# New Directions for Reproductive Lifespan and Healthspan

Dr Zhongwei Huang

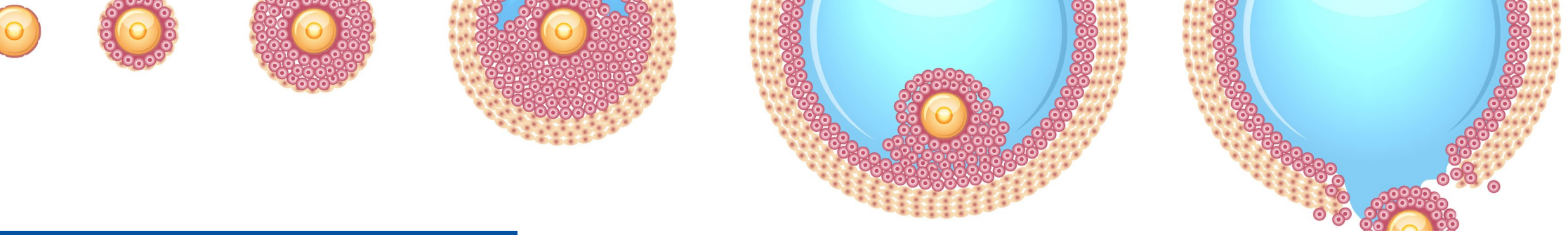
Dr Paula Benny

FEBRUARY 2025

doi.org/10.33548/SCIENTIA1258

MEDICAL & HEALTH SCIENCES

Scientia



# New Directions for Reproductive Lifespan and Healthspan

Balancing starting a family with career goals is a difficult challenge many women have to face, which can lead to inequalities in various aspects of their lives. Dr Zhongwei Huang and the team at NUS Bia-Echo Asia Centre for Reproductive Longevity and Equality (ACRLE) are pioneers in reproductive health research. They work to improve female reproductive longevity and equality, exploring novel approaches to tackle fertility and conception problems, and ways to maintain optimal healthspan later in life.



## Inevitable Fertility Decline

Many women have to carefully balance their work life and career goals with having a family. Unlike men, who are generally able to father children into their later years, women are faced with a decline in their fertility when they hit their late 30s, making it harder to conceive. By the age of around 50 years old, many women will have experienced menopause. As their reproductive hormone levels fall, their ovaries stop releasing eggs, meaning that they cannot become pregnant. The World Health Organization says that the age at which this happens varies from woman to woman, but generally, it occurs between 45 and 55 years. After menopause, women are then at a higher risk of a plethora of age-related health conditions due to a drastic decline in hormone levels in the body.

Women faced with this dilemma can be forced into making less-than-ideal choices due to the ticking of their biological clock. New research into female reproductive health at the NUS Bia-Echo Asia Centre for Reproductive Longevity and Equality (ACRLE) offers much-needed hope for women confronting these difficulties. Dr Zhongwei Huang says that the overarching focus of their work at ACRLE is using data from clinical studies coupled with bench-bedside research approaches to change the narrative for women, with a focus on reproductive longevity in women, in particular for the Asian population.

## Impact of Low Oestrogen

Fertility in women starts to decline after around 37 years old, and it is rare to fall pregnant after 45. As women face menopause, this comes with an increased risk of age-related diseases. During this period of life, the levels of oestrogen, one of the main female reproductive hormones, drop significantly. Lower levels of oestrogen are linked to a myriad of physiological and health issues, including systemic inflammation, impaired glucose and lipid metabolism, decline in cardiovascular health, and bone problems such as osteoporosis and fractures.

