1)	10 (17.5)	5 (8.8)
Loss of privacy	44 (77.2)	2 (3.5)	5 (8.8)	6 (10.5)
Deep sorrow/ despair	37 (64.9)	11 (19.3)	5 (8.8)	4 (7.0)
Strain on the couple life	44 (77.2)	9 (15.8)	3 (5.3)	1 (1.8)
Pessimism	39 (68.4)	11 (19.3)	5 (8.8)	2 (3.5)
Inconvenience	37 (64.9)	9 (15.8)	5 (8.8)	6 (10.5)

Table 13: Patient assessment of the treatment and hFSH products: urinary purified urinary highly purified and recombinant

Patient assessment of the treatment	Urinary purified hFSH Number (%)	Urinary highly purified hFSH Number (%)	Recombinant hFSH Number (%)	Total Number (%)	X^2	*P*
Negative experience	14 (51.9)	5 (45.5)	7 (36.8)	26 (45.6)	1.013	0.603
Severe psychological strain	14 (51.9)	6 (54.5)	7 (36.8)	27 (47.4)	1.289	0.525
Loss of privacy	9 (33.3)	2 (18.2)	2 (10.5)	13 (22.8)	3.186	0.203
Deep sorrow/ despair	12 (44.4)	4 (36.4)	4 (21.05)	20 (35.8)	2.689	0.261
Strain on the couple life	8 (29.6)	1 (9.1)	4 (21.05)	13 (22.8)	1.923	0.382

Pessimism	11 (40.7)	4 (36.4)	3 (15.8)	18 (31.6)	3.358	0.187
Inconvenience	13 (48.1)	3 (27.3)	4 (21.05)	20 (35.8)	3.960	0.138
Total	27	11	19	57		

Table 14: Patient assessment of the treatment and hFSH products: urinary purified versus recombinant

Patient assessment of the treatment	Urinary purified hFSH Number (%)	Recombinant hFSH Number (%)	Total Number (%)	X^2	*P*
Negative experience	14 (51.9)	7 (36.8)	21 (45.6)	0.314	1.013
Severe psychological strain	14 (51.9)	7 (36.8)	21 (45.6)	1.013	0.314
Loss of privacy	9 (33.3)	2 (10.5)	11 (23.9)	2.888	0.089
Deep sorrow/ despair	12 (44.4)	4 (21.05)	16 (34.8)	2.690	0.101
Strain on the couple life	8 (29.6)	4 (21.05)	12 (26.1)	0.425	0.514
Pessimism	11 (40.7)	3 (15.8)	14 (30.4)	3.279	0.070
Inconvenience	13 (48.1)	4 (21.05)	17 (37.0)	3.514	0.06
Total	27	19	46		

The period of treatment was seen as a severe psychological strain by 47.4% of the patients, as a negative experience by 45.6%, as sorrow and despair by 35.1% , as a strain on the couple life by 22.8% and as a period of loss of privacy by 22.8% also. Of all the patients,35.1% reported that the treatment is inconvenient and 31.6% were pessimistic about the treatment outcome. The period of treatment was considered as a period of important loss of privacy by 10.5% of the patients, as a severe psychological

strain by 8.8%, as a deep sorrow and despair by 7.0% and as a severe strain on the couple life by 1.8%. Severe inconvenience with the treatment was reported by 10.5% of the participants and extreme pessimism about the treatment outcome was reported by 3.5%. When comparing the different hFSH products with respect to the patient assessment of the treatment,13 patients of urinary purified group were inconvenient with the treatment versus 3 patients of urinary highly purified group and 4 patients of recombinant group. Comparison of the urinary purified and recombinant groups showed that 9 versus 2 patients respectively evaluated the period of treatment as a period of loss of privacy. Sorrow and despair during the period of treatment was reported by 12 patients of the urinary purified group and by 4 patients of the recombinant group.

Pessimism about the treatment outcome was reported by 11 patients on urinary purified hFSH and by only 3 patients on recombinant hFSH .

These differences were not statistically significant.

Willingness to take the treatment:

Patient acceptance of the treatment is described in table 15.

