

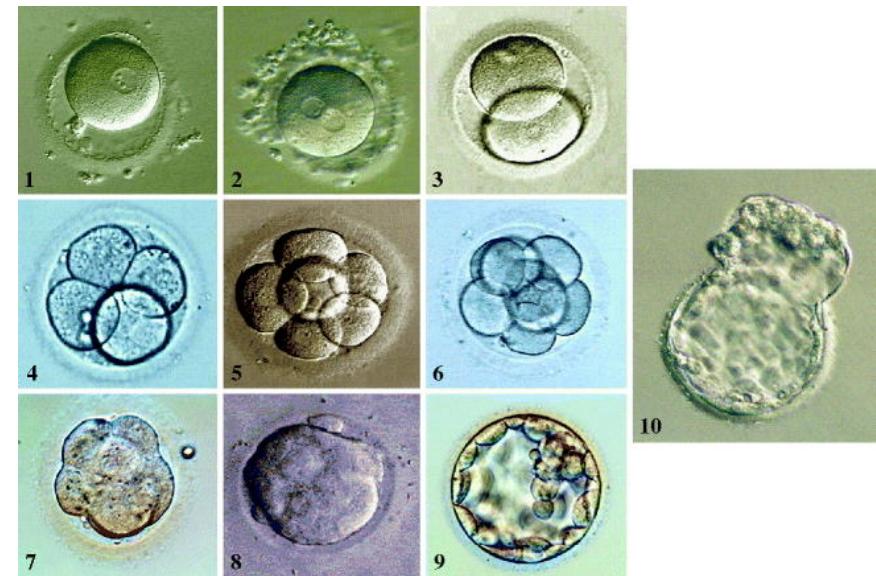
# Assisted Reproductive technologies and human evolution

Dr Jessica Dudley



# Outline

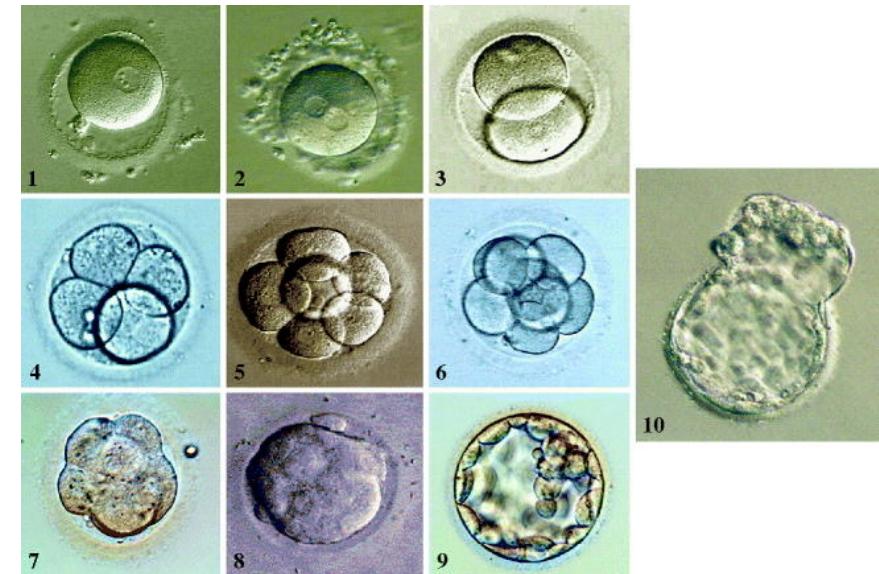
## Part 1: Types of ARTs



# Outline

Part 1: Types of ARTs

Part 2: History of ARTs and emerging ART technologies

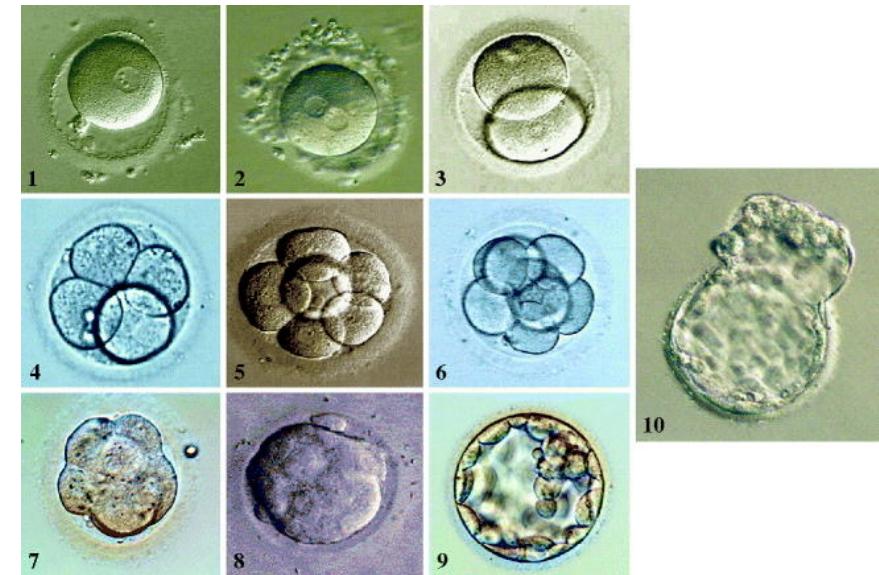


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Part 1: Types of ARTs

Part 2: History of ARTs and emerging ART technologies

Part 3: Overall health effects, DNA methylation and epigenetics



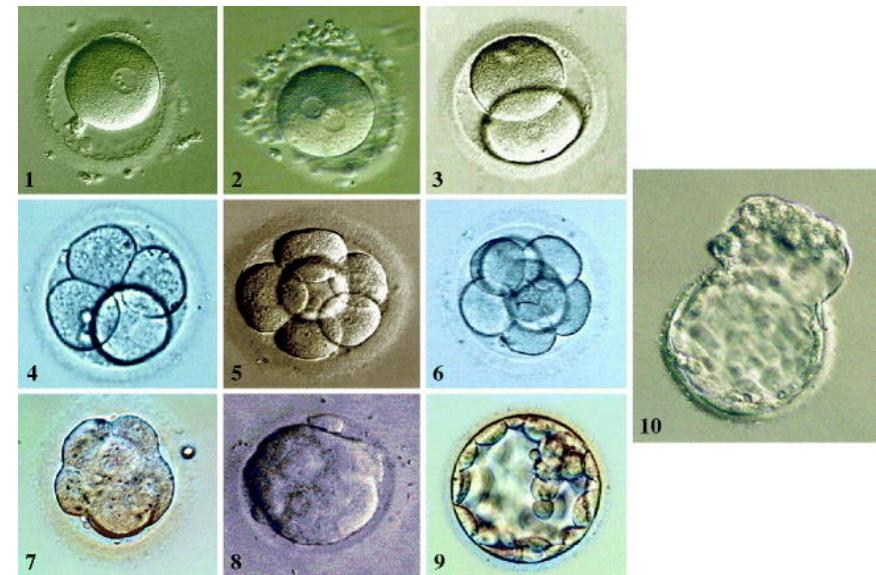
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Part 1: Types of ARTs

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Part 4: The future of ARTs and human evolution



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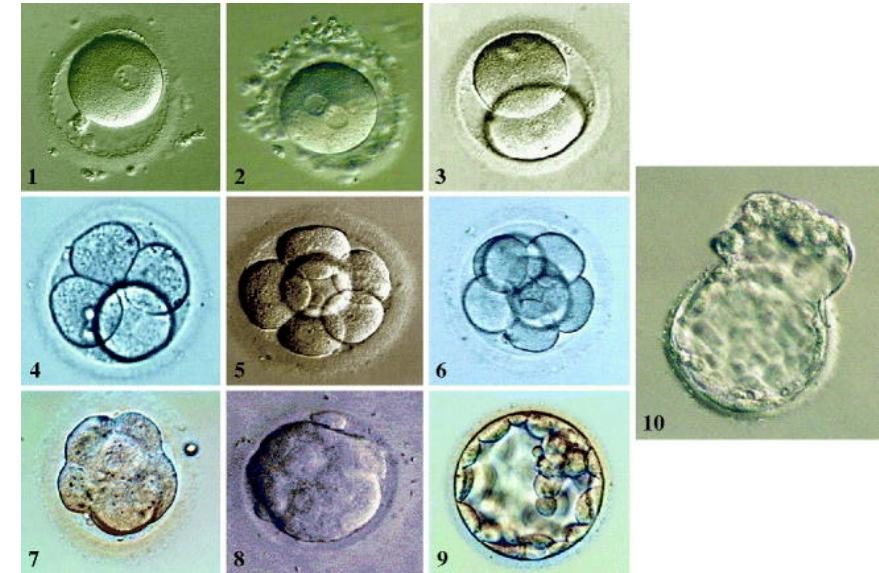
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Part 3: Overall health effects, DNA methylation and epigenetics

