History and Fundamentals of Oocyte Maturation in Vitro

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History of IVM

1935	Pincus & Enzmann	IVM in rabbit
1965	Edwards	IVM of human oocytes
1983	Veeck	First IVM baby (‘GV rescue‘)
1989	Cha et al.	First IVM babies (triplets) (unstimulated, donor)
1993	Cha et al.	Further 4 IVM babies
1994	Trounson et al.	First IVM baby from PCOS
1995	Barnes et al.	PCOS
From 1996	Increasing number of groups worldwide	

- End of 2006: Probably around 500 IVM babies worldwide

- so we thought!

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Deliveries and ongoing pregnancies (facts and educated guesses)

Countries	Deliveries and ongoing pregnancies
Scandinavia	150
Italy	77
France	40
Germany	20
Rest of Europe	33
Total Europe	320

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Deliveries and ongoing pregnancies (facts and educated guesses)

Countries	Deliveries and ongoing pregnancies
Middle East	21
Japan	100
Vietnam	26
China (incl. HK)	60
Korea (Cha Hosp.)	57
Korea (Maria Cl.)	≈ 400
Rest of Asia	15
Total Asia	679

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Deliveries and ongoing pregnancies (facts and educated guesses)

Countries	Deliveries and ongoing pregnancies
Canada	120
USA	5
Australia	5
Total	130

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Deliveries and ongoing pregnancies (facts and educated guesses)

Countries	Deliveries and ongoing pregnancies
Asia	679
Europe	320
North America	125
Australia	5
Grand Total	1129

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Why do IVM ?

OHSS in PCO(S) patients

male factor

- patients
- community
- IVF Center

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Why do IVM ?

- Poor (slow) responders
- Repeated poor embryo quality
- Repeated failure of ovulation induction

- Cryopreservation prior to cancer treatment
- Career and life style considerations

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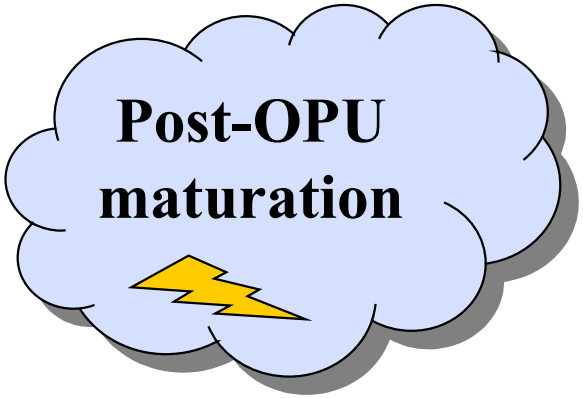
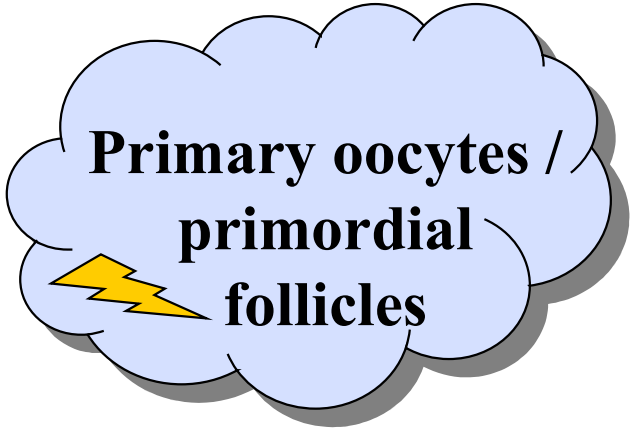
Why do IVM ? - future

GV oocytes from stimulated cycles



Stimulated cycles



Ovarian biopsies

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Scientific background for IVM

- Oogenesis
- Follicular development
- Follicular selection
- Follicular atresia

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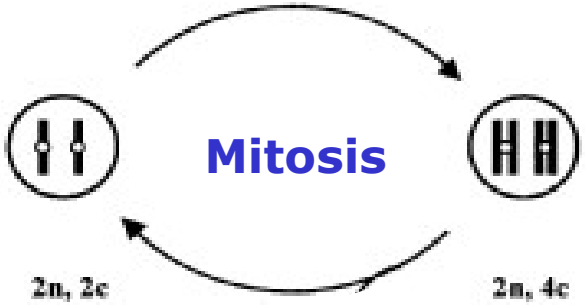
Gametogenesis

