ASRM 2024
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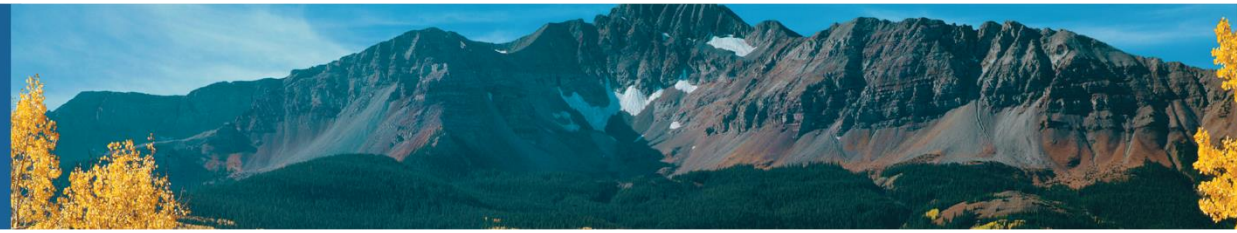

Impact of Gonadotropin Selection on Risk of Ovarian Hyperstimulation Syndrome in Predicted Higher Responders Undergoing Ovarian Stimulation: a MEGASET-HR Trial Analysis

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Disclosures & Acknowledgements

- Russell Foulk, Cristin C. Slater, and Vishvanath Karande were investigators in the MEGASET-HR trial
- Lindsay Kelly, and Sasmira Lalwani are current employees of Ferring Pharmaceuticals, Inc.
- Gaurang Daftary, Eric Foster, and Patrick Heiser were employees of Ferring Pharmaceuticals, Inc. at the time this work was conducted
- The MEGASET-HR trial was funded by Ferring Pharmaceuticals, Inc.

Ovarian Hyperstimulation Syndrome (OHSS)

- Iatrogenic complication of ovarian stimulation in ART
- Occurs in early and late forms[1]
  - Early OHSS (≤9 days post trigger) relates to magnitude of gonadotropin stimulation
  - Late OHSS (>9 days post trigger) is generally associated with pregnancy
- Classified into mild, moderate and severe grades[2]
- Overall risk of 1-5% in all ART cycles[3-5]
- Associated with brisk ovarian stimulation, high estradiol, high oocyte recovery[3,6,7]
- Young, high-responder and those with PCOS are at a higher risk of OHSS[8-10]

1. Mathur RS, et al. Fertil Steril. 2000;73:901-7. 2. Golan A, et al. Obstet Gynecol Surv 1989;44:430–440. 3. Broer SL, et al. Fertil Steril 2013;100:420-9.e7. 4. Nelson SM, et al. Thromb Res 2017;151 Suppl 1:S61-S64. 5. Nastri, CO, et al. Ultrasound Obstet Gynecol. 2015;45:377-393. 6. Steward RG et al. Fertil Steril 2014;101:967-73. 7. Magnusson Å, et al. Hum Reprod 2018;33:58-64. 8. Arce JC, et al. Gynecol Endocrinol 2014;30:444-50. 9. Mascarenhas M, et al. Hum Fertil (Camb) 2017;20:155-67. 10. Oudshoorn SC, et al. Hum Reprod 2017;32:2506-14.

GnRH Agonist Trigger as an OHSS Preventive Strategy

- Use of GnRH agonist trigger has reduced the incidence of moderate and severe OHSS,[1,2] but…
  - Impairs endometrial receptivity, which prevents fresh transfer and potentially increases costs
  - Delays time to pregnancy, particularly if patient is not undergoing PGT

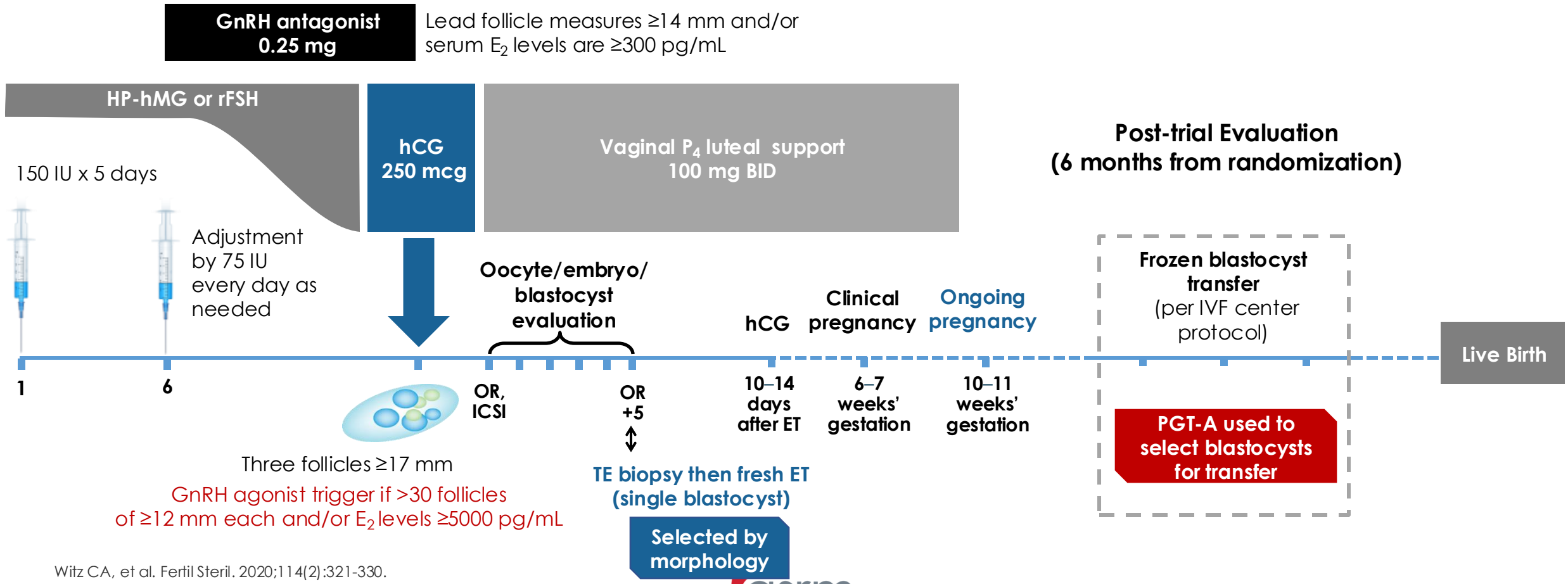
1. Toftager M, et al. Hum Reprod 2016;31:1253-64.
2. Youssef MA, et al. Cochrane Database Syst Rev 2014:CD008046.