Part 4: The future of ARTs and human evolution

Learning objectives:

- Understand the different types of ARTs
- Identify the potential health impacts of ARTs
- Explain the genetic mechanisms that are impacted by ARTs during development
- Evaluate the long-term consequences of widespread ART use on human evolution
- Engage with scientific data



# What are ARTs?

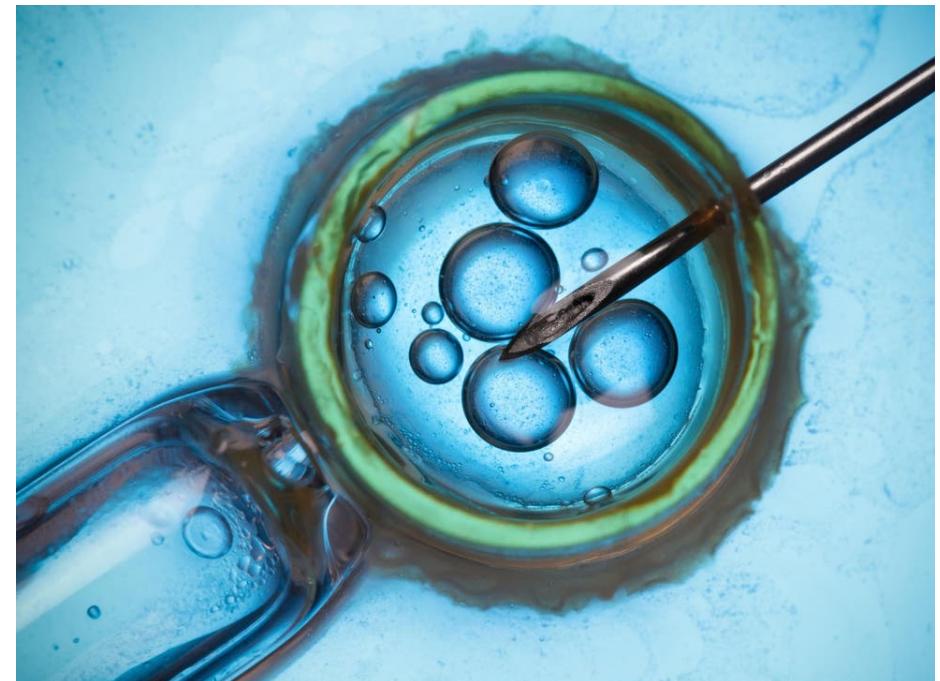
## Definitions

In-vitro: outside of a living organism  
Oocytes and sperm: sex gametes  
Embryos: fertilised eggs

- Assisted Reproductive technologies
  - treatments or procedures that initiate pregnancy via *in vitro* handling of oocytes and sperm

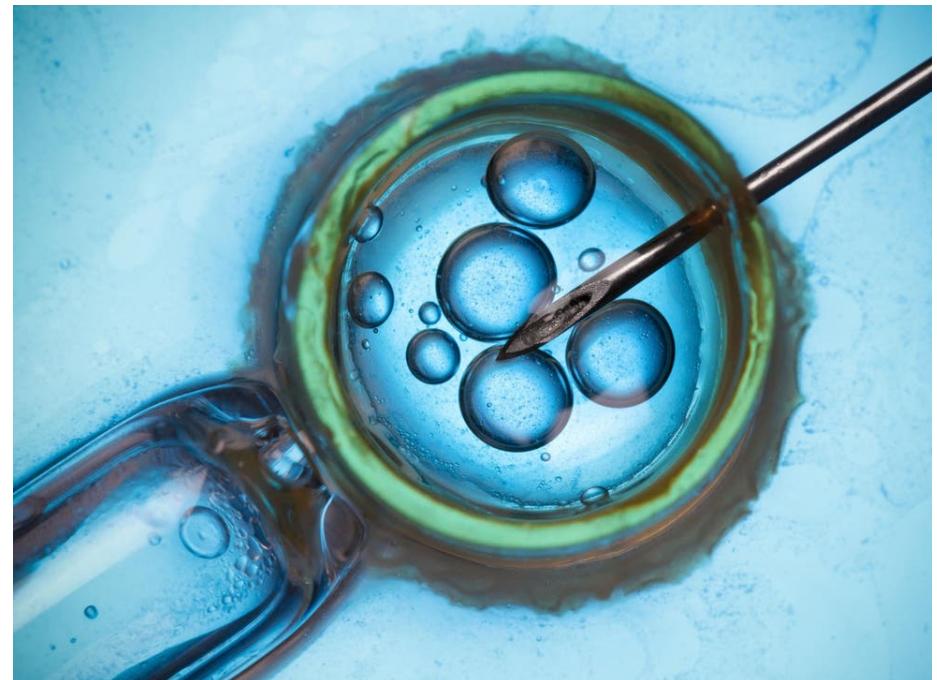
# Why do we need ARTs?

- Reduction in fertility over time
  - Unexplained
  - Endocrine disrupting chemicals
  - Genetic disorders
  - COVID



# Why do we need ARTs?

- Reduction in fertility over time
  - Unexplained
  - Endocrine disrupting chemicals
  - Genetic disorders
  - COVID
- Society changes
  - Increased age at first birth
  - Access to contraception

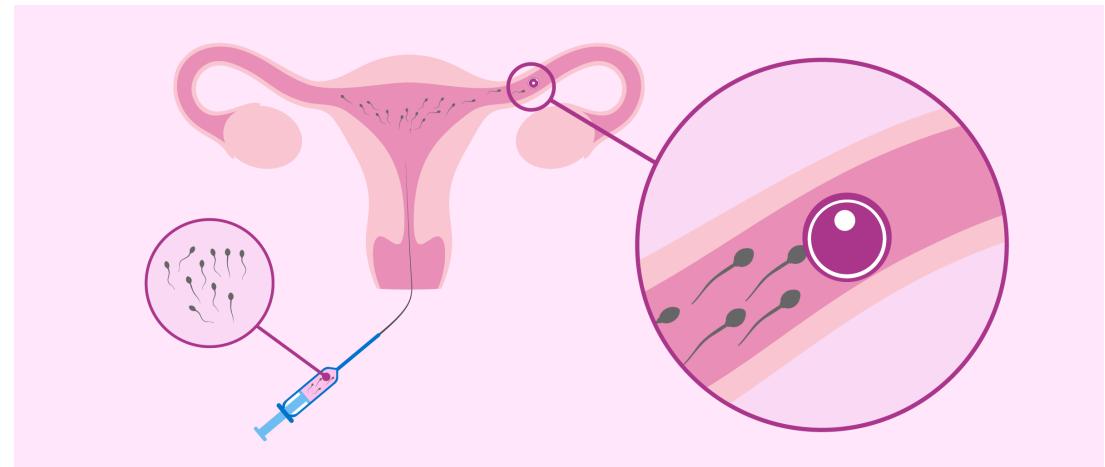


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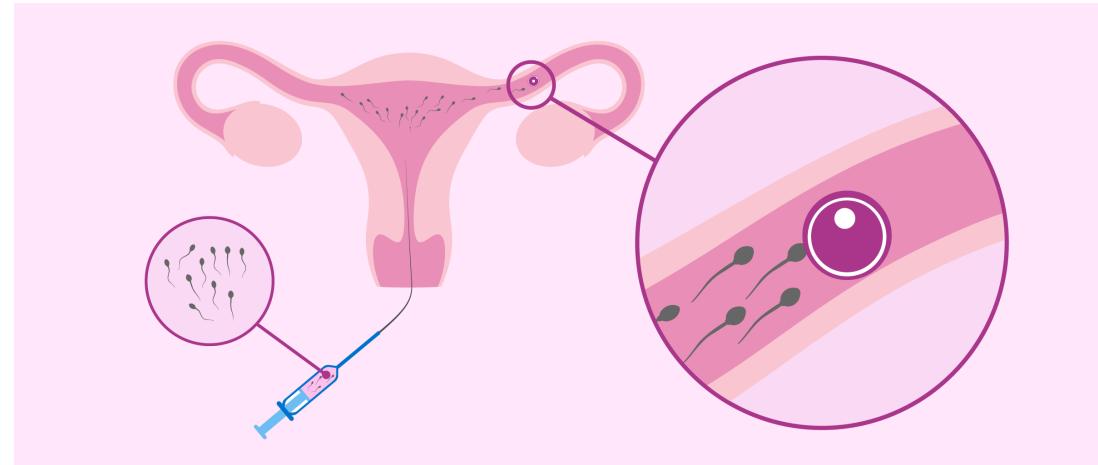
# Types of ARTs -