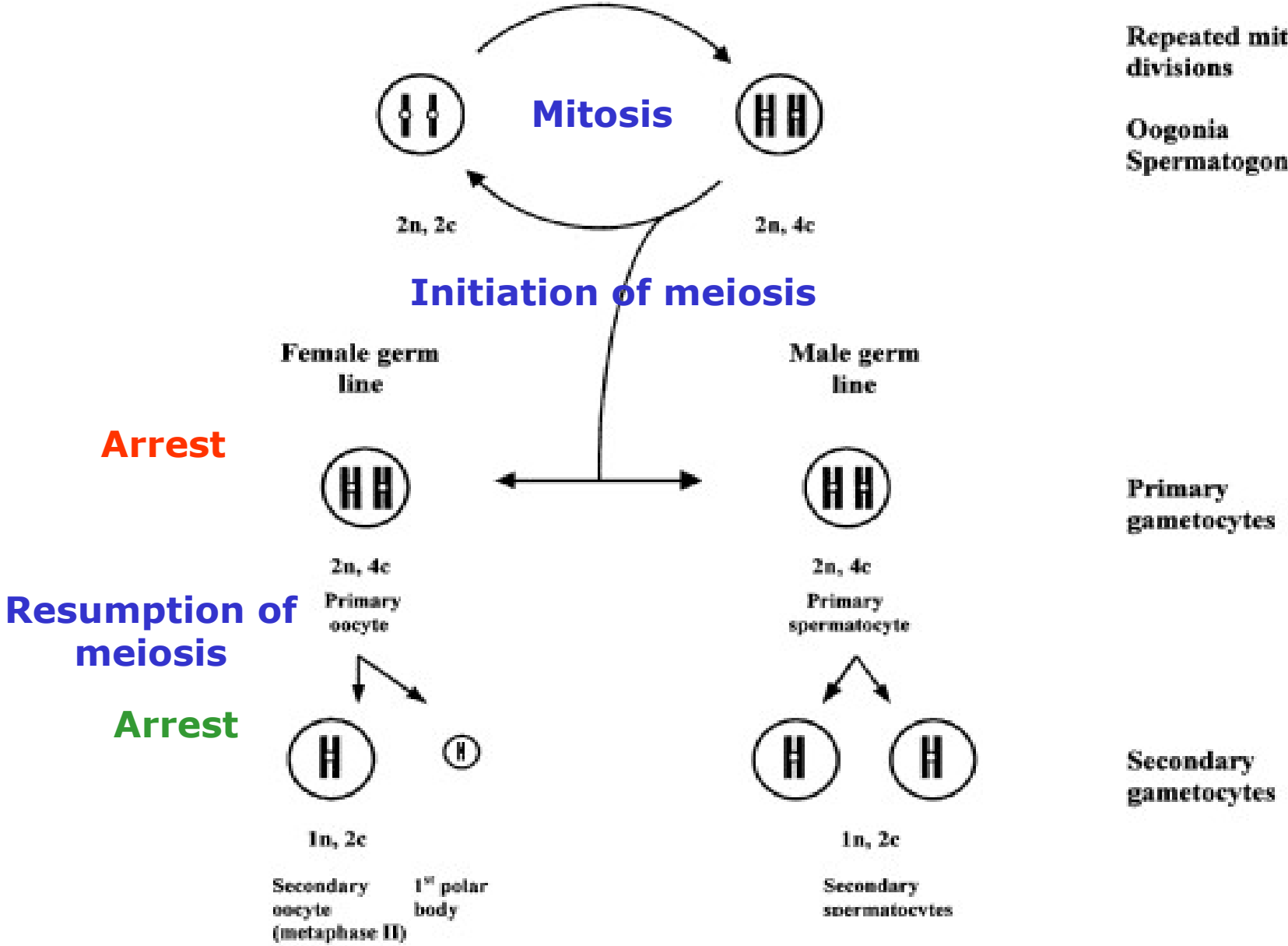


Repeated mitotic divisions

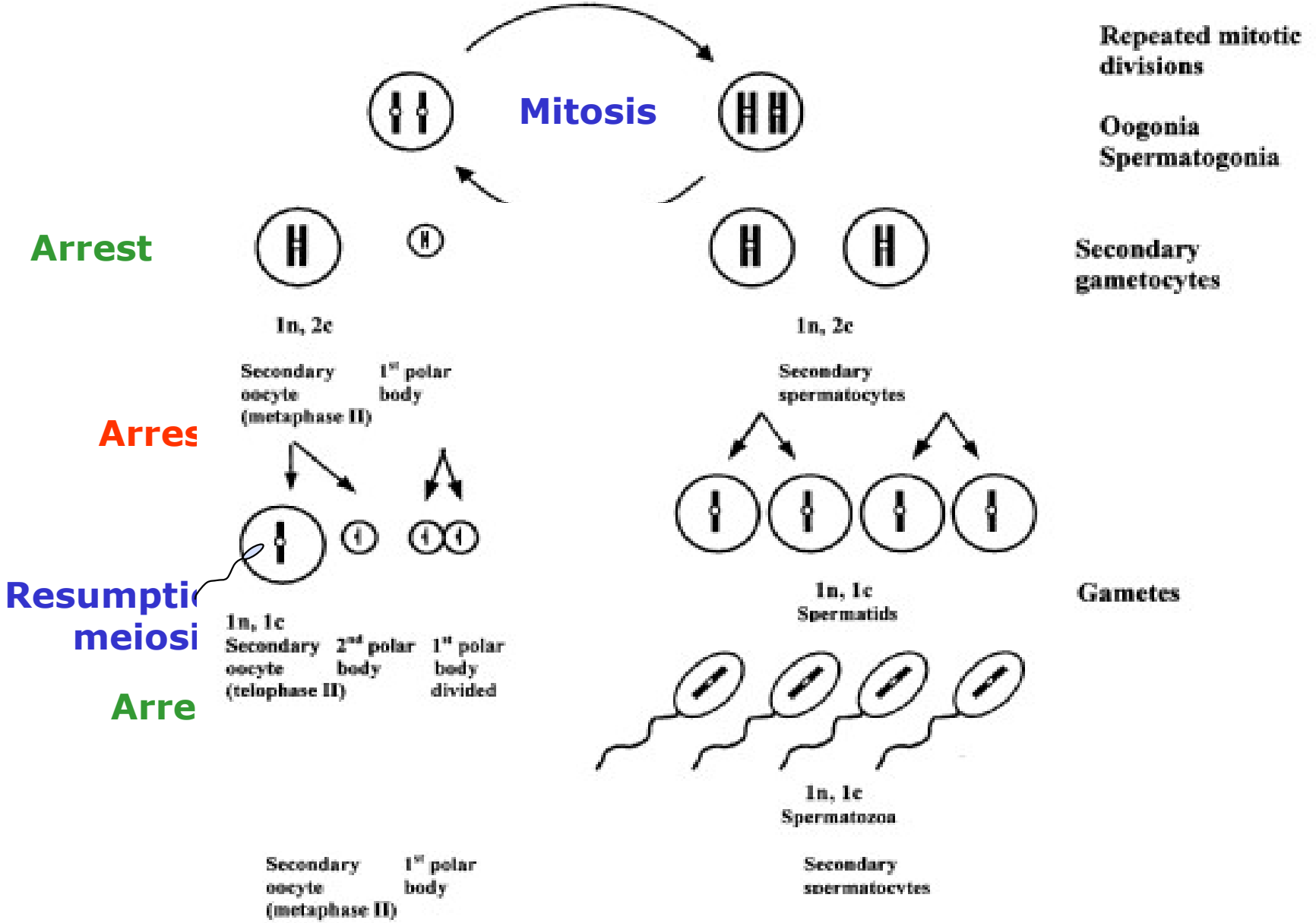
