# Debate: Natural vs. Stimulated Cycles

Stimulated Cycles

Norbert Gleicher, MD
Medical Director And Chief Scientist, Center For Human Reproduction, New York, NY
President, Foundation For Reproductive Medicine, New York, NY
Professor (Adj), Rockefeller University, New York, NY
Professor (Adj), Department Of Obstetrics & Gynecology, Vienna University School Of Medicine, Vienna, Austria

Ovarian Club 2016, Paris, France, November 4-6

# Conflict Statement

Dr. Gleicher is listed as co-inventor on a number of pending patent applications claiming diagnostic and therapeutic benefits from determination of CGG repeat numbers and ovarian *FMR1* genotypes and sub-genotypes.

Dr. Gleicher is co-inventor of awarded U.S. patents, claiming therapeutic benefits for supplementation of DHEA in women with diminished ovarian reserve, a topic discussed in this talk. Other patent applications in regards to DHEA and other fertility-related claims, with no relationship to this talk, are pending. Dr. Gleicher receives royalties from, and owns shares in Fertility Neutraceuticals, LLC, a distributor of a DHEA product.

Dr. Gleicher is co-inventor of three pending patent applications claiming potential therapeutic benefit for anti-Müllerian hormone (AMH) in infertile women. Dr. Gleicher owns shares in OvaNova Laboratories, LLC.

# Outline

- Rationale for both options
- Outcomes with both options
- Consequences of both options
- Conclusions

# Outline

- **Rationales for both options**
- Outcomes with both options
- Consequences of both options
- Conclusions

# Rationales

- IVF started with natural cycle

- Went to Clomid

- Went to gonadotropins

# Rationales

- Gonadotropins

- Went to Clomid

- Went to natural cycles

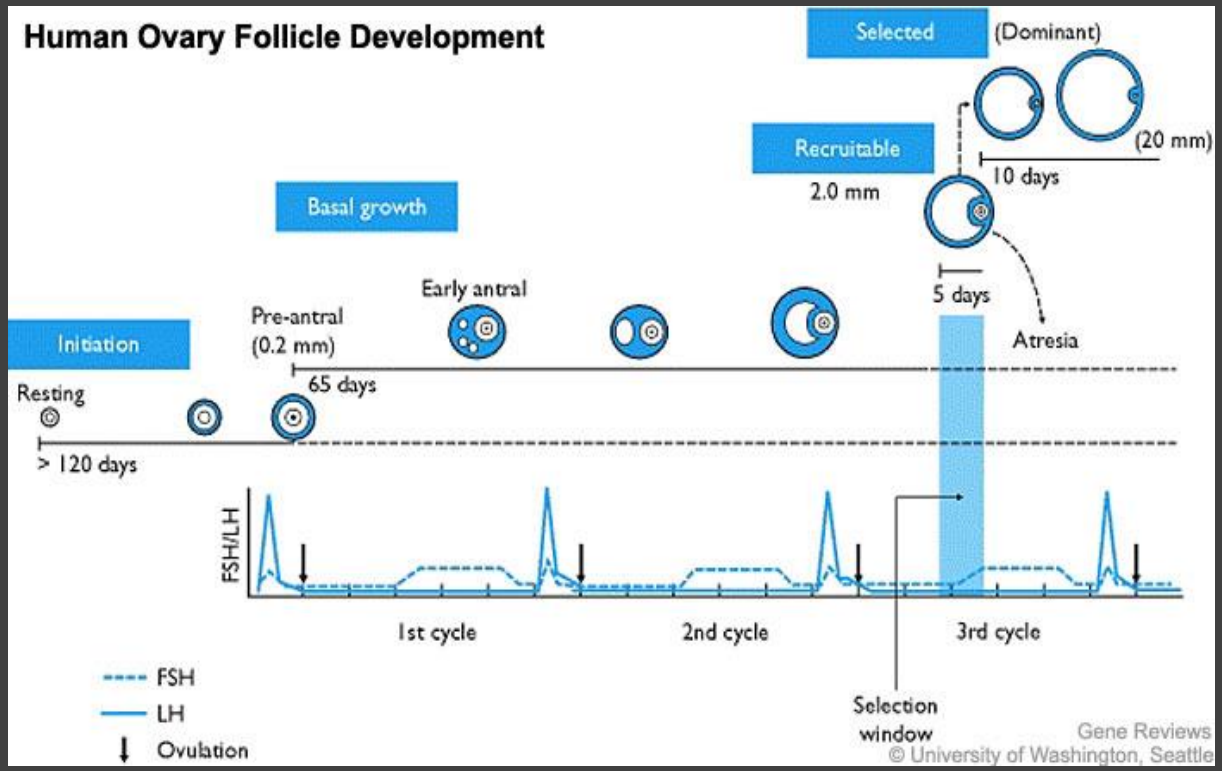
# Under the arguments

- More “patient-friendly”
- Less “invasive”
- More “natural”
- Less “costly”
- Better embryos
- Less multiples
- Less OHSS

Just not under the argument of better cycle outcomes!