- Problem:
  - Infertility: inability to conceive after 12 mths



# Types of ARTs - IUI (intrauterine insemination)

- **Problem:**
  - Infertility: inability to conceive after 12 mths
- **Solution:**
  - Sperm is collected and placed directly into the uterus at time of ovulation



## Definitions

In-vitro: outside of a living organism  
Oocytes and sperm: sex gametes  
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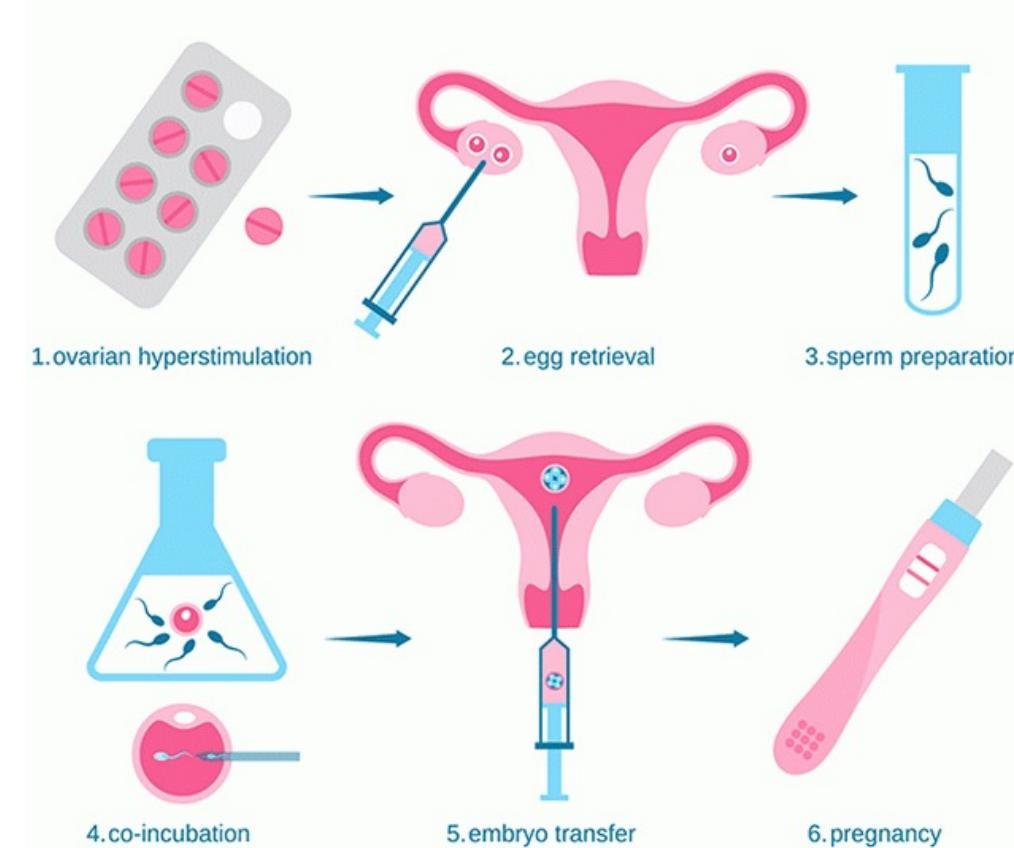
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- Cause: female reproductive system (40% couples struggling with infertility)



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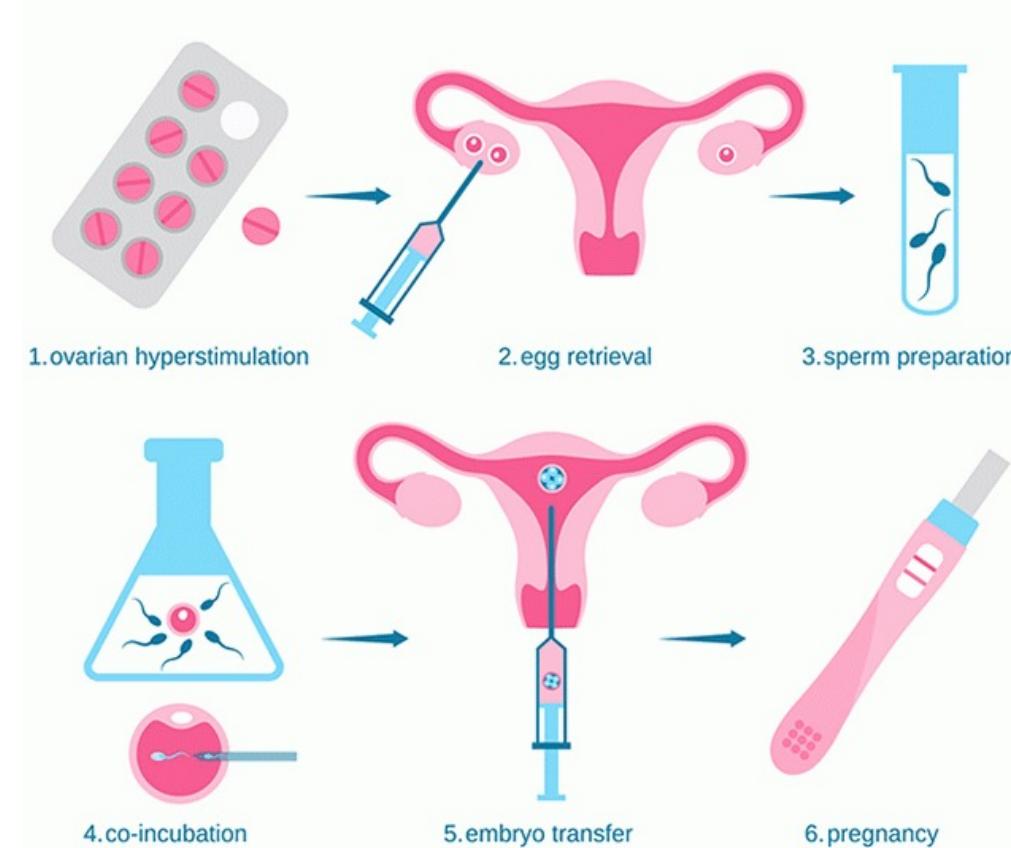
# Types of ARTs – IVF (in-vitro fertilisation)

- **Problem:**

- Infertility: inability to conceive after 12 mths
- Cause: female reproductive system (40% couples struggling with infertility)

- **Solution:**

- IVF
- Hormone stimulation

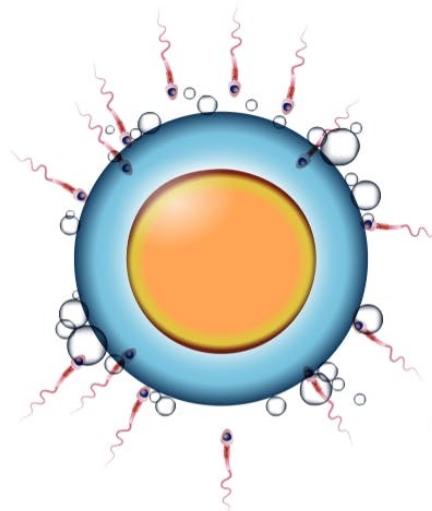


# Types of ARTs -

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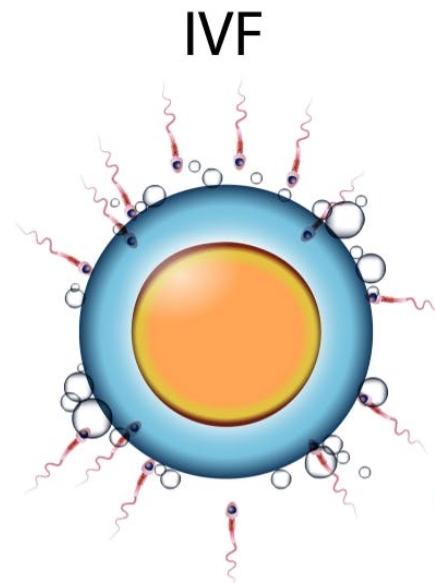
IVF



# Types of ARTs - ICSI (Intracytoplasmic Sperm Injection)

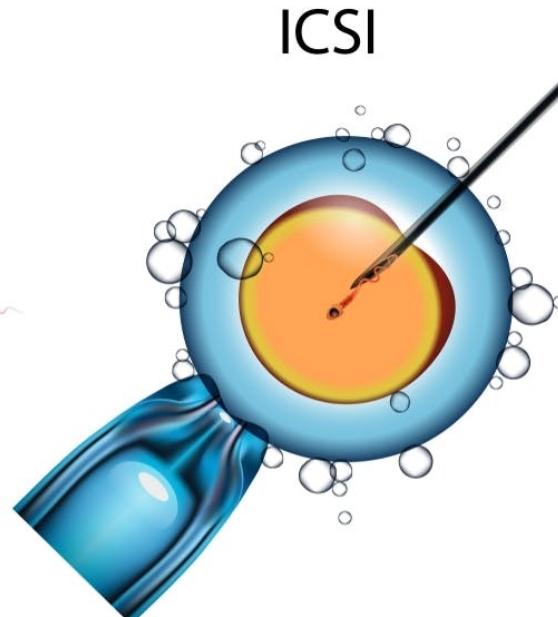
- **Problem:**

- Infertility: inability to conceive after 12 mths
- Cause: male sperm factor (40% couples struggling with infertility)



