A journey into the future of IVF

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Conflict Statements

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.
“The trouble with our times is that the future is not what it used to be”

- Paul Valery
Louise Brown, the world’s first IVF baby, was born just before midnight on 25th July 1978 at Oldham General Hospital in the North of England. Following fertilisation of a natural cycle oocyte, she was delivered by Cesarean section because, according to John Webster who was in the delivery room, ‘it was the only way to show the world that [her mother] had no fallopian tubes’. Both Louise and her sister Natalie, an IVF baby conceived at Bourn Hall, both now have children of their own, all naturally conceived. Progress in IVF after the birth of Louise remained slow: the world’s third IVF baby was not delivered until June 1980, in Melbourne.

*Focus on Reproduction, May 2008*
Robert Edwards, PhD | Cambridge University

2001 Albert Lasker Clinical Medical Research Award

“For the development of in vitro fertilization, a technological advance that has revolutionized the treatment of human infertility.”

But, amazingly, the Nobel Prize in medicine has not been felt warranted for over 3 million IVF births worldwide. In 2013, he died on April 10th.
“What the future has in store for you depends largely on what you place in store for the future”

- Anonymous
US annual live birth rates after autologous IVF cycles 1995-2014

The data for this figure are derived from annual CDC ART Success Rate Reports (www.cdc.gov/art/artdata/), accessed 3/20/17. Live birth rates demonstrate almost steady improvements until 2002, a decline between 2003 and 2007, reaching a similar new peak to the 2002 between 2008 and 2010, only to again decline to below 2004 rates between 2011 and 2014. We in this analysis attempt to associate changes in IVF practice patterns to these variations.
Volume of Fresh Autologous Oocyte 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.
Worldwide autologous IVF cycle live birth rates 2004-2014

The data in this figure are derived from annual reports from Australian & New Zealand Assisted Reproduction Database (ANZARD) (https://npesu.unsw.edu.au/), accessed March 20, 2017), Canada Fertility & Andrology Society Annual Reports (CARTR) (https://cfas.ca/cartr-annual-reports/, accessed March 20, 2017), Japan Society of Obstetrics & Gynecology (JSOG), Latin American Network of Assisted Reproduction (REDLARA) (www.redlara.com, accessed March 20, 2017), Human Fertilisation and Embryology Authority (HFEA) for United Kingdom (www.hfea.gov.uk/fertility-clinics-success-rates.html, accessed March 20, 2017) and CDC for United States. Live birth rates in most regions of the world stagnated. The most obvious deviation from this international trend is Japan, which over this decade lost approximately two-third of her live birth rate. Similarly, Canada demonstrated a significant drop off in live birth rates in the second half of the decade, while Australia and New Zealand gradually lost approximately 25% of their respective live births over the decade. Modified with permission from Kushnir et al.
Why the declines?
Why the declines?

- Extended culture to blastocyst
- eSET
- Embryo banking
- Mild stimulation and natural cycle IVF
- PGS/PGT-A
Percentage of elective single embryo transfers in fresh ART cycles

Sources for the presented data are described in the footnote of slide 14. The figure demonstrates uniform increases in eSET in all regions of the world. Australia/New Zealand adopted eSET much earlier than other regions and increased utilization more, except for Canada and to a lesser degree the UK.

Correlations between live birth rates and numbers of autologous cycles performed in Japan and Australia/New Zealand

Japan (a), and Australia/New Zealand (b) data were retrieved from in Figure 2 described sources. Both countries demonstrate associations between declining live birth rates and increasing cycle numbers. This association is most profound in Japan, which between 2004 and 2012 lost two-thirds of her live births and tripled IVF cycle numbers. Also noteworthy is the perfect inverse relationship between live births and initiate IVF cycles in both regions. Modified with permission from Kushnir et al.

National US embryo banking cycles 1997-2014

These data are retrieved from the CDC’s Annual ART Success Rate reports, as described in slide 6. The figure demonstrates exponential increases in embryo banking starting around 2006 but largest year-to-year increases starting around 2010-2011.
PGS/PGT-A

- Plays a significant role in the decline
The incorrect assumptions of constance

- Same normal lab values for all?
- Same ovarian stimulation for all?
- LH for all?
- Same luteal support for all?
- PGS/PGT-A for all?

