# The future of IVF: Can we do better?

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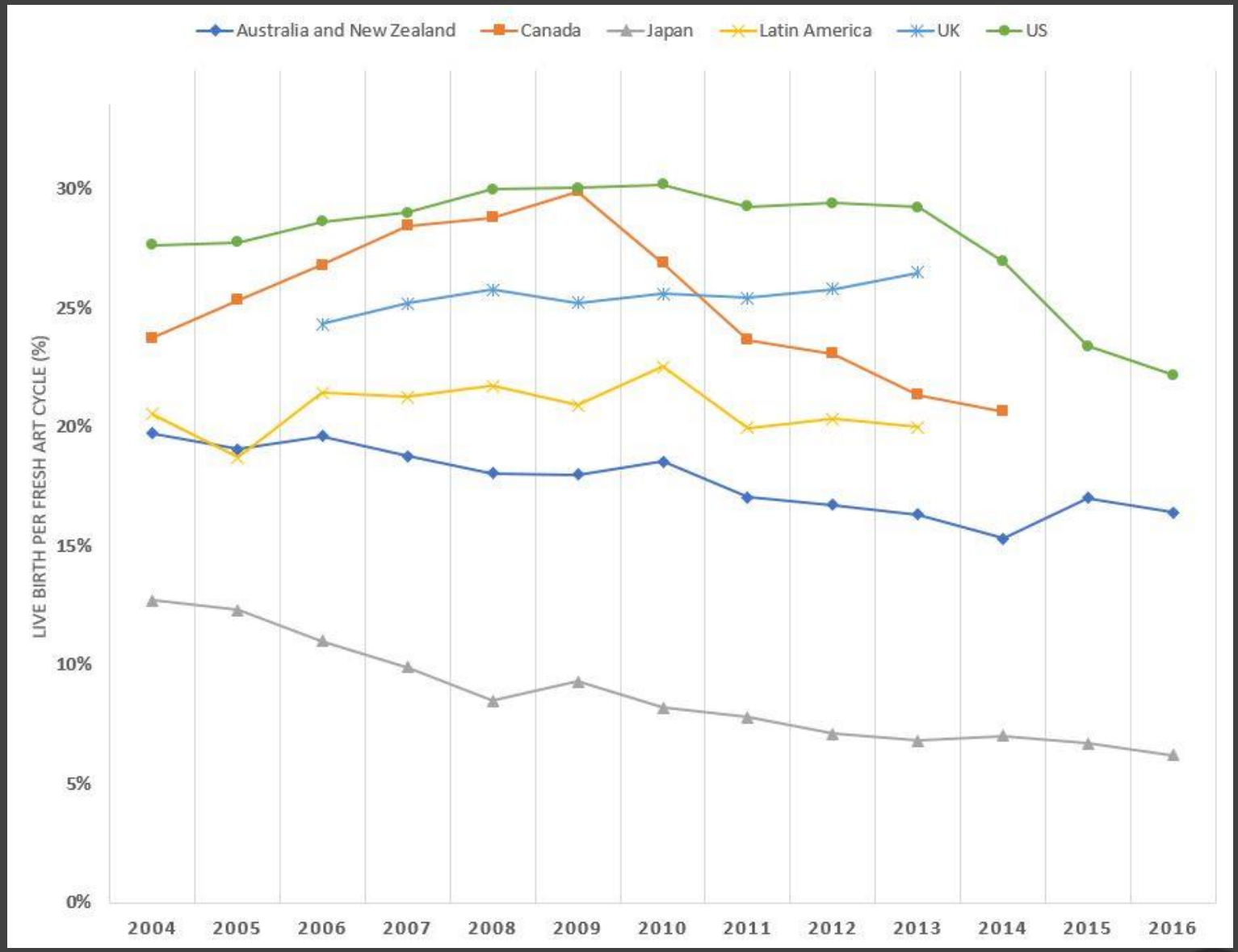
# Conflict Statement

- 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.

- It is no longer a question of whether we can do better
- We know we can do better because we used to do better
- **WE NOW MUST DO BETTER!**

# Autologous non-donor live birth rates, 2004-2016




*Gleicher et al, in press.*

- Why these declines?
- Irresponsible add-ons!

