Successful Pregnancy by In Vitro Fertilization Using Corifollitropin Alfa (ELONVA) for Controlled Ovarian Stimulation: The First Reported Local Experience*

Florely Joy Estrella-Gregorio, MD; Leonardo A. Almeda MD, FPOGS,FPSRM, FPSGE and Michelle Enriquez-Gamboa, MD, FPOGS, FPSRM, FPSGE
Section of Reproductive Endocrinology and Infertility, Consortium of
Far Eastern University-Nicanor Reyes Medical Foundation
Medical Center and Jose R. Reyes Memorial Medical Center

The need for simplified in-vitro fertilization (IVF) treatment approaches with the aim of reducing treatment burden and to prevent drop-outs after a failed IVF cycle can be met by the use of corifollitropin alfa for COS in association with a GnRH antagonist protocol. This is a report of the first local case of a successful pregnancy using corifollitropin alfa in IVF. This is a case of a 33 year-old G3 P0 (0030) whose partner has teratozoospermia. COS using corifollitropin alfa yielded eight mature oocytes with no occurrence of OHSS. Six oocytes were fertilized using ICSI with six good quality embryos reaching cleavage stage. Two grade 1 embryos at day 3 cleavage stage were transferred. A clinical pregnancy was documented at 7 weeks age of gestation. Congenital anomaly scanning at 24 weeks age of gestation revealed a grossly normal fetus. Patient delivered a healthy, live, term baby boy. Review of literature suggests that corifollitropin alfa is as effective as rFSH in delivering live birth rate, ongoing pregnancy rate and clinical pregnancy rate. The sustained and higher FSH immunoreactivity concentrations and the inability for dose adjustment after treatment with a single dose of corifollitropin compared with the daily rFSH regimen underscores the need for careful patient selection in the use of corifollitropin alfa.

Key words: Corifollitropin alfa (ELONVA), recombinant follicle stimulating hormone (rFSH), controlled ovarian stimulation (COS), in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI)

Introduction

Infertility is a life crisis with a wide range of socio-cultural, emotional, physical and financial problems for a couple. While the infertility is not a disease, it can affect all aspects of the couple's life, which can cause various psychological-emotional disorders or consequences including turmoil, frustration, depression, anxiety, hopelessness, guilt and feelings of worthlessness in life. On the other hand, the occurrence of pregnancies with poor obstetric outcomes such as abortions, ectopic pregnancies or fetal deaths is even more a devastating experience for a couple. Such pregnancy losses can bring along with it emotional trauma from the loss itself, as well as financial strain to the couple due to repeated hospital admissions and treatment of resulting pelvic pathologies after the pregnancy losses. For

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couples whose pregnancy losses result to tubal factor infertility, in vitro fertililization (IVF) is often recommended.

As part of IVF programs, controlled ovarian stimulation with gonadotropins during each cycle is the first step. Traditionally, hMG, highly purified FSH, or recombinant FSH (rFSH) are used to stimulate development and maturation of a sufficient number of oocytes to improve chances for conception. These injections have to be administered daily to maintain adequate levels of FSH during controlled ovarian stimulation because of their half-life and rapid metabolic clearance.[1] This regimen is quite cumbersome for some patients as this requires multiple self-injections within one cycle of controlled ovarian stimulation, or in several cycles if pregnancy does not occur on the first cycle.

Verberg, et al. (2008) showed that the most frequent cause of couples dropping out from IVF programs was the physical and psychological burden of treatment.[2] This stress is not only due to the physical burden of multiple self-injections but also due to the frequent monitoring associated with controlled ovarian stimulation.[3] This treatment burden, along with the stress related to medication injection contributed to discontinuation rates ranging from 39.9% after the first cycle to 62.2% after the fourth cycle among couples participating in assisted reproductive technology or IVF programs without achieving a live birth of a child even before completion of all cycles for which costs were covered.[4,5] There is then a need for simplified IVF treatment approaches with the aim of reducing treatment burden and to prevent drop-out rate after a failed IVF cycle.

Recombinant DNA technologies have produced a recombinant molecule which is a long-acting FSH named corifollitropin alfa (ELONVA) or FSH-CTP. A single dose of long-acting FSH is able to keep the circulating FSH level above the threshold necessary to support multifollicular growth for an entire week (Figure 1).[6] A single injection of corifollitropin alfa (ELONVA) can replace the first seven injections with standard gonadotropins and stimulation can be continued with daily FSH injections if the need arises. This makes corifollitropin alfa (ELONVA) potentially more patient-friendly and may lead to lower drop-out rate of patients.[1]

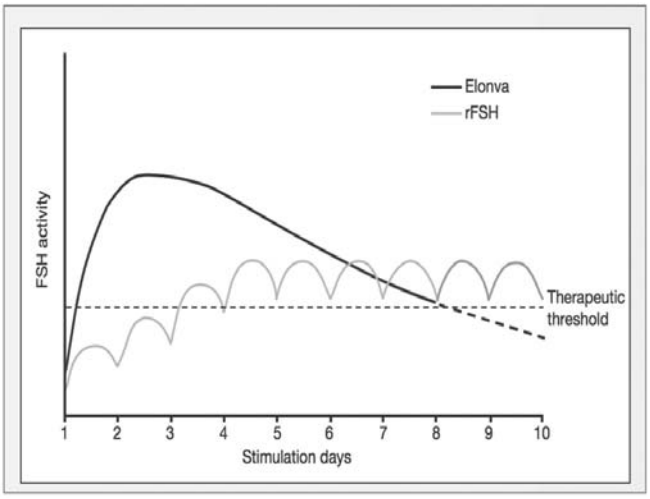

Figure 1. A single Elonva injection sustains FSH activity beyond the minimum threshold for at least 7 days and resembles a natural step-down protocol (adapted from ELONVA (corrifollitropin alfa): A simplified, patient-friendly approach to controlled ovarian stimulation, http://www.elonva.no/static/images/Elonva_Monograph_Jan_2010__tcm1872-273164.pdf - accessed July 31, 2015).