- **Solution:**

- Morphology and motility based selection of sperm
- Single sperm injected into each egg



# Types of ARTs -

- Problem:
  - Lifestyle changes
  - Cancer therapies



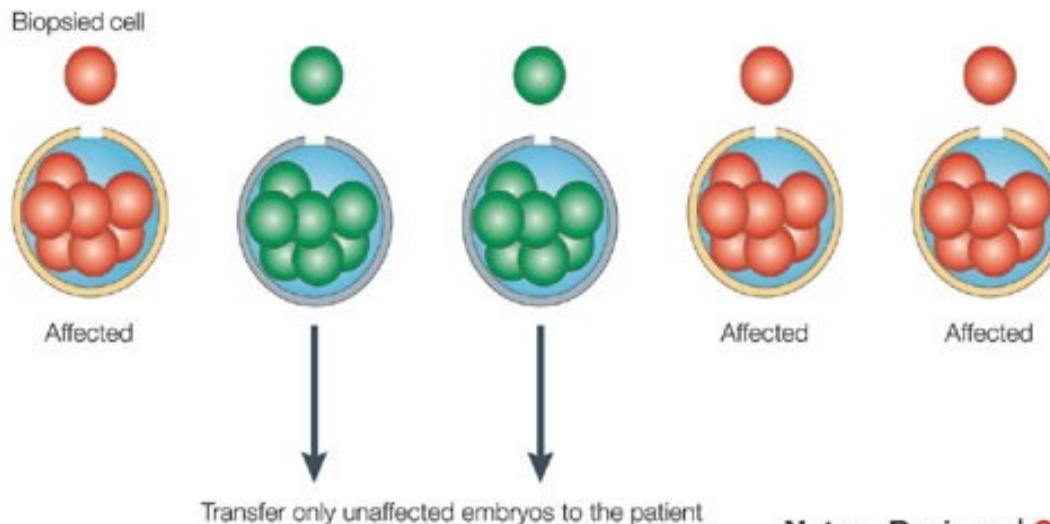
# Types of ARTs – Cryopreservation of gametes

- **Problem:**
  - Lifestyle changes
  - Cancer therapies
- **Solution:**
  - Freeze eggs and sperm to save a persons ability to conceive in the future



# Types of ARTs –

- Problem:
  - Aneuploidy
  - Post-conception diagnostic procedures lead to difficult decisions



Nature Reviews | Genetics



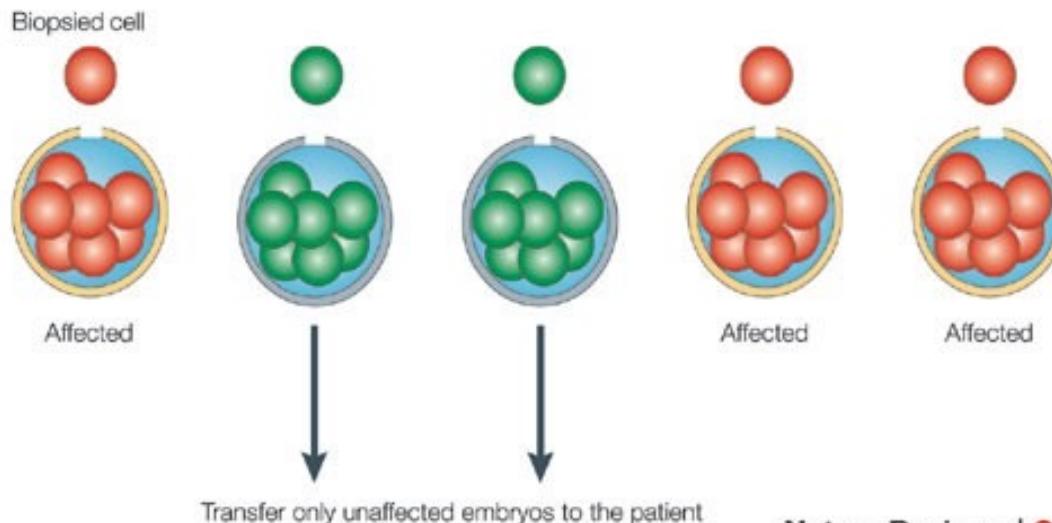
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Cleavage stage biopsy

# Types of ARTs – pre-implantation genetic screening

- Problem:

- Aneuploidy
- Post-conception diagnostic procedures lead to difficult decisions



- Solution:

- PGD
- Enhances success of IVF



Cleavage stage biopsy

# History

## Definitions

IVF: In-Vitro Fertilisation

1978

- First IVF baby



# History

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**IVF:** In-Vitro Fertilisation

**Implantation:** attachment of an early embryo to the wall of the uterus in early pregnancy

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- Development of Pre-implantation genetic diagnosis



# History

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**ICSI:** Intra-cytoplasmic sperm injection

1978

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1980

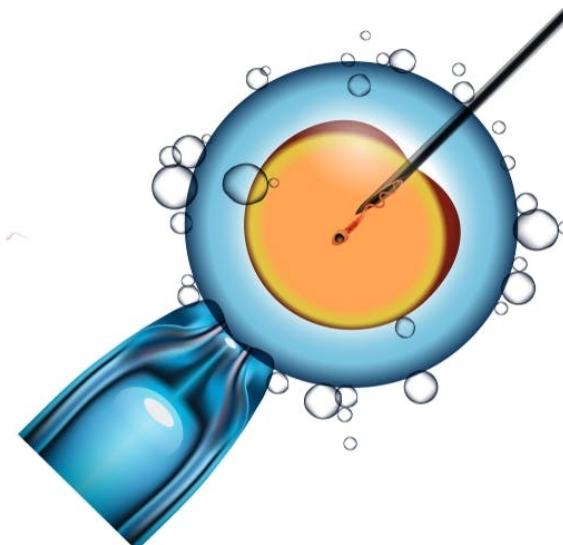
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1992

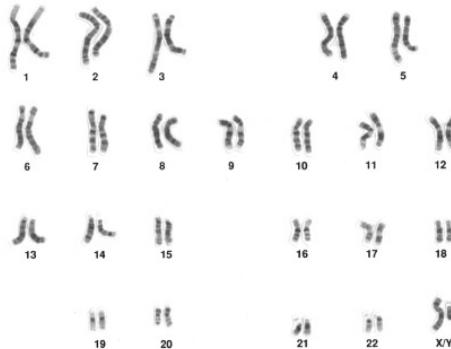
- Development of ICSI



# History

1995

- Aneuploidy testing
- Birth after IVM + ICSI + assisted hatching



## Definitions

**Aneuploidy:** abnormal number of chromosomes

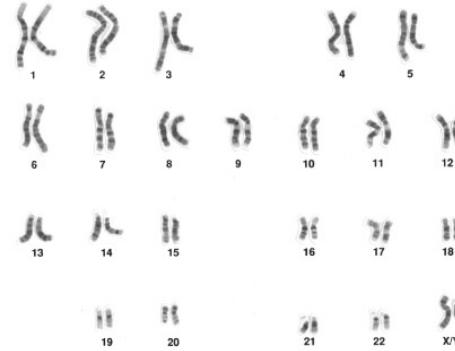
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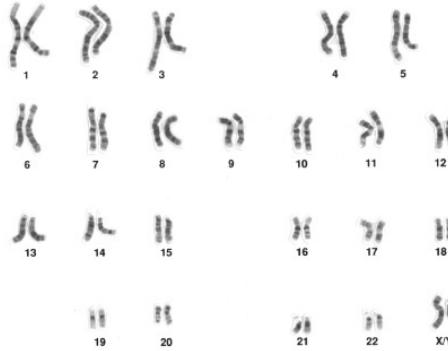
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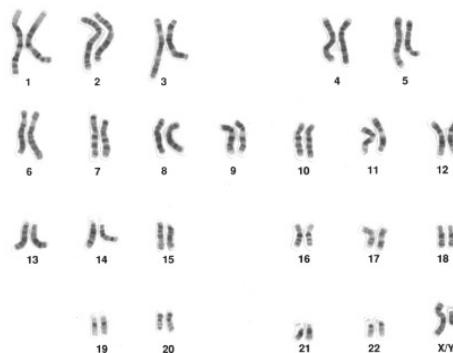
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2001

- Birth of the first cryopreserved embryo
- UK law updated to allow embryonic stem cell research for serious diseases and to ban reproductive cloning in humans



# History

2004

- Birth of the first single embryo transfer

Fertilization



Day 2



Day 3



Day 4  
Morula



Day 5  
Blastocyst



Blastocyst  
hatching



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© Colin Davey

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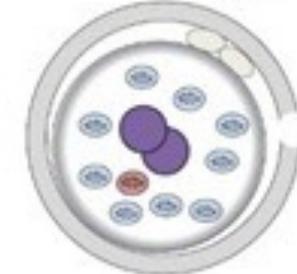


2015

- UK legalises mitochondrial donation techniques

Fertilised egg containing:

- Patient's nuclear DNA,
- Healthy mitochondrial DNA from the egg donor.



