State of the ART:
Improving Fertility Treatment through Research and Technological Innovation

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Fertility Specialist
MD MSc (Res) MSc (HCM) PhD FRANZCOG CSST ReproMed (EBCOG/ESHRE)

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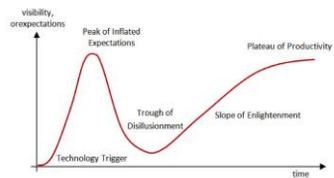## Fertility management in 2019

The demand for fertility treatment is on the rise

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Research focused on improving outcome

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Research focused on improving outcome

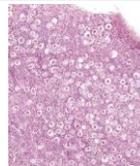The Gartner Hype Curve

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From hype to actual clinical value

- AMH: setting things straight
- Oocyte freezing: keeping it real
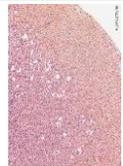- State of the ART: technological innovations that improve safety and efficacy for patients

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AMH & Ovarian reserve in humans
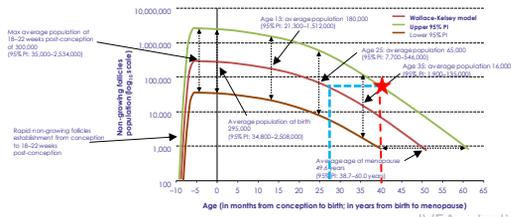

Infant   Reproductive age   Menopause

Dramatic loss of primordial follicles with advancing age

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AMH & Ovarian reserve in humans

PI, prediction interval
Figure reproduced from Wallace WH, Kelsey TW. PLoS One 2010;5:e8772

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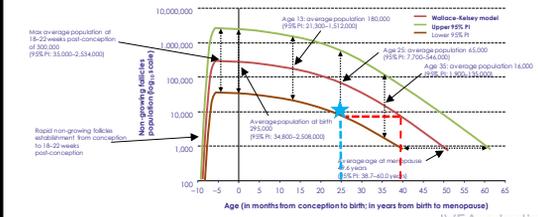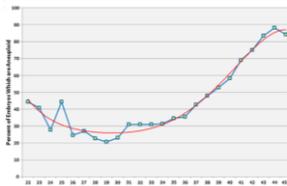## AMH & Ovarian reserve in humans

PI, prediction interval
Figure reproduced from Wallace WH, Kelsey TW. PLoS One 2010;5:e8772

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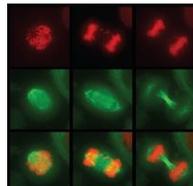## What about egg quality?

Aneuploidy increases with female age

Stefano Santaguida and Angelika Amon, MIT

Franasiak et al., F&S, 2014

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Can we assess the ovarian reserve?

The era of AMH

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AMH: a blessing or a curse?

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AMH: a blessing or a curse?

Nicole (late 20s)

Nicole thought it would be useful to do the test. She hoped it would buy her some time, or put the subject off the agenda once and for all. So off she went to the GP to ask for one.

https://www.abc.net.au/news/science/2018-11-04/egg-timer-fertility-test:-your-stories/10428004

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AMH: a blessing or a curse?

Nicole (late 20s)

Her results were very low.

The doctor told her she would have difficulty conceiving and immediately referred her to an IVF clinic.
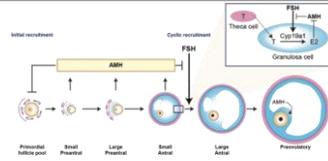
"I remember leaving the GP — it was my lunch break at work — and I couldn't go back to work," Nicole says.

"I remember just wandering around the shops aimlessly, thinking 'what does this mean for my relationship?'"

https://www.abc.net.au/news/science/2018-11-04/egg-timer-fertility-test:-your-stories/10428004

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What is AMH?

**Dimeric glycoprotein
Member of the TGF-β superfamily**

AMH, anti-Müllerian hormone; Cyp19a1, cytochrome P450 family 19 subfamily A member 1; E2, estradiol; FSH, follicle-stimulating hormone
Figure reproduced from Dewailly D, et al. Hum Reprod Update. 2014;370–85

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How is AMH measured?

**Results are not directly comparable
and have to be interpreted in an assay specific manner**

AMH, anti-Müllerian hormone; ELISA, enzyme-linked immunosorbent assay
Table reproduced from Iliodromiti S, et al. Hum Reprod Update. 2015;21:698–710

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Issues with AMH measurement?

<u>Inter-individual factors</u>

- Age
- Ovarian surgery/ Endometriosis/ Prior gonadotoxic chemotherapy
- Ethnicity (Chinese, Black African, Hispanic and South Asian< Caucasian)
- Smoking
- Pregnancy, GnRH analogues, combined hormonal contraceptives
- Chronic disease/ malignancies

<u>Intra-individual factors</u>

- Minimal cyclic variation during the menstrual cycle (late follicular phase)
- Low variability between menstrual cycles

AMH, anti-Müllerian hormone; GnRH, gonadotropin-releasing hormone
Dewailly D, et al. Hum Reprod Update. 2014;370–85; Iliodromiti S, et al. Hum Reprod Update. 2015;21:698–710; McCredie S, et al. Reprod Biomed Online. 2017;34:522–533

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What AMH does not reveal?

AMH does not reveal anything about oocyte quality
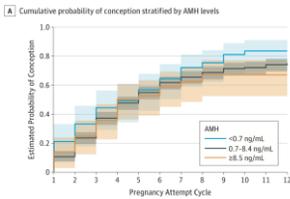
Prospective study
N=981; 30-44yo
Actively attempting to conceive
Adjustment for age

No association between AMH levels and time to conception

Steiner et al., 2017, JAMA

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What AMH does not reveal?
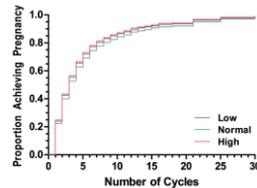
Prospective study
N=1202; 18-40yo with 1-2 pregnancy losses
Actively attempting to conceive
F/U: up to 30 menstrual cycles

No association between AMH levels and fecundability

Zarek et al., 2015, JCEM

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Is there a measure of oocyte quality?

