Urinary follicle-stimulating hormone is not different than recombinant follicle-stimulating hormone on embryo quality and karyotype makeup during induction of ovulation in women with recurrent pregnancy failure

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Background and objectives
Follicle-stimulating hormone (FSH) is critical for the onset and duration of follicular development. This can be promoted medically by drugs such as follitropin beta and recombinant follicle-stimulating hormone (rFSH) technology. The former is purified from CHO cell culture supernatant (111 amino acid) and has a high biochemical purity (>99%), with specific biological activity (about 10 000 IU/mg protein), and no luteinizing hormone activity. The drugs used for ovulation induction during in vitro fertilization may affect the number and quality of follicles produced. This in turn may affect the quality and the integrity of the embryos generated. Bad-quality embryos may cause recurrent pregnancy failure. We aimed to assess the relationship of urinary follicle-stimulating hormone (uFSH) versus recombinant follicle-stimulating hormone (rFSH) drugs in producing embryos with chromosomal abnormalities.
Patients and methods
Seven women were enrolled for the intracytoplasmic sperm injection trial: Three had highly purified uFSH and four had rFSH. All embryos had blastomere extraction on day 3 after injection but the preimplantation genetic screening was carried out 6 weeks after embryo transfer. Only one embryo was transferred to each woman.
Results and conclusion
The results revealed that there was no difference between the two drugs in terms of number and quality of embryos fertilized or abnormal karyotype assessed. Overall, 71% of the women included had some form of chromosomal abnormality (4/7). However, two of them miscarried between 2 and 3 weeks later. Either of uFSH or rFSH did not improve the quality or integrity of the embryos. However, preimplantation genetic screening is a valuable tool in the selection of embryos in assisted conception cycles to increase the take-home baby rate.

Keywords:
IVF, miscarriage, next-generation sequencing, PGM system, preimplantation genetic screening, recombinant follicle-stimulating hormone, urinary follicle-stimulating hormone

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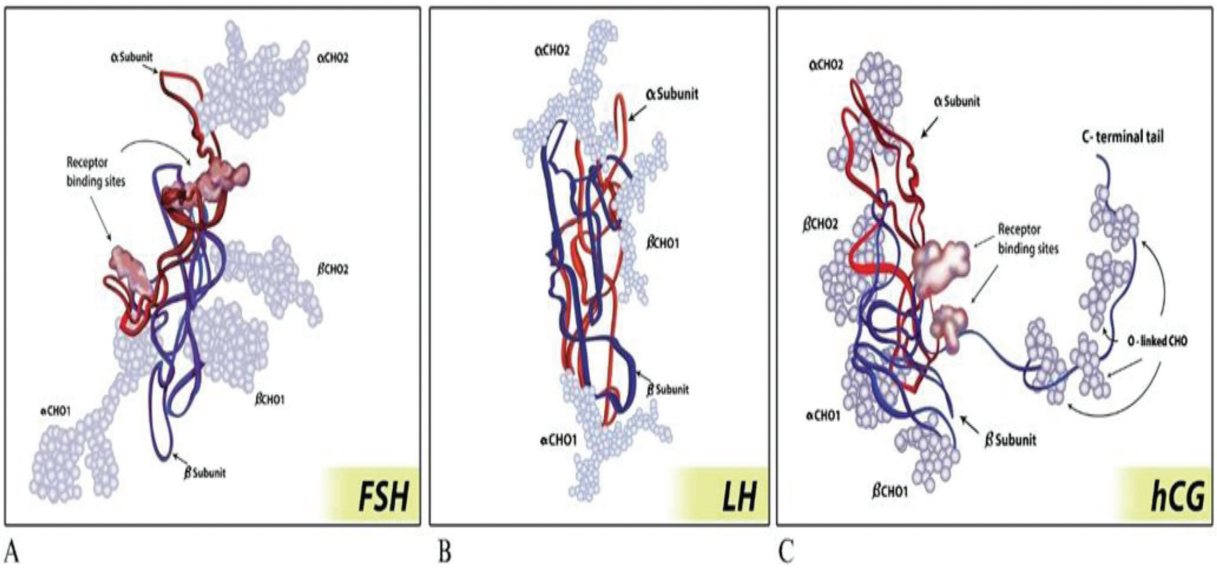
Introduction

Follicle-stimulating hormone (FSH) is a glycoprotein called follitropin that regulates the development, growth, pubertal maturation, and reproductive processes of the body. Follitropin consists of two noncovalent nonidentical glycoproteins known to be the alpha and beta-subunits, which are human FSH preparations of recombinant DNA origin. The alpha-subunit and beta-subunit consist of 92 and 111 amino acids, respectively. Asn 51 and Asn 78 are glycosylated for the alpha subunit, whereas Asn 7 and Asn 24 are glycosylated for the beta subunit (Fig. 1) [1].

