ClinicalTrials.gov PRS DRAFT Receipt (Working Version)
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ClinicalTrials.gov ID: NCT02738580

Study Identification

Unique Protocol ID:	1512-VLC-066-EB
Brief Title:	Follicular Steroid Genesis in Controlled Ovarian Stimulation (ESTEFOL)
Official Title:	Analysis of Follicular Steroid Synthesis During Controlled Ovarian Stimulation With Recombinant FSH vs HMG in GnRH Antagonist Cycles
Secondary IDs:	

Study Status

Record Verification:	February 2020
Overall Status:	Completed
Study Start:	October 18, 2016 [Actual]
Primary Completion:	June 15, 2018 [Actual]
Study Completion:	June 15, 2018 [Actual]

Sponsor/Collaborators

Sponsor:	Instituto Valenciano de Infertilidad, IVI VALENCIA
Responsible Party:	Sponsor
Collaborators:	Roche Pharma AG

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	

U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: 03/29/2016 Board Name: CEIC IVI Valencia Board Affiliation: ministry of Health Spain Phone: 963050900 Email: miguel.moreno@ivi.es Address: Plaza de la Policia local, 1 46015 Valencia, Spain
Data Monitoring:	Yes
FDA Regulated Intervention:	No

Study Description

Brief Summary:	Serum concentrations of the different hormones involved in follicular steroid genesis during a cycle of controlled ovarian stimulation with recombinant FSH or HMG will be compared in this study. Serum Progesterone (P) levels at the end of Controlled Ovarian Stimulation (i.e. the day of triggering) have been related to cycle outcome, in terms of ongoing pregnancy and live birth rates. Large cohort studies show that P levels above a certain threshold are associated with poorer cycle outcome. The mechanisms behind P elevation are not well understood yet. It has been shown that P levels are positively related to ovarian response and to the dose of FSH given during COS. Furthermore, it has been well documented that P levels at the end of stimulation are significantly higher when recombinant (r) FSH is used for COS when compared to HMG, either in a GnRH agonist long protocol or in a GnRH antagonist protocol. Some authors suggest that this finding is explained by the fact that COS with rFSH provides a higher oocyte yield than when hMG is given, so the higher P levels observed would be explained by the larger number of follicles developed when rFSH is used. On the other hand, other authors explain this event by a different follicular esteroidogenesis when HMG is used for COS compared to rFSH The hypotheisis behind this assumption is that rFSH enhances P synthesis from its precursor pregnenolone in the granulosa cells. This P is unable to be further metabolized into androgens because of the lack of 17-20 lyase in the human granulosa cells, and therefore is delivered into circulation. On the other hand, when HMG is given for COS, the $\Delta 4$ pathway is promoted, and pregnenolone will be catabolized in to Dehidroepiandrostenodione (DHEA), in the theca cells, and this one to Androstenodione, which will be finally aromatized in to estrogens. This mechanism will explain the lower P and higher E2 levels observed in HMG cycles in comparison to rFSH cycles.
Detailed Description:	

Conditions

Conditions:	Infertility Controlled Ovarian Hyperstimulation
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 4
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	None (Open Label)
Allocation:	Randomized
Enrollment:	112 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Active Comparator: rFSH Controlled ovarian hyperstimulation with GnRH antagonists and rFSH in women with normal ovarian function.	Drug: COS with GnRH antagonists and rFSH Controlled ovarian hyperstimulation with GnRH antagonists and rFSH in women with normal ovarian function. Other Names: • GnRH antagonists and rFSH
Active Comparator: HP-HMG Controlled ovarian hyperstimulation with GnRH antagonists and HP-HMG with normal ovarian function.	Drug: COS with GnRH antagonists and HP-HMG Controlled ovarian hyperstimulation with GnRH antagonists and HP-HMG in women with normal ovarian function. Other Names: • GnRH antagonists and HP-HMG

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	35 Years
Sex:	Female
Gender Based:	

Accepts Healthy Volunteers: Yes

Criteria: Inclusion Criteria:

- Good physical and psychological condition
- Normal menstrual cycle (25-35 days)
- Normal ovarian reserve defined by serum ANH010-30 pMol/L
- All other criteria to fulfill by oocyte donors

Exclusion Criteria:

- Kidney failure
- Ovarian Polyquistic syndrome
- Any systemic or metabolic disfunction that counter indicates the use of gonadotrophins
- Any other reason that involves exclusion of the oocyte donation program

Contacts/Locations

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IPDSharing

Plan to Share IPD: No

References

Citations:

Links:

Available IPD/Information:

Documents

Study Protocol and Statistical Analysis Plan
Document Date: December 17, 2015
Uploaded: 12/13/2019 05:56

Study Results

Participant Flow

Pre-assignment Details	Not applicable

Reporting Groups

	Description
rFSH	Controlled ovarian hyperstimulation with GnRH antagonists and rFSH in women with normal ovarian function. COS with GnRH antagonists and rFSH: Controlled ovarian hyperstimulation with GnRH antagonists and rFSH in women with normal ovarian function.
HP-HMG	Controlled ovarian hyperstimulation with GnRH antagonists and HP-HMG with normal ovarian function. COS with GnRH antagonists and HP-HMG: Controlled ovarian hyperstimulation with GnRH antagonists and HP-HMG in women with normal ovarian function.

Overall Study

	rFSH	HP-HMG
Started	56 [1]	56
Completed	52 [2]	52 [3]
Not Completed	4	4
Adverse Event	1	0
Lack of Efficacy	3	2

	rFSH	HP-HMG
Withdrawal by Subject	0	1
EXCLUDED FROM DONNOR PROGRAM	0	1

[1] 56 patients were assigned to this arms.
[2] 3 cycles cancelled due to por response to stimullation.

1 cycle cancelled due to SAE.
[3] 2 cycles cancelled due to por response to stimullation

1 patient withdrawal

1 excluded

Baseline Characteristics

Reporting Groups

	Description
rFSH	Controlled ovarian hyperstimulation with GnRH antagonists and rFSH in women with normal ovarian function. COS with GnRH antagonists and rFSH: Controlled ovarian hyperstimulation with GnRH antagonists and rFSH in women with normal ovarian function.
HP-HMG	Controlled ovarian hyperstimulation with GnRH antagonists and HP-HMG with normal ovarian function. COS with GnRH antagonists and HP-HMG: Controlled ovarian hyperstimulation with GnRH antagonists and HP-HMG in women with normal ovarian function.

Baseline Measures

		rFSH	HP-HMG	Total
Overall Number of Participants		56	56	112
Age, Categorical Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	56 participants	56 participants	112 participants
	<=18 years	0 0%	0 0%	0 0%
	Between 18 and 65 years	56 100%	56 100%	112 100%

		rFSH	HP-HMG	Total
	>=65 years	0 0%	0 0%	0 0%
Sex: Female, Male Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	56 participants	56 participants	112 participants
	Female	56 100%	56 100%	112 100%
	Male	0 0%	0 0%	0 0%
Race and Ethnicity Not Collected [1] Measure Type: Count of Participants Unit of measure: participants	Number Analyzed	0 participants	0 participants	0 participants
		---	---	0
		[1] Measure Analysis Population Description: Race and Ethnicity were not collected from any participant.		

Outcome Measures

1. Primary Outcome Measure:

Measure Title	SERUM PROGSTERONE CONCENTRATION
Measure Description	Compare hormonal blood serum concentrations of progesterone during ovarian stimulation implied in follicular steroidogenesis during a cycle of Controlled Ovarian Stimulation with either r-FSH or HP-HMG.
Time Frame	21 days

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
rFSH	Controlled ovarian hyperstimulation with GnRH antagonists and rFSH in women with normal ovarian function. COS with GnRH antagonists and rFSH: Controlled ovarian hyperstimulation with GnRH antagonists and rFSH in women with normal ovarian function.
HP-HMG	Controlled ovarian hyperstimulation with GnRH antagonists and HP-HMG with normal ovarian function. COS with GnRH antagonists and HP-HMG: Controlled ovarian hyperstimulation with GnRH antagonists and HP-HMG in women with normal ovarian function.