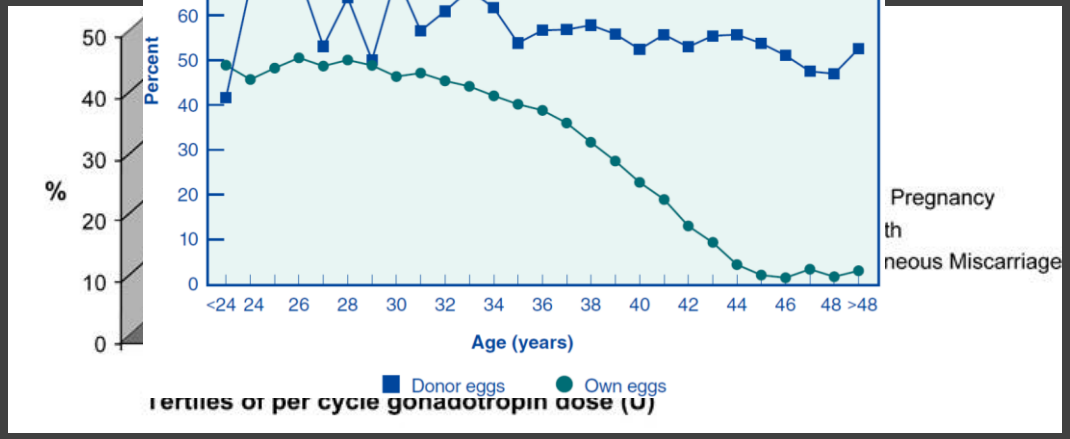
# Nature will select the best oocyte

- Hundreds of follicles initiate maturation in each cycle
- Only a few ever reach the late antral stage for recruitment
- Ovulation induction techniques are already acting on a highly selected group of follicles



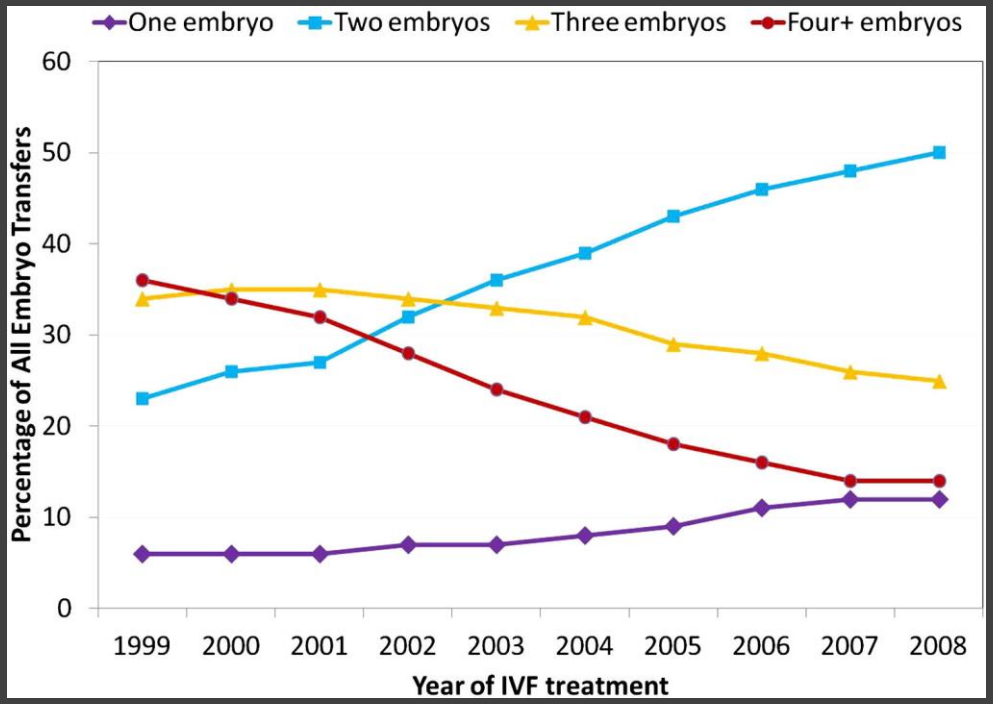
# Effects of gonadotropins

- Observational studies of this effect are confounded by the fact that women with worse ovarian reserve receive higher doses of gonadotropins
- In any IVF center the highest pregnancy rates are among donor recipient cycles
  - This confounding is not entirely controlled by adjusting for age since young women may also have poor ovarian reserve
  - No IVF Center recommends that donors undergo natural or minimal stimulation cycles
- Mini IVF has less OHSS a
- Does a risk of lower Clin decreased risk?