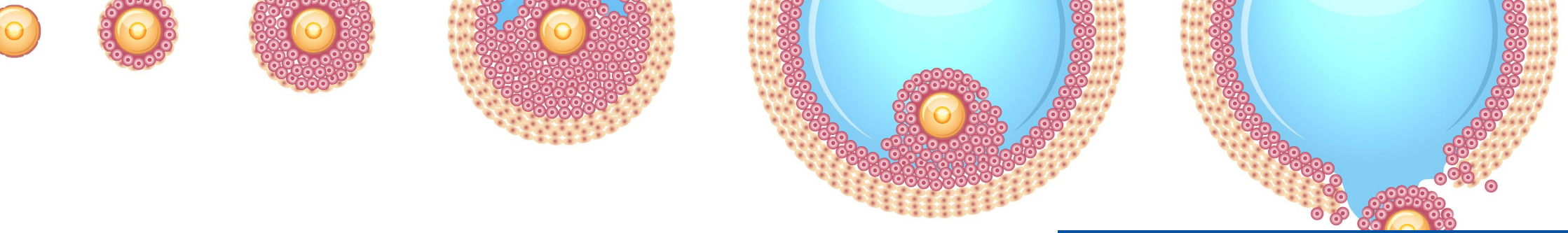
Unfortunately, a decline in fertility and the potential to conceive is just the tip of the iceberg when it comes to female health and ageing. Reproductive longevity is currently a very understudied field – but Dr Huang is working to put that right. It is critical that medical advances start being focused on mitigating female reproductive ageing in order to not only maintain fertility for longer but also to preserve hormone functions. This would offer women increased life choices as well as enhance healthy lifespan.

## Unravelling the Biology of the Ovary

The research at ACRLE focuses on four main tracks, one of which is dedicated to ovarian biology and senescence – the process of deterioration of ovarian function with ageing. Here, the team aims to acquire a better understanding of the changes that happen to the reproductive system as women grow older.

To this end, the team reviewed the literature about the biology of the ovary and its ageing process to better understand the molecular events that drive ovarian ageing and menopause, and explore strategies that could offset these events and inform the development of new treatments.

It is established that the ovaries contain follicles – fluid-filled sacs, each of which contains an oocyte, more commonly known as an egg. Each month, a follicle bursts, releasing a mature egg, a cycle which continues until menopause. These follicles also release hormones, which eventually begin to decline as menopause approaches.



Dr Huang explains that current knowledge about the mechanisms of ovarian ageing remains limited. That said, promising avenues of research are emerging from pre-clinical model studies in which attempts have been made to maintain the quality and quantity of follicles by manipulating the pathways involved. He adds these could potentially prolong the female reproductive lifespan and hopefully improve healthspan.

## Mysteries of Ovarian Senescence

The team also reported a compelling need to develop novel strategies and set out clear directions for future research. Dr Huang argues that once the mysteries behind ovarian senescence are unravelled, they hope to offer women greater flexibility when it comes to choosing when they want to have a baby. He adds that it is vital to protect and enhance the reproductive lifespan and thus healthspan of women, and they aim to explore innovative solutions, finding options that are safe with minimal side effects to counteract the negative issues linked to reproductive ageing and hormone decline.

Additionally, the researchers at ACRLE concluded that it is critical to advocate for reproductive longevity and equality in women. The clinical management of fertility issues is always complicated by age, with limited outcomes and a higher risk of reproductive failure and pregnancy complications the older the woman is. Even natural menopause is not fully understood yet because of a lack of information on the biology of ovarian senescence. Using science to fight the inevitable reproductive ageing process so future generations can lead happier, healthier lives is vital. Dr Huang adds that new strategies could target the root causes of reproductive ageing at the cellular and molecular level, which is also organ-specific.