Oogonia
Spermatogonia

Initiation of meiosis

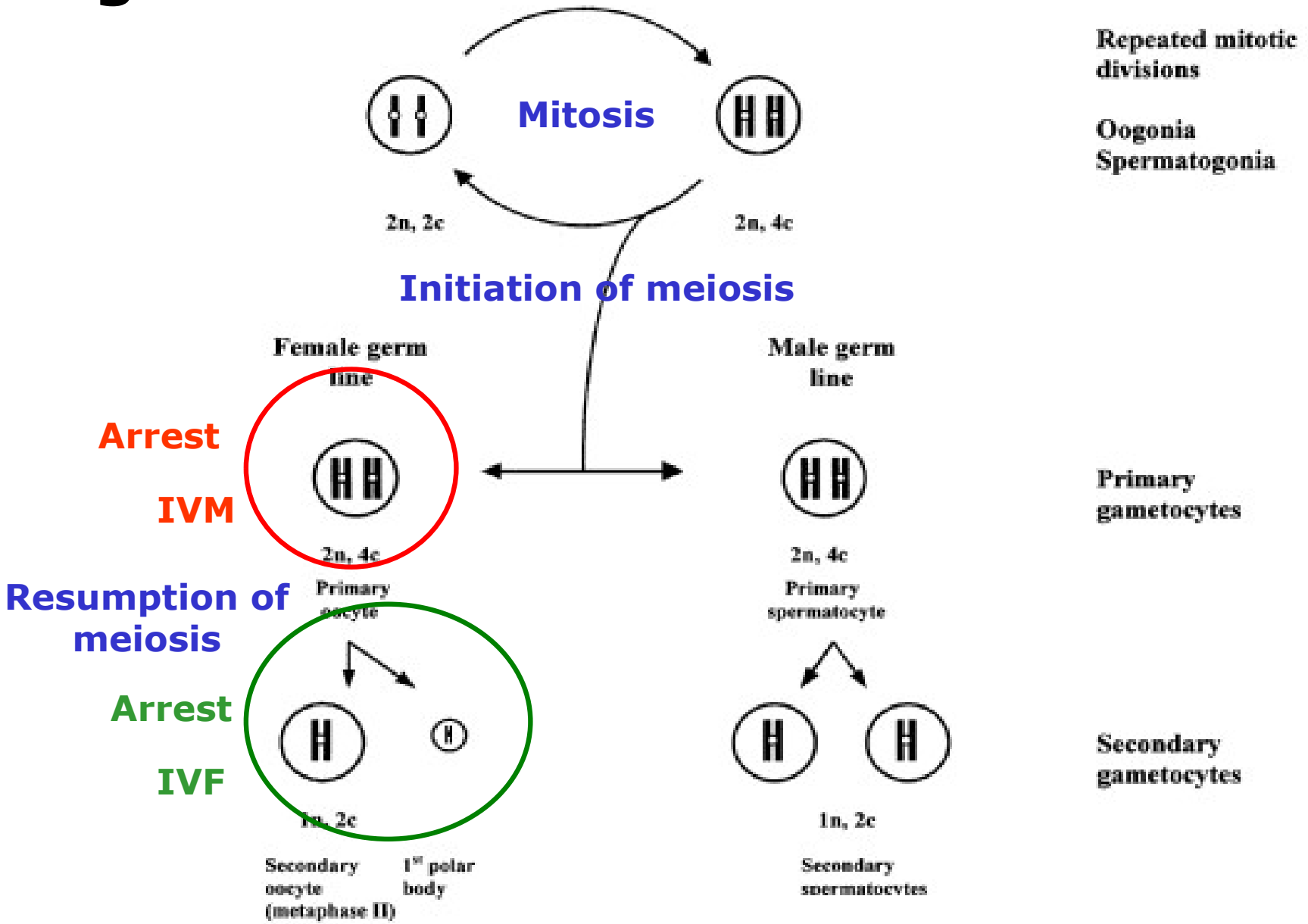