This paper presents a case of a 33 year-old G3 P0 (0030) with 1 induced abortion and 2 ectopic pregnancies who underwent left salpingectomy and right salpingostomy, and whose male partner has teratozoospermia. With a history of tubal and male factor infertility, IVF with ICSI was performed. This paper aimed to present the first reported local case of a successful pregnancy by in vitro fertilization using Corifollitropin alfa (ELONVA) for controlled ovarian stimulation.

The Case

This is a case of JM, 33 years old G3 P0 (0030), Roman Catholic, residing at Quezon City, married for 1 year to MM, 28 years old, who consulted for in vitro fertilization after three first trimester pregnancy losses.

The patient has no history of hypertension, diabetes, bronchial asthma, tuberculosis, cancer,

or thyroid disease. She has no known allergies to any food or drugs. Hypertension and diabetes are noted on both paternal and maternal sides. JM is a college graduate and works as a government employee. She is a 2-year pack smoker and an occasional alcoholic beverage drinker.

The patient had her menarche at 13 years old, with subsequent menses occurring regularly every 28-30 days, lasting for 4-5 days, using up 2-3 moderately-soaked pads per day, and with dysmenorrhea.

Patient is a gravida 3 para 0 (0030), with the first pregnancy (2003) ending in an induced abortion at 4 weeks age of gestation for which no curettage was done. Second pregnancy (2013) was a ruptured left tubal pregnancy for which patient underwent exploratory laparotomy with left salpingectomy. Third pregnancy (June 29, 2014) was an unruptured right tubal pregnancy and patient underwent diagnostic laparoscopy followed by exploratory laparotomy and right salpingostomy.

The methods of contraception used were oral contraceptive pills for 2 years and barrier method (condom). Coitarche was at 20 years old with 4 sexual partners. She is currently in a monogamous relationship.

Upon examination, patient had stable vital signs with a weight of 49 kg and body mass index of 22.4 kg/m^2. Pelvic examination revealed a nulliparous introitus, vagina admits two fingers with ease, cervix firm and smooth with an anteverted, unenlarged uterus and no adnexal masses or tenderness.

Transvaginal ultrasound revealed a normal-sized uterus with normal bilateral ovaries. For the male partner, semen analysis revealed teratozoospermia of 3% (Table 1). With a history of tubal and male factor infertilty, the couple was advised to undergo IVF with ICSI.

Controlled Ovarian Stimulation and Preparation of the Oocytes

Day 2 transvaginal ultrasound scan revealed an antral follicle count of 12. Controlled ovarian stimulation was started (based on the patient's weight of 49 kg) by administering Corifollitropin alfa (ELONVA) 100 μg subcutaneously on the same day (stimulation day 1). Cetrorelix acetate (CETROTIDE) 0.25 mg was given subcutaneously on stimulation days 5 to 11 to prevent premature LH surges. Follicle monitoring on stimulation day 8 revealed 8 follicles measuring at least 10-12 mm and follitropin beta (PUREGON) 100 iu was given on stimulation days 8 and 9 based on follicle growth. Hormone levels determined at day 10 showed an E2 of 5,927 pmol/L and progesterone of 0.81ng/mL. Transvaginal ultrasound done on day 10 revealed 12 follicles measuring at least 17mm in diameter, thus 10,000 iu of HCG (PREGNYL) was administered to trigger final oocyte maturation.

Oocytes were recovered by ultrasound-guided puncture 36 hours after HCG administration. Fifteen follicles were aspirated and eight oocytes were recovered (Figure 2). Endometrial lining was 0.87 cm after ovum pick-up (Figure 3). After retrieval, the oocytes were stored in a 37° C minc incubator with mixed gas composed of 6% CO2, 5% O2 and 89% Nitrogen for 2-4 hours. Micromanipulation and examination of the oocytes were then performed under an inverted microscope at 200x magnification to assess the integrity and maturation stage of each oocyte. All of the eight oocytes retrieved were metaphase II (MII) stage oocytes.

Intracytoplasmic Sperm Injection and Embryo Culture

Intracytoplasmic sperm injection was performed on all of the eight metaphase II oocytes between 37 and 41 hours after HCG administration. Of the eight oocytes retrieved, six were fertilized. Development of the embryos were observed over the next 2 days. Two excellent (top) quality embryos of grade 1 quality (Figure 4) were transferred on the third day after fertilization while the remaining four embryos at cleavage stage of good quality at grades 1-2 were frozen (Figure 5).

Table 1. Semen analysis result of male partner.

Semen Analysis Report (9/26/2014): Teratozoospermia

Date of abstinence	3 days	Time produced	1150H
Produced at		Time submitted	1152H
Method of collection	Masturbation	Time examined	1154H

Macroscopic Analysis	Result	Reference value
Completeness of sample	Complete	
Liquefaction time	Within 30 minutes	Within 30 minutes
pH	8.0	≥ 7.2
Appearance	Heterogeneous with gelatinous materials, yellowish-opalescent	Homogeneous, gray-opalescent
Viscosity	Slightly viscous	
Debris	+ 4	**

Microscopic Analysis	Result		Reference value
Volume	3.7	mL	≥ 1.5Ml
Sperm concentration	25	x 10^6/mL	≥ 15 x 10^6/Ml
Total sperm count	92.5	x 10^6/ejaculate	≥ 39 x 10^6/ejaculate
Total motility (PR + NP)	61	%	≥ 40%
Total Motile Count	56.4	x 10^6	
Progressive motility (PR)	13	%	≥ 32%
Non-progressive (NP)	48	%	
Immotile	39	%	
Sperm Vitality	72	%	58%
Agglutination	None	/ HPF	None
White Blood Cells	< 1.0	x 10^6/mL	≤ 1.0 x 10^6/Ml
Normal Forms	3	%	4%