# Emerging technologies - Mitochondrial donation

## Problem:

- Mitochondrial diseases passed down maternally

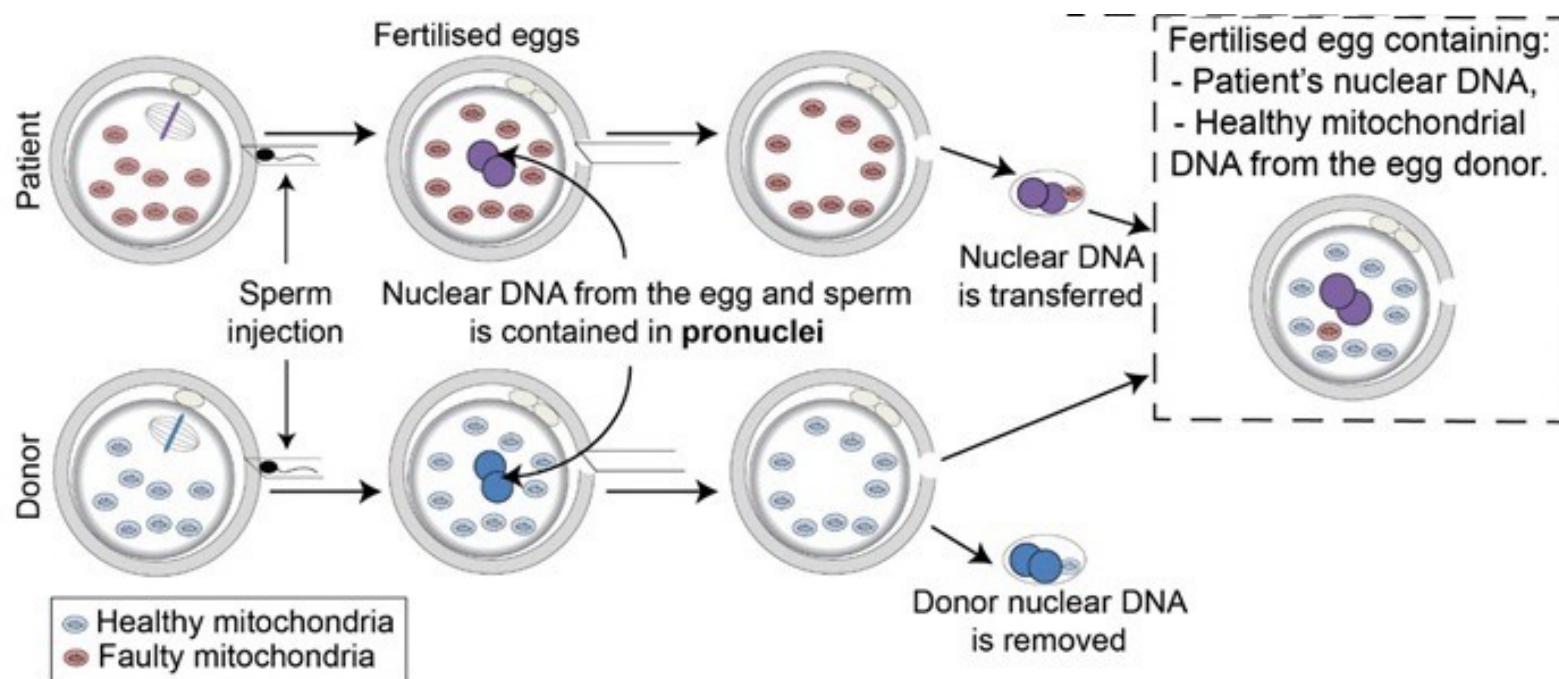
# Emerging technologies - Mitochondrial donation

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## Solution:

- three parent IVF

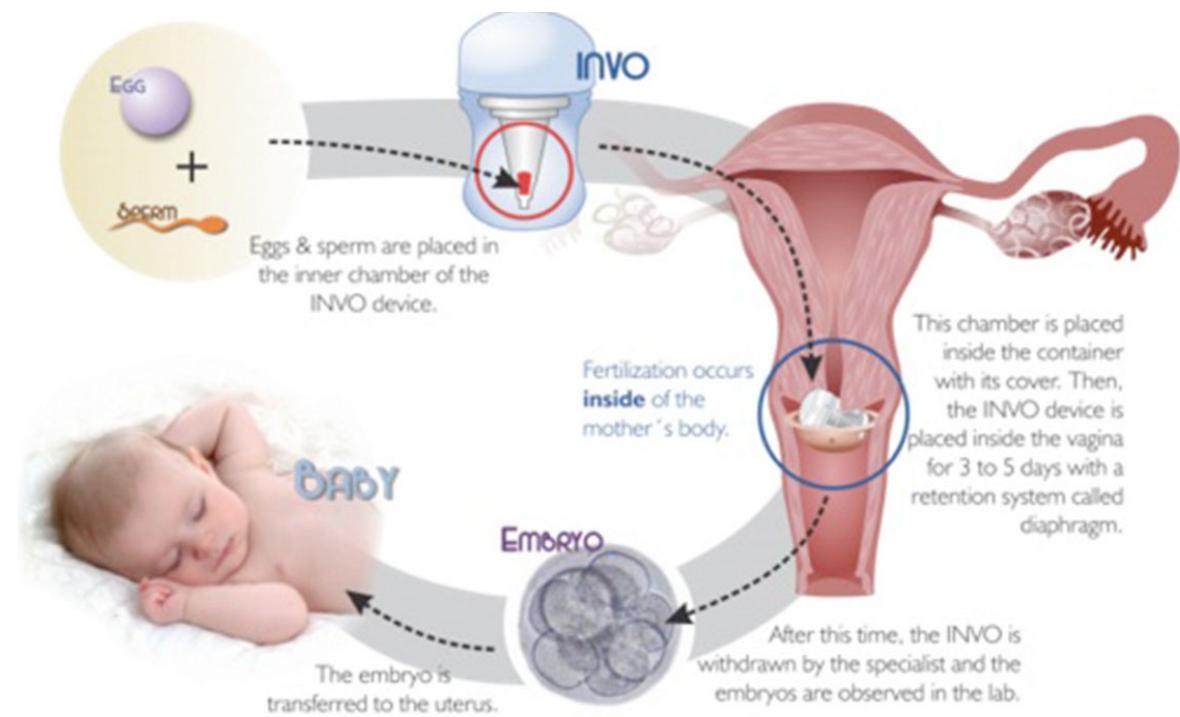


# Emerging technologies – INVOcell capsule IVF

- **Problem:** high cost of IVF

# Emerging technologies – INVOcell capsule IVF

- Problem: high cost of IVF
- Solution: incubating embryos inside a capsule within the vagina instead of a lab

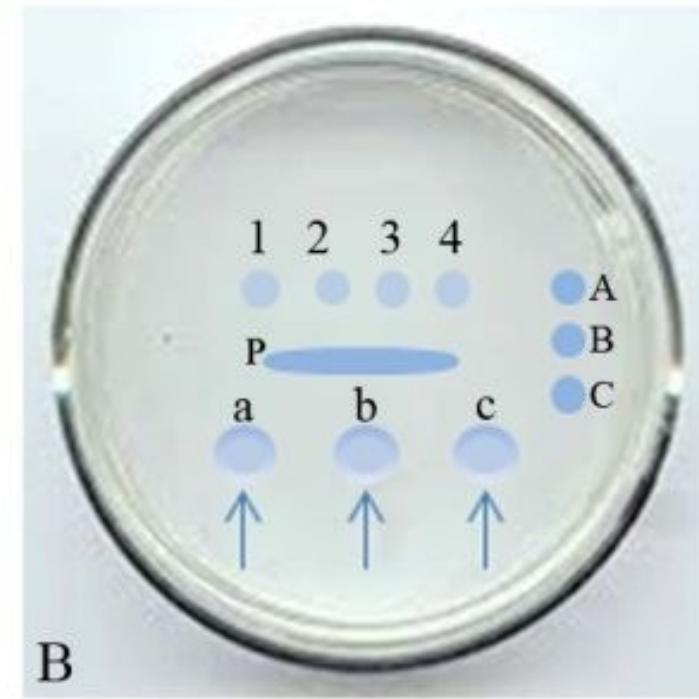


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  - Low sperm binding to hyaluronic acid
  - High sperm DNA fragmentation
- 
- **Solution:** physiological intracytoplasmic sperm injection



PICSI dish: Each arrow is pointing to a dot containing hyaluronic acid. A, B and C are oocyte washing drops, P is a sperm immobilisation agent

# Overall health effects of ART vs natural conception

- Biggest problem is the increased risks associated with having multiples

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**Table I** Fetal, neonatal and perinatal mortality following ART, Australia and New Zealand 2004–2008.