MEGASET-HR Post-hoc OHSS Analysis

Objective: To evaluate risk of developing ovarian hyperstimulation syndrome (OHSS) with use of highly purified human menotropin (HP-hMG)versus recombinant follicle stimulating hormone (rFSH) for ovarian stimulation in predicted high responder patients

MEGASET-HR: Treatment Protocol

Randomized, non-inferiority trial conducted in 31 US centers
619 potential high-responders (serum AMH ≥5 ng/mL [≥35.8 pmol/L])



Witz CA, et al. Fertil Steril. 2020;114(2):321-330.

MEGASET-HR: Key baseline characteristics

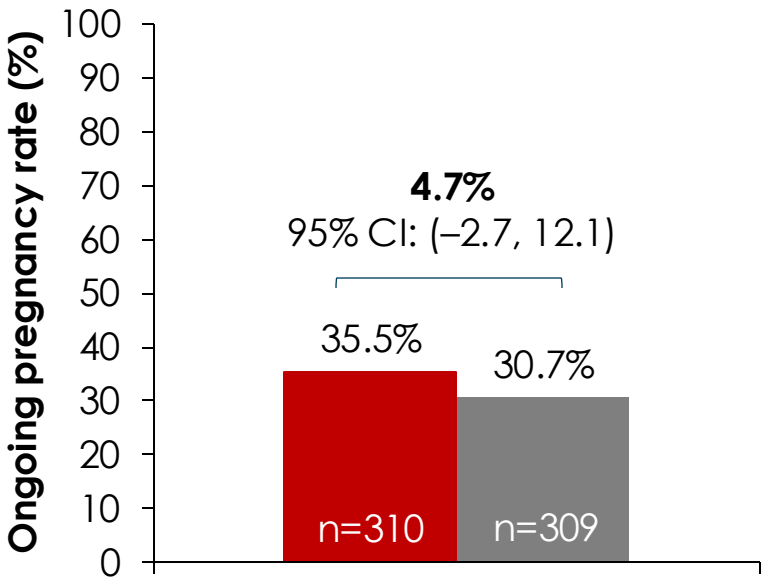
Parameters	HP-hMG (N=310)	rFSH (N=309)
Age, years	30.0 ± 3.08	30.4 ± 3.02
BMI, kg/m^2	24.4 ± 3.29	24.3 ± 3.39
Duration of infertility, months	36.7 ± 25.79	37.1 ± 28.38
Cause of infertility, n (%)*		
Oligo-ovulation	50 (16.1)	56 (18.1)
Endometriosis	20 (6.5)	25 (8.1)
Male factor	136 (43.9)	129 (41.7)
Tubal factor	44 (14.2)	43 (13.9)
Idiopathic	105 (33.9)	112 (36.2)
Other	28 (9.0)	29 (9.4)
AFC	30.5 ± 15.47	31.0 ± 12.24
AMH, pmol/L (ng/mL)	56.1 ± 25.96 (7.8 ± 3.61)	53.9 ± 17.47 (7.5 ± 2.43)
≥35.7 (≥5.0)	310 (100)	309 (100)
≥42.9 (≥6.0)	217 (70.0)	216 (69.9)
≥50.0 (≥7.0)	143 (46.1)	141 (45.6)
≥57.1 (≥8.0)	92 (29.7)	96 (31.1)
LH, U/L	6.9 ± 4.04	6.4 ± 3.49
FSH, U/L	6.4 ± 1.55	6.2 ± 1.55

Values are mean ± SD or n (%) unless otherwise indicated.
AFC, antral follicle count; AMH, anti-Müllerian hormone.
Witz CA, et al. Fertil Steril. 2020;114(2):321-330.

MEGASET-HR: Primary Endpoint

Population: mITT

HP-hMG rFSH



HP-hMG demonstrated to be **non-inferior** to rFSH for the primary endpoint of **ongoing pregnancy after fresh transfer per cycle start**

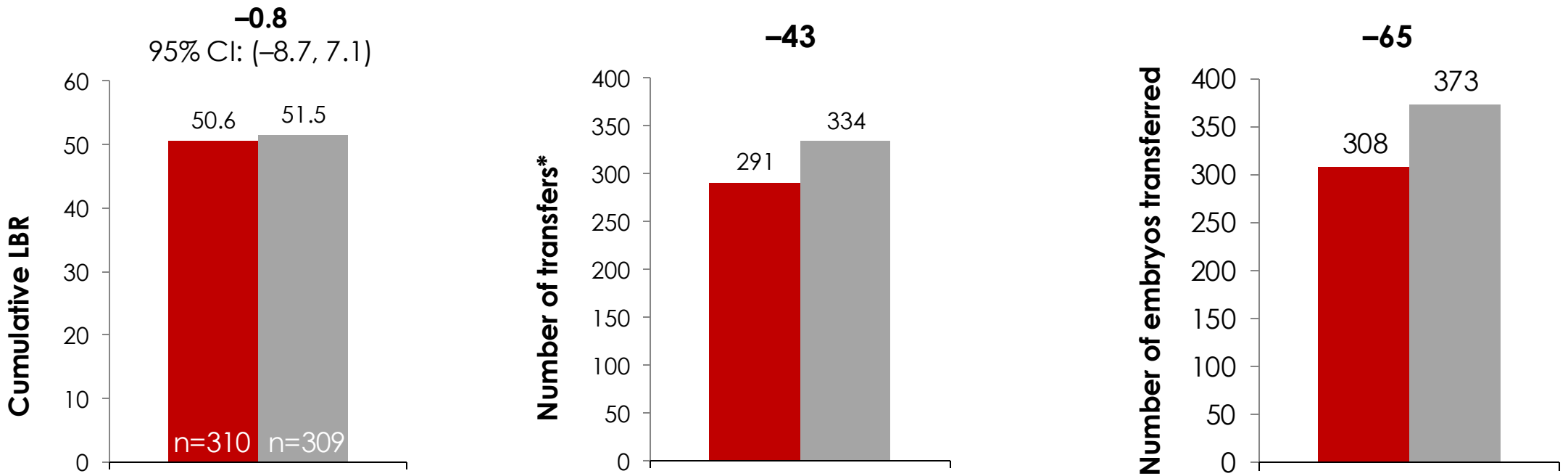
Witz CA, et al. Fertil Steril. 2020;114(2):321-330.

Ongoing pregnancy was defined as ≥1 intrauterine pregnancy with a detectable fetal heartbeat 8-9 weeks after fresh transfer (10-11 weeks gestation).
mITT=modified intent-to-treat (i.e., randomized and treated, according to randomization).