Abnormal Forms: 97%	Amorphous, tapered, small, pyriform heads, residual cytoplasm, coiled tail, bent neck and hairpin loop tail

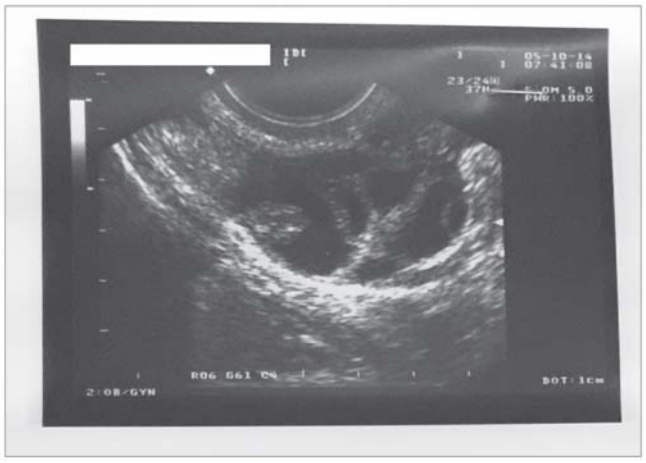

Figure 2. Right ovary after controlled ovarian stimulation with Corifollitropin alfa (ELONVA).

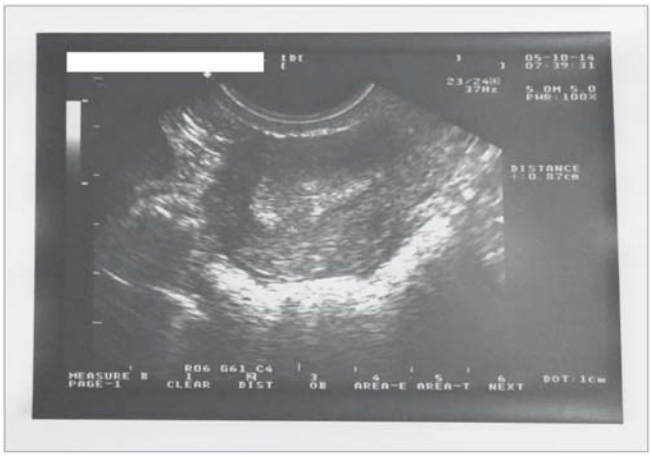

Figure 3. Endometrial lining after ovum pick-up.

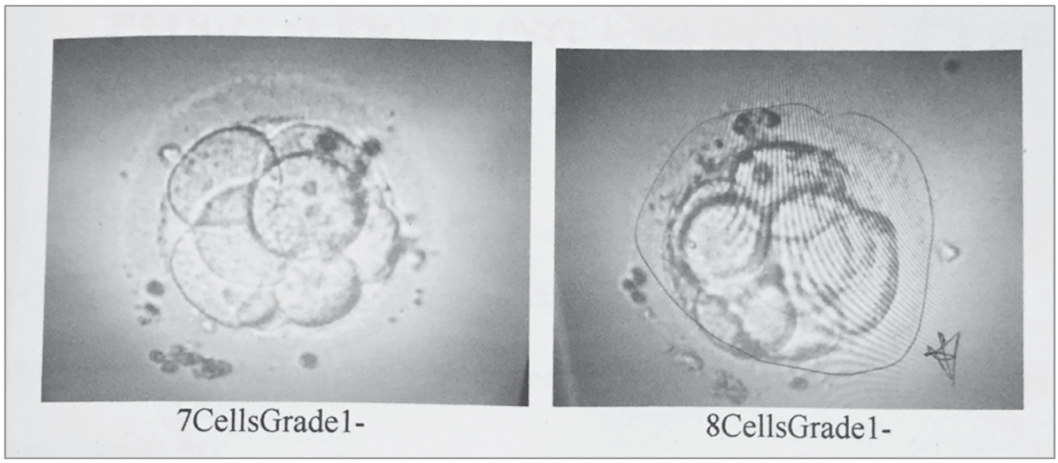

Figure 4. Two day-3 embryos transferred.

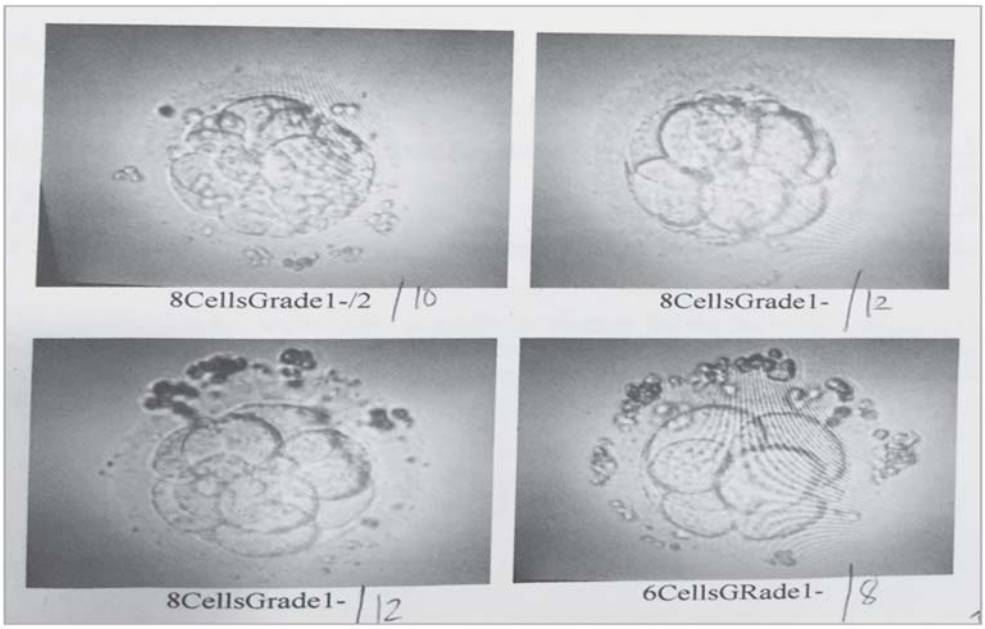

Figure 5. Four good quality embryos frozen.