	Plurality		Embryo transfer		Total <sup>a</sup>
	Singletons	Twins	Single	Double	
Number					
Live birth/survived	39 133	10 010	24 887	24 060	49 445
Fetal death (stillbirth)	411	197	277	346	630
Neonatal death	82	89	57	122	183
Perinatal death	493	286	334	468	813
All births	39 626	10 296	25 221	24 528	50 258
Rate per 1000 births (95% CI)					
Fetal deaths (stillbirth) <sup>b</sup>	10.4 (9.4–11.4)	19.1 (16.6–22.0)	11.0 (9.7–12.4)	14.1 (12.7–15.7)	12.5
Neonatal deaths <sup>c</sup>	2.1 (1.7–2.6)	8.9 (7.1–10.9)	2.3 (1.7–3.0)	5.1 (4.2–6.1)	3.7
Perinatal death	12.4 (11.4–13.6)	27.8 (24.7–31.2)	13.2 (11.9–14.7)	19.1 (17.4–20.9)	16.2

<sup>a</sup>Includes all births.

<sup>b</sup>Fetal and perinatal mortality rates calculated using all births (live births and fetal deaths) as denominator.

<sup>c</sup>Neonatal mortality rates calculated using live births as denominator.

# Overall health effects of ART vs natural conception

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- Low birth weight
- Pre-term delivery
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**Table 11: Outcomes of autologous fresh embryo transfer cycles by women's age and number of embryos transferred, Australia and New Zealand, 2019**

Stage/outcome of treatment	Age group (years) <sup>(a)</sup>							
	< 35		35–39		≥ 40		All	
	SET <sup>(b)</sup>	DET <sup>(c)</sup>	SET <sup>(b)</sup>	DET <sup>(c)</sup>	SET <sup>(b)</sup>	DET <sup>(c)</sup>	SET <sup>(b)</sup>	DET <sup>(c)(d)</sup>
Embryo transfer cycles	8,279	370	8,027	794	4,686	1,475	20,992	2,679
Clinical pregnancies	3,534	152	2,760	258	759	227	7,053	642
Live births	3,024	129	2,080	182	448	130	5,552	441
<i>Clinical pregnancies per embryo transfer cycle (%)</i>	42.7	41.1	34.4	32.5	16.2	15.4	33.6	24.0
<i>Live births per embryo transfer cycle (%)</i>	36.5	34.9	25.9	22.9	9.6	8.8	26.4	16.5

(a) Age at start of a treatment cycle.

(b) SET: single embryo transfer.

(c) DET: double embryo transfer.

(d) Includes 40 cycles where three or more embryos were transferred

Newman et al., *Assisted reproductive technology in Australia and New Zealand 2019*. National Perinatal Epidemiology and Statistics Unit, the University of New South Wales (2021)

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Outcome	IVF/ICSI conceptions, n	Overall effect (RR, 95% CI), fixed effect
APH	20 807	2.49 (2.30–2.69)
Congenital anomalies	4382	1.67 (1.33–2.09)
Hypertensive disorders of pregnancy	16 923	1.49 (1.39–1.59)
PPROM	14 141	1.16 (1.07–1.26)
Caesarean Section	12 950	1.56 (1.51–1.60)
Birthweight < 2500 g	28 352	1.65 (1.56–1.75)
Birthweight < 1500 g	27 105	1.93 (1.72–2.17)
Perinatal mortality	14 054	1.87 (1.48–2.37)

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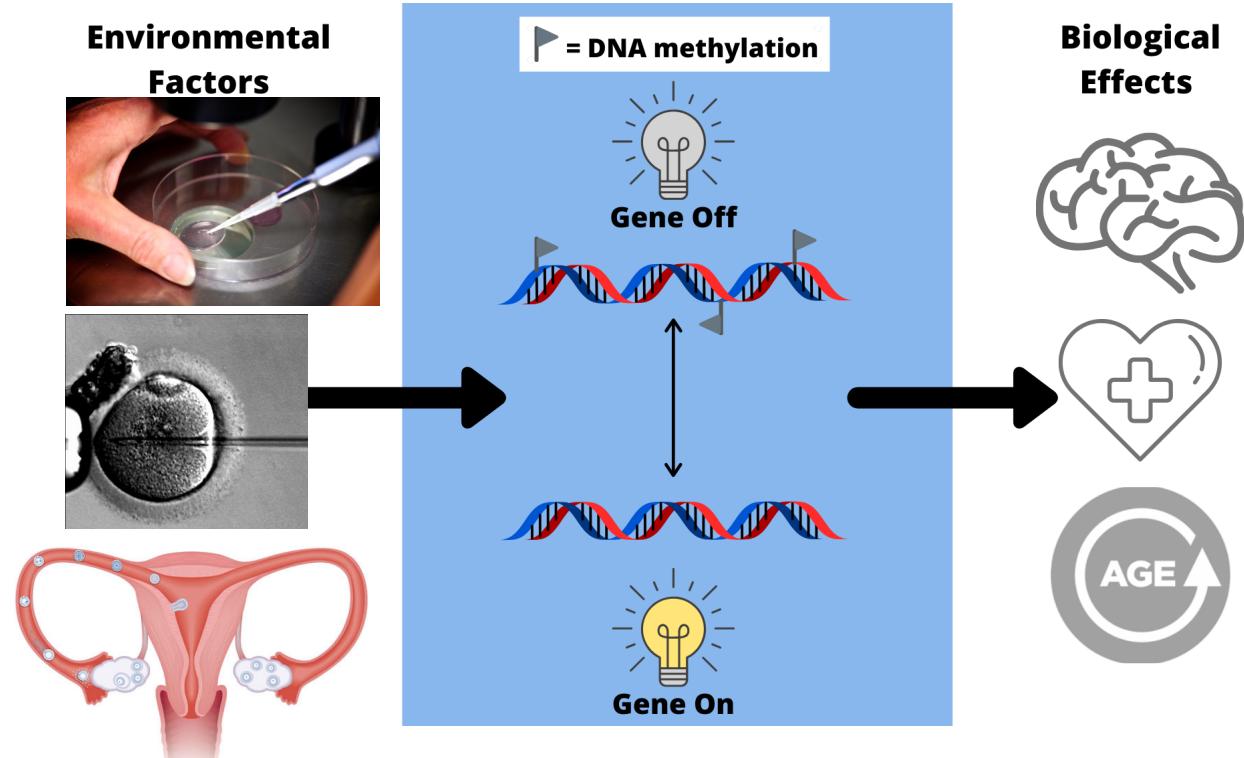
# Overall health effects of ART vs natural conception