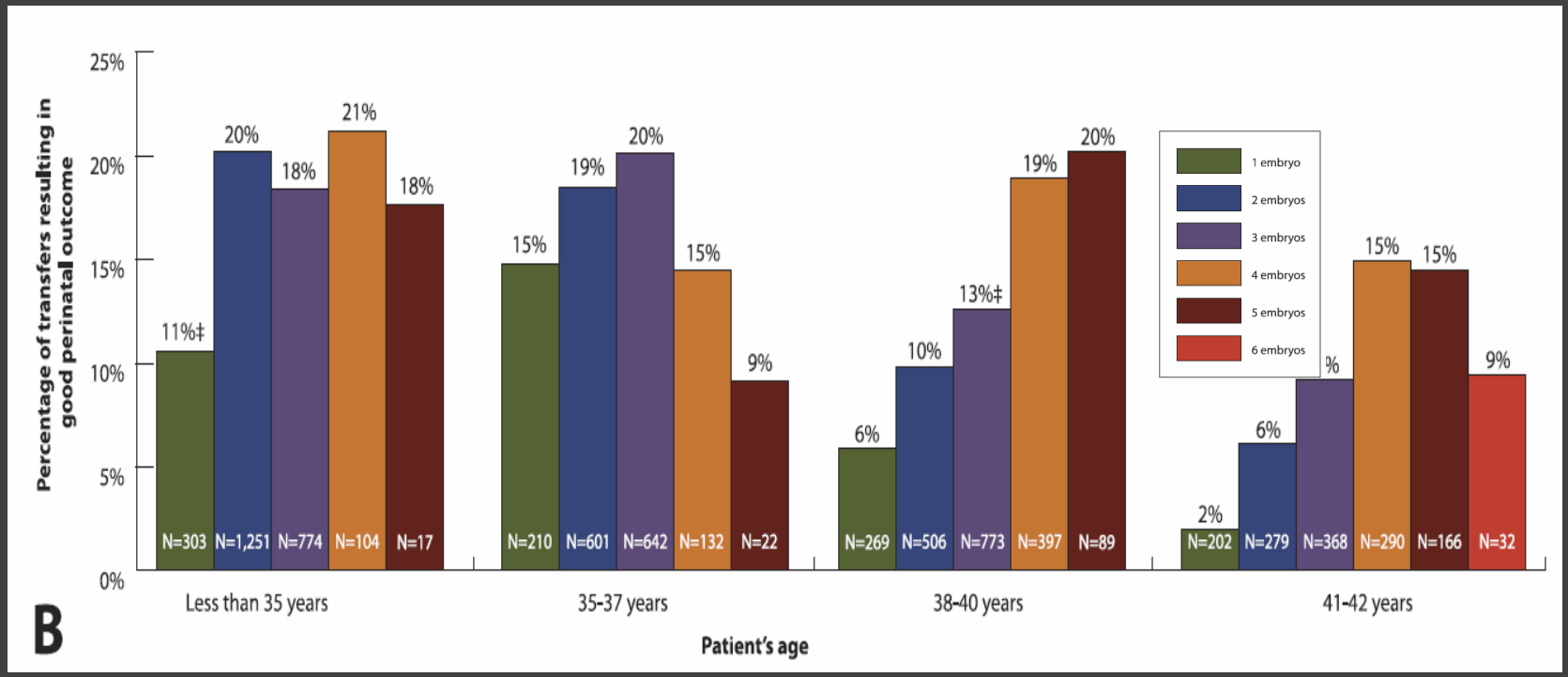



L. Pal et al. Fertil Steril. 2008 Jun; 89(6): 1694–1701.

# Embryo transfer in the United States




*Fertility and Sterility, Volume 97, Issue 4, 2012, 835 - 842*




*Kissin. Number of Embryos Transferred and Perinatal Outcome. Obstet Gynecol 2014.*

# Patients with a less favorable prognosis – Cleavage Stage

# Outline

- Rationales for both options
- **Outcomes with both options**
- Consequences of both options
- Conclusions

Reprod Biomed Online. 2010 Oct;21(4):485-95. doi: 10.1016/j.rbmo.2010.06.033. Epub 2010 Jun 30.

# Minimal ovarian stimulation (mini-IVF) for IVF utilizing vitrification and cryopreserved embryo transfer.

Zhang J[1], Chang L, Sone Y, Silber S.

Author information

**Erratum in**
Reprod Biomed Online. 2011 Sep;23(3):396.

**Abstract**

Gentle ovarian stimulation protocols, such as 'mini-IVF', have several potential advantages over conventional IVF protocols, including less medication and fewer injections, producing fewer eggs, but eggs of higher quality. The particular 'mild' stimulation protocol called 'mini-IVF' is described. This protocol requires a reliable and cheap method for embryo cryopreservation such as vitrification, because of the negative impact of clomiphene citrate on the endometrium and since cryopreserved embryo transfers with this protocol have yielded much higher pregnancy rates than fresh transfers. In this series, patients were not denied treatment based on their day-3 FSH value or ovarian reserve. Yet very acceptable pregnancy rates were achieved (20% for fresh embryo transfers and 41% for cryopreserved embryo transfers). These results strengthen the argument for a mini-IVF protocol and vitrification as an alternative to standard conventional IVF stimulation protocols. Now a randomized control trial with cryopreserved single-embryo transfer is required.