VERY OLD
FRESH
A WEEK OLD
3-4 WEEKS OLD

There is no reliable way to measure oocyte quality without performing ART

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What AMH **does** reveal?

Low or high ovarian reserve

Indicative of time to menopause

Response to ovarian stimulation

Rarely might be indicative of Granulosa Cell Tumor

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Patient with low AMH: What to do?

- Ensure not on the OCP or other forms of HC
- Low but how low? Always adjust for age
- <5th centile: consider genetic testing (karyotype/ Fragile X syndrome)
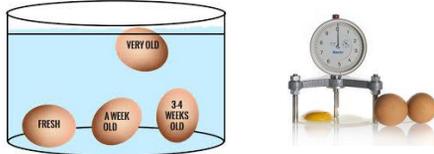- Advise to complete family ASAP
- Consider referring to Fertility Specialist

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AMH: a blessing or a curse?

Nicole (late 20s)

"After a whole lot of tests that all "came out fine", the fertility specialist suggested the couple should try to conceive naturally."

After two months of trying, Nicole got pregnant and has since given birth twice, which she says seems to be "the exact opposite of what the [AMH] test indicated".

https://www.abc.net.au/news/science/2018-11-04/egg-timer-fertility-test-your-stories/10428004

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Oocyte freezing: keeping it real

Is social egg freezing the future?

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Oocyte freezing: keeping it real

How many eggs do I need?

| 30 | 24 | 19 | 12 | 3 |

Oocytes Collected | Mature oocytes | Oocytes Thawed & survived | Oocytes fertilised | Day 5 Embryos
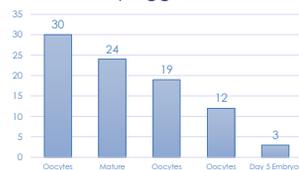
Depending on age a day 5 embryo could have a 5-40% implantation rate

Hence 3x Day 5 embryos for a 34 year old (30% IR) translate to ~60% CLBR

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Oocyte freezing: Main messages

There is no guarantee that a live birth will occur

Oocyte freezing is far more successful in younger women (usually ≤36 years old)

The more eggs the better

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IVF in 2020: modern ovarian stimulation

More attention to endometrial receptivity

Progesterone elevation and probability of pregnancy after IVF: a systematic review and meta-analysis of over 60 000 cycles

C.A. Venetis, E.M. Kolibianakis, J.K. Bosdou, and B.C. Tarlatzis

Higher probability of live-birth in high, but not normal, responders after first frozen-embryo transfer in a freeze-only cycle strategy compared to fresh-embryo transfer: a meta-analysis

J.K. Bosdou, C.A. Venetis, B.C. Tarlatzis, G.F. Grimbizis, and E.M. Kolibianakis

Bosdou, Venetis et al., 2019, Hum Reprod
Venetis et al., 2019, Hum Reprod Update

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IVF in 2020: modern ovarian stimulation

More oocytes lead to:

Human Reproduction, pp. 1–6, 2018

SHORT COMMUNICATION *Infertility*

Is more better? A higher oocyte yield is independently associated with more day-3 euploid embryos after ICSI

Christos A. Venetis[1,2,3,4], Liza Tilia[4], Erin Panlilio[4], and Andrew Kan[2,3]

More genetically normal embryos
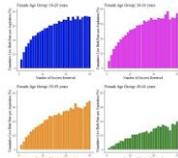
Higher chance of having a baby

Venetis et al., 2018, Hum Reprod

Law, Venetis et al., 2019, under Review

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IVF in 2020: technological innovation

- Optimising culture environment
- Selecting the best embryo
- Shortening time-to-pregnancy

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Time-lapse in the IVF laboratory

Photographs taken every 5-20 mins

Uninterrupted culture

More information regarding embryo growth and development

Stable culture environment

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The future: selecting the best embryo
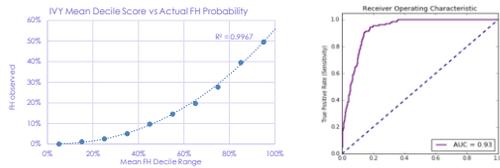

MACHINE LEARNING

ARTIFICIAL INTELLIGENCE

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IVY: selecting the best embryo

Artificial Neural Network predicting clinical pregnancy

IVY Mean Decile Score vs Actual FH Probability

Receiver Operating Characteristic

$R^2 = 0.9967$

AUC = 0.93

Trans et al., 2018, ASRM

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Main Messages

- Research and technological innovation should focus on improving patient outcomes
- It usually takes time to fully ascertain the true clinical value of new technologies and optimize their use

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Main Messages

- Ovarian reserve assessment using AMH is useful but it should be performed & interpreted appropriately
- Low AMH does not mean low fertility
- However, it can indicate that time is running out

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Main Messages

- Social oocyte freezing is a modern tool that can help some women achieve their life goals
- Younger women have much higher success rates but are also less likely to use their cryopreserved eggs
- Women should be consulted about the the realistic chances of success with oocyte freezing

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Main Messages

- Modern ovarian stimulation protocols increase efficacy of each stimulated cycle and are much safer
- Technological advancements in the lab have been significant in the last few years
- Time-lapse technology with the power of AI is a promising tool that could improve embryo culture, optimize embryo selection and shorten time-to-pregnancy for patients

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Thank you

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