- metabolic syndromes
- diabetes
- heart disease
- obesity



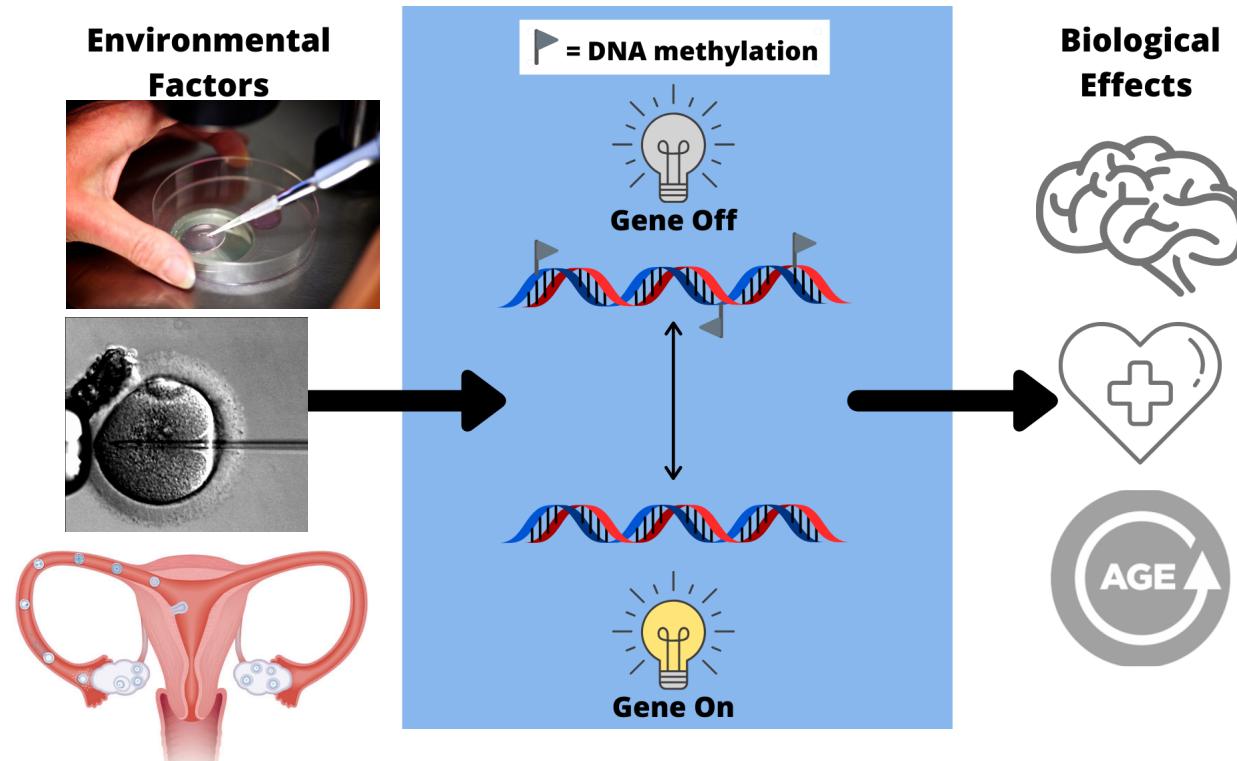
# Possible mechanisms: DNA methylation and epigenetics

- Developmental origins of health and disease hypothesis



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- Developmental origins of health and disease hypothesis
- Epigenetic instability:
  - Imprinting disorders
  - Altered DNA methylation
  - Histone modifications
  - Micro-RNAs

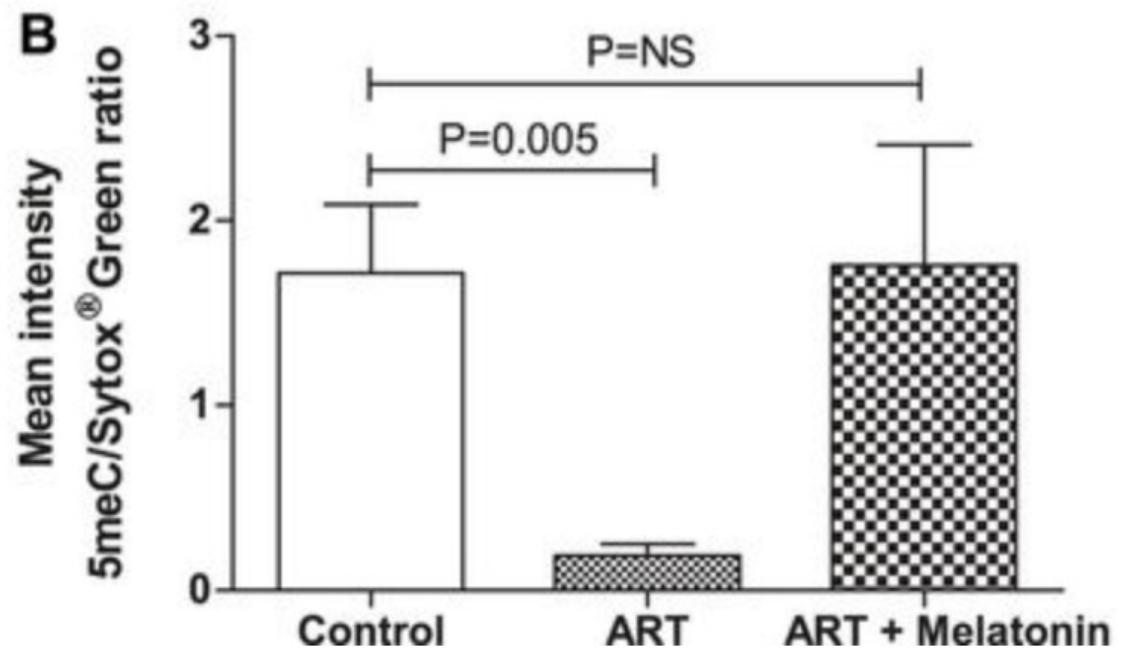


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(physical environment)

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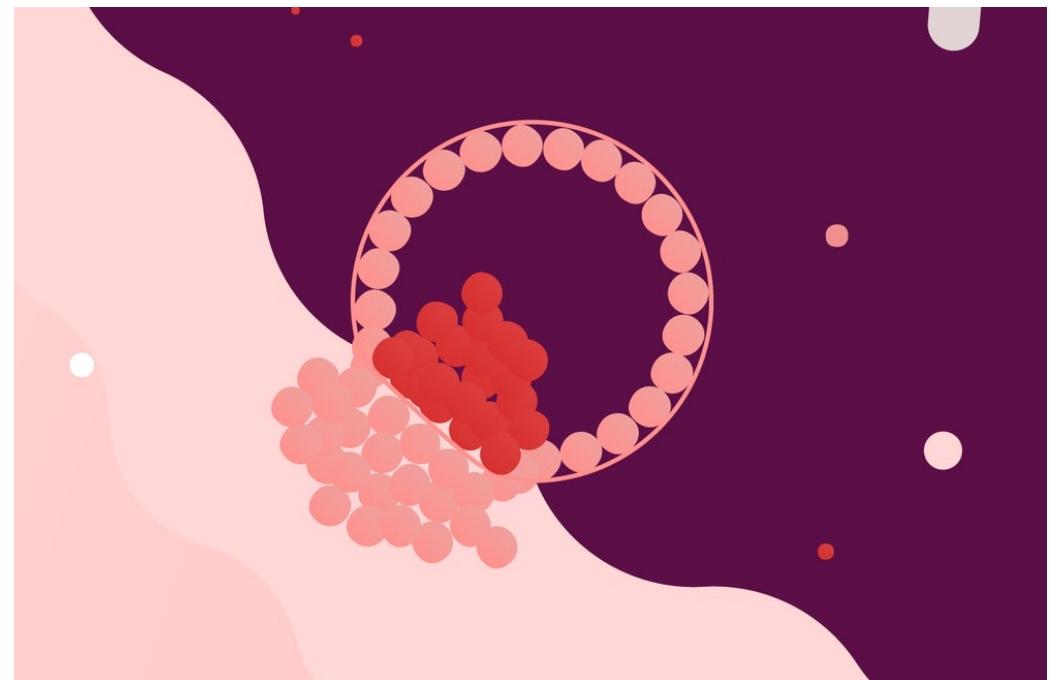
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- Improved follicular development



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- Better culture media system  
(physical environment)
- Improved follicular development
- **Improved implantation rates**



# The future of ARTs

- Better culture media system (physical environment)
- Improved follicular development
- Improved implantation rates
- **Improved genetic screening**
  - Using next-generation sequencing technologies