Structural studies indicate that the follitropin beta amino acid sequence is the same as the normal human hormone activating the follicle. In addition, the side chains of oligosaccharides are extremely close but not identical with natural FSH. These minor changes, compared with natural FSH, do not, nevertheless, affect bioactivity. Exogenous FSH has been used to promote ovarian follicular growth and maturation in female and spermatogenesis in male. The relative short elimination half-life and rapid metabolic clearance of current versions of FSH require a daily or twice-daily scheduled subcutaneous injection to maintain stable FSH level being not below the threshold during ovarian stimulation. A number of technological strategies have been explored to develop recombinant longer-acting FSH (rFSH) [2]. This may

Figure 1

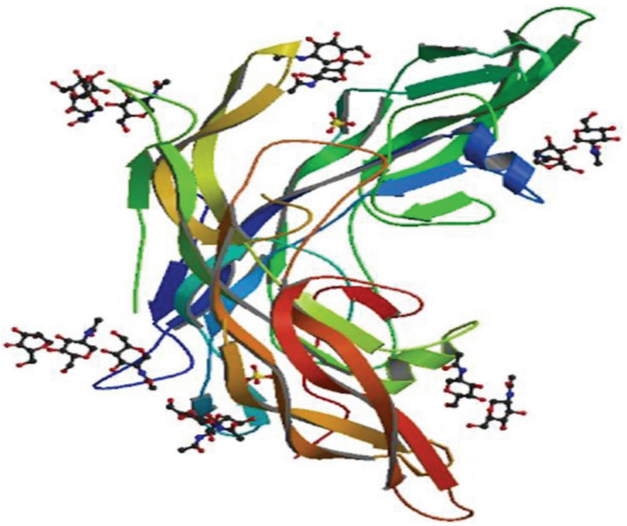


Three gonadotropin molecules. (a) Follicle-stimulating hormone (FSH) is a glycoprotein composed of two subunits (alpha and beta subunits are represented by red and blue strands, respectively), whereas the four carbohydrate chains are represented by light blue balls. (b) Luteinizing hormone (LH) is a glycoprotein with two subunits (alpha and beta subunits are represented by red and blue strands), which is similar to FSH, with two carbohydrate attachment sites, and the beta subunit (blue) with only one carbohydrate attachment site. (c) Human chorionic gonadotropin. HCG has structural features similar to LH. With the exception of having a long carboxy-terminal cross-section of O-glycosylated (O-linked CHO), which confers a longer half-life of HCG [1]. HCG, human chorionic gonadotropin.

be helpful for less injection, thus improving patient compliance and reducing patient stress and error rates. The pharmacokinetics of the rFSH and urinary follicle-stimulating hormone (uFSH) after a single intravenous injection in 12 pituitary-down-regulated healthy women showed remarkably comparable findings in in vitro and in vivo studies. The authors observed that following injection of 15 IU of uFSH and rFSH, the mean concentration profiles were virtually comparable and the mean profile was double than that for the 150 IU dosage after 300 IU of rFSH. With both products, exposure to drugs was similar, and for rFSH, the exposure would rise directly with the dose. Both preparations had an initial half-life (distribution) of 2 h and an actual elimination of 17 h [3,4]. Puregon is a rFSH that binds to the G-connected FSH hormone receptor. Binding the FSH to the sensor seems to cause phosphorylation and activation, which in the cells are known to affect many other cellular metabolic and associated activities of survival/maturation of phosphatidylinosite-3-kinase and Akt signaling pathway (Fig. 2).

Cetrorelix is an anti-human luteinizing hormone (LH) that binds to the gonadotropin-releasing hormone receptor and acts as a potent inhibitor of gonadotropin secretion. It competes with natural GnRH for binding to membrane receptors on pituitary cells and thus controls the release of LH in a dose-dependent manner (Fig. 3).