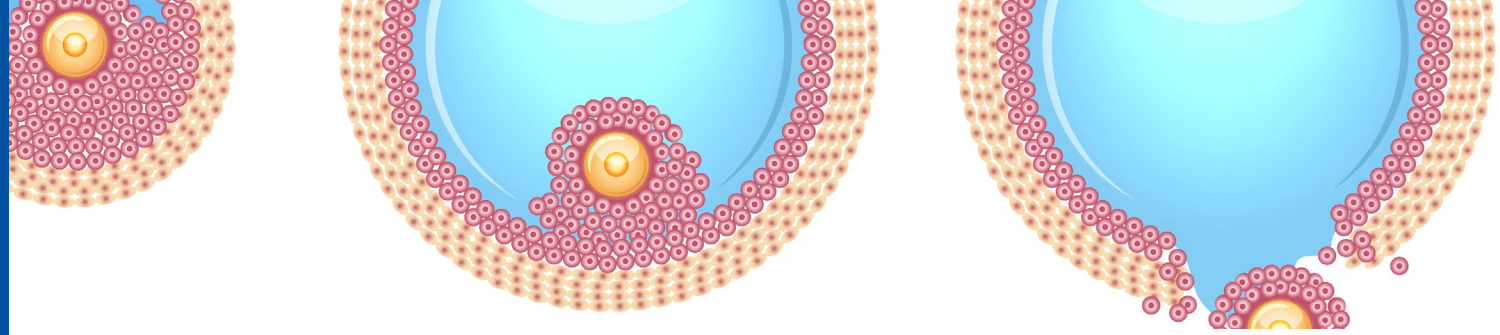
## Assisted Reproductive Technology

Assisted reproductive technologies (ART) help people with fertility problems to conceive. The most common type of ART is in vitro fertilisation (IVF), where the egg and sperm are retrieved from the parents, combined in the lab to allow fertilisation to occur, and then the embryo created is placed into the woman's uterus. Dr Huang says that ART has advanced greatly in the last forty years, but when examining the clinical outcomes of ART, shocking differences between Asian women and Caucasians came to light. The majority of the studies reported far lower reproductive success amongst Asian women. The stark contrast between these outcomes spurred the team to investigate the possible causes *in silico*.

Dr Huang explains that they first investigated the genes associated with ART clinical outcomes, focusing on Asian ethnicities. Although humans are 99.9% identical genetically, the remaining 0.1% of genes determine a variety of differences, including some health outcomes, such as predisposition to particular diseases and varied responses to certain drugs in different ethnic groups. The team considered the idea that genetics could play a part in governing female fertility, and carried out a thorough literature review to integrate all the studies linked with reproductive outcomes in women of different ethnic backgrounds.

“

Using science to fight the inevitable reproductive ageing process so future generations can lead happier, healthier lives is vital.

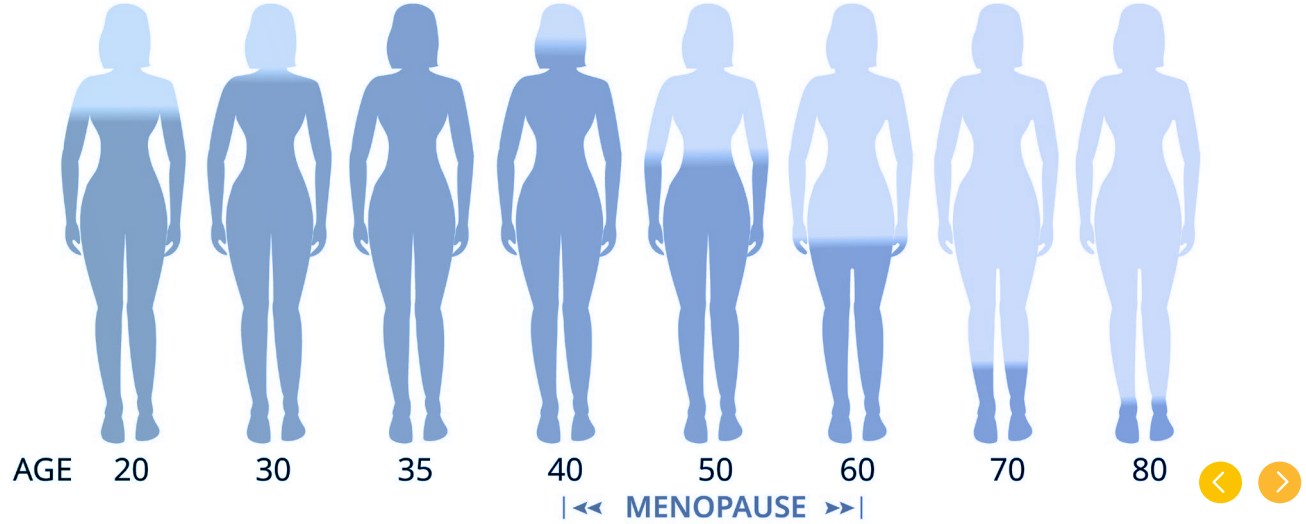


> Based on their findings, the team at ACRLE propose the development of personalised fertility treatments based on ethnic-specific biomarkers to address every woman's unique reproductive potential.

## The Future of Female Fertility

The team analysed a total of 128 studies exploring bioinformatic genetics analyses. They also reviewed data such as the age at menarche (AAM), when a girl gets her first menstrual period, and the timing of her first pregnancy. Dr Huang says they found several groups of genes associated with reproductive processes which could impact fertility. For example, the FMR1 gene was most linked to ovarian reserve, and mutations to the LIN28 gene were associated with AAM and were found to be prevalent in both Chinese and American populations. They also found several other genes closely associated with the menstrual cycle and ovarian follicle development.