Table 15: Willingness to take the treatment

Willingness to take the treatment	Yes Number (%)	No Number (%)
Break within the treatment	2 (3.5)	55 (96.5)
Repeat the treatment	55 (96.5)	2 (3.5)
Try every possible treatment	56(98.2)	1 (1.8)

96.5% of the patients refuse to break within the treatment and are willing to repeat it in case of failure. 98.2% want to try every possible treatment available.

DISCUSSION

Excluding local reactions to injections, the most frequently reported adverse effects for all hFSH products in this study were irritability, fatigue, abdominal pressure and then headache. In the recombinant human FSH study (16), abdominal pain and headache were the most frequently reported adverse effects following the local reactions to injections. Difference in adverse effects profile was noted when comparing the difference preparations of hFSH.

Comparing three available hFSH products revealed significantly higher frequency of body rash in the urinary purified group. Moreover, when comparing urinary purified group with recombinant group, a significantly higher percentage of breast tenderness was reported in the urinary purified group.

Irritability and chills were also more frequently reported in the urinary group. The lack of significant here is probably due to the small sample size.

Difference between recombinant and urinary hFSH that might explain the difference in adverse effects include the contaminating proteins in the urinary preparations, the pharmaceutical formulation, the isohormone profile and the small difference in the oligosaccharide structure (5).

In fact, body rash and chills are immune mediated reactions, and their occurrence in higher frequencies in the urinary purified group is related to the fact that the later preparation contains more than 95% of protein bands. These proteins co-administrated as impurities with conventional gonadotropin preparations might increase the rate of allergic reactions in the recipients even if all of the proteins were human origin. It is

documented that exogenous human proteins can induce immune reactions in patients as described by insulin, human growth hormone, hCG....

Anaphylactic chock was reported in women undergoing stimulation for IVF with urinary HMG...(28). Similarly, a patient who had shown an immune mediated type reaction using HMG was treated without allergic symptoms with recombinant hFSH(29).The same conclusion can be drawn from recent case report showing that delayed type hypersensitivity reactions to HMG were avoided by using highly purified hFSH(30).

In addition, some gonadotropins were shown to modulate parameters of immune function in vitro (13). However, different product gave a substantially different pattern of activity.

Recombinant preparations and highly purified preparations which are pure hFSH preparations did not show any effect in any of the tests performed, thus, ruling out that the effects observed with other preparations were caused by hFSH(13). Moreover, preparations from different manufacturer have different in vitro immunological effects, reflecting a different profile of contaminants.

Other adverse effects including headache, abdominal pain, breast tenderness, and irritability are known events associated with hFSH treatment, and are undoubtedly related to ovarian stimulation, which leads to some increase in ovarian size and to elevated serum estrogen levels (32).

In fact, breast tenderness and irritability were higher in the urinary purified group, this maybe due to the higher estradiol level on the day of hCG.

In fact, in a study comparing urinary purified hFSH and recombinant hFSH(13), a significant difference was observed in estradiol levels on the day of hCG with higher

levels in the urinary purified hFSH. This is probably related to the slightly lower number of large follicles (>14mm) recorded in the study (31). Other studies reported also lower estradiol level when using urinary highly purified preparations as compared to purified or HMG preparations (12,15).

The lower estradiol levels were not correlated with higher cancellation rates or lower embryo transfer, embryo implantation rate or pregnancy rate and pregnancy outcome. These serum estradiol levels are however well above the physiologic preovulatory estradiol level (300 to 900 pmol/l) (12,16).

Another fact, which may account for the different adverse effects profile of the three preparations is the different isohormone profile.

It has recently been shown that the distribution of hFSH isoforms in the urinary purified and urinary highly purified preparations deviates significantly from that of the recombinant hFSH , being far more acidic in nature than in the latter(5, 14,15).

Moreover, the terminal sialic acid dictates the clearance of hFSH. So, acidic isoforms have a longer half life than basic isoforms of hFSH. It might be expected that urinary preparations stays longer in serum than do recombinant hFSH (5).

As for the potency in vivo, acidic isoformes are less bioactive than the alkaline one(5).

Recombinant hFSH preparations are supplied as 50IU/ampoule, and when calculating the total dose supplied, a significant difference was found with much lower total dose needed for recombinant therapy.This is in agreement with other studies where not only the total dose of the recombinant group was significantly lower than the urinary hFSH groups, but also the number of ampoules given and the total days of stimulation were also significantly lower (15).