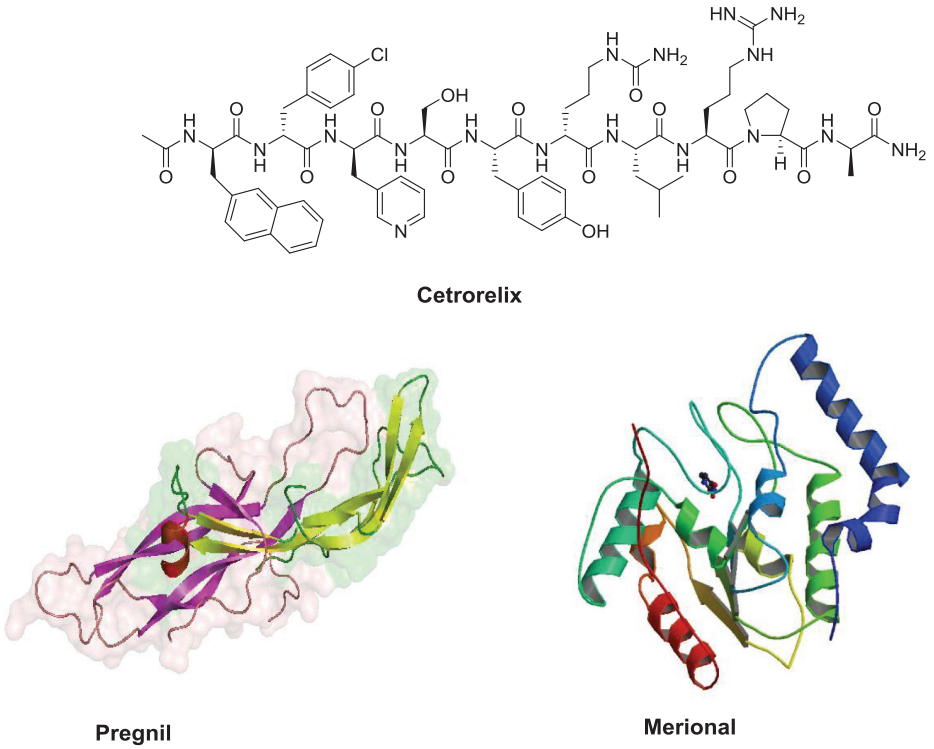
Figure 2



Protein chemical formula of rFSH Puregon ($C_{975}H_{1513}N_{267}O_{304}S_{26}$). rFSH, recombinant follicle-stimulating hormone.

Some studies found an association between type of FSH used in assisted conception and chromosomal abnormality of the embryo. This could explain the recurrent implantation failure in assisted conception cycles [5,6]. These chromosomal anomalies can be detected by the new technology of next-generation sequencing (NGS) of DNA. This has emerged and developed over the last decades such that the accomplishments today exceed the challenges and restrictions faced over the past few years. DNA

Figure 3



Chemical structures of Cetrorelix ($C_{70}H_{92}ClN_{17}O_{14}$), human chorionic gonadotropin (Pregnil), and human gonadotropin (Merional).

contains the layout of life [7]. NGS is a strobe podium that enables the sequencing of millions of DNA molecules concomitantly. NGS offers a high-throughput option with the power to sequence several members at the same time and focuses on reading aligned to a reference sequence using various bioinformatics mapping tools to call sequence variants in genomes [8]. Embryo quality was not related to multiple birth risk but was associated with increased live-birth rates when fewer embryos were transferred. Nevertheless, this hypothesis did not improve IVF outcomes and reduced miscarriage rates [9,10]. For sex selection, the presence of numerical chromosome abnormalities in human embryos was first accomplished by fluorescent in situ hybridization with four or additional chromosome-specific probes. Once most cells of embryos are analyzed, the fluorescent in situ hybridization technique allows differentiation to be made between aneuploidy, mosaicism, haploid, and polyploidy [11]. Now, the hypothesis of preimplantation genetic screening (PGS) inspires the disposal of aneuploidy embryos before the use in IVF procedures, which improves implantation rates, increases pregnancy and live birth rates, and reduces miscarriages [12,13]. Most missed miscarriages are caused by chromosomal abnormalities in fetuses. Only about 30% of the embryos cleaved when selected for transfer in IVF indeed implant in the uterus [14,15]. The reason for this high failure rate is unrecognized, but the hidden genetic mutations and abnormalities in chromosomes may be the main reason. We need to look for smart active technology with high accuracy screenings to lower costs and confer benefits to a much larger group of women [16,17]. There are several reports that have linked the type of drug used in ovulation induction with poor quality embryos and reduced pregnancy rate in intracytoplasmic sperm injection (ICSI) cycles [18,19]. Therefore, we conducted this pilot study to assess whether rFSH versus uFSH would increase the likelihood of chromosomal abnormality among women attending for ICSI trial. Chromosomal integrity was carried out by NGS.

Patients and methods

Criteria of patient

This pilot study included seven women aged more than 35 years, with history of at least two implantation failures with assisted conception, and were eligible to be recruited within this pilot study irrespective of their semen parameters or ovulation potential. We extracted

one blastomere from each embryo on day 3 of the ICSI cycle to check for its genetic makeup. This was carried out 6 weeks after transfer using an Ion ReproSeq PGS 316 View Kit for ion torrent technology. Ethics approval and consent to participate: The study was approved by the Ethical research committee (IRB) of Beni-Suef University under reference number protocol (151) in February 2019. Where we were using the transfer aspecting quality or number of embryo transfer, also using one blastomer from every embryo to check the genetic income of these embryos. The participants approved the publication and their participation in the study was written by all participant because the study did not disclose the identity of them.