Reproductive BioMedicine Online (2011) **23**, 274–278

www.sciencedirect.com
www.rbmonline.com


COMMENTARY

# Low-intensity IVF: real progress?

**Norbert Gleicher [a,b,*], Andrea Weghofer [a,c], David H Barad [a,d]**

[a] *Center for Human Reproduction, New York and Foundation for Reproductive Medicine, New York, NY, USA;* [b] *Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA;* [c] *Department of Obstetrics and Gynecology, Vienna University School of Medicine, Vienna, Austria;* [d] *The Center for Human Reproduction, Department of Epidemiology and Population Health, New York, NY, USA*
[*] Corresponding author. *E-mail address:* ngleicher@thechr.com (N Gleicher).

**Abstract** A recent publication in this journal strongly advocated low-intensity IVF (LI-IVF) after presenting the authors' experience with minimal ovarian stimulation (mini-IVF). The data presented failed to support their conclusions. Therefore, presented here is a critique of their manuscript and of uncontrolled clinical use of LI-IVF, in general. In the absence of properly controlled studies, all forms of LI-IVF should be considered experimental and be offered only in well-controlled research settings and with appropriate informed consent.

# Our recalculations concluded that per intent to treat (i.e., cycle start) clinical pregnancy rates were:

- 4.6% (normal FSH)
- 3.1% (high FSH)
- 10.4 - 15.6% with FET
- 15.1 – 18.7% cumulative

Every halfway decent IVF program achieves higher pregnancy rates in a single fresh IVF cycle

GYNECOLOGY

# Minimal stimulation IVF vs conventional IVF: a randomized controlled trial

John J. Zhang, MD, PhD; Zaher Merhi, MD; Mingxue Yang, MD, PhD; Daniel Bodri, MD, PhD; Alejandro Chavez-Badiola, MD; Sjoerd Repping, PhD; Madelon van Wely, PhD

**BACKGROUND:** Minimal stimulation in vitro fertilization (mini—in vitro fertilization) is an alternative in vitro fertilization treatment protocol that may reduce ovarian hyperstimulation syndrome, multiple pregnancy rates, and cost while retaining high live birth rates.

**OBJECTIVE:** We performed a randomized noninferiority controlled trial with a prespecified border of 10% that compared 1 cycle of mini—in vitro fertilization with single embryo transfer with 1 cycle of conventional in vitro fertilization with double embryo transfer.

**STUDY DESIGN:** Five hundred sixty-four infertile women (<39 years old) who were undergoing their first in vitro fertilization cycle were allocated randomly to either mini—in vitro fertilization or conventional in vitro fertilization. The primary outcome was cumulative live birth rate per woman over a 6-month period. Secondary outcomes included ovarian hyperstimulation syndrome, multiple pregnancy rates, and gonadotropin use. The primary outcome was cumulative live birth per randomized woman within a time horizon of 6 months.

**RESULTS:** Five hundred sixty-four couples were assigned randomly between February 2009 and August 2013 with 285 couples allocated to mini—in vitro fertilization and 279 couples allocated to conventional in vitro fertilization. The cumulative live birth rate was 49% (140/285) for mini—in vitro fertilization and 63% (176/279) for conventional in vitro fertilization (relative risk, 0.76; 95% confidence interval, 0.64-0.89). There were no cases of ovarian hyperstimulation syndrome after mini—in vitro fertilization compared with 16 moderate/severe ovarian hyperstimulation syndrome cases (5.7%) after conventional in vitro fertilization. The multiple pregnancy rates were 6.4% in mini—in vitro fertilization compared with 32% in conventional in vitro fertilization (relative risk, 0.25; 95% confidence interval, 0.14-0.46). Gonadotropin consumption was significantly lower with mini—in vitro fertilization compared with conventional in vitro fertilization (459 ± 131 vs 2079 ± 389 IU; $P < .0001$).

**CONCLUSION:** Compared with conventional in vitro fertilization with double embryo transfer, mini—in vitro fertilization with single embryo transfer lowers live birth rates, completely eliminates ovarian hyperstimulation syndrome, reduces multiple pregnancy rates, and reduces gonadotropin consumption.