Embryo Transfer and Luteal Phase Support

Transfer of two excellent (top) quality embryos at cleavage stage (7 cells grade 1 and 8 cells grade 1) was performed on day 3. A Bourne Wallace catheter was used for the embryo transfer. After the catheter was rinsed with transfer medium, the embryos were loaded and the catheter was handed to the clinician who inserted it through the endocervical canal without any difficulty. The insertion of the catheter and the location of the embryos were guided with the use of pelvic ultrasound (Figures 6 & 7). Luteal phase support in the following forms were started on the day of embryo transfer and was continued until assessment of pregnancy 15 days after embryo transfer: Crinone 8% vaginal suppository BID, Utrogestan 200mg/cap 1 cap TID and Progynova 2mg/tab 1 tab BID. Folic acid 5mg/tab 1 tablet OD was also continued. There were no signs and symptoms of ovarian hyperstimulation syndrome during the course of IVF.

Course of Pregnancy

Fifteen days after embryo transfer, home urine pregnancy test was positive. The serum β-HCG level 15 days after embryo transfer was 383 mIu/mL (Table 2). A clinical pregnancy for our patient was documented when transvaginal ultrasound showed a fetal heartbeat 7 weeks and 3 days age of gestation (Figures 8 & 9). Luteal phase support using progesterone was continued until 14 weeks age of gestation (Crinone 8% vaginal suppository until 10 weeks age of gestation and Utrogestan until 14 weeks age of gestation). Aspirin 80 mg 1 tablet OD was also given until 28 weeks age of gestation.

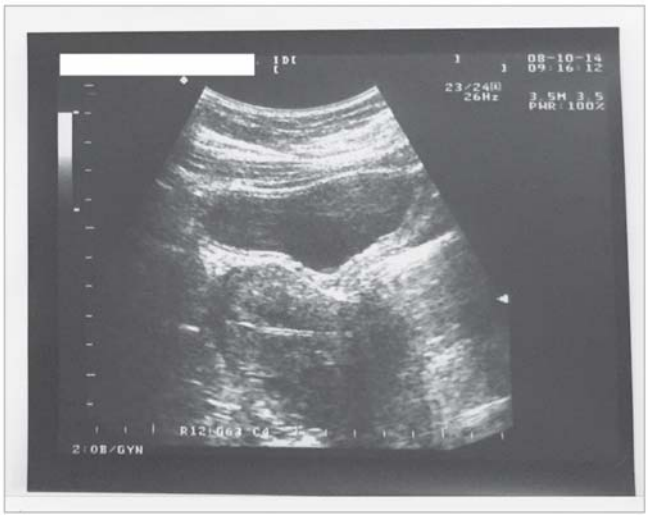

Figure 6. Sagittal view of the uterus prior to fresh embryo transfer.

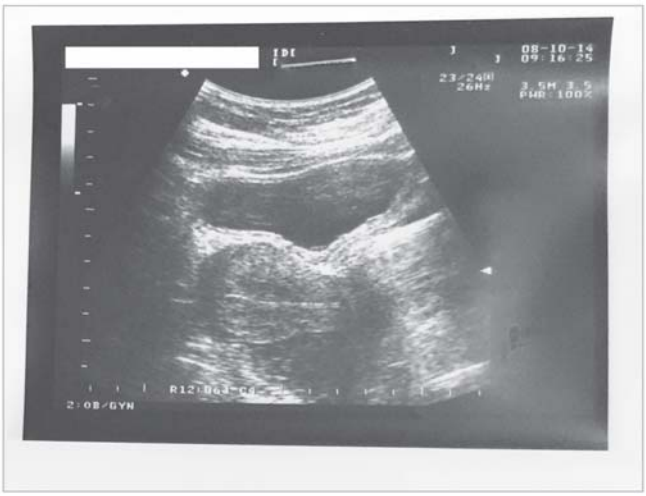

Figure 7. Sagittal view of the uterus during the ultrasound-guided transfer of two day 3 embryos.

Regular prenatal check-ups were done by the patient with her attending obstetrician. A congenital anomaly scan at 23 weeks and 4 days revealed a grossly normal fetus (Table 3). At 39 1/7 weeks age of gestation, patient underwent trial of labor but Emergency Primary Low Segment Cesarean Section was performed due to Non-reassuring Fetal Heart Rate Pattern (Fetal bradycardia). A live term baby boy was delivered with a birth weight of 2420 grams, birth length of 49 cm and an Apgar scores of 7 and 10 at 5 and 10 minutes of life, 39 weeks by pediatric aging, small for gestational age.