Biochemical and stimulation protocol for intracytoplasmic sperm injection women evaluation

Blood samples were collected from the studied women in sterile test tubes and centrifuged for 15 min at 50 g. Serum was separated and kept at −80°C until used. Serum FSH, LH, and E2 were determined using enzyme-linked immunosorbent assays (R&D Systems, Minneapolis, Minnesota, USA) according to the manufacturer's instructions. We used the antagonist protocol for induction for all women. One group (three women) was administered highly purified (uFSH) (Merional, IBSA, Italy) at 150–225 international units (IU) daily starting on the second day of the cycle, whereas four women were administrated with rFSH (Puregon, USA) at 100–200 IU daily. We used cetrolix as the anti-human chorionic gonadotropin (HCG) drug in a dose of 0.25 mg daily subcutaneous injection from day 7 after menstruation onward for both groups. The adjustment of gonadotropin dose is based on the antral follicle count and FSH level before induction. Thereafter, the dose was adjusted according to the number and size of follicular development. Then, on day 7 or when follicular size reached more than or equal to 14 mm, cetrorelix was begun; both are continued until the administration of HCG injection (Pregnil, 100 00 IU, Elnil, Cairo, Egypt) when follicles reached a size between 17 to 19 ml. We monitored the women via transvaginal sonography every other day starting from day 8 and measuring estrogen level every other day to avoid hyperstimulation. Ovum pickup was scheduled 34–36 h after HCG administration.

Oocyte collection

Under ultrasound guidance, the woman was sterilized and a double-lumen needle was inserted through the vaginal wall into the ovarian follicles. The other end of the needle was attached to a suction device (pressure range, 90–110 mmHg). Once the follicle was entered, suction is gently applied to aspirate follicular fluid and with it, the cellular material, including the oocyte. The follicular fluid was delivered to an embryologist in the ICSI laboratory to identify and quantify the ova. Next, other follicles were aspirated. Once all the follicles have been aspirated from one ovary, the needle is withdrawn, and the procedure repeated for the other ovary. After completion, the needle was withdrawn, and hemostasis was achieved. The procedure usually lasted between 20 and 30 min.

Fertilization of the oocytes

The procedure was carried out using multiple micromanipulation devices (micromanipulator, microinjectors, and micropipettes). A holding pipette stabilizes the mature oocyte with gentle suction applied by a microinjector. From the opposite side, a thin, hollow micropipette is used to collect a single sperm, after having been immobilized it by cutting its tail with the point of the micropipette. The oocyte is pierced through the oolemma, and the sperm is directed into the inner part of the oocyte (cytoplasm). The sperm head is then released into the oocyte. The oocyte injected has to have an extruded polar body to indicate its maturity (MII stage). The polar body is positioned at the 12 or 6 o'clock position to ensure that the inserted micropipette does not disrupt the spindle inside the egg. After the procedure, the oocyte was placed into cell culture and checked on the following day for signs of fertilization. The fertilized oocyte is kept in the incubator for 5 days. On the third day, embryo development is checked for number of the blastomeres, their regularity, and granulation content, and accordingly, their quality was graded as A, B, and C grades, with A being the best quality and C being the least.

One blastomere from each embryo with grade A or B was extracted on day 3 and subjected to PGS technique. We conducted the genetic analysis after 7 weeks after embryo transfer to assess the pregnancy rate, and we did not interfere with the decision of transfer or not to transfer policy. This was left to the discretion of the couple and their treating consultant based on the quality of these embryos physically.

Blastomere aspiration and extraction

This was achieved through a noncontact laser that was adapted to the microscope to open the zona pellucida. Laser is transmitted through a 45× objective and then the chosen cell to biopsy was placed at the 3o'clock position. The chosen cell has to have a single, clearly visible nucleus, and the aspiration pipette for

blastomere aspiration has an inner diameter of 35–40 μm. The cell was partially aspirated and then pulled out. Then, we placed the biopsied cell far from the embryo. Thereafter, we placed the embryo immediately in the incubator. All the cells extracted were cryo-frozen to be subjected to analysis later.