Gametogenesis



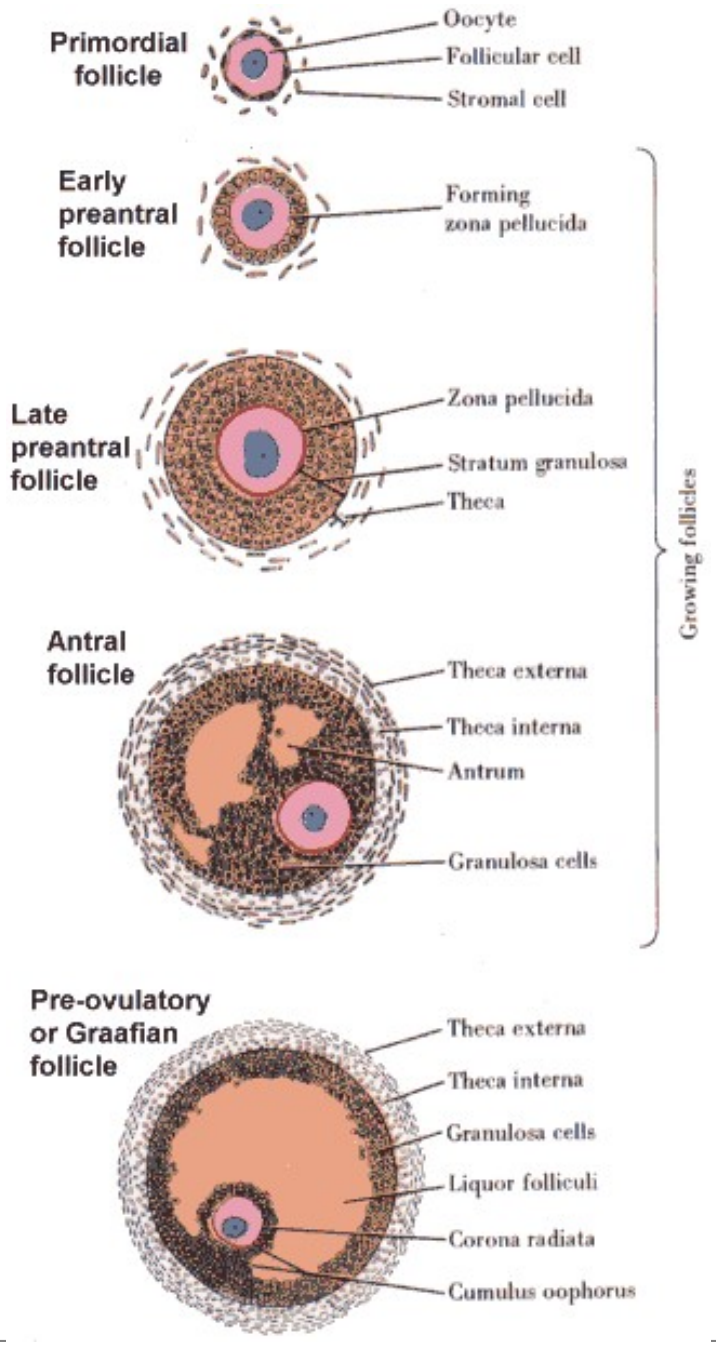
Gametogenesis



Gametogenesis



Development of an Ovarian Follicle



IVM

IVF

Modified from Ross et al. Histology A Text and Atlas, 3rd Ed.