Discussion

Assisted reproduction techniques such as IVF and ICSI can help subfertile couples create a family. Along with the hope of creating a family, infertility and the IVF treatment process in itself brings along with it physical, psychological and

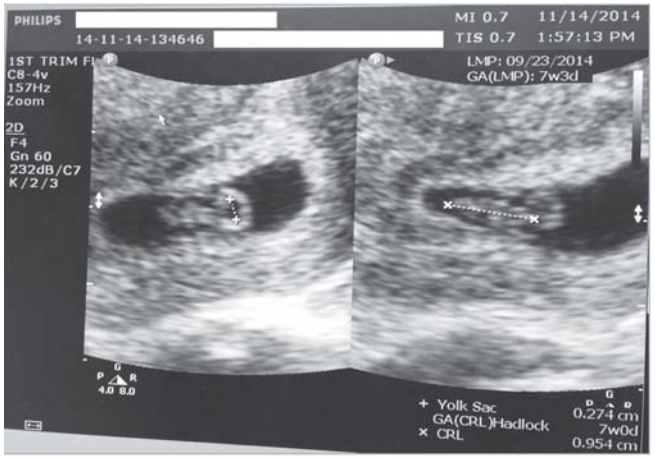

Figure 8. Transvaginal sonogram image of embryo at 7 weeks age of gestation.

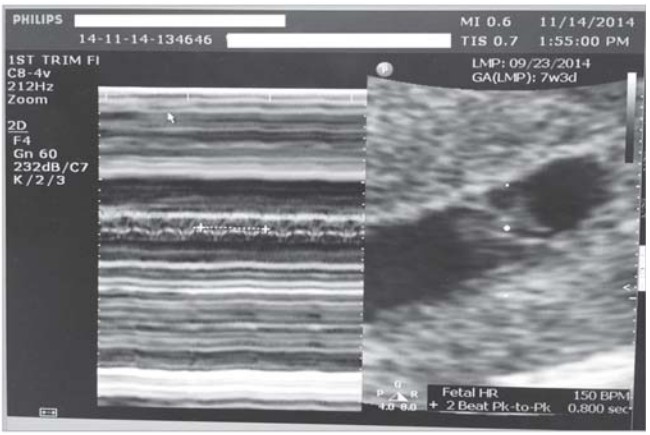

Figure 9. Clinical pregnancy documented by presence of fetal heart beat at 7 weeks age of gestation.

Table 2. β-HCG results post-embryo transfer.

	October 23, 2014	October 30, 2014	Normal value
β-HCG	383.00	3,578	0.5 mIU/mL

Table 3. Ultrasound results for pregnancy.

Date	Type of ultrasound done	Impression
November 14, 2014	Transvaginal sonography	Single, live, intrauterine pregnancy 7 weeks age of gestation by crown-rump length with good cardiac activity. Normal ovaries with corpus luteum on the right. EDD: June 30, 2015
March 7, 2015	Congenital anomaly scan	No gross congenital anomalies noted at the time of scan

emotional burden to infertility patients. Studies have shown that infertile patients experience high levels of distress and their level of anxiety and depression is equivalent to that experienced by women with cancer or heart disease.[7] Drop-out rates have been recorded to be well above 50% before completion of IVF cycles largely due to the psychological impact of treatment, with the primary reason for treatment discontinuation not based on physician recommendation, but because patients are too distressed to continue.

A prospective cohort study comparing a reduced duration of stimulation using GnRH antagonist protocol with a conventional long GnRH agonist protocol demonstrated a significantly reduced drop-out rate in the antagonist group, indicating that the impact of treatment strategy is an important factor determining the risk of drop-out (Figure 10).[2,9] The need for simple treatment regimens that lessen the burden of IVF such as fewer injections to be given may improve drug compliance and / or prevent errors during drug administration can be met by the recently available long-acting rFSH - corifollitropin alfa (ELONVA).

Corifollitropin alfa (ELONVA) is a new hybrid molecule with sustained follicle stimulating

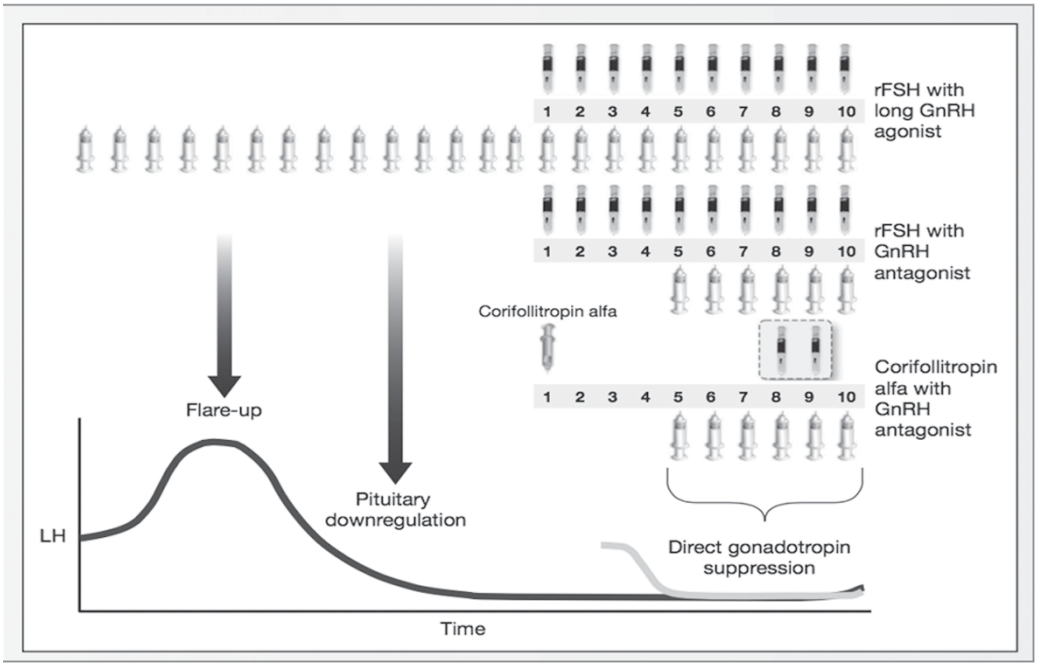

Figure 10. The number of injections COS requires has been reduced with the advent of the GnRH antagonist protocol (adapted from ELONVA (corrifollitropin alfa): A simplified, patient-friendly approach to controlled ovarian stimulation, http://www.elonva.no/static/images/Elonva_Monograph_Jan_2010__tcm1872-273164.pdf - accessed July 31, 2015).