**Key words:** IVF, mini-IVF, clomiphene citrate, OHSS, multiple pregnancy

**TABLE 4**

**Outcome of fresh and frozen-thawed embryo transfers in both arms**

| In vitro fertilization | Fresh embryo transfer | Frozen embryo transfer | | | | |
|---|---|---|---|---|---|---|
| | | First | Second | Third | Fourth | Fifth |
| Mini | | | | | | |
| Total embryo transfers, n | — | 228 | 80 | 26 | 6 | — |
| Transferred embryos per cycle, n[a] | — | 1 ± 0 | 1 ± 0 | 1 ± 0 | 1 ± 0 | — |
| Clinical pregnancy, n (%) | — | 106 (47)* | 38 (48) | 14 (54) | 3 (50) | — |
| Implantation rate, n/N (%) | — | 106/228 (47)* | 38/80 (48) | 14/26 (54) | 3/6 (50) | — |
| Live birth, n (%) | — | 90 (39)[b] | 33 (41)[c] | 14 (54)[d] | 3 (50)[e] | — |
| Multiple pregnancy, n (%) | — | 9 (9.3) | 0 | 0 | 0 | — |
| Conventional | | | | | | |
| Total embryo transfers, n | 120 | 111 | 67 | 25 | 9 | 2 |
| Transferred embryos per cycle, n[a] | 1.7 ± 0.5 | 1.7 ± 0.5 | 1.6 ± 0.5 | 1.5 ± 0.5 | 1.5 ± 0.5 | 1.6 ± 0.5 |
| Double embryo transfer/total embryo transfers, n/N (%) | 87/120 (72) | 84/111 (75) | 37/67 (55) | 8/25 (32) | 4/9 (44) | 1/2 |
| Clinical pregnancy, n (%) | 89 (74) | 76 (68)** | 33 (49) | 10 (40) | 3 (33) | 0 |
| Implantation rate, n/N (%) | 117/207 (56) | 113/195 (58)** | 42/104 (40) | 10/33 (30) | 5/13 (38) | 0 |
| Live birth, n (%) | 74 (62)[f] | 67 (60)[g] | 24 (36)[h] | 8 (32)[i] | 3 (33)[j] | 0 |
| Multiple pregnancy, n (%) | 27 (34) | 31 (45) | 6 (22) | 0 | 2 (66) | 0 |

[a]Data are given as mean ± SD; Chi-square test: b vs f, $P = .0001$, relative risk, 0.73 (95% CI, 0.62–0.86); b vs g, $P = .0003$, relative risk, 0.76 (95% CI, 0.65–0.88); c vs h, $P = .61$, relative risk, 1.11 (95% CI, 0.82–1.49); d vs i, $P = .16$, relative risk, 1.54 (95% CI, 0.89–2.63); e vs j, $P = .62$, relative risk, 1.50 (95% CI, 0.44–5.09); * vs **, $P < .05$.

*Zhang et al. Mini-IVF vs conventional IVF. Am J Obstet Gynecol 2016.*

# Systematic Review of Worldwide Trends in Assisted Reproductive Technology 2004-2013

*Vitaly A. Kushnir, David H. Barad, David F. Albertini, Sarah K. Darmon, Norbert Gleicher*

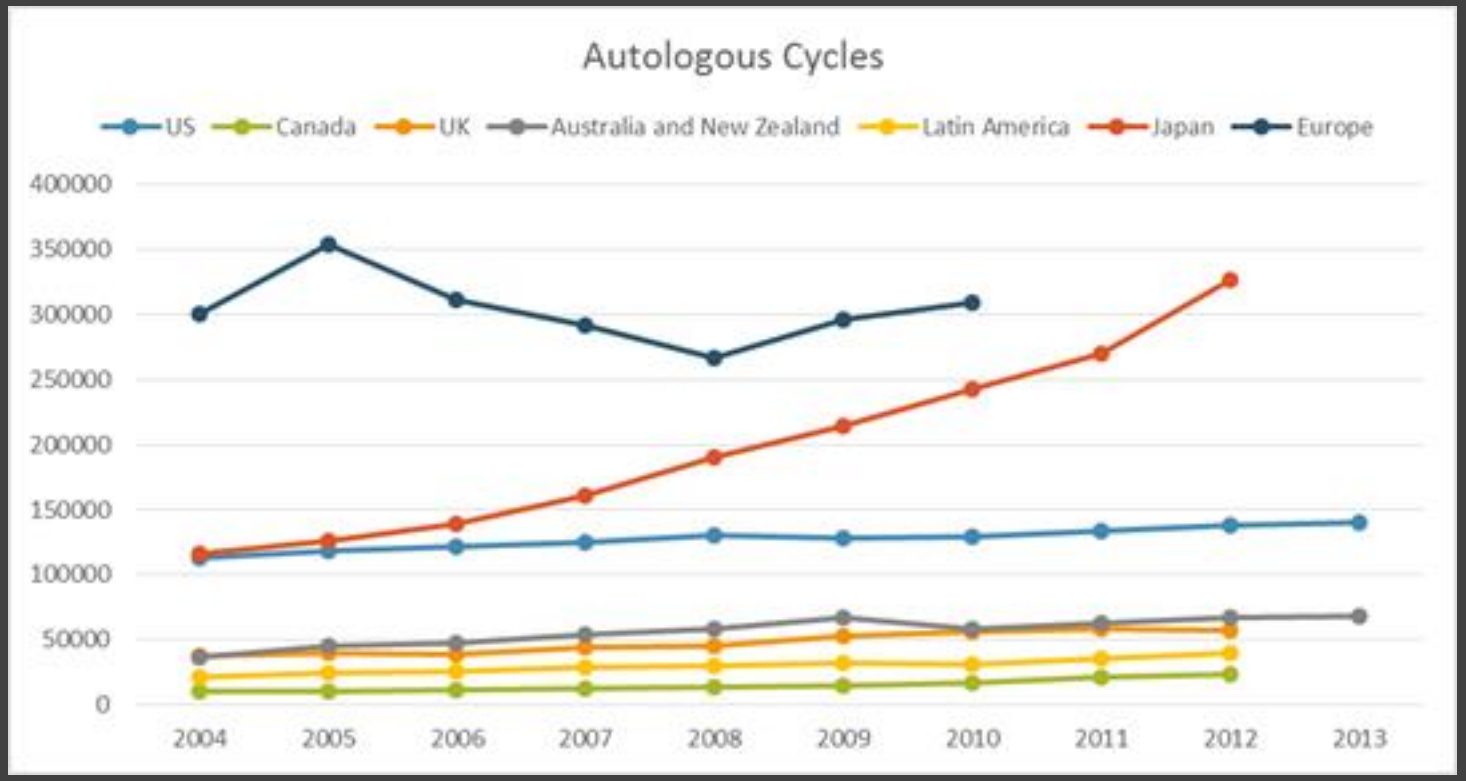
The Center for Human Reproduction, New York, NY, USA (all authors); Foundation for Reproductive Medicine, New York, NY, USA (D.H. Barad, MD, MS and N. Gleicher, MD); Albert Einstein College of Medicine, New York, NY, USA (D. H. Barad, MD, MS) Wake Forest School of Medicine, Winston-Salem, NC, USA (V.A. Kushnir, MD); University of Kansas Medical Center, Kansas City, KS, USA (D.F. Albertini, PhD); The Rockefeller University, New York, NY, USA (N. Gleicher, MD)