Sequencing using Ion Torrent PGM system and preimplantation genetic screening workflow

This was carried out 6 weeks after embryo transfer for mothers from extracted cryo-frozen cells to assess the integrity of the chromosomal makeup of the embryos. For NGS analysis, cell samples and negative controls were first lysed and genomic DNA was randomly fragmented and amplified. DNA indexing was performed to simultaneously analyze embryos from different women. A basic workflow for NGS sequencing comprised four major steps: library building, template preparation, sequencing, and data analysis. Libraries were prepared at the life technology laboratory. The semiconductor sequencing technology uses sequencing by the synthesis method and emulsion PCR, similar to other sequencing platforms, but without using fluorescence or chemiluminescence. It depends on the detection of the hydrogen ion released during base incorporation. The sequencer uses new chips that allow them to push into the high throughput. The advantage of this sequencing technology is figurative on read lengths which are greater in length to other sequencers and fast sequencing time. The Ion Torrent Technology Concepts explicitly transform chemically encoded information (A, C, G, and T) on a semiconductor chip into digital information (0, 1).

Applying their standard protocol website (https://www.thermofisher.com/eg/en/home/life-science/sequencing/dna-sequencing/preimplantation-genetic-screening.html).

where our workflow in Ion ReproSeq PGS 316 View Kit for Ion torrent technology. Single cell library preparation and sequencing on the Ion PGM System was 1–10 cells per sample were prepared in up to 2.5 μL 1× PBS in Polymerase Chain Reaction tube (PCR tube). The DNA from the biopsied cells was extracted and amplified using the Ion SingleSeq Kit (Part No. A28955; 24 reactions/kit) used to extract, amplify, and barcode genomic DNA. Library pooling, purification, and quantification were done following the manufacturer's protocol. Quantification of the Ion SingleSeq library pool was done using the Qubit dsDNA HS (high sensitivity) assay. Template-positive Ion PGM Template IA Ion Sphere particles were prepared using Ion PGM Template IA 500 Kit followed by enrichment of the template-positive Ion PGM Template IA Ion Sphere particles. The IA reaction was performed. Sequencing was done by creating a planned run, cleaning, and initializes the Ion PGM sequencer and loading the chip and starting the sequencing run. Analysis of data on Ion Reporter analyzer was done using the ReproSeq low-pass whole-genome aneuploidy workflow. Website software (https://ionreporter.thermofisher.com/ir/).

All women had one embryo transferred; this was usually the best quality embryo. A Cook catheter was used under ultrasound guidance with full bladder on day 5. All the procedures were carried out by the same consultant to avoid operator bias.

Results and discussion

Criteria of patient

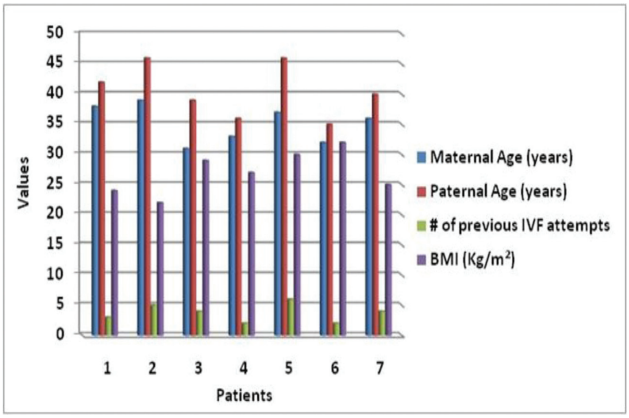
The women included in the study had a mean age of 35.14±3.13 years. They had a mean of 4 previous attempts of ICSI cycles before, and their BMI (kg/m^2) was 27.00±3.56 (Fig. 4). The mean endometrial thickness for the women was 9.86±1.35 mm (Table 1).

Table 1 The clinico chemical characteristics of the studied women

Items	Mean ±SD	Range
Maternal age (years)	35.14 ±3.13	31–39
Paternal age (years)	40.57 ±4.39	35–46
Number of previous IVF attempts	3.71 ±1.50	2–6
BMI (kg/m^2)	27.00 ±3.56	22–32
Basal FSH (mIU/ml)	7.16 ±1.11	5.7–8.6
Basal LH (mIU/ml)	5.50 ±1.80	3.9–9.3
E2 Level the day before HCG administration (pg/ml)	2097 ±710.72	1086–3419
Endometrial thickness on HCG administration (mm)	9.86 ±1.35	8–12
Number of eggs retrieved	7.57 ±3.69	4–15
Number of eggs fertilized	5.86 ±3.29	3–13
Number of blastocysts analyzed for PGS	3.57 ±1.27	2–6
Number of embryos transferred	1.00±0	1

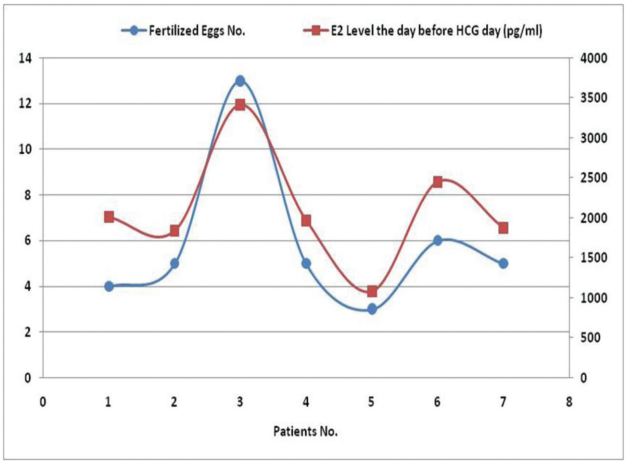
FSH, follicle-stimulating hormone; HCG, human chorionic gonadotropin; LH, luteinizing hormone; PGS, preimplantation genetic screening.