activity, approved by the European Commission in January 2010 for use in controlled ovarian stimulation in combination with a GnRH antagonist for the development of multiple follicles in women participating in an ART program. It is a fusion product of human FSH and the C-terminal peptide from the ß-subunit of HCG produced by recombinant DNA technology. It has the same pharmacologic activity as FSH and recombinant FSH but with a slower absorption[7] and a 2-fold longer elimination half-life, interacting only with FSH receptors without LH activity which provides a plasma activity of ~65 hours, and an almost 4-fold extended time-interval to peak serum levels. Due to this pharmacokinetic profile, corifollitropin alfa can function as a sustained follicle stimulant with a similar pharmacodynamic profile as rFSH, but with the ability to initiate and sustain multiple follicular growth for an entire week. From phase II and III studies, it was concluded that a single injection of corifollitropin alfa (ELONVA) can replace the first seven injections of recombinant FSH (rFSH) using a gonadotropin-releasing hormone antagonist protocol in ovarian stimulation prior to IVF or ICSI.[7] Stimulation can be continued with daily FSH injections if the need arises. This makes corifollitropin alfa (ELONVA) potentially more patient-friendly and may lead to lower drop-out rate of patients.[1]

Corifollitropin alfa (ELONVA) is administered as a single subcutaneous injection, preferably in the abdominal wall, during the early follicular phase of the menstrual cycle based on body weight and antral folllicle count (AFC) of ≤ 20 on day 2 or 3 of menstrual cycle (Stimulation day 1). The optimal corifollitropin dose has been calculated to be 100 µg for women with a body weight of ≤ 60kg and 150 µg for women with a body weight >60 kg. On stimulation day 5 or 6, treatment with a GnRH antagonist is started to prevent premature LH surges depending on ovarian response, i.e. number and size of growing follicles and/or the amount of circulating estradiol. Daily injections of rFSH are started on stimulation day 8 until the criteria for

triggering final oocyte maturation (3 folllicles ≥17mm) have been reached. Daily rFSH dose is dependent on ovarian response: daily dose of 150 IU is advised on normal responders. As soon as 3 follicles ≥17mm are observed, a single injection of 5,000 up to 10,000 IU HCG is administered the same day or day after to induce final oocyte maturation.[8]

Two randomized, double-blind, active-controlled, non-inferiority trials were conducted to investigate the efficacy and safety of a new treatment regimen using corifollitropin alfa (ELONVA) based on patient's weight. The ENGAGE trial was designed to compare corifollitropin alfa (ELONVA) 150 mcg to 200 IU rFSH at 34 IVF clinics in North America and Europe. A total of 1,506 subjects (with body weight > 60 kg and body mass index (BMI) of ≥18 and ≤ 32 kg/m^2) with ages less than 36 years and considered not at risk of developing OHSS (antral follicle count ≤ 20) were randomized. Seven hundred fifty-six subjects were given single 150 µg-injection of corifollitropin alfa (ELONVA) followed by daily treatment with rFSH injection from stimulation day 8 onwards up to and including the day of HCG administration. A second group of 733 subjects (active control) were treated with daily injections of 200 IU rFSH (follitropin beta). Both treatments included daily administration of the GnRH antagonist Ganirelix (0.25mg SC) starting on day 5 up to and including the day of HCG to induce final oocyte maturation. Progesterone for luteal support was initiated on the day of oocyte retrieval and continued for at least 6 weeks, unless menses, or a negative pregnancy test was performed at least 14 days after embryo transfer.[10] Ongoing pregnancy rates of 38.9% for the corifollitropin alfa group and 38.1% for rFSH were achieved, with an estimated non-significant difference of 0.9% in favor of corifollitropin alfa. Clinical outcomes (including the different pregnancy rates, miscarriage rate, and ectopic pregnancy rate) following COS were also similar between treatments (Table 5). A slightly higher follicular response with corifollitropin alfa resulted in a higher number of cumulus-oocyte-complexes compared with rFSH. The number and quality of oocytes, fertilization rates, number and quality of embryos, and implantation rates following COS were all similar between treatments. The mean number of good-quality embryos transferred was 1.4 in both groups (Table 5). Median duration of stimulation was equal (9 days) and incidence of (moderate/severe) ovarian hyperstimulation was the same.[11]

Like the ENGAGE trial, The ENSURE clinical trial was performed to investigate the efficacy and safety of a single injection of 100 µg corifollitropin alfa (ELONVA) to initiate and sustain multifollicular development for controlled ovarian stimulation in women with a body weight of < 60 kg. The ENSURE study concluded that use of ELONVA delivered a 13.3 mean number of oocytes versus 10.6 with daily rFSH ($p > 0.001$), a 3.4 mean number of good quality embryos versus 3.0 with daily rFSH, and ongoing pregnancy rate per cycle started of 25.4% vs 34.4% with daily rFSH (see Table 6)[12].

Table 4. Clinical outcomes (pregnancy rates) following ELONVA or rFSH in the Engage trial (adapted from: http://www.elonva.no/hcp/clinicalexperience/theengagestudy/index.xhtml).