There is no constance in biology!
There is only relativity!
Relativity in reproduction

- Lab results are age-dependent
- Lab results vary depending on other hormones (ratios)*
- Different ovarian stimulations require different end points
- Different ages/ovarian function respond differently to LH, luteal support, etc.
- PGS/PGT-A may be most efficient in younger women

* Weghofer and Gleicher. Hum Reprod 2009
The new paradigm

INDIVIDUALIZATION!
Individualization

- Ovarian preparation
- Medical preparation
- Ovarian stimulation
- Timing of retrieval: HIER
- IVF laboratory
- OB care
The graying of infertility treatments
Birth rates by age of mother, United States, 1990-2015
2017 median age: 43 years!
Pregnancy as a stress test

- Every medical problem increases in prevalence and severity with advancing maternal age
Pregnancy management

- Avoid twins
- Close medical control of mother
- Close fetal monitoring
- Increased CS rate
- Be cognizant of postpartum risks
Expected scientific progress

- In vitro maturation of primordial follicles
- Creating oocytes and sperm from autologous stem cells
- Embroids (artificial embryos)
**Figure 1** Photomicrographs illustrating each step in the multi-step culture system. (A–D) Illustrate the device are prepared by removing underlying cortex and creating strips that are then prepared into fragments. The 1 mm² (A) and then cut into fragments of ~1 x 1 x 0.5 mm³. Tissue prepared for culture and examined by predominantly primordial and primary follicles (B). After 8 days in culture growing follicles can be observed. Histological evaluation of cultured pieces in vitro for 8 days shows the presence of growing follicles (D). (E–G) Cultured for 8 days with growing follicles ready to be dissected out (E) multi-laminar follicles tend to be isolated follicle after dissection from a cultured fragment (F) the follicle is kept within stromal cells and culture of a multi-laminar follicle dissected from cultured fragment after 8 days (G). Note the healthy oocyte and granulosa cells (H). Histological section of in vitro grown follicle/ oocyte showing mural and cumulus granulosa cells (I) isolated from in vitro grown follicles and placed on membranes for further growth (J) during Step 3.

**Figure 5** Bright field (A, C) and confocal images (B, D, E) of in vitro grown and in vitro matured metaphase-II human oocytes. The compact cumulus is separated from the oocytes (A–C) that display an enlarged first polar body (A–C). The spindle (green) with tapered poles anchored to the oocyte cortex (red) in juxtaposition to the polar body (B). Equatorially aligned chromosomes (blue in B, D; white in E) on the spindle. An enrichment of F-actin is seen at the interface between the polar body and oolemma where the spindle is attached (D, E). (D) An additional F-actin with more typical broad spindle poles (green) and chromosome alignment (blue) on the metaphase spindle relative to the polar body seen by light microscopy in (C).
Synthetic embryology: controlling geometry to model early mammalian development

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Differentiation of embryonic stem cells in vitro is an important tool in dissecting and understanding the mechanisms that govern early embryologic development. In recent years, there has been considerable progress in creating organoids that model gastrulation, neurulation or organogenesis. However, one of the key challenges is reproducibility. Geometrically confining stem cell colonies considerably improves reproducibility and provides quantitative control over differentiation and tissue shape. Here, we review recent advances in controlling the two-dimensional or three-dimensional organization of cells and the effect on differentiation phenotypes. Improved methods of geometrical control will allow for an even more detailed understanding of the mechanisms underlying embryologic development and will eventually pave the way for the highly reproducible generation of specific tissue types.
Disruption of current IVF practice

- No need for ovarian stimulation
- Centralized laboratories
- Radically different business models
- Extended embryo culture?
Disruption of societal norms

- Single gender conceptions
- Extended reproductive lifespans
- Genome editing?
Will it be a better world?
“The most incomprehensible thing about the world is that it is comprehensible”

- Albert Einstein
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