Figure 4



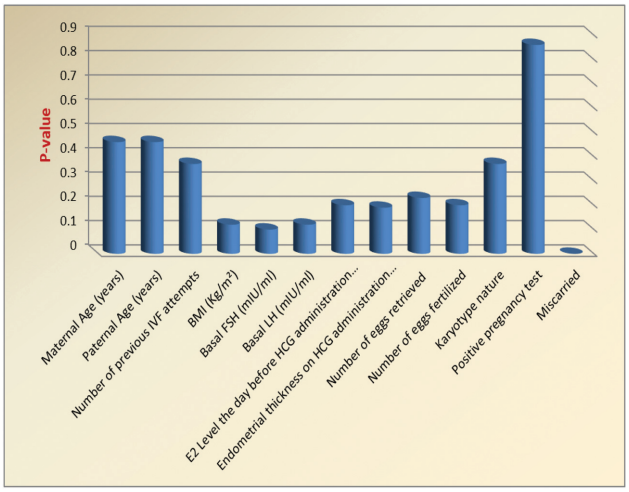
The proportions between the ages of mothers and fathers as well as the effect of BMI with previous attempts of intracytoplasmic sperm injection (ICSI) cycles before the miscarriage.

Figure 5



The graphic illustrates the apparent effect between the estrogen level and the number of eggs fertilized according to the stimulation protocol for intracytoplasmic sperm injection (ICSI) women.

Figure 6



This figure schemes clinical demographic characteristics of couples.

Biochemical and stimulation protocol for intracytoplasmic sperm injection women evaluation

Their mean basal FSH and LH levels were 7.16±1.11 and 5.50±1.80, respectively. The mean estrogen level the day before egg collection was 2097±710.72 pg/ml, as illustrated in Fig. 5.

The women had an average of 7.57±3.69 eggs retrieved. The fertilization rate was 77.36±3.29%. There was no statistically significant difference between women receiving rFSH versus uFSH in terms of age (P=0.46), BMI (25.5±3.11 vs. 29.00±3.61; P=0.12) and number of previous IVF attempts (P=0.37). Moreover, there was no difference between both groups regarding basal FSH, LH, or E2 the day before HCG administration levels (P=0.1, 0.12, and 0.2, respectively). Furthermore, there was no difference

Table 2 Clinical demographic characteristics of couples enrolled in the study stimulated by recombinant follicle-stimulating hormone versus highly purified uFSH

Items	Mean±SD		*P* value
	rFSH	HP uFSH	
Maternal age (years)	35.25±3.86	35.00±2.65	0.46
Paternal age (years)	40.75±4.27	40.33±5.51	0.46
Number of previous IVF attempts	3.5±1.29	4.00±2.00	0.37
BMI (kg/m^2)	25.5±3.11	29.00±3.61	0.12
Basal FSH (mIU/ml)	6.7±1.30	7.77±0.47	0.1
Basal LH (mIU/ml)	6.175±2.18	4.60±0.62	0.12
E2 level the day before HCG administration (pg/ml)	2313±740.85	1808.67±688.52	0.2
Endometrial thickness (mm)	10.25±1.71	9.33±0.58	0.19
Number of eggs retrieved	8.5±4.51	6.33±2.52	0.23
Number of eggs fertilized	6.75±4.19	4.67±1.53	0.2
Karyotype nature	3/4 abnormal	1/3 abnormal	0.37
Positive pregnancy test	3/4 (75)	2/3 (66.66)	0.86
Miscarried	2/4 (50)	0/3	0

FSH, follicle-stimulating hormone; HCG, human chorionic gonadotropin; LH, luteinizing hormone; rFSH, recombinant follicle-stimulating hormone; HP uFSH, highly purified urinary follicle-stimulating hormone.

in endometrial thickness between rFSH and uFSH groups (10.25±1.71 vs. 9.33±0.58, respectively; *P*=0.19) and number of eggs retrieved or fertilized (*P*=0.23 and 0.2, respectively). The four embryos in the rFSH group showed 75% chromosomal abnormality incidence versus almost 66% for the uFSH group. This was statistically nonsignificant (*P*=0.37) (Fig. 6). As well, the pregnancy rate was nonsignificant among the two groups (*P*=0.86). However, there was a significant difference in the miscarriage rate among the rFSH group versus the uFSH women (50 vs. 0%; *P*=0) (Table 2).