MEGASET-HR: Cumulative LBR

Population: mITT

HP-hMG rFSH

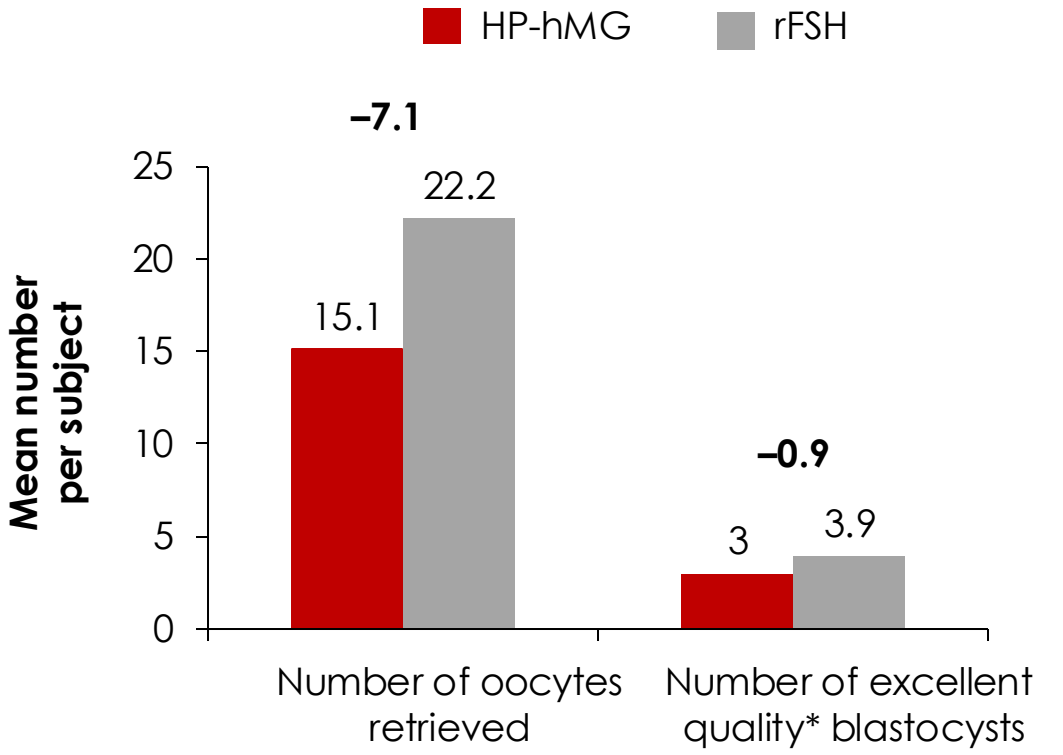


Cumulative LBR at 6 months was **achieved with fewer transfers and fewer embryos** in the HP-hMG group

*Transfers involving multiple embryos were considered protocol deviations – all but 3 occurred with FET.
Live birth rate (LBR) was a secondary endpoint.

Witz CA, et al. Fertil Steril. 2020;114(2):321-330.

MEGASET-HR: Maintaining Efficacy with a Lower Ovarian Response



	Number of oocytes retrieved	Number of excellent quality* blastocysts
Difference (95% CI)†	-7.00 (-8.00, -5.00)	0.00 (-1.00,0.00)

The HP-hMG group had **fewer oocytes retrieved but comparable number of excellent quality blastocysts*** compared to the rFSH group

*Defined as blastocyst expansion and hatching status 4–6, inner cell mass grade A, and trophectoderm grade A or B.
†Differences between HP-hMG and rFSH were calculated by the Hodges-Lehmann estimate.
Oocytes retrieved was a secondary endpoint.

Witz CA, et al. Fertil Steril. 2020;114(2):321-330.

OHSS in MEGASET-HR

	HP-hMG n/n (%)	rFSH n/n (%)	Difference % (95% CI)
Any OHSS	30/310 **(9.7)**	66/309 **(21.4)**	-11.7 (-17.3, -6.1)
Early OHSS	19/310 **(6.1)**	54/309 **(17.5)**	-11.3 (-16.4, -6.3)
Late OHSS	11/310 (3.5)	12/309 (3.9)	-0.3 (3.3, 2.6)

Early and late OHSS were defined as onset ≤9 days or >9 days after trigger, respectively.
Witz CA, et al. Fertil Steril. 2020;114(2):321-330.

Patient Factors Associated with Early OHSS

Parameter	No OHSS		Early OHSS		P value
	n	Value	n	Value	
Age (years), mean (±SD)	546	30.3 (3.03)	73	29.5 (3.15)	**0.0232**
Weight (kg), mean (±SD)	546	66.2 (10.33)	73	63.8 (11.87)	**0.0406**
BMI (kg/m^2), mean (±SD)	546	24.5 (3.31)	73	23.6 (3.45)	**0.0319**
Duration of infertility (months), mean (±SD)	545	37.7 (27.58)	73	31.0 (22.46)	**0.0217**
Cause of infertility, n (%)					
Oligoovulation		90 (16.5)		16 (21.9)	0.2487
Endometriosis		44 (8.1)		1 (1.4)	0.0501
Male factor		226 (41.4)		39 (53.4)	0.0588
Tubal factor		81 (14.8)		6 (8.2)	0.1520
Idiopathic		197 (36.1)		20 (27.4)	0.1531
Other		46 (8.4)		11 (15.1)	0.0819
Antral follicle count, mean (±SD)	544	30.4 (12.93)	71	33.8 (19.97)	0.1340
Baseline AMH (ng/mL), mean (±SD)	546	7.6 (2.95)	73	8.4 (3.83)	0.2161
Luteinizing hormone (U/L), mean (±SD)	536	6.5 (3.50)	70	7.4 (5.43)	0.1886
Follicle-stimulating hormone (U/L), mean (±SD)	536	6.3 (1.53)	70	6.2 (1.67)	0.7036
Estradiol (pg/mL), mean (±SD)	455	37.48 (20.54)	64	44.31 (23.52)	**0.0299**
Progesterone (ng/mL), mean (±SD)	534	0.22 (0.71)	70	0.16 (0.34)	0.6007
Testosterone (ng/dL), mean (±SD)	525	28.84 (12.69)	70	31.73 (18.75)	0.1063
End of stimulation, mean (±SD)					
Estradiol (pmol/L)	479	10,672.95 (7,002.79)	61	13,934.53 (6,288.09)	<0.0001
Number of follicles observed/subject	504	28.8 (14.65)	70	34.6 (15.78)	0.0018
Number of follicles ≥12 mm observed/subject	504	16.4 (7.58)	70	21.2 (7.48)	<0.0001
Number of oocytes retrieved/subject	526	17.5 (10.53)	72	27.9 (13.44)	<0.0001