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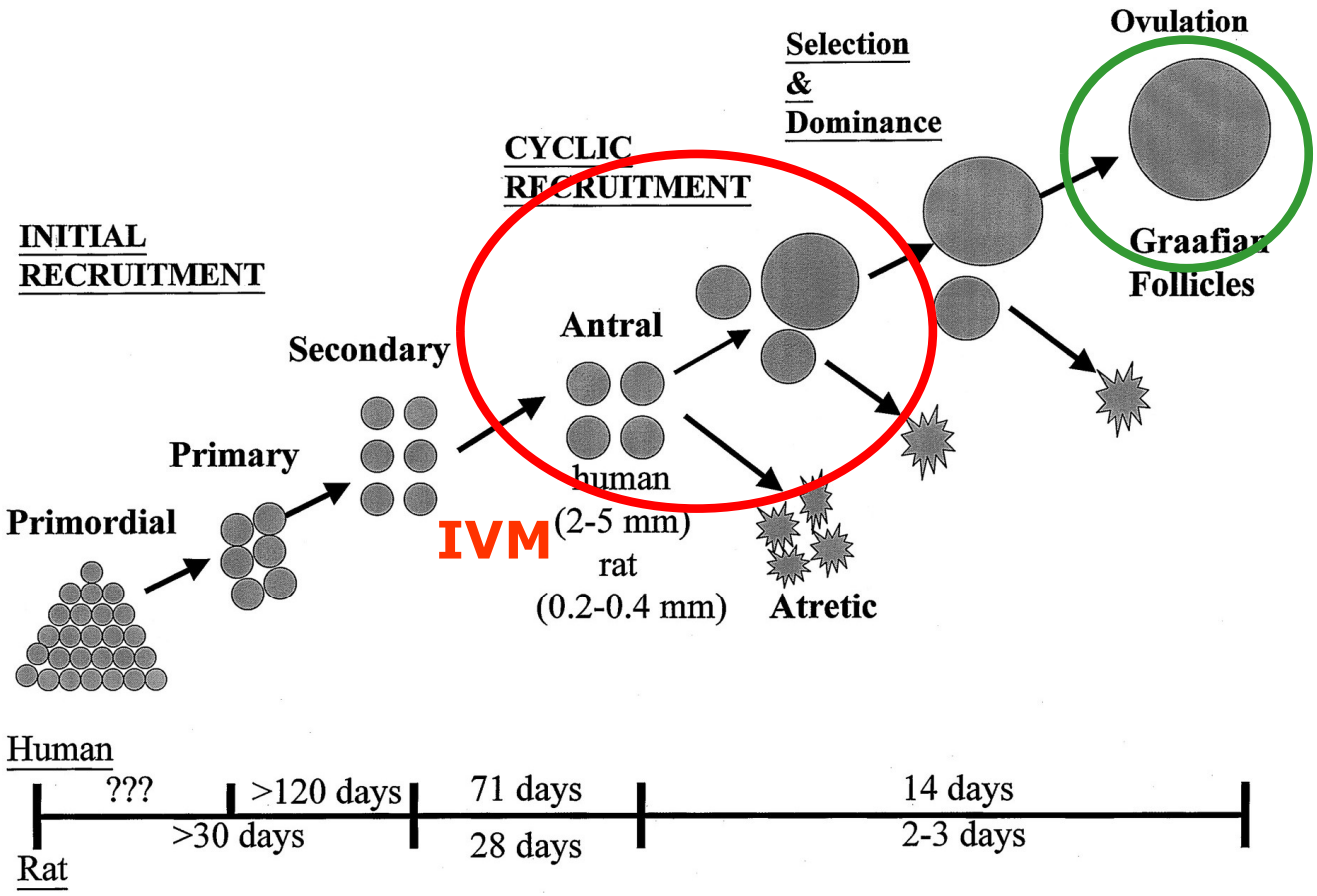
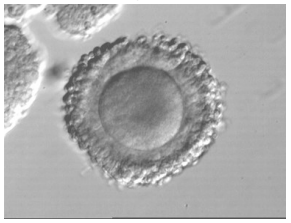
Follicle selection and atresia



