Factors affecting success rates in two concurrent clinical IVF trials: an examination of potential explanations for the difference in pregnancy rates between the United States and Europe

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Background

- Pregnancy and live birth rate from ART

  → US > Europe

  (Gleicher , 2007; CDC, 2008; Andersen, 2008)

- 2 Similar trails in US and Europe have been reported
  - HP-hFSH vs rFSH in pts with ART
  - Similar inclusion criteria and protocols
  - Clinical pregnancy rate : US > Europe

Purpose of this study

- Identify the baseline and tx – associated variables of both trails that might explain the difference in clinical pregnancy rates.

Materials and methods

- Study designs of both US and Europe trails
  - prospective , assessor – blinded and randomized
  - US trails → conducted at 4 sites ; Europe →France and Hungary
  - HP-hFSH was compared with rFSH in cycles down-regulated with GnRH agonist .
  - Similar baseline , tx and outcome variables
  - Clinical pregnancy rate : sac + FHB

Materials and methods

- All baseline, tx , and outcomes variables that were similar in both trails were included in this analysis .
- Compared all US pts (HP-hFSH + rFSH) with all European pts (HP-hFSH + rFSH) .

Materials and methods

- Logistic regression
  - to determine if any of the variable measured in both studies might explain the difference of clinical pregnancy rate .

- Regression analysis
  - 81 baseline and tx variables --> considered as possible predictors of likelihood of pregnancy
  - Some variables were part of study design → not included to analyze , but could account for differences

Variables

- Baseline variables
- Process variables involving ovarian stimulation
- Process variables involving oocyte retrieval, laboratory culture , and embryo transfer .

Results

TABLE 1

Comparison of study protocols between US and European trial.

	US	Europe
ICSI plan	if indicated	all cycles
Birth control pill pretreatment	yes	no
Normal TSH required	yes	no
Baseline FSH <10 required	yes	yes
Baseline estradiol <80 pg/mL	yes	no
≥10 antral follicles required	yes	no
Exclude if prior IVF cycle had <3 oocytes retrieved	yes	yes
Exclude if hydrosalpinx untreated	yes	no
Exclude if Stage III or IV endometriosis	yes	no
Down-regulation endometrium	≤5 mm	<7 mm
Starting FSH dose	300 IU	225 IU
Gonadotropin day on which dose adjustment permitted	3	6
Luteal progesterone support	IM	Vaginal

Notes: ICSI = intracytoplasmic sperm injection.

Baker. Comparison of 2 IVF trials (US, Europe). Fertil Steril 2010.

TABLE 2

Comparison of baseline characteristics in the US and European trials for those volunteers who received at least one dose of FSH.

	US	Europe
Number of patients treated	152	145
Completed study	135	135
Canceled prior to hCG[a]	11	3
Canceled after retrieval[b]	6	7
Age[c]	34.6 (3.1, 25.8–39.9)	33.4 (3.8, 21.5–39.4)
BMI	23.6 (3.13, 15.3–30.0)	23.5 (3.38, 17.0–33.0)
Duration of infertility (years)[c]	3.1 (2.4, 0.3–14.0)	4.0 (2.1, 1.0–13.0)
Previous pregnancies	40.1%	31.7%
Prior IVF cycle[c]	9.2%	37.9%
Prior IUI cycle[c]	52.6%	11.0%
Male factor infertility[c]	50.0%	98.6%
Tubal factor infertility	21.1%	24.1%
Baseline FSH	6.4 (1.5, 0.7–10.0)	6.0 (2.2, 1.1–19.3)
Baseline estradiol (pg/mL)[c]	41.2 (18.3, 1.0–126)	65.4 (57.2, 11–325)
Prolactin (ng/mL)[c]	12.6 (7.1, 1–43)	15.3 (22.6, 1–226)
Endometrial thickness at baseline (mm)[c]	7.4 (1.1, 1.3–8.7)	4.1 (1.3, 1.0–9.3)

Notes: When means are expressed, standard deviation and range are listed in parentheses. BMI = body mass index.

[a] Reasons for cancellation in the US study prior to hCG included risk of OHSS (n = 1), uterine polyp (n = 1), poor ovarian response (n = 8). Reasons for cancellation in the European study prior to hCG included risk of OHSS (n = 1) and poor ovarian response (n = 2).

[b] Reasons for cancellation in the US study after oocyte retrieval included no oocytes retrieved (n=1), risk of OHSS (n = 1), no fertilization (n = 3), and no progression of embryo (n = 1). Reasons for cancellation in the European study after oocyte retrieval included risk of OHSS (n = 3), no fertilization (n = 3) and no progression of embryo (n = 1).

[c] Denotes statistically significant difference between studies ($P < .05$).

Reference: Comparison of 2 IVF trials (US, Europe). Ferring Data 2010.

TABLE 3

Treatment variables in the US and European trials.

	US	Europe
Days of FSH treatment*	9.4 (1.5, 3–13)	10.7 (1.6, 8–18)
Total FSH dose (IU)*	2,675 (871, 900–5,550)	2,459 (723, 1,275–5,650)
Daily FSH dose (IU)*	282 (84, 142–421)	224 (47, 113–419)
Total number follicles*	21.2 (10.4, 4–57)	13.5 (4.7, 5–30)
Number follicles ≥15 mm	10.3 (5.0, 0–34)	11.0 (4.5, 0–30)
Cancellation prior to hCG*	7.2%	2.1%
Intramuscular hCG (not SQ)*	50.4%	73.9%
Total oocytes retrieved*	16.7 (9.3, 0–54)	11.6 (5.2, 0–32)
2 PN on day 1**	10.5 (5.5, 0–29)	8.2 (3.2, 1–17)
Total embryos including fertilization noted on day 2**	10.3 (5.2, 1–26)	7.2 (3.3, 1–19)
Fertilization rate (2 PN oocytes exposed to sperm)	66.6%	70.1%
Embryos transferred**	2.3 (0.6, 0–5)	2.6 (1.0, 0–4)
Embryos frozen**	3.5 (3.9, 0–21)	2.1 (3.1, 0–17)
Day of embryo transfer*	3.5 (0.9, 2–6)	2.7 (0.7, 2–6)

Notes: Data are expressed as mean with standard deviation and range in parentheses. All other *P* values are >.05.