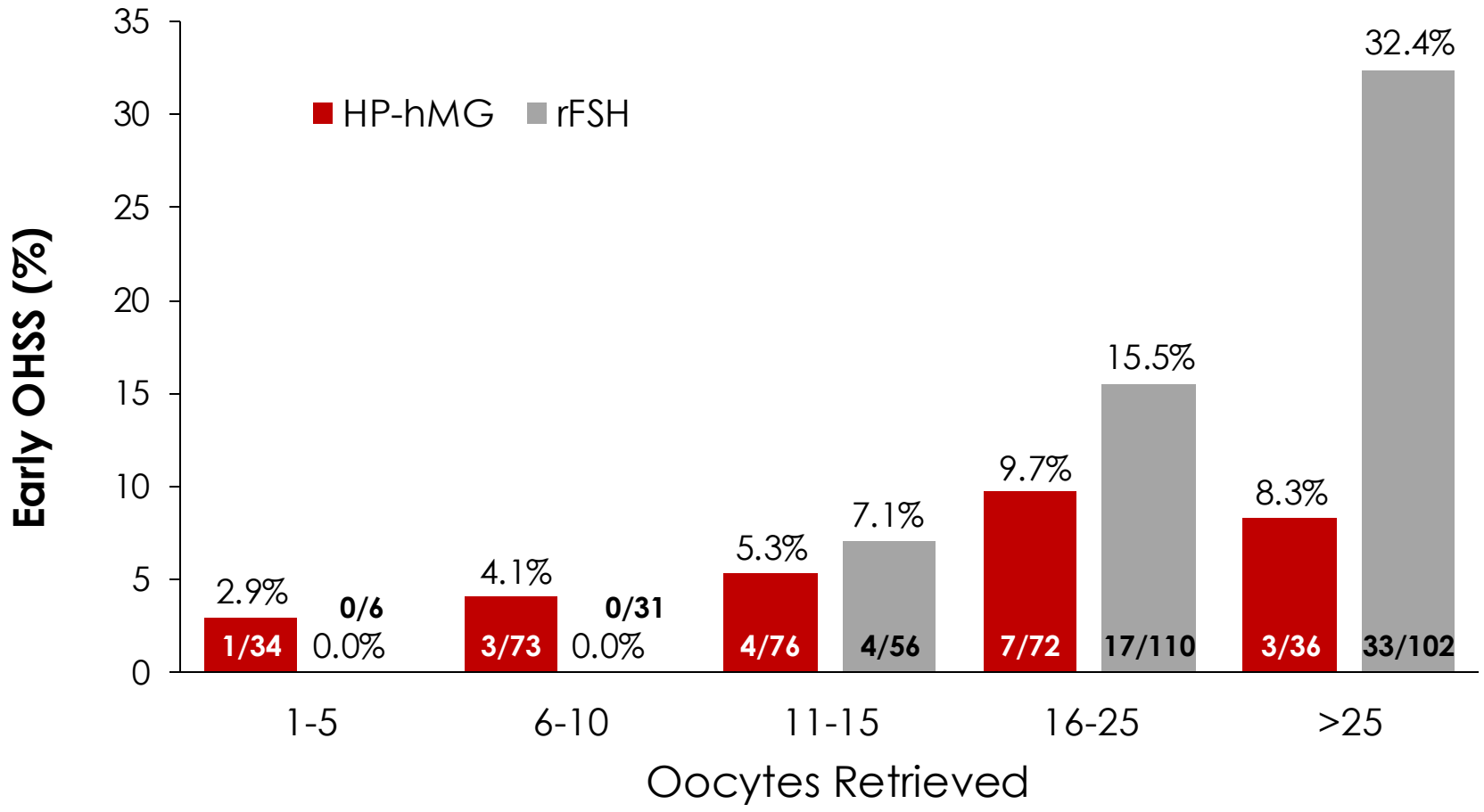
Patient Factors Associated with Early OHSS by Treatment Arm

Parameter	rFSH		HP-hMG		P value
	N	Value	n	Value	
Age (years), mean (±SD)	54	29.6 (3.12)	19	29.2 (3.29)	0.6584
Weight (kg), mean (±SD)	54	62.3 (12.23)	19	67.9 (9.97)	**0.0368**
BMI (kg/m^2), mean (±SD)	54	23.1 (3.43)	19	24.8 (3.27)	0.0673
Duration of infertility (months), mean (±SD)	54	30.3 (20.43)	19	32.9 (28.01)	0.8402
Cause of infertility, n (%)					
Oligoovulation		10 (18.5)		6 (31.6)	0.3330
Endometriosis		1 (1.9)		0 (0.0)	1.0000
Male factor		30 (55.6)		9 (47.4)	0.5994
Tubal factor		5 (9.3)		1 (5.3)	1.0000
Idiopathic		14 (25.9)		6 (31.6)	0.7659
Other		9 (16.7)		2 (10.5)	0.7167
Antral follicle count, mean (±SD)	53	32.5 (13.57)	18	37.7 (32.50)	0.8739
Baseline AMH (ng/mL), mean (±SD)	54	7.8 (3.22)	19	9.8 (4.99)	0.1205
Luteinizing hormone (U/L), mean (±SD)	52	6.7 (3.54)	18	9.2 (8.79)	0.4721
Follicle-stimulating hormone (U/L), mean (±SD)	52	6.0 (1.58)	18	6.8 (1.82)	0.0716
Estradiol (pg/mL), mean (±SD)	47	42.72 (21.29)	17	48.70 (29.11)	0.6373
Progesterone (pg/mL), mean (±SD)	52	0.15 (0.39)	18	0.09 (0.08)	0.3404
Testosterone (ng/dL), mean (±SD)	52	31.72 (16.72)	18	40.38 (22.50)	0.0552
End of stimulation, mean (±SD)					
Estradiol (pmol/L)	45	14,362.97 (6,025.14)	16	12,729.54 (7,040.89)	0.3172
Number of follicles observed/patient	52	34.9 (12.98)	18	33.7 (22.44)	0.2088
Number of follicles ≥12 mm observed/patient	52	23.3 (6.83)	18	15.4 (6.27)	**0.0002**
Number of oocytes retrieved/patient	54	30.1 (11.62)	18	21.1 (16.41)	**0.0010**