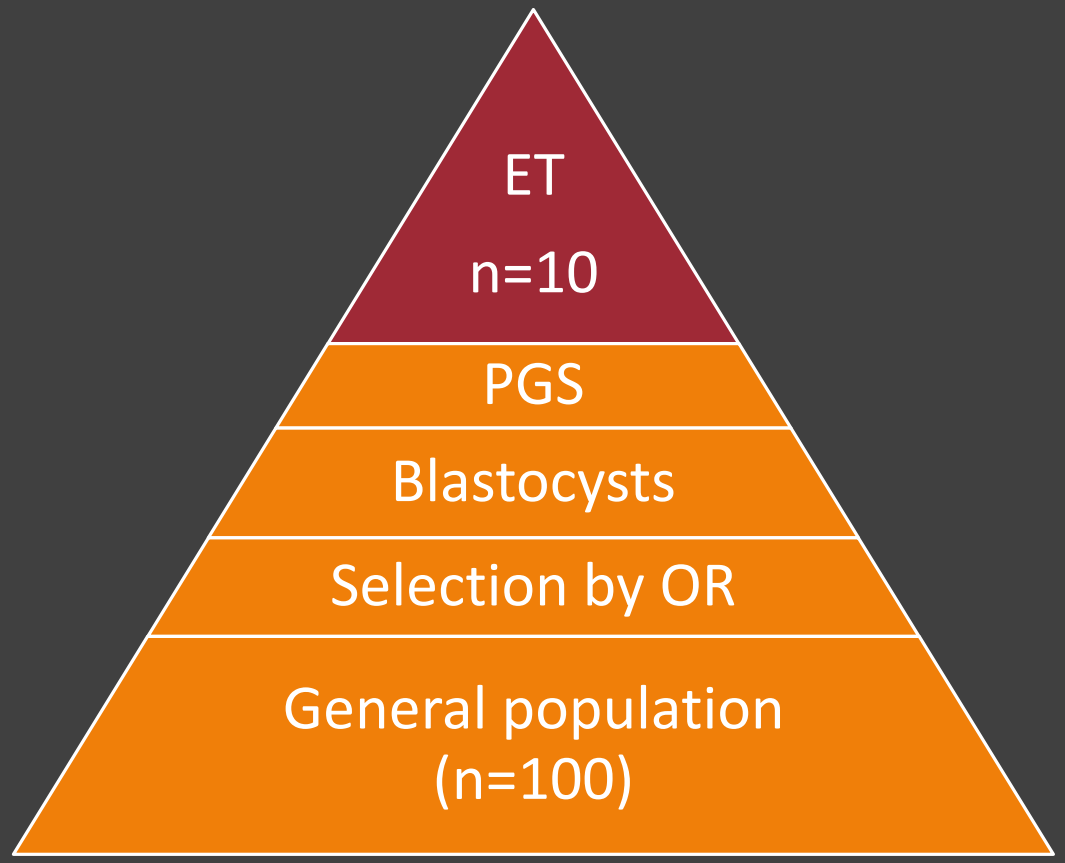
- Irresponsible add-ons are often based on incorrect outcome reporting

- The most important issue is IVF outcome reporting with reference ET and claiming results for an unselected patient population

# This has been the case for:

- Extended embryo culture
- Single embryo transfer
- All-freeze/FET cycles
- PGS/PGT-A
- Etc.

# The errors in IVF outcome assessments with reference embryo transfer




- Assuming 8 live births, the live birth rate will be 80% with reference ET, but only 8% with reference cycle start (“intent to treat”)

# Differences in reporting of live birth rates depending on reference points, 2005-2016

| Study year | 2005 | 2010 | 2015 | 2016 |
|---|---|---|---|---|
| Fresh, non-donor cycles (n) | 27,947 | 30,425 | 21,771 | 19,137 |
| Live birth rates per cycle start (%) | 27.8 | 30.2 | 23.9 | 22.2 |
| Live birth rates per embryo transfer (%) | 34.5 | 36.8 | 36.7 | 36.3 |
| Gain in absolute percentage points | +6.7 | +6.4 | +12.8 | +14.1 |

*Gleicher et al, in press.*

# What can timing tell us?

- The year 2010 was crucial

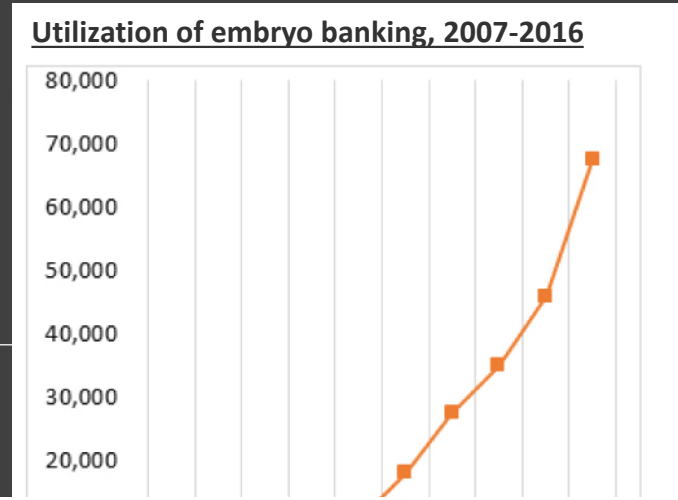
# Longitudinal view of single and multiple fetus clinical pregnancy rates, 2005-2016