	ELONVA (150 µg) n = 756	rFSH (200 IU/day) n = 750
Biochemical pregnancy (%)	364 (38.1)	352 (46.9)
Clinical pregnancy (%)	322 (42.6)	308 (41.1)
Vital pregnancy (%)	302 (39.9)	293 (39.1)
Ongoing pregnancy (%)	294 (38.9)	286 (38.1)
Singleton (%, as a percentage of ongoing pregnancy)	211 (71.8)	220 (76.9)
Multiple pregnancy (%, as a percentage of ongoing pregnancy)	83 (28.2)	66 (23.1)
Miscarriage (%)	27 (8.4)	21 (6.8)
(Ruptured) Ectopic pregnancy (%)	7 (0.9)	9 (1.2)
Live birth rate	35.6	34.4

Table 5. Efficacy outcomes following ELONVA or daily rFSH in the Engage trial (adapted from: http://www.elonva.no/hcp/clinicalexperience/theengagestudy/index.xhtml).

	ELONVA (150 µg) n = 756	rFSH (200 IU/day) n = 750
Mean (SD) number of oocytes retrieved	13.7 (8.2) *	12.5 (6.7) *
Number of subjects with oocyte quality assessment[a]	n = 413	n = 417
Number of oocytes	13.8 (7.6)	12.1 (6.3)
Number of metaphase I oocytes	1.1 (1.5)	0.9 (1.3)
Number of metaphase II oocytes	10.8 (6.5)	9.2 (5.1)
Number of germinal vesicles stage oocytes	1.5 (1.9)	1.7 (2.2)
Number of metaphase II oocytes as a percentage of total (%)	78.9 (18.9)	77.4 (18.1)
Number of subjects with fertilization assessment[b]	n = 727	n = 737
Fertilization rate (%)	66.0 (23.4)	67.6 (22.9)
Number of subjects with embryo assessment at day 3[c]	n = 714	n = 729
Total	8.3 (5.6)	7.4 (4.8)
Good quality	4.6 (4.3)	4.4 (3.9)
Number of subjects with embryo transferred[d]	n = 672	n = 704
Total number of embryos transferred	1.7 (0.4)	1.7 (0.4)
Number of subjects with 1 embryo transferred	173 (25.7)	190 (27.0)
Number of subjects with 2 embryos transferred	496 (73.8)	514 (73.0)
Number of subjects with 3 embryos transferred	3 (0.4)	0
Good quality transferred	1.4 (0.7)	1.4 (0.7)
Implantation rate (%)	36.2 (41.6)	32.2 (40.1)

* p = 0.001
[a] including 3 subjects for whom the quality of oocytes assessed, but for whom ICSI was not performed
[b] restricted to subjects with IVF and/or ICSI
[c] excluding subjects who had embryos transferred or cryopreserved before day 3
[d] restricted to subjects with embryo transfer (defined as 100 times the maximum number of gestational sacs as assessed by USS after ET divided by the number of embryos transferred (per subject), maximized to 100%)

Table 6. Fertilization rate, number of good quality embryos, and clinical outcomes following a single dose of ELONVA (100 µg) or daily rFSH (150 IU) in the Ensure trial (adapted from http://www.elonva.no/HCP/ClinicalExperience/TheENSUREStudy/index.xhtml).

	ELONVA (100 µg)	rFSH (150 IU/day)
Fertilization rate, mean percent (SD)	67.6 (22.5) n = 264	67.7 (25.4) n = 124
Number of good quality embryos, mean (SD)[a]	3.4 (3.0) n = 264	3.0 (3.0) n = 124
Number of good quality embryos transferred, mean (SD)[b]	1.3 (0.8) n = 246	1.3 (0.8) n = 121
Clinical outcome	n = 268	n = 128
Biochemical pregnancy, percent	37.7	45.3
Clinical pregnancy, percent	29.1	37.5
Vital pregnancy, percent	25.7	35.2
Ongoing pregnancy, percent	25.4	34.4

[a] Good quality embryos at day 3, restricted to subjects with IVF / ICSI
[b] restricted to subjects with embryo transfer
* p = 0.06

In a systematic review and meta-analysis of 4 randomized controlled trials (ENGAGE and ENSURE trials included) using corifollitropin alfa (ELONVA) with 2,326 enrolled women, it was concluded that combination of corifollitropin alfa with fixed daily GnRH antagonist seems to be an alternative for daily rFSH injections in normal-responder patients undergoing ovarian stimulation in IVF/ICSI treatment cycles. Corifollitopin alfa (ELONVA) yielded similar pregnancy rates, as well as significantly higher numbers of oocytes, MII oocytes and obtained embryos, with less amount of used FSH compared with women stimulated with daily rFSH injections. The median duration of stimulation with FSH was 9 days in both treatment groups, which means that, on average, recipients of corifollitropin alfa and daily rFSH required only two further days of stimulation with rFSH before final oocyte maturation triggering.[1]

Also based on this meta-analysis, corifollitropin alfa was associated with a higher cycle cancellation rate than daily rFSH, although the differences were not statistically significant. The incidence of moderate/severe OHSS in corifollitropin alfa was increased by almost 50% in the corifollitropin alfa group compared with the rFSH group. The higher ovarian response and the risk of OHSS in corifollitropin alfa group could be explained by the sustained and higher FSH immunoreactivity concentrations and the inability for dose adjustment after treatment with a single dose of corifollitropin. Compared with the daily rFSH regimen (where the dose can be adjusted according to the ovarian response to avoid low or high ovarian response), a rapid increase of serum E2 and inhibin levels and development of more medium-size follicles (11–14 mm) on day 8 (7.8 % vs. 6.4%) and day of hCG (6.4% vs. 5.2%) were noted on the corifollitropin alfa group. More multiple pregnancies in the corifollitropin alfa group compared with the daily rFSH group was also noted, although the differences were again not statistically significant. Corifollitropin alfa was well-tolerated and nonimmunogenic and there was no significant difference between corifollitropin alfa and rFSH regarding the most commonly reported side effects, such as pelvic pain, pelvic discomfort, headache, and drug-related local or systemic reactions.[1]