No Significant Difference in OHSS by Trigger Type

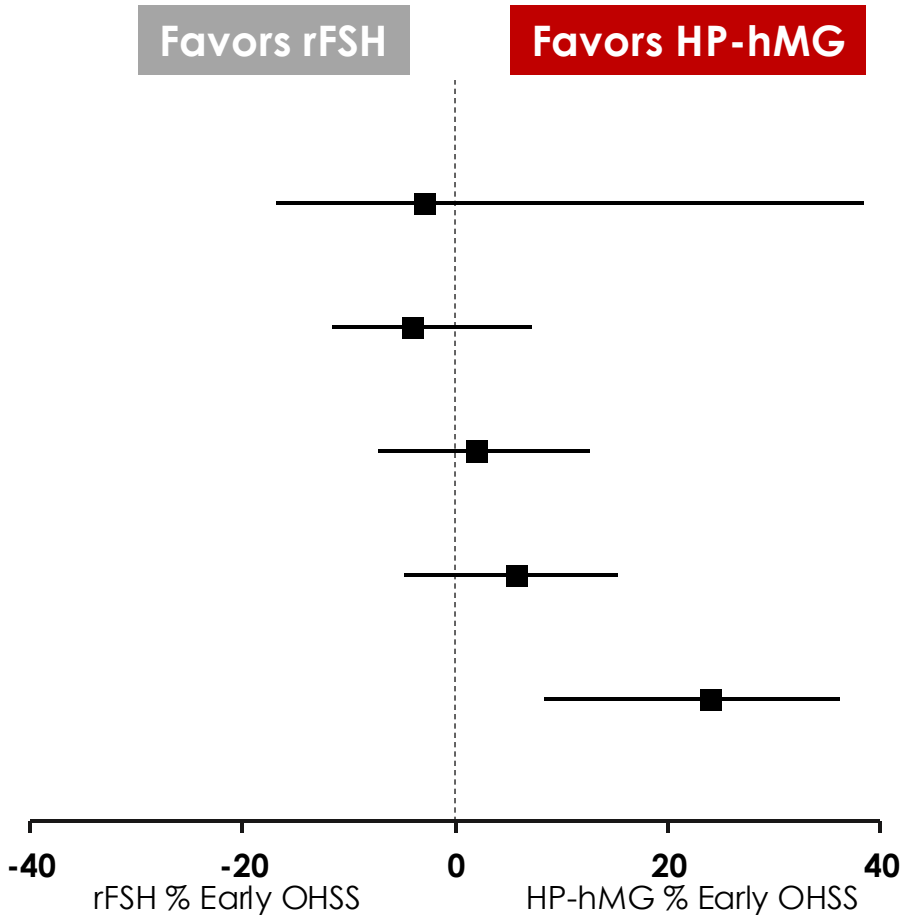
OHSS	GnRH agonist		hCG		Difference (95% CI)	P value
	N	n (%)	N	n (%)		
Early	91	15 (**16.5**)	509	57 (**11.2**)	5.3 (-2.2, 14.7)	0.1618
Late	91	1 (**1.1**)	509	22 (**4.3**)	-3.2 (-5.7, 1.8)	0.2311
Any	91	16 (**17.6**)	509	79 (**15.5**)	2.1 (-5.3, 11.6)	0.6403
Mild	91	9 (9.9)	509	15 (2.9)	6.9 (2.0, 15.1)	0.0053
Moderate	91	6 (6.6)	509	48 (9.4)	-2.8 (-7.5, 4.5)	0.5497
Severe	91	1 (1.1)	509	16 (3.1)	-2.0 (-4.4, 3.0)	0.4913

Early OHSS Incidence Increases with Oocyte Yield

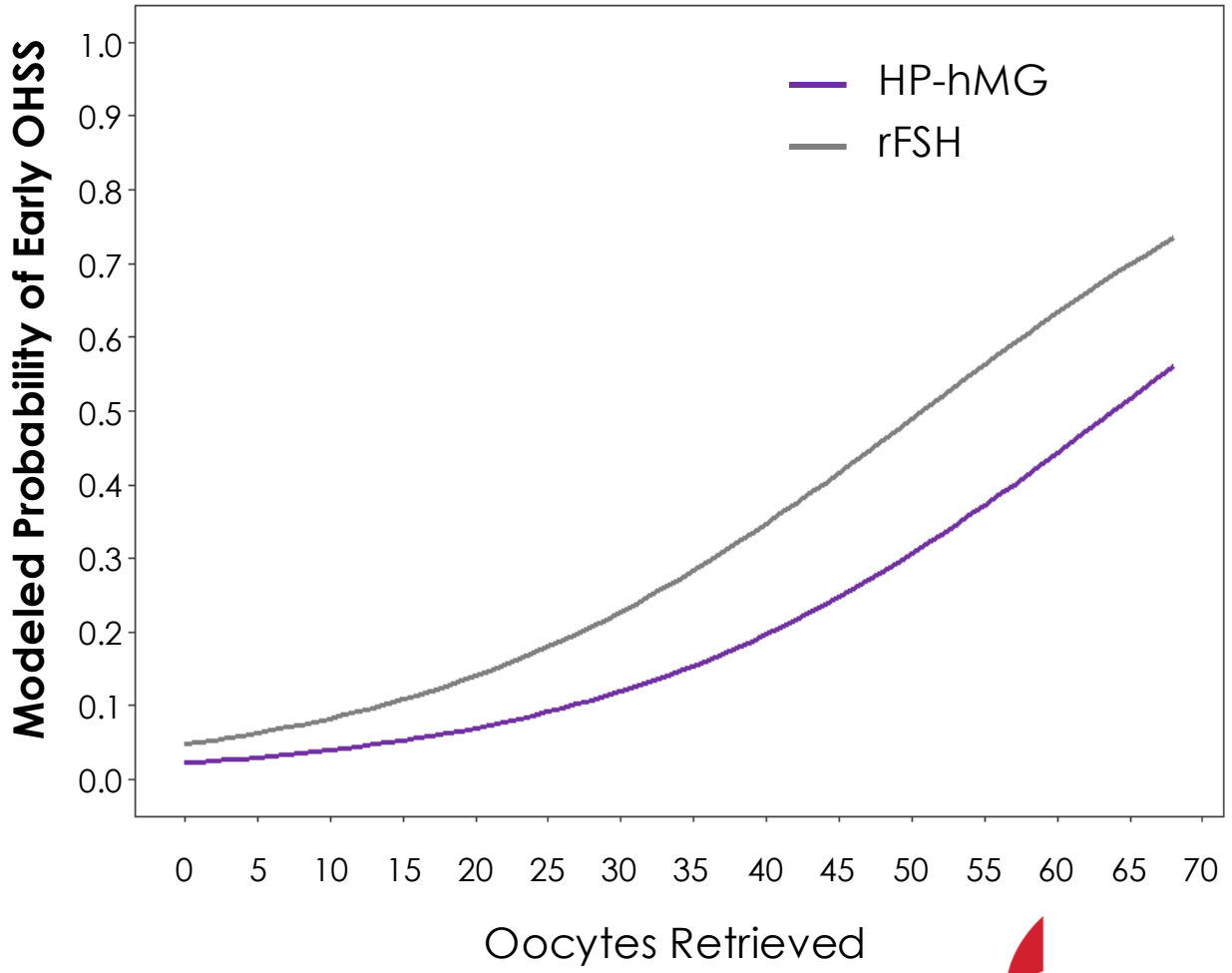


Highest Incidence of Early OHSS: rFSH-treated Patients with >25 Oocytes Retrieved

Oocytes retrieved	Diff in Pct (95% exact CI)
1–5	-2.9% (-16.9%, 38.5%)
6–10	-4.1% (-11.6%, 7.3%)
11–15	1.9% (-7.2%, 12.6%)
16–25	5.7% (-4.9%, 15.4%)
>25	24.0% (8.3%, 36.2%)