**Table 1.** Total number of ART cycles and live births by region for study period 2004-2013

| | Fresh Embryo Cycles | Frozen Embryo Cycles | Live Births |
|---|---|---|---|
| US | 995,410 | 281,237 | 376,067 |
| Canada* | 96,489 | 37,044 | 32,273 |
| UK** | 289,347 | 62,736 | 85,469 |
| Australia and New Zealand | 357,494 | 20,7678 | 101,012 |
| Latin America* | 228,822 | 40,135 | 55,656 |
| Japan* | 1,199,715 | 585,670 | 224,170 |
| Europe*** | 1,709,207 | 498,597 | 460,968 |
| **Total** | 4,876,484 | 1,713,097 | 1,335,615 |
| | 6,589,581 | | |

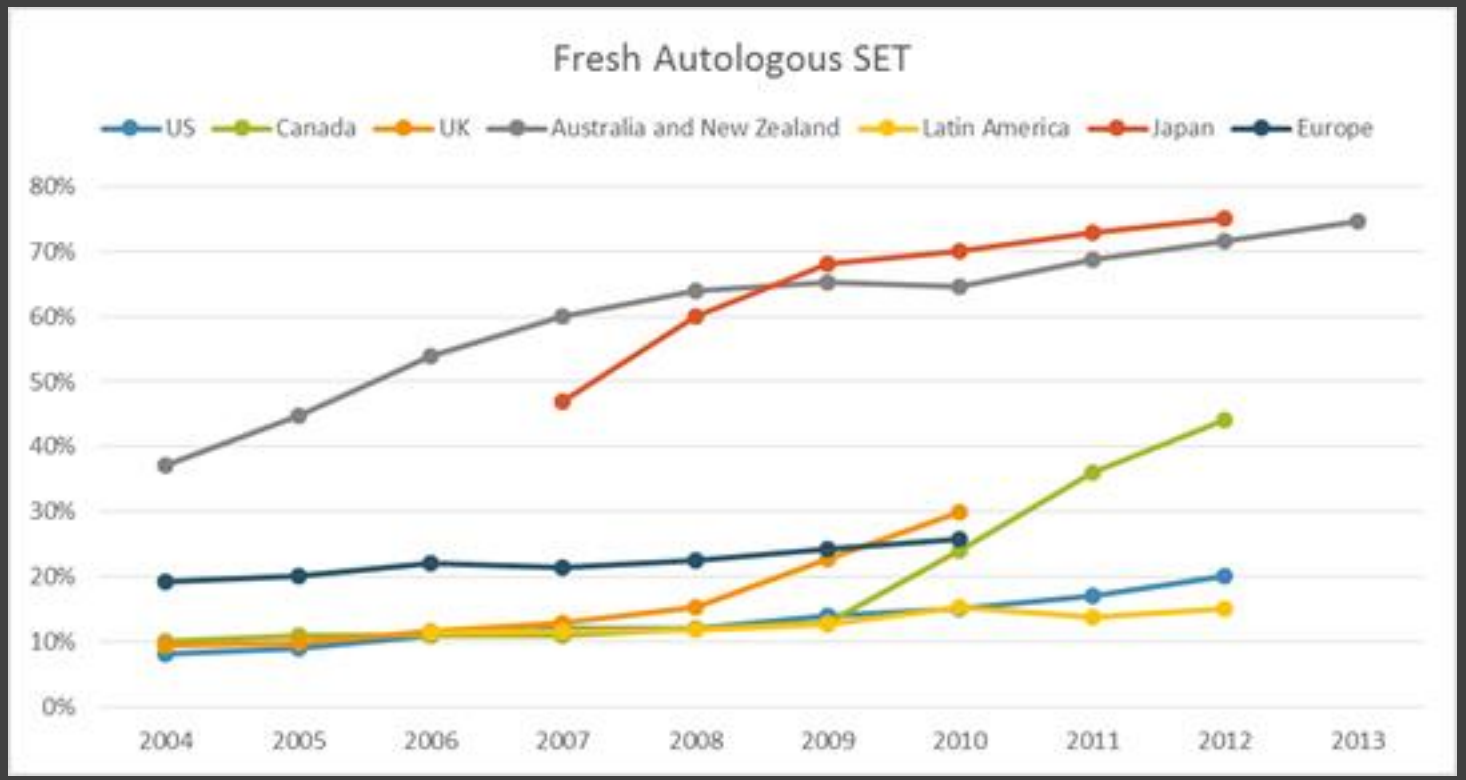
Partial data available only for years *2004-2012, ** 2006-2012, ***2004-2010