A more recent meta-analysis of published randomized controlled trials evaluating the outcomes of IVF cycles using corifollitropin alfa for controlled ovarian stimulation in comparison with daily rFSH examined seven randomized controlled trials including 2138 patients receiving corifollitropin alfa and 1788 women receiving daily rFSH for controlled ovarian stimulation. There were no significant differences between corifollitropin alfa and rFSH with respect to the majority of the clinical parameters considered, and comparable were the outcomes in terms of live birth rate (4 RCTs; OR 1.12, 95 % CI 0.96–1.31; p = .15), clinical pregnancy rate (4 RCTs; OR 1.01, 95 % CI 0.84–1.20; p = .95), and ongoing pregnancy rate (6 RCTs; OR 1.04, 95 % IC 0.90–1.20; p = .62). The risk of spontaneous abortion is the same in pregnancies obtained in women undergoing controlled ovarian stimulation with corifollitropin alfa and rFSH. Ovarian response to stimulation with corifollitropin alfa demonstrated a significantly higher number of oocytes retrieved (7 RCTs; WMD 1.37, 95 % CI 0.58–2.16; p = .0007), a significantly higher number of metaphase II oocytes at ovum pick-up (6 RCTs; WMD 1.54, 95 % CI 0.66–2.43; p = .0006), and significantly higher number of formed embryos (6 RCTs; WMD 0.77, 95 % CI 0.41–1.13; P < .0001) in comparison to daily rFSH.[13]

The risk of cycle cancellation due to overstimulation was significantly higher in the corifollitropin alfa group (3 RCTs; OR 3.19, 95 % CI 1.07–9.45; P = .03;) than in the daily rFSH group. Ovarian hyperstimulation syndrome incidence was statistically comparable between patients receiving long lasting or daily rFSH. Nevertheless, in view of the fact that corifollitropin alfa resulted in a higher number of metaphase II oocytes collected and a higher number of cycles cancelled due to overstimulation, corifollitropin alfa should be cautiously considered in women with the potential of being hyper responders.[13]

From the studies cited, corifollitropin alfa (ELONVA) can be an alternative for daily rFSH injections in normal-responder patients undergoing ovarian stimulation in IVF/ICSI treatment cycles.

Its use is already approved in Europe. However, it is still not available in the Philippines. As part of ongoing open-label clinical trials to test for its safety and efficacy, an IVF center in the Philippines was given the privilege to assess the responses of Filipino women undergoing controlled ovarian stimulation for IVF/ICSI. Inclusion criteria are the following: antral follicle count of < 20 (both ovaries), no polycystic ovary syndrome, and no prior hyper-response or OHSS. Our patient is 33 years old with a body weight of 49 kg and an antral follicle count of 12. With an expected normal response to controlled ovarian stimulation with corifollitropin alfa (ELONVA), she was therefore eligible to participate in the trial. An optimal response to corifollitropin alfa (ELONVA) was noted in our patient as evidenced by the development of 12 mature follicles and aspiration of eight oocytes at metaphase II, with no detrimental effect on the endometrial lining (0.87cm). There were also no noted signs and symptoms of ovarian hyperstimulation during the course of IVF.

Intracytoplasmic sperm injection (ICSI) is better indicated for male factor infertility such as presented in our case, and for those with poor or failed fertilization in a previous IVF treatment cycle. A systematic review of 10 RCTs showed that for couples with very poor semen quality (concentration < 10 million per ml, motility <30%, morphology < 4% normal forms), ICSI has better fertilization rates than with subzonal sperm injection and additional IVF.[14] Patient's male partner has teratozoospermia of 3% hence ICSI was performed which yielded fertilization of six oocytes, all of which reached cleavage stage with resultant good quality embryos.

Patient's age, quality of the embryo and endometrial receptivity are the most important factors for the success of IVF.[15] A successful pregnancy was achieved in our case since our patient is young with optimal response to controlled ovarian stimulation with corifollitropin alfa (ELONVA) in association with a GnRH antagonist protocol and with an endometrial lining receptive for implantation.

In summary, we have presented the first locally-reported case of a successful pregnancy in a 33 year-old G3 P0 (0030) who underwent controlled ovarian stimulation in IVF using corifollitropin alfa (ELONVA) with no noted signs and symptoms of hypertimulation.

Corrifollitropin alfa (ELONVA) is administered as a single subcutaneous injection during the early follicular phase of the menstrual cycle based on body weight and antral folllicle count (AFC) of ≤ 20 on day 2 or 3 of menstrual cycle (Stimulation day 1). On stimulation day 5 or 6, treatment with a GnRH antagonist is started depending on ovarian response. Daily injections of rFSH are started on stimulation day 8 until the criteria for triggering final oocyte maturation have been reached. As soon as 3 follicles ≥ 17 mm are observed, a single injection of 5,000 up to 10,000 IU HCG is administered the same day or day after to induce final oocyte maturation. Luteal phase support with progesterone is initiated on the day of oocyte retrieval and continued for at least 6 weeks, unless menses, or a negative pregnancy test was performed at least 14 days after embryo transfer.

Review of literature suggests that corifollitropin alfa is as effective as rFSH in delivering live birth rates, ongoing pregnancy rates and clinical pregnancy rates. The increased number of eggs at metaphase II retrieved under corifollitropin alfa regimen reflects the elevated effectiveness of this long-acting follicle stimulant. However, this property of sustained and higher FSH immunoreactivity concentrations and the inability for dose adjustment after treatment with a single dose of corifollitropin compared with the daily rFSH regimen (where the dose can be adjusted according to the ovarian response to avoid low or high ovarian response) underscores the need for careful patient selection in the use of corifollitropin alfa so as to prevent ovarian hyperstimulation syndome.

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