Lower Risk of Early OHSS with HP-hMG Across Oocyte Yields



In both groups, for each additional oocyte retrieved, the likelihood of early OHSS increased **1.06** fold

After adjusting for the number of oocytes retrieved, the odds of early OHSS with HP-hMG was **0.45** times that with rFSH

Conclusions

- In predicted high-responders, HP-hMG stimulation was associated with **significantly lower overall and early OHSS rates** compared to rFSH, even **after adjusting for oocyte yield**
- HP-hMG provides comparable efficacy to rFSH with lower incidence of OHSS suggesting an **optimized risk/benefit profile**
- Safety considerations in predicted high-responders could drive **improved protocol individualization** based on gonadotropin type
- Further studies are warranted to explore the potential protective mechanism of HP-hMG in predicted high-responders

References

1. Mathur RS, et al. Fertil Steril. 2000;73:901-7
2. Golan A, et al. Obstet Gynecol Surv 1989;44:430–440.
3. Broer SL, et al. Fertil Steril 2013;100:420-9.e7.
4. Nelson SM, et al. Thromb Res 2017;151 Suppl 1:S61-S64.
5. Nastri, CO, et al. Ultrasound Obstet Gynecol. 2015;45:377-393.
6. Steward RG et al. Fertil Steril 2014;101:967-73.
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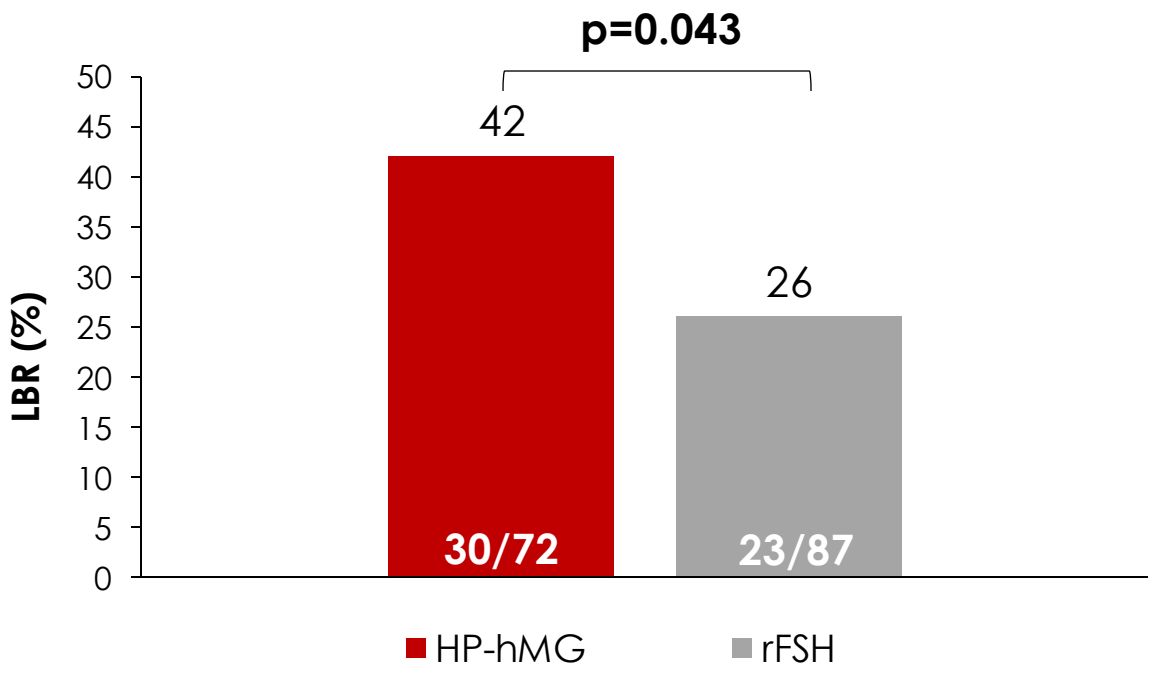
10. Oudshoorn SC, et al. Hum Reprod 2017;32:2506-14.
11. Toftager M, et al. Hum Reprod 2016;31:1253-64.
12. Youssef MA, et al. Cochrane Database Syst Rev 2014:CD008046.
13. Witz CA, et al. Fertil Steril. 2020;114(2):321-330.

Thank You

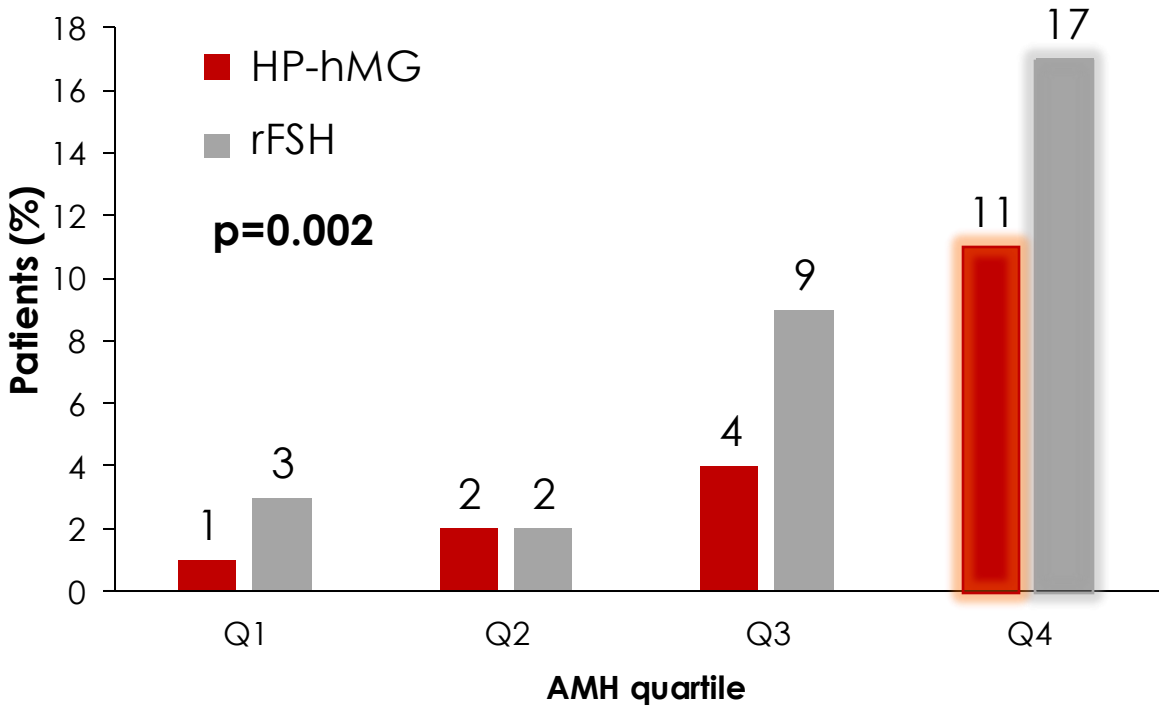
Back-up

Potential Benefit of the Stimulation Protocol: Post-hoc Analysis of the MEGASET Trial

Live Birth Rate per Fresh Embryo Transfer (Fourth AMH quartile: >37 pmol/L [>5.2 ng/mL])[1]



Early OHSS or Safety Interventions* due to Excessive Ovarian Response[2]



*Interventions: cycle cancellation due to excessive response, paracentesis, albumin administration. *P* value per AMH quartile calculated by Chi-square test.