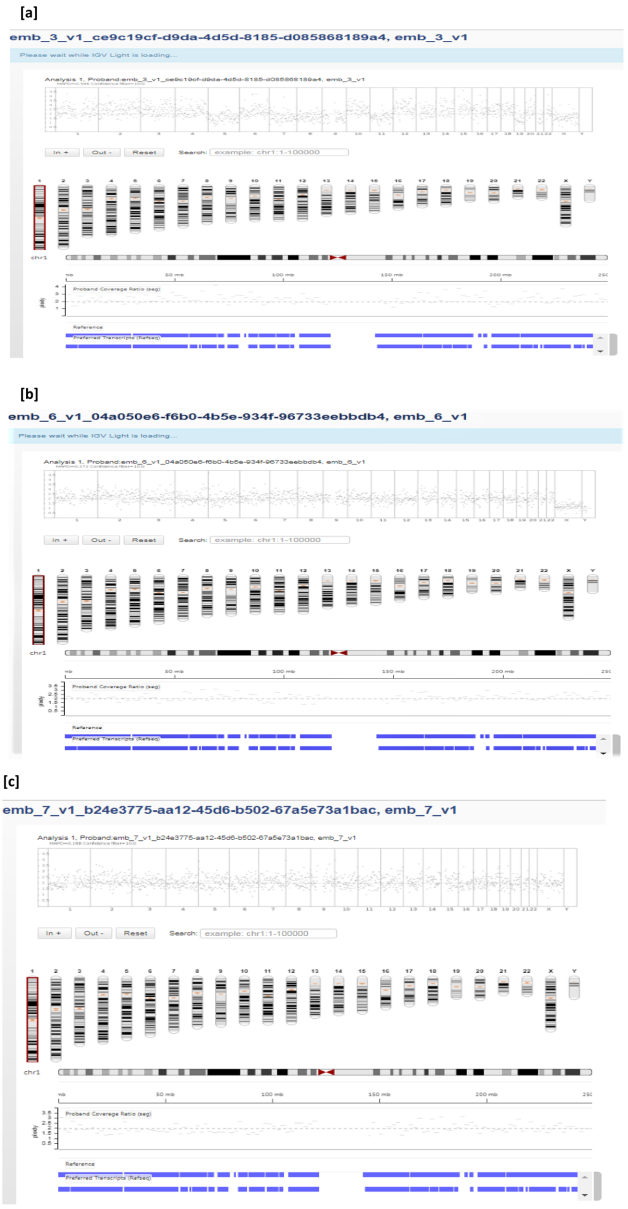
Sequencing using Ion Torrent PGM system and preimplantation genetic screening workflow

The cell that was taken from the biopsy, which was previously cryo-frozen, was followed up after 6 weeks of embryo transfer for mothers by NGS analysis for biopsies. All embryos except embryo numbers 3, 6, and 7 showed varying degrees of chromosomal abnormalities (Fig. 7).

Embryo number 1 showed three chromosomal loss aberrations in chromosomes 5, 14, and 15. Embryo number 2 showed a deletion at chromosome number 5 only (De15q11.1). Embryo number 4 revealed multiple chromosomal insertion defects affecting chromosomes 1, 5, 9, and 20 (Is1q21.1, Is5q11.1, Is9p12, and Is20q11.2). Moreover, embryo number 5 showed defects in chromosomes 2, 3, 13, and 16 (De12p25.3, Is3q24, De113q11, and Is16q11.2) (Fig. 8).

Indeed, after the examination and follow-up of cases, we found that upon transfer of these embryos to the mothers, five women had positive pregnancy test results 2 weeks after the transfer with 71.4% implantation rate. Nevertheless, two of them miscarried between 2 and 3 weeks later (Table 3).

Figure 7



Next-generation sequencer representation. (a) Embryo number 3 shows normal chromosomes, (b) embryo number 6 shows normal chromosomes, and (c) embryo number 7 shows normal chromosomes. The three figures illustrated that embryos with normal chromosomal makeup continued the pregnancy till the end of the study.

Discussion

The high rate of chromosomal blunders is among the main etiologies for recurrent miscarriage and implantation failure. Approximately 70% of human conceptions fail to achieve viability, with almost 50% of them ending in miscarriage before the clinical recognition of a missed period [20,21]. Most chromosome abnormal embryos will either fail to implant in the uterus or will result in miscarriage. PGS is a powerful test to screen for numerical and structural chromosomal abnormalities and helps physicians and the couple to decide which embryos to transfer to increase pregnancy and birth rate.