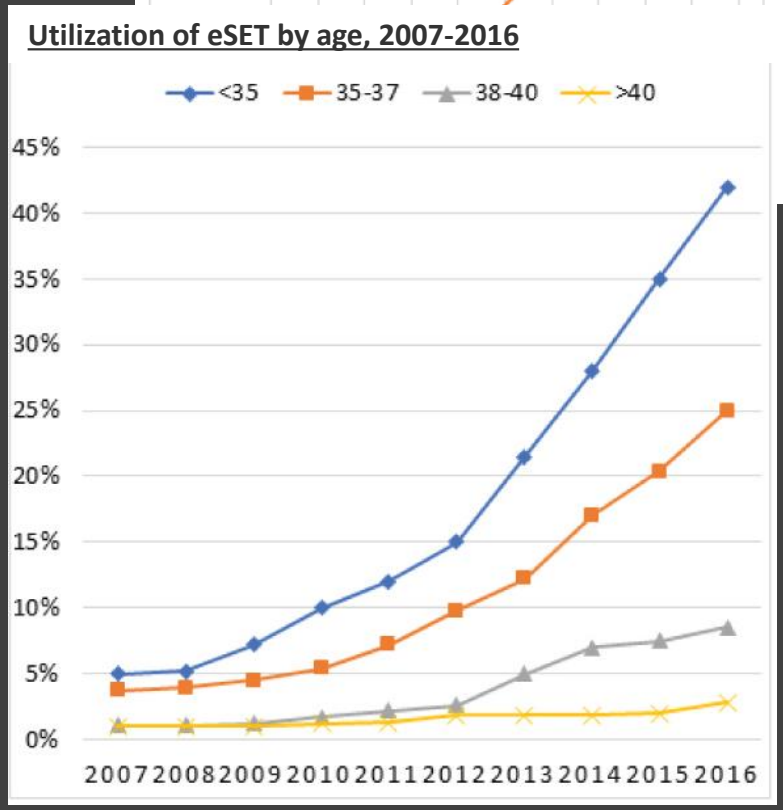
| Study year | 2005 | 2010 | 2015 | 2016 |
|---|---|---|---|---|
| Clinical pregnancies (%) | 34.0 | 36.8 | 29.3 | 25.4 |
| Singleton (%) | 20.5 | 23.1 | 20.4 | 19.8 |
| Multiples (%) | 11.2 | 11.5 | 6.9 | 5.6 |
| No pregnancy (%) | 65.4 | 62.4 | 70.2 | 72.2 |

*Gleicher et al, in press.*

# PGS/PGT-A

- 2007: Paper by Mastenbroeke, et al *N Engl J Med 2007;357:9-17*
- 2008: Practice Committee of the ASRM, *Fertil Steril 2008;90:S136-143*
- 2008/9: Switch from PGS 1.0 to PGS 2.0
  - Increase in extended embryo culture
  - Increase in all-freeze cycles
  - Increase in eSET
- All associated with lower live birth rates