1. Arce JC, et al. Gynecol Endocrinol 2014;30:444–450.
2. Arce JC, et al. Fertil Steril 2013;99:1644–1653.

MEGASET-HR: Key Inclusion/Exclusion Criteria

Main inclusion criteria

- Serum AMH ≥5 ng/mL (≥35.8 pmol/L) at screening
- 21–35 years of age
- Infertility for ≥1 year
- Menstrual cycles of 21–45 days
- Normal total testosterone, prolactin and thyroid-stimulating hormone
- BMI of 18–30 kg/m^2
- Willing to accept single ET (one blastocyst)

Main exclusion criteria

- Antral follicle count (diameter 2–10 mm) <10 for both ovaries combined
- Use of hormonal birth control in previous 3 months
- History of recurrent miscarriage Previous IVF or ART failure from poor response
- Stage III-IV endometriosis
- Uncontrolled systemic disease

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MEGASET-HR: Outcomes

Primary outcome

- Ongoing pregnancy rate in the fresh cycle

Secondary outcomes

- Cumulative ongoing pregnancy
- Early pregnancy loss
- OHSS frequency
- Follicular development
- Endocrine profile
- Endometrial development
- Number of oocytes retrieved
- Blastocyst quality
- Safety: TEAEs

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MEGASET-HR: Participant Demographics

Parameter	HP-hMG (n=310)	rFSH (n=309)
Age, years	30.0 ± 3.1	30.4 ± 3.0
BMI, kg/m^2	24.4 ± 3.3	24.3 ± 3.4
FSH, IU/L	6.4 ± 1.6	6.2 ± 1.6
AMH, pmol/L	**7.8 ± 3.6**	**7.5 ± 2.4**
Antral follicle count	**30.5 ± 15.5**	**31.0 ± 12.2**
Duration of infertility, months	36.7 ± 25.8	37.1 ± 28.4
Cause of infertility, n (%)†		
Male factor	136 (44%)	129 (42%)
Idiopathic	105 (34%)	112 (36%)
Oligoovulation	50 (16%)	56 (18%)
Tubal factor	44 (14%)	43 (14%)
Other	28 (9%)	29 (9%)
Endometriosis	20 (6%)	25 (8%)

Unless otherwise noted, data are presented as mean ± standard deviation.
*AMH conversion: 1 ng/mL=7.14 pmol/L.
†Patients may have had >1 cause of infertility.
AMH=anti-Müllerian hormone; BMI=body mass index; HP-hMG=highly purified human menotropin; rFSH=recombinant follicle stimulating hormone.

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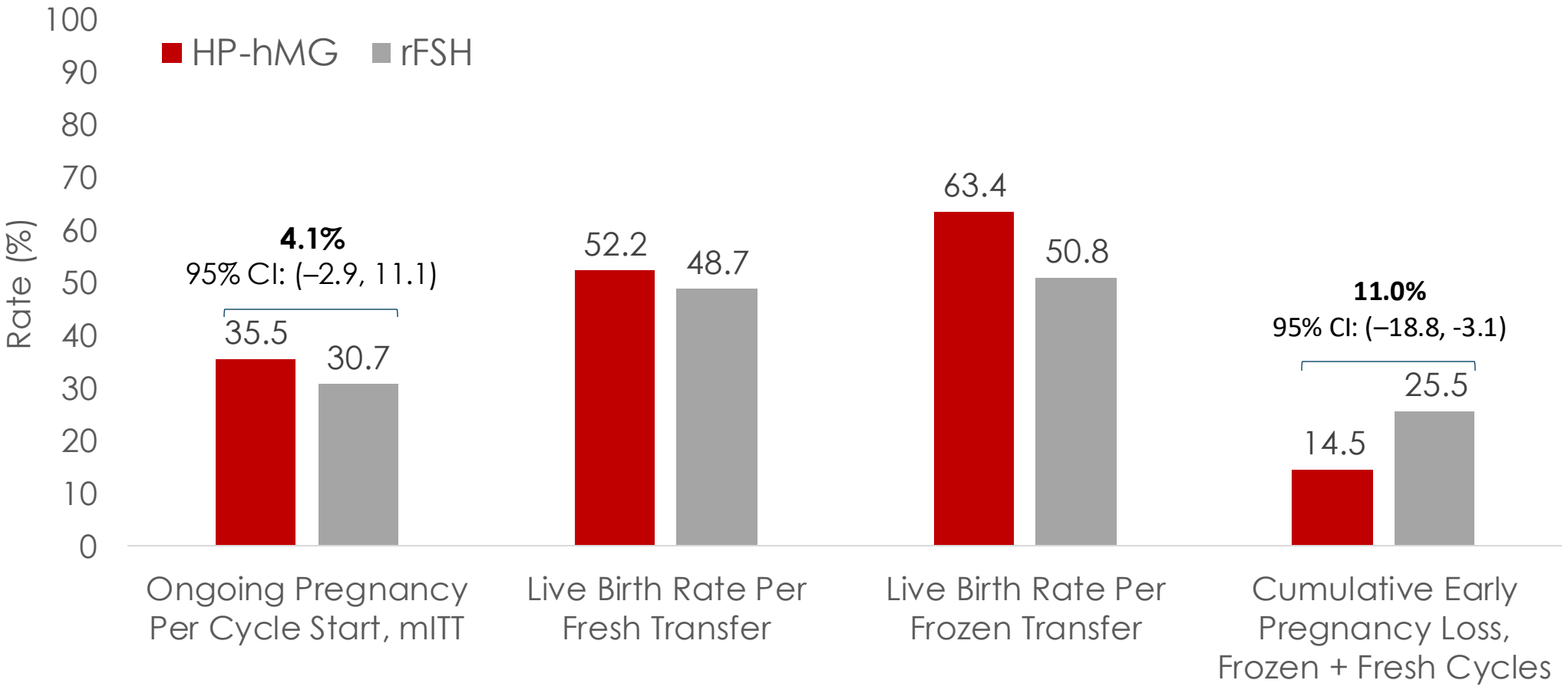
MEGASET-HR: Secondary Endpoints



Ongoing pregnancy was defined as ≥1 intrauterine pregnancy with a detectable fetal heartbeat 8-9 weeks after fresh transfer (10-11 weeks gestation).
mITT=modified intent-to-treat (i.e., randomized and treated, according to randomization).