Natural ovulation

Unstimulated IVM cycle

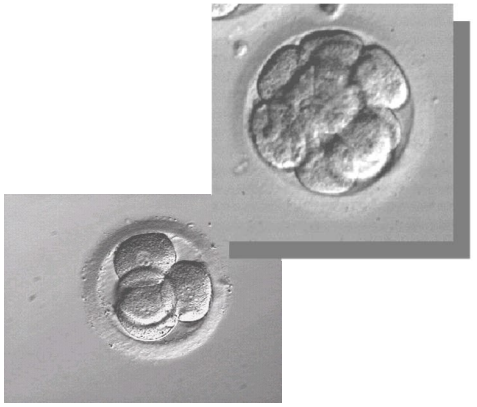


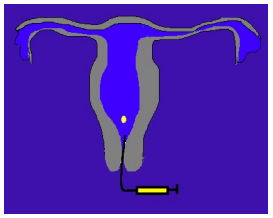
Day -1

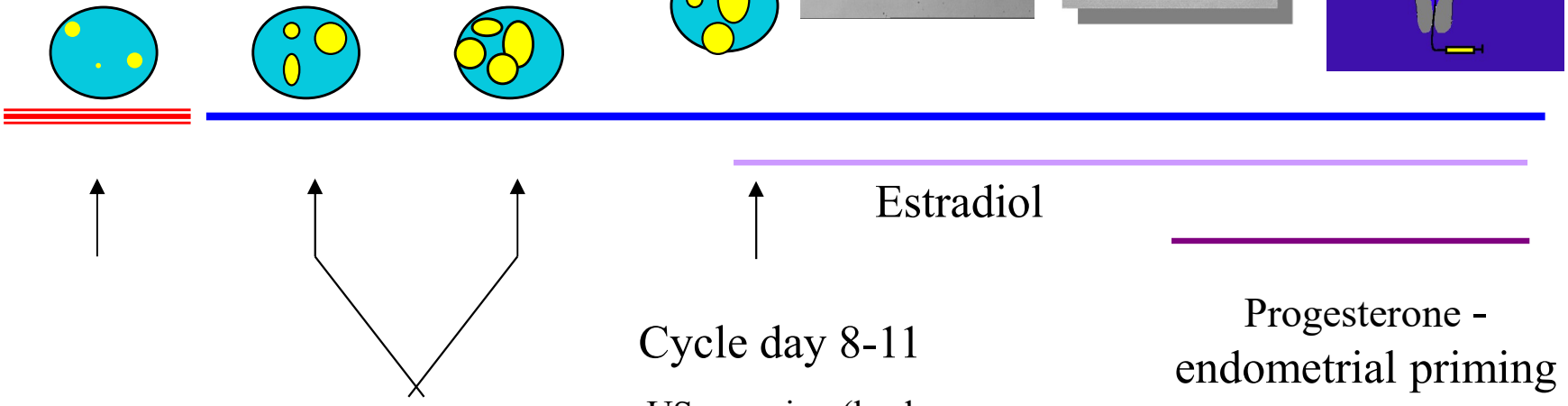
Day 0

Day 1

Day 2 or day 3







Estradiol

Progesterone - endometrial priming

Cycle day 3

US scanning

(Blood sample)

Cycle day 7-10

US scanning

(Blood sample)

Cycle day 8-11

US scanning (lead follicle 10-14 mm)

Blood sample

Oocyte pick-up

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Traditional IVF versus IVM

Traditional IVF

- Relatively many oocytes/embryos
- 'High' pregnancy rate / OPU
- Down regulation
- Daily hormone injections
- hCG injection
- Emotional stress
- Long treatment time - 4-6 weeks
- Potential side effects (e.g. OHSS)

IVM®

- Fewer oocytes and embryos
- Lower pregnancy rate / OPU - **BUT**
- No down regulation, no manipulation of hormone balance
- No hormone injections – or
- Minimal hormone injections (PCOS)
- (No hCG injection)
- Reduced psychological impact
- Reduced treatment time – 2 weeks
- Reduced interference with daily life
- No known side effects (e.g. OHSS)

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TABLE 1

Clinical outcome of IVM cycles in PCO and PCOS patients.