* $P < .001$.

† $P = .014$.

‡ $P = .003$.

§ $P = .006$.

¶ Values are based on patients with at least one embryo (n = 538 US; n = 519 Europe).

Ideal Comparison of 2 IVF trials: US, Europe; Nov/Dec 2011

TABLE 4

Pregnancy outcomes in the US and European trials.

Variable	US	Europe	*P* value
Gestational sac	46.7%	30.3%	.004
Fetal heartbeat	43.4%	29.7%	.016
Live birth	38.2%	27.6%	.064
Multiple birth	37.9%	22.5%	.126
Implantation rate	35.4%	16.5%	< .001
Successful implantation rate	25.9%	14.0%	.001

Notes: The denominator for the clinical pregnancy and live birth rates is all treated patients (n = 162 for US, n = 145 for Europe). Multiple birth rates were calculated by dividing the number of patients with a multiple live birth by the total number of patients with a live birth (n = 58 for US, n = 40 for Europe). Implantation rate was calculated by dividing the number of gestational sacs by the number of embryos transferred. Successful implantation rate was calculated as the number of babies born divided by the total number of embryos transferred (n = 309 for US, n = 367 for Europe).

Boker Comparison of 2 IVF trials (US, Europe). Fertil Steril 2010.

Results of logistic regression analysis

- The best predictors of clinical pregnancy
  - Lower number of days on FSH
  - Lower EM thickness at baseline
  - Higher total follicle count

Results of forward regression/backward regression

- The significant predictors of pregnancy
  - Shorter FSH dosing duration
  - Thinner endometrium at baseline
- The max rescaled R^2 of this model : 0.95

  → most of the variance was not explained by the variables included in the regression analysis .

Discussion

- Clinical pregnancy rate in pts undergoing IVF
  →US (43.3%) **>** Europe (29.7%)
- Different study design
  → different clinical practice
  → might explain differences in clinical pregnancy rate

Logistic regression analysis

- 2 predictors of outcome :
    1. EM thickness at the end of down-regulation ;
    2. duration of FSH exposure
- Low R^2 : other predictor variables that were not captured in this analysis are important .

  →e.g. Index of embryo quality

Percentage of embryo transfer at blastocyst

- US → 26 %
- Europe → 2.2%
- Likely a reflection of preference or better cohort of embryos available in the US.

Ovarian stimulation protocols

- US → higher starting dose of FSH (300IU) , often decreased as needed → slight higher total dose .
- Europe → lower starting dose of FSH (225IU) , often increased.
- Higher starting dose→ not address very different issue of much higher doses (Pal et al., 2008)
- A step-up approach in Europe was less successful at recruiting oocytes .

Ovarian stimulation protocols

- Larger no. of oocytes → greater no. of embryo transfer
  → clinical pregnancy rate and liver birth rate ↑

  (Jun, 2008; CDC, 2008)

  → But this study did not . (less no. of ET , higher pregnancy rate))

- The earlier dose change in US study
  → more individualized care

- EM thickness was greater in Europe → may explain the difference.
- Age and no. of ET→ could not explain the difference .
  - Higher no. of ET in US contributes only slightly to the overall higher pregnancy rate . (Gleicher,2006)
- Higher implantation rate in US → may be the difference of laboratory condition

- Luteal phase support (Progesterone)
  - US : IM ; Europe : VT
  - Possible to explain some of the differences in pregnancy rate
- Prior IVF cycles
  - Greater % in Europe
  - But unlikely to explain the difference because
    - Slightly decreased in IVF success rate for the first 3~4 cycles (Malizia, 2009)
    - Exclusion criteria in our study : > 2 cycles

- ICSI rate
  - US : 70.4% ; Europe : 100%
  - Male factor infertility : US→ 50% ; Europe→96.6%
  - ICSI is not thought to lead to a lower pregnancy rate than conventional IVF if male factor is present . (CDC,2008)

- The study of Europe conducted in France and Hungary only → results may be different in other European countries . (Andersen, 2008)
- Some countries in Europe face legislative mandates that limits no. of ET and no. of oocytes for insemination.
  → reduce the efficiency of fresh IVF cycles
- But in this study →no limits of no. of oocytes that could be expose to sperm or the no. of ET.

Limitation of this study

- Retrospective , small sample size
- The two clinical trails were prospective → but the purpose was to compare HP-hFHS and rFSH, not the differences in IVF pregnancy rates .
- No follow-up information about outcome from cryopreserved cycle.
- This report can not offer definitive explanations for the difference in US and Europe .

Conclusion

- The causes behind the differences between Europe and the US are not well-understood.
- This study suggests US pregnancy rates may be higher in part because of differences in down-regulation and gonadotropin dosing .
- Other factors not assessed likely also contribute to the difference in pregnancy rates.
- Further studies attempting to elucidate reasons for differences in success between the US and Europe .

Thank you !!!