Measured Values

	rFSH	HP-HMG
Overall Number of Participants Analyzed	52	52
SERUM PROGSTERONE CONCENTRATION Mean (95% Confidence Interval) Unit of measure: ng/mL	0.74 (0.22 to 1.26)	0.45 (0.19 to 0.71)

Statistical Analysis 1 for SERUM PROGSTERONE CONCENTRATION

Statistical Analysis Overview	Comparison Group Selection	rFSH, HP-HMG
	Comments	[Not specified]
	Type of Statistical Test	Superiority
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.05
	Comments	The proportion of patients with elevated Progesterone on last day of stimulation(>1.5 ng/mL) was compared between both groups using the Chi-square test.
	Method	t-test, 2 sided
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.29
	Parameter Dispersion	Type: Standard Deviation Value: 0.26
	Estimation Comments	[Not specified]

2. Primary Outcome Measure:

Measure Title	OVARIAN RESPONSE
Measure Description	NUMBER OF FOLICLES REACHED AND PUNCTURED AFTER CONTROLED OVARIAN STIMULATION
Time Frame	21 days

Analysis Population Description
[Not Specified]

Reporting Groups

	Description
rFSH	Controlled ovarian hyperstimulation with GnRH antagonists and rFSH in women with normal ovarian function. COS with GnRH antagonists and rFSH: Controlled ovarian hyperstimulation with GnRH antagonists and rFSH in women with normal ovarian function.
HP-HMG	Controlled ovarian hyperstimulation with GnRH antagonists and HP-HMG with normal ovarian function. COS with GnRH antagonists and HP-HMG: Controlled ovarian hyperstimulation with GnRH antagonists and HP-HMG in women with normal ovarian function.

Measured Values

	rFSH	HP-HMG
Overall Number of Participants Analyzed	52	52
OVARIAN RESPONSE Mean (95% Confidence Interval) Unit of measure: folicles	16.5 (9 to 24)	17.5 (9.6 to 25.4)

Statistical Analysis 1 for OVARIAN RESPONSE

Statistical Analysis Overview	Comparison Group Selection	rFSH, HP-HMG
	Comments	[Not specified]
	Type of Statistical Test	Superiority
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.49
	Comments	[Not specified]
	Method	t-test, 1 sided
	Comments	[Not specified]

Reported Adverse Events

Time Frame	21 Days
Adverse Event Reporting Description	Coagulation panel alteration.

Reporting Groups

	Description
rFSH	Controlled ovarian hyperstimulation with GnRH antagonists and rFSH in women with normal ovarian function. COS with GnRH antagonists and rFSH: Controlled ovarian hyperstimulation with GnRH antagonists and rFSH in women with normal ovarian function.
HP-HMG	Controlled ovarian hyperstimulation with GnRH antagonists and HP-HMG with normal ovarian function. COS with GnRH antagonists and HP-HMG: Controlled ovarian hyperstimulation with GnRH antagonists and HP-HMG in women with normal ovarian function.

All-Cause Mortality

	rFSH		HP-HMG	
	Affected/At Risk (%)	# Events	Affected/At Risk (%)	# Events
Total All-Cause Mortality	0/56 (0%)		0/56 (0%)	

Serious Adverse Events

	rFSH		HP-HMG	
	Affected/At Risk (%)	# Events	Affected/At Risk (%)	# Events
Total	1/56 (1.79%)		0/56 (0%)	
Blood and lymphatic system disorders				
COAGULATION PANEL ALTERATION A [1] *	1/56 (1.79%)	1	0/56 (0%)	0

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, Vitamin K Deficiency

[1] PT: 15,4 seg; INR: 1,3; Quick Index: 69%; TTPA: 38 seg. Hemmatic parameters at minimum normal limits She was reffered to hemathologist department. There was not more information about patient since january 2018.

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 0%

	rFSH		HP-HMG	
	Affected/At Risk (%)	# Events	Affected/At Risk (%)	# Events
Total	0/56 (0%)		0/56 (0%)	

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

All Principal Investigators ARE employed by the organization sponsoring the study.

Results Point of Contact:

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