*Gleicher et al, in press.*

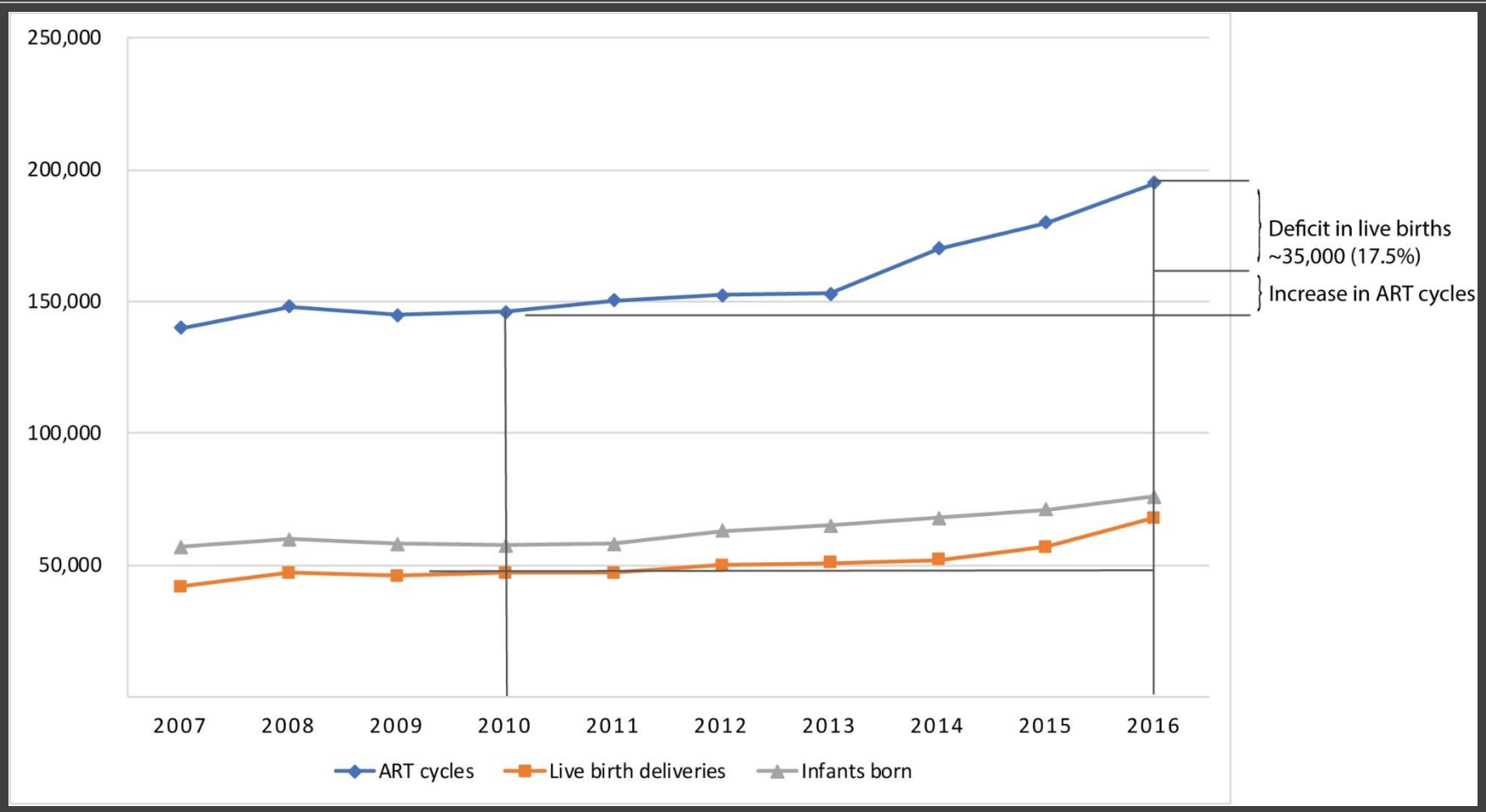
# PGS/PGT-A does NOT:

- Improve pregnancy and live birth rates
- Reduce miscarriage rates
- Reduce time to pregnancy
- Permit differentiation between mosaic embryos with better or poorer pregnancy chances
- Differentiate between chromosomally normal and abnormal embryos
- Allow to determine which embryo to transfer and which to discard

# PGS/PGT-A does:

- Increase costs significantly for an already expensive procedure with low success rates
- Financially significantly benefit IVF centers and especially the genetic testing industry

# Comparison of total ART cycle starts with live births and infants born, 2007-2016




*Gleicher et al, in press.*

# Conclusions

- IVF results are declining at an accelerating pace since peaks were reached in 2010
- This decline is caused by add-ons to IVF, without proper prior validation studies added to routine practice
- Though various add-ons contribute to the decline, PGS/PGT-A, likely, plays an outsized role since PGS 2.0 is also associated with extended embryo culture and (falsely) with eSET

# What can be done?

- Stop PGS/PGT-A utilization as a routine procedure
- Stop extended embryo culture as a routine procedure
- Stop eSET as a routine procedure
- Stop voluntary freezing of embryos
- Stop mild ovarian stimulation in women with low ovarian reserve
- **Bring personalized medicine to IVF: Individualized care**

# Where else can we do better?

- Treating older women
- Improving access to IVF
- Finally understanding that every patient we treat with donor eggs represents a failure of our profession

# Where else will we do better?

- Deferral of menopause
- *In vitro* maturation of primordial follicles
- Production of gametes from peripheral cells
- Cure of genetic diseases in embryos rather than their disposal
- Better understanding of implantation
- Etc.

# But:

- *The future is hidden even from the men who make it*

-Anatole France

- *The trouble with our time is that the future is not what it used to be*

-Paul Valéry

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