In addition, urinary preparations show large batch to batch variation in the amount of bioactive hFSH available per ampoule, and in the composition of isoforms, whereas recombinant preparations are more consistant (5).

The higher bioactivity, shorter half –life and the batch consistency of the recombinant hFSH products may account for the lower frequency of adverse effects observed in this study.

Because of their high purity, urinary highly purified hFSH and recombinant hFSH can be administered SC. Several studies agreed that the administration of hFSH SC by the patient herself is an attractive and convenient alternative to patients and greatly simplifies patient management (12, 14, 16,17). The present study confirmed this finding but failed to show a reduction in the level of stress experienced by IM preparations as was detected in another study (12).

Local tolerance to injections was good and did not differ significantly between IM and SC administration. This is in agreement with previous studies (16).

Anxiety test scores before and after hFSH therapy were significantly different from baseline scores. Although anxiety disorder was not detected by the Beck scale, significant increase in the scores was seen, and mild to moderate anxiety was present in many patients. This suggest that the items in the Beck anxiety scale (i.e. feeling hot, nervous, unable to relax, heart pounding or racing etc..) are adverse effects of the infertility medications. Some of the items are already documented adverse effects of the GnRHa and hFSH treatment. For instance, feeling hot is a known adverse effect of GnRH analogues and irritability an adverse effect of hFSH treatment (4).

With respect to anxiety scores, no significant difference was found between the different hFSH preparations.

So, in contrast to other studies that attributed the anxiety of the infertile patients to their medical condition, to the medical interventions (IVF, ICSI), and the treatment cost, (19-23), the present study confirms the role of the infertility medications in the genesis of anxiety.

Moreover, the patient's own assessment of the treatment revealed that an important number of patients showed a depressed mood, and experienced a severe psychological strain during the period of treatment.

In conclusion, the present study suggests that anxiety is an adverse effect of the infertility medications and that the different hFSH products differ in their adverse effects profile. The study limitation is that of a small sample size. Moreover, filling of the questionnaire retrospectively for seventeen cycles represents another limitation.

So, further studies are needed to check if the infertility medications are responsible of psychological disorders as anxiety and depression, and to confirm the finding that different hFSH products differ in their adverse effects. A large sample would give the study more credibility.

By knowing which infertility drug has a better adverse effects profile, patient's tolerance and acceptability of the treatment would be maximized and the patient's different needs would be considered.

PHYSICAL AND PSYCHOLOGICAL CHANGES ASSOCIATED WITH INDUCTION OF OVULATION SPECIFICALLY WITH FSH TREATMENT

Patient initials:

Patient age:

Patient HT:

Patient WT:

Good physical health	Yes	No
Good mental health	Yes	No

Semen analysis of the partner

Count:

Motility:

Morphology:

NL uterine cavity and fallopian tube:	Yes	No

Infertility: Primary

Secondary

Causes of infertility: Primary

Secondary

Duration of infertility:

G...P...A...L...

Baseline	US
	E2
	FSH

FSH treatment given:

Type: hMG

UFSH

HP-UFSH

Rec-FSH

Date of starting the drug:

Date of stopping the drug:

Total days of stimulation:

Total number of ampoules:

Chorionic Gonadotropin

DATE	DOSE

Use of GnRH agonist with the above treatment Yes No

If Yes: Long Protocol

Short Protocol

Day	CD1	CD2	CD3	CD4	CD5	CD6	CD7	CD8	CD9
Dose									

Use of Assisted Reproductive techniques

Yes No

If Yes: a) IVF

b) GIFT

c) ICSI

Monitoring

Date	CD
US (# of follicles)	
E2	

HCG titer on day of retrieval:

Oocytes characteristics:

Total # of eggs collected:

Mature eggs:

Immature eggs:

Postmature eggs:

Mature eggs:

GI:

GII:

GIII:

Embryos characteristics:

Total # of embryos:

Normal embryos:

Abnormal embryos:

# of embryos transferred:

Normal embryos:

GI:

GII:

GIII:

Pregnancy status: + ve

- ve

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