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Post-hoc OHSS Analysis Endpoints

- Incidence of OHSS by treatment arm
- Patient factors associated with OHSS overall and by treatment arm
- Incidence of OHSS by trigger type and oocytes retrieved
- Risk of OHSS in potential high responders

Methods

A post-hoc analysis was performed on the MEGASET-HR trial to analyze differences between participates who experienced OHSS and those that did not

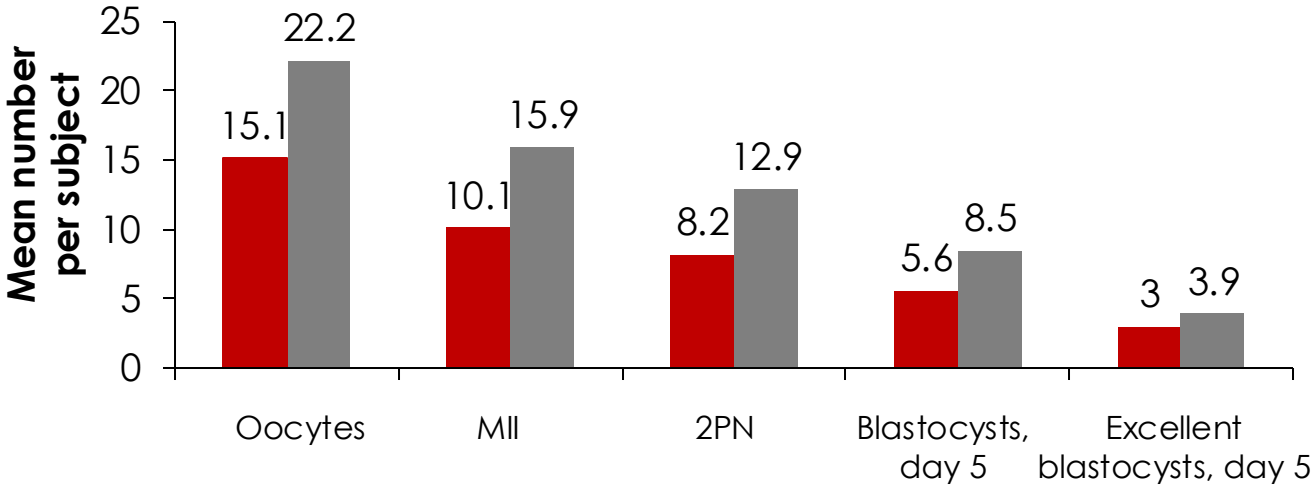
- Non-parametric tests (Kruskal-Wallis test for continuous variables and the Fisher's exact test for categorical variables) were used to compare demographics, baseline characteristics, and end-of-stimulation values.
- A linear regression model was used to model oocytes retrieved as a function of both treatment and baseline AMH.*
- A logistic regression model was used to model the probability of early OHSS as a function of treatment and oocytes retrieved.*

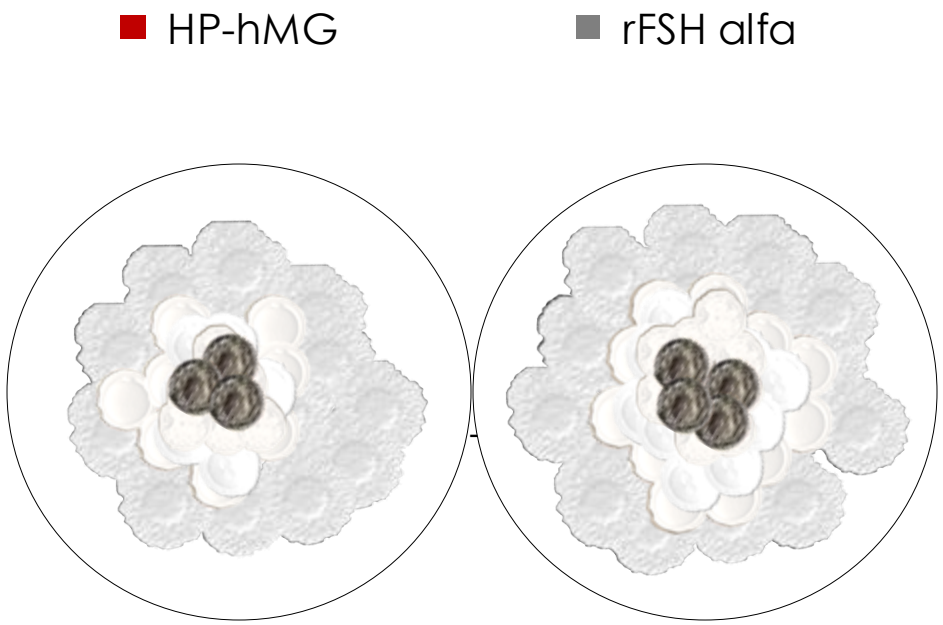
*Both models were fit with and without an interaction term, using the interaction model if the interaction term was statistically significant at the 5% significance level. Otherwise, the main effects model was used for inference. For summaries based on type of OHSS or categories of oocytes retrieved, 95% exact confidence intervals for differences in proportions were created using the Agresti-Min methodology.

MEGASET-HR: Secondary outcome

Population: Subjects with data for respective endpoint

Numerical difference:	–7.1	–5.8	–4.7	–2.9	–0.9
Hodges-Lehmann estimate difference (CI 95%)	–7.0 (–8.0, –5.0)	–5.0 (–7.0, –4.0)	–4.0 (–5.0, –3.0)	–3.0 (–3.0, –2.0)	0.0 (–1.0, 0.0)





Witz CA, et al. Fertil Steril. 2020;114(2):321-330.

MEGASET-HR: Overall safety

Parameter[1]	HP-hMG (N=310)	rFSH alfa (N=309)
TEAE*	58%	71%
Procedural pain	23%	23%
Nausea	12%	13%
Abdominal distension	8%	11%
Constipation	7%	12%
Headache	9%	7%
Abdominal pain	7%	8%
Vaginal hemorrhage	7%	7%
OHSS†	10%‡	21%‡
Mild	2%	6%
Moderate	5%	13%
Severe	3%	3%
Serious AEs	3%	4%
AE-related discontinuation of trial product	1%	1%
Death of mother	0%	0%

*TEAEs with an incidence of at least 5% by MedDRA System Organ Class and Preferred Term (Safety Analysis Set); †Classification of grade was determined using Golan's classification system;[2]; ‡Difference in OHSS incidence: 11.7%, (confidence interval –17.3, –6.1%).

1. Witz CA, et al. Fertil Steril 2020;114:321–330;
2. Golan A, et al. Obstet Gynecol Surv 1989;44:430–440.

Safety was a secondary endpoint in this trial. The clinical trial was neither designed nor powered to assess results based on secondary outcomes, therefore no final conclusions can be drawn from the results.