We have achieved 90% rate of fertilization in our group of women. However, the positive pregnancy test was only 71%. There is a very high incidence of structural aneuploidies in embryos produced from couples attempting assisted conception cycles. This could be one of the explanations of this discrepancy between the two figures.

However, not all chromosomal abnormalities are responsible for failure of implantation or miscarriage later on. If there was any chromosomal abnormality in the transferred embryo, there are some good evidence with delivery of normal embryos physically even with

Figure 8

Chromosome abnormalities were detected by next-generation sequencing. Twenty-four chromosome aneuploidy screening analysis target resolution gains or losses of chromosomal materials (a) for control sample showing aneuploidy screening for chromosome (16). The result of screening four embryos showing varying degrees of chromosomal abnormalities. (b) Embryo number one barcoded as (sample 3) showing loss aberrations in chromosomes 5, 14, and 15. (c) Embryo number 2 shows a deletion at chromosome number 5 (De15q11.1). (d) Embryo number 4 revealed multiple chromosomal insertion defects affecting chromosomes 1, 5, 9, and 20. (e) Embryo number 5 shows deletion defects in chromosomes 2, 3, and 13 and insertion in chromosome 16 (De12p25.3, Is3q24, De113q11, and Is16q11.2).

some chromosomal abnormalities [22]. Moreover, not all chromosomal derangements are lethal or handicapping. None of the abnormalities we encountered in this study were termed fatal after delivery. We have shown that from our results it is not necessary that every case that has chromosomal abnormalities will not be able to achieve positive pregnancy test or live birth rate. Where, 50% of the embryos with chromosome abnormalities that have been transferred in utero did implant. This may be owing to the importance of chromosome number in continuation of life [23,24]. Furthermore, this study opens up another interesting perspective that not all chromosomal abnormality will end in miscarried, but the most important factor may be the nature of the abnormality rather than the presence or absence of abnormality. Among the cases described in this study, two embryos had abnormalities in chromosome 5 in the point (5q11.1); all of them had positive pregnancies, and only one continued the pregnancy. Several authors [25,26] reported correlations between the 5p duplicated segment and the phenotype. Meanwhile, others have shown that the defect resulting from deletion of variable size occurring on the short arm of chromosome 5 (5p-) without mention any reason regarding the danger of a deletion in the point of long arm (5q11.1). This is what the studies by Shapiro and colleagues, and Bagchi and Bhanja, confirmed, where the deletion of variable length of short arm of chromosome 5(5p) had a bad effect on the embryos

Table 3 Pregnancy rate and state among the studied women

Item case	1	2	3	4	5	6	7
Maternal age (years)	38	39	31	33	37	32	36
Paternal age (years)	42	46	39	36	46	35	40
Number of previous IVF attempts	3	5	4	2	6	2	4
BMI (kg/m^2)	24	22	29	27	30	32	25
Basal FSH (mIU/ml)	6.4	6.1	5.7	8.6	7.6	8.3	7.4
Basal LH (mIU/ml)	5.2	4.3	9.3	5.9	4.8	3.9	5.1
E2 level the day before HCG day (pg/ml)	2014	1845	3419	1974	1086	2457	1883
Endometrial thickness on HCG day (mm)	8	11	12	10	9	10	9
Number of eggs retrieved	6	5	15	8	4	9	6
Number of eggs fertilized	4	5	13	5	3	6	5
Number of blastocysts analyzed for PGS	3	3	6	4	2	4	3
Number of embryos transferred	1	1	1	1	1	1	1
Karyotype nature	Abn.	Abn.	N	Abn.	Abn.	N	N
Positive pregnancy test	Pos.	Neg.	Pos.	Pos.	Neg.	Pos.	Pos.
Miscarried	Mis.	–	OP	Mis.	–	OP	OP
Sex	M	M	F	M	M	M	f

Abn., abnormal; F, female; FSH, follicle-stimulating hormone; HCG, human chorionic gonadotropin; LH, luteinizing hormone; M, male; N, normal; PGS, preimplantation genetic screening.

and was lethal [27–29]. We did not show any difference in the pregnancy rate, the implantation rate, and the abnormal chromosomal karyotype makeup in embryos among women receiving either rFSH or uFSH drugs. However, the women with uFSH had less miscarriage rate as compared to the rFSH group. These findings need larger sample size and randomized controlled trials to substantiate the results.

Conclusion

uFSH is no different than rFSH in producing embryos with chromosomal abnormality. It showed even a less miscarriage rate. This study highlights the importance of good selection criteria including chromosomal parameters among others to help couples struggling with recurrent pregnancy loss following IVF to achieve live birth rate.

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Conflicts of interest

There are no conflicts of interest.

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