# Volume of Fresh, Autologous Ooocyte ART Cycles 2004-2013



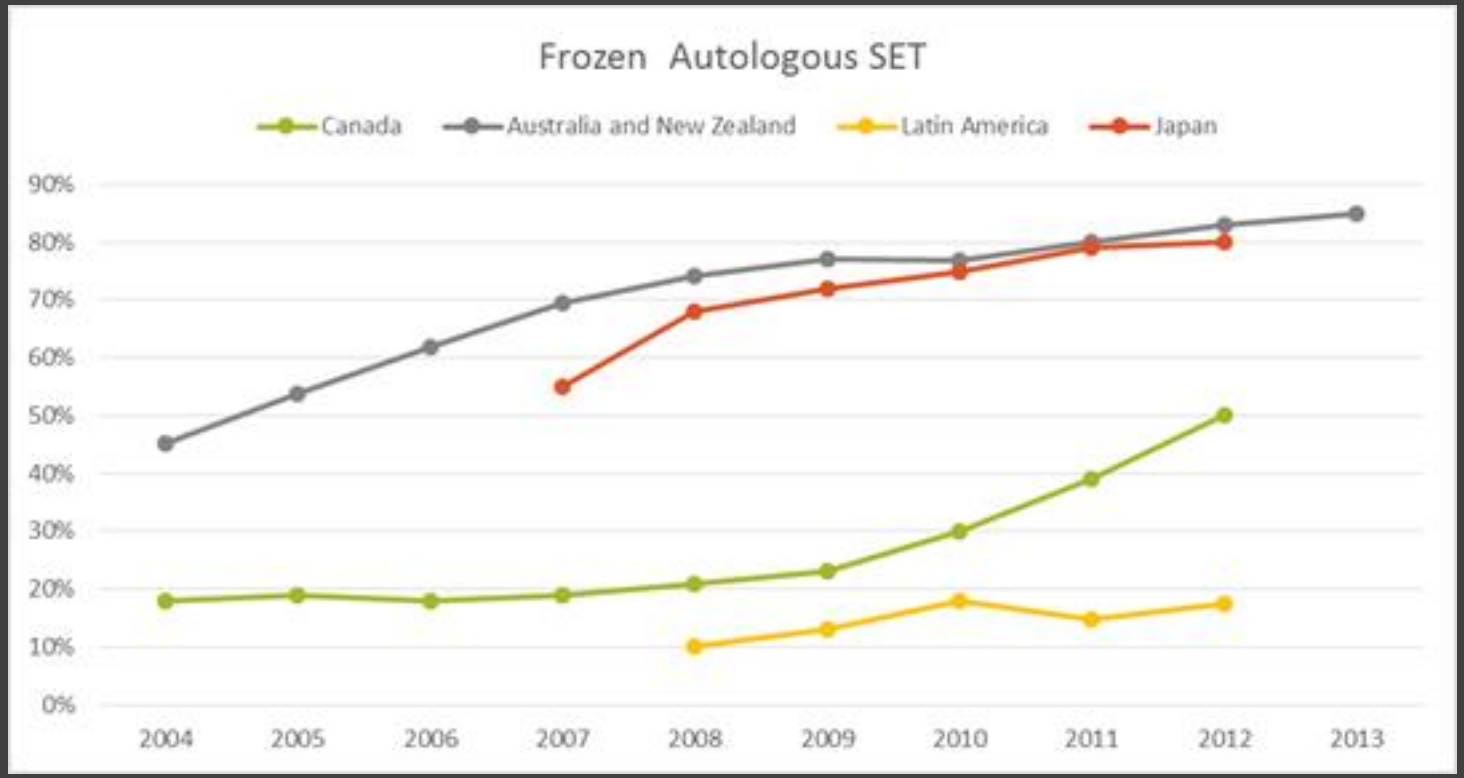

The figure demonstrates in most regions flat to mildly increasing ART cycle numbers, except for Japan, which demonstrates a significant increase in numbers.