First author and year published (reference citation no.)	No. of cycles	Priming	Average no. of oocytes retrieved	% Maturation (duration of culture in h)	% Fertilization (type of insemination)	% Cleaved embryos	Average no. of embryos transferred	PR (%) per ET	IR (%)	No. of live births	% SAb
Cha 2000 (41)	94	None	13.6	62.2 (48)	68 (ICSI)	88	4.9	27.1	6.9	20	20
Cha 2005 (51)	203	None	15.5	NA	NA	NA	5.0	21.9	5.5	24	37
Chian 2000 (36)	13	hCG vs.	7.6	76.2/85.2 (24/48)	90.7 (ICSI)	94.9	2.8	38.5	16.6	3	40
	11	none	7.4	4.9[a]/68.0[a] (24/48)	83.9 (ICSI)	95.7	2.5	27.3	14.8	3	0
Child 2001 (38)	53 (PCO) vs.	hCG	10.0	76 (48)	76.3 (ICSI)	94.6	3.3	23.1	8.9	9	40
	66 (PCOS)	hCG	11.3	77 (48)	79.3 (ICSI)	91.3	3.2	29.9	9.6	10	52.3
Child 2002 (40)	107	hCG	10.3	76 (48)	78 (ICSI)	74	3.2	21.5	9.5	17	26.1
LeDu 2005 (10)	45	hCG	11.4	54.2/63 (24/48)	70.1 (ICSI)	95.3	2.5	22.5	10.9	6	40
Lin 2003 (39)	35	FSH + hCG vs.	21.9	43.2/76.5 (24/48)	75.8 (ICSI)	89.4	3.8	31.4	9.7	21	19
	33	hCG	23.1	39.2/71.9 (24/48)	69.5 (ICSI)	88.1	3.8	36.4	11.3		
Mikkelsen 2001 (37)	12	None vs.	6.9	44 (24)	69 (ICSI)	64	1.7	0	0	0	0
	24	FSH	6.5	59 (24)[a]	70 (ICSI)	66	1.8	39[a]	21.6	3	62.5
Soderstrom-Anttila 2005 (12)	20 (PCO) vs.	None	9.3	54.9 (30–48)	35.0 (IVF, 13)	85.7	1.7	22.2	13.3	2	0
					72.4 (ICSI, 7)	61.9	2.0	0	0	0	0
	26 (PCOS)	None	14.3	58.2 (30–48)	43.8 (IVF, 16)	82.5	1.7	52.9	34.5	6	33.3
					76.4 (ICSI, 10)	70.9	1.8	22.2	12.5	1	50

Note: NA = not available; PR = pregnancy rate; IR = implantation rate; SAb = spontaneous abortion.
[a] Statistically significant difference compared with the other arm of that study.

Average 3.0 29

Jarvis: A new maturation of human oocyte. Fertil Steril 2006.

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TABLE 2

Clinical outcome of IVM cycles in women with normal ovaries and regular cycles.

First author and year published (reference citation no.)	No. of cycles	Priming	Average no. of oocytes retrieved	% Maturation (duration of culture in h)	% Fertilization (type of insemination)	% Cleaved embryos	Average no. of embryos transferred	PR (%) per ET	IR (%)	No. of live births	% SAb
Child 2001 (36)	56	hCG	5.1	78.4 (48)	72.5 (ICSI)	93.1	2.6	4	1.5	1	50
Mikkelsen 1999 (50)	10	None vs.	3.7	76 (36)	62 (ICSI)	54	1.8	33.3	18.8	4	20
	10	FSH × 3 d	4	85 (36)	65 (ICSI)	62	1.9	22.2	11.8		
	5	FSH × 3 d, vs.	4.2	71 (48)	61 (ICSI)	48	1.4	20	14.3	1	0
	7	FSH × up to 6 d	2.4	71 (48)	61 (ICSI)	59	1.1	0	0		
Mikkelsen 2000 (48)	87	None	6.1	80 (28–36)	77 (ICSI)	87	2.0	17.4	8.6	9	18.9
Mikkelsen 2001 (49)	132	None	3.8	80 (28–36)	73 (ICSI)	87	NA	18	NA	12	20
Soderstrom-Anttila 2005 (12)	91	None	6.3	66.9 (30–48)	35.9 (IVF) vs. 67.1[a] (ICSI)	84.6	1.4	31	22.6	12	33.3
	100	None	6.5	54.5 (30–48)		85.6	1.5	21	20.0	15	16.7
Yoon 2001 (47)	69	None	9.0	40.7/71.5/74.3 (24/48/56)	72.6 (IVF and ICSI)	89	3.6	17.6	6.5	6	33.3

Note: NA = not available; PR = pregnancy rate; IR = implantation rate; SAb = spontaneous abortion.
[a] Statistically significant difference compared with the other arm of that study.

Average 2.0 20

Jarvis: In vitro maturation of human oocyte. Fertil Steril 2006.

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What needs to be improved in IVM?

- **IVM has a lower pregnancy rate per OPU - due to lower no. of oocytes/embryos resulting in lower transfer rate**
- **IVM has a lower pregnancy rate per ET - due to lower no. of embryos resulting in lack of selection possibilities, and possibly in a smaller no. of embryos transferred**
- **IVM has a lower implantation rate - due to lower no. of embryos resulting in lack of selection possibilities**
- **IVM has probably a higher rate of early pregnancy loss?**

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Shukran

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