# The future of ARTs

- Improve gamete health for older couples



Erramatti Mangayamma gave birth to twins in India at the age of 74

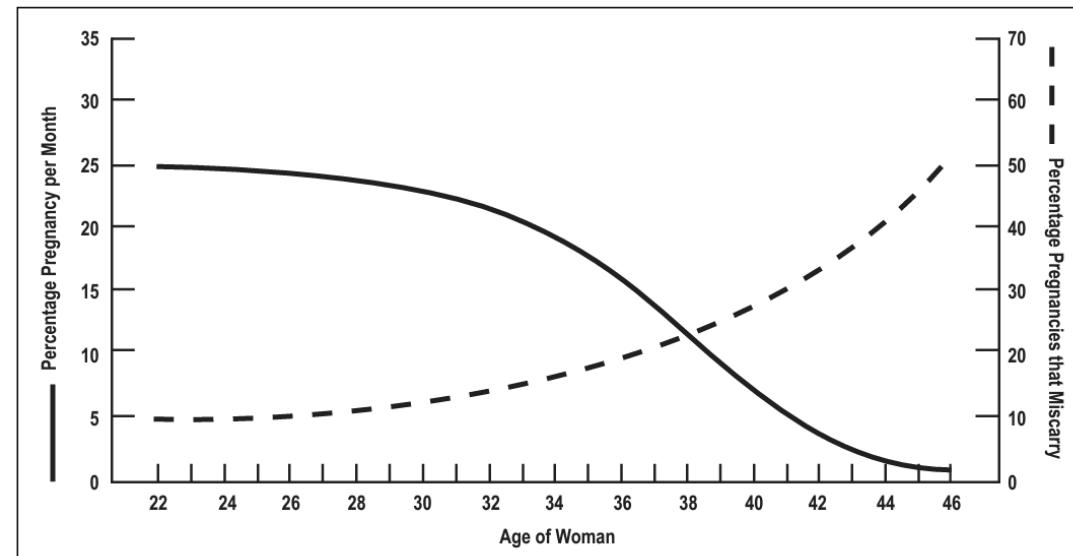
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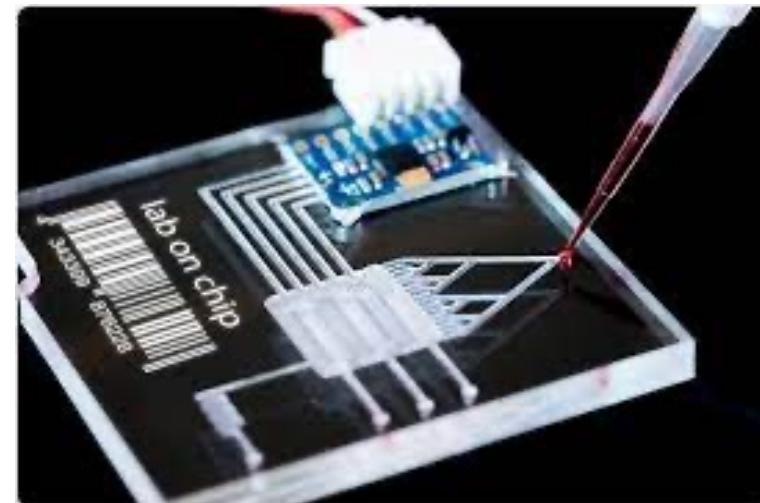
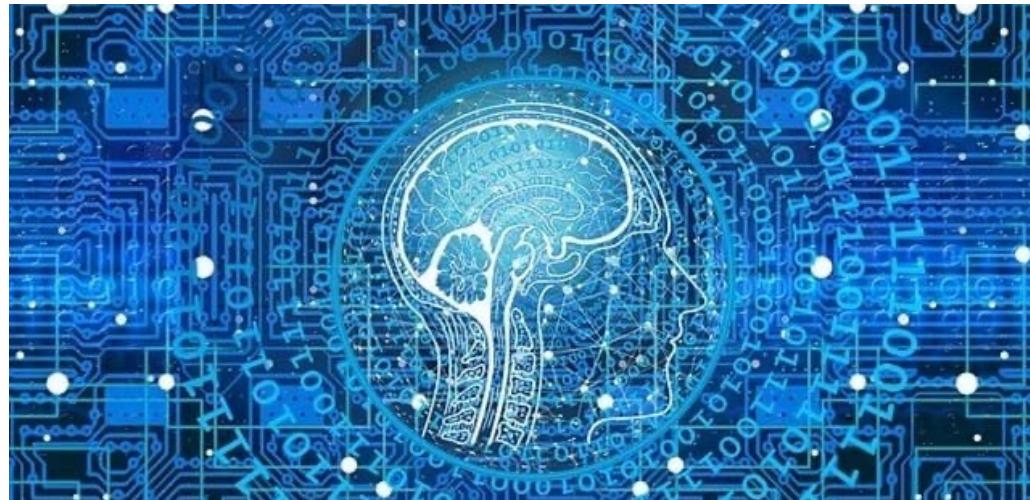
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**Figure 1. Natural conception: schematic demonstrating trends in pregnancy and miscarriage rates according to age**



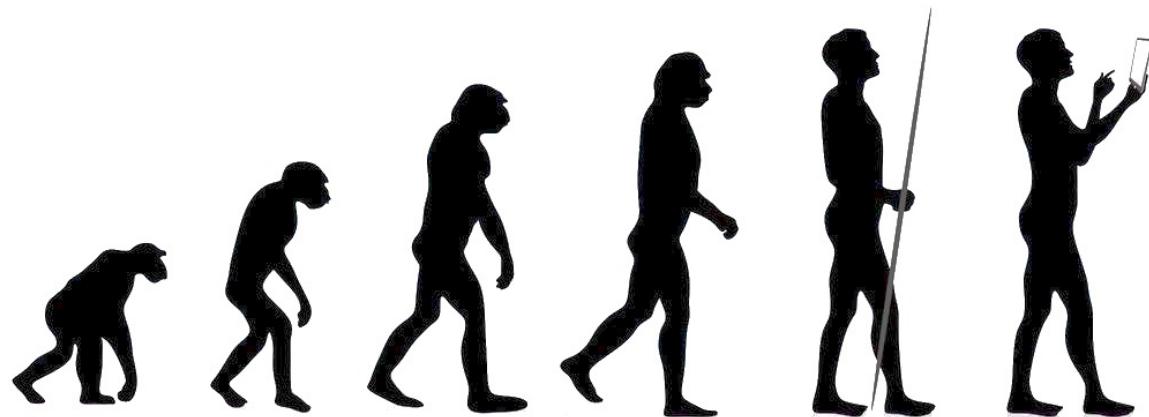
# The future of ARTs

- Integration with Artificial intelligence and machine learning:
  - Automated systems for embryo culture



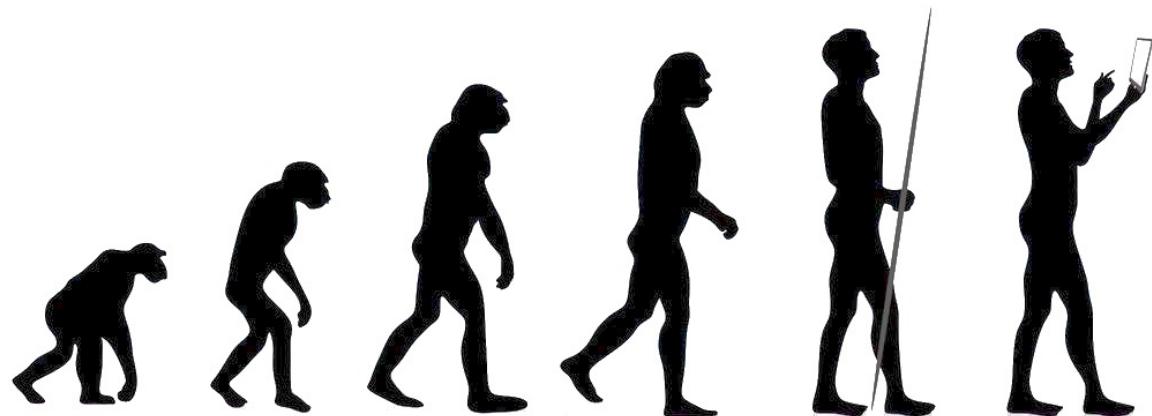
# Human evolution

- Selection pressures:
  - IVF vs. natural reproduction



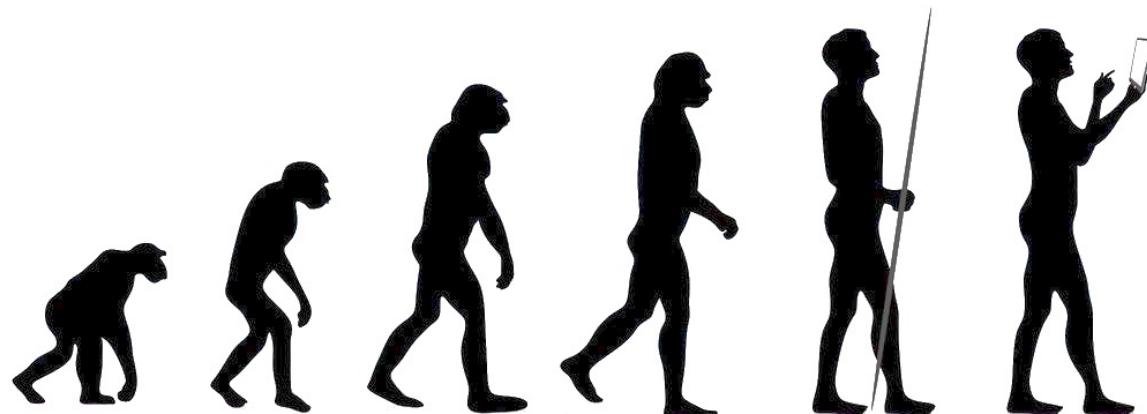
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# Human evolution

- Selection pressures:
  - IVF vs. natural reproduction
  - IVF favours sub-fertile individuals
- Increased reliance on ARTs for reproduction into the future



# Take home messages

- Many types of Artificial Reproductive Technologies
- Have potential health impacts
- Genetic mechanisms underpin differences
- long-term consequences of widespread ART use on human evolution



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