# Utilization of SET in Fresh Autologous Oocyte ART Cycles



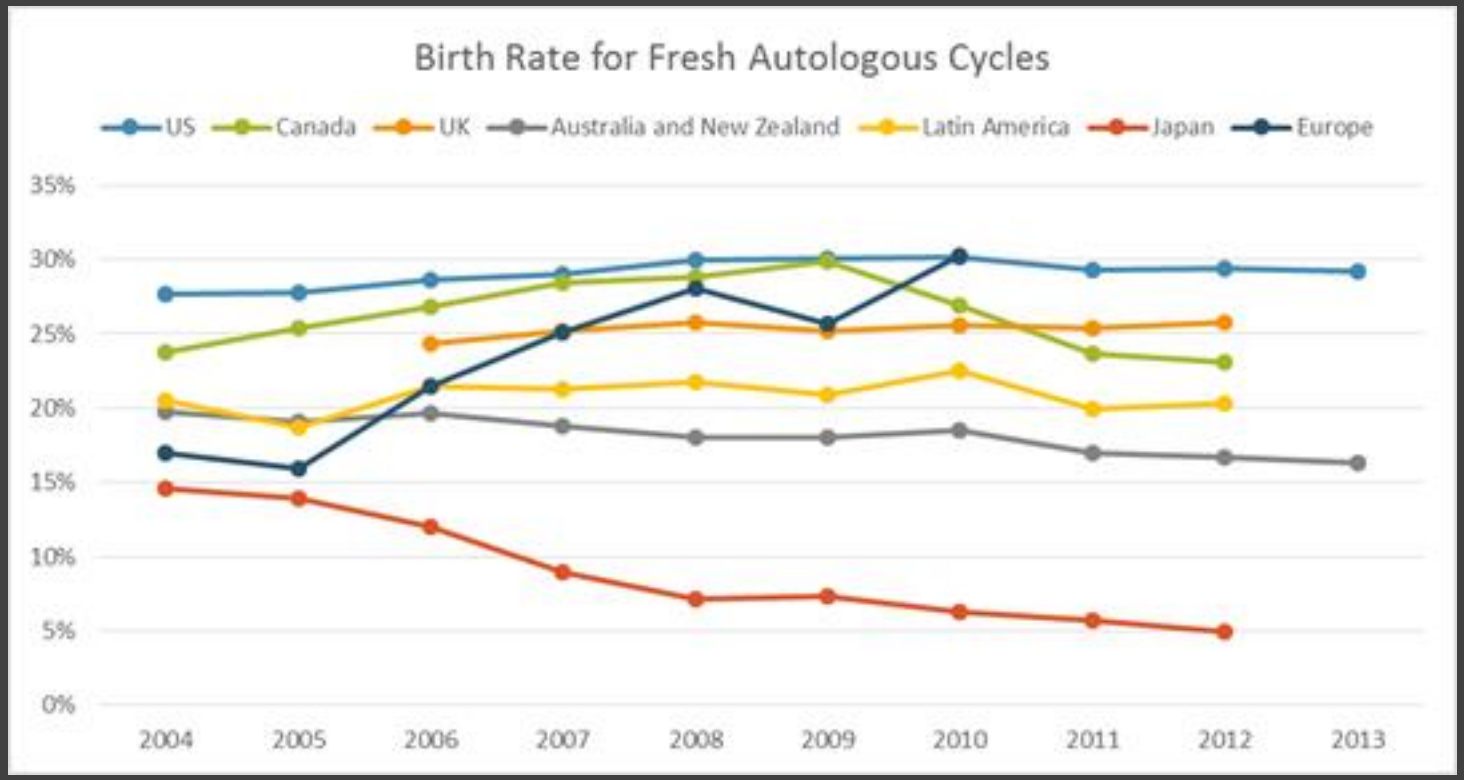

The figure demonstrates a uniform increase in utilization of SET.

# SET Utilization in Frozen-Thawed Autologous Oocyte ART Cycles




The figure demonstrates a uniform increase in utilization of SET.

# Live birth rates in fresh autologous oocyte ART cycles




The figure demonstrates stable or slightly increasing live birth rates in most regions. Increasing live birth rates are noted in continental Europe while most pronounced decreases are noted in Japan and in Canada after 2009.

# Does this make sense??

# CHR Staff

(* Visiting Scientists)

**David F Albertini**, PhD
**David H Barad**, MS, MD
**Ali Brivanlou**, PhD, MD*
**Sarah Darmon**, PhD, MS
**Norbert Gleicher**, MD
**Vitaly A Kushnir**, MD
**Emanuela Lazzaroni-Tealdi**, MS
**Nicolas Santiquet**, PhD
**Kenneth Seier**, MS*
**Aya Shohat-Tal**, PhD*
**Andrea Vidali**, MD*
**Qi (Vicky) Wang**, PhD
**Andrea Weghofer**, PhD, MS, MBA, MD*
**Yan-Guang Wu**, PhD*
**Yao Yu**, PhD*


# Affiliates

*University of Rochester School of Medicine and Dentistry*:
**Aritro Sen**, PhD

*Rockefeller University:*
**Ali Brivanlou**, PhD, MD
**Gist Croft**, PhD

*Salk Institute for Biological Studies:*
**Pradeep Reddy**, PhD