Dr Huang says that the health disparities associated with ART highlight the need for personalised medicine. Based on their findings, the team at ACRLE propose the development of personalised fertility treatments based on ethnic-specific biomarkers to address every woman's unique reproductive potential. Certainly, the team's hard work and ground-breaking research are paving the way for new strategies to improve female reproductive health, striving for equality and new perspectives on fertility treatments.



## MEET THE RESEARCHERS

### Asia Centre for Reproductive Longevity and Equality (ACRLE)

Yong Loo Lin School of Medicine, National University of Singapore, Singapore

The National University of Singapore's Bia-Echo Asia Centre for Reproductive Longevity and Equality (ACRLE) specialises in women's reproductive health, ageing, and digital medicine. The team works to help women preserve and improve their reproductive systems for conception, enabling them to conceive safely in their later years and to remain generally healthy for longer. Their vision is to prioritise female reproductive longevity and equality through scientific and clinical discoveries coupled with powerful narratives. They lead the way in women's reproductive health, advocating and educating on reproductive equality. They work closely with other academic institutions and stakeholders to change the narrative of reproductive equality and longevity, particularly for Asian women. To achieve their vision, ACRLE investigations explore four main tracks: ovarian biology and senescence, translational and clinical studies, population health studies, public health education and outreach. The specialist team at ACRLE is led by Dr Brain Kennedy (Director) and Dr Zhongwei Huang (Deputy Director).

### CONTACT


obgzwh@nus.edu.sg

acrle@nus.edu.sg

https://www.acrle.com/

@ACRLE_NUS


### KEY RESEARCHERS

Dr Brian Kennedy, PhD (Director)
Dr Zhongwei Huang, MBBS, DPhil, AFHEA, M Med, MRCOG, FAMS (Deputy Director)
Dr Paula Benny, PhD
Dr Min Gong, PhD
Dr Vani Khare, PhD
Dr Chervin Lam, PhD
Miss Qian Yang, MPH
Miss Lang Chu Lau, MSc
Miss Shaili Sashidharan, BSc
Miss Devi Nadjaja, MSc
Mr Abraham Lau, BEng
ACRLE Administrative Leads: Miss Eunice Sim, BSc and Miss Dione Ng, BIHTM

### FORMER LAB MEMBERS

Dr Huili Guo, PhD
Miss Jovin Lee, BSocSci
Miss Xue Ting Tan, BSc

### KEY COLLABORATORS

Ferring Pte Ltd, Singapore
Merck Pte Ltd, Singapore
HeyVenus Integrated Healthscience, Singapore
Temasek Life Sciences Laboratory, Singapore
National University Hospital, Singapore
Shenzhen Zhongshan Urology Hospital, China
KK Women's and Children's Hospital, Singapore
Institute for Human Development and Potential, A*STAR, Singapore

### FUNDING


Bia-Echo Foundation
NUS Yong Loo Lin School of Medicine
Ferring Pharmaceuticals Pte Ltd
Merck Pte Ltd
NUHS Seed Grant Junior PI 2019
NUHS Seed Grant Junior PI 2020
NUHS Clinician-Scientist Unit Programme Award
Seah Cheng Siang Memorial Research Award, Academy Medicine of Singapore 2022
Ministry of Health Healthy Longevity Catalyst Awards 2021
Ministry of Health, National Medical Research Council Transition Award 2023
NUHS Seed Grant Junior PI 2024


### FURTHER READING


C Long, P Benny, J Yap, *et al.*, A Systematic Review of Genetics and Reproductive Health Outcomes: Asian Perspective, *Reproductive Sciences*, 2023, 31(2), 309–319. DOI: https://doi.org/10.1007/s43032-023-01311-y

L Dong, DBL Teh, BK Kennedy, *et al.*, Unraveling female reproductive senescence to enhance healthy longevity, *Cell Research*, 2023, 33(1), 11–29. DOI: https://doi.org/10.1038/s41422-022-00718-7


NUS National University of Singapore | Bia-Echo Asia Centre for Reproductive Longevity & Equality Yong Loo Lin School of Medicine


Find out more at **scientia.global**