Low Cost Approaches to IVF

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Why?

- Traditional IVF is expensive
  - Average cost: $15-18,000 in US - Forbes 2014
- Cycles require extended time commitment
  - Frequently 2-3 months to initiate
  - 1-3 months between failed attempts, including FET
- Aversion to ovarian stimulation
  - Fear of needles/injections
  - Fear/high risk of OHSS
- History of low oocyte yield/evidence for diminished ovarian reserve impedes patient retention
- Access to technology/infrastructure is not universal

Introduction

- ASRM White Paper: Access to Care Summit, 2015
  - In 2014 only 24% of infertile couples received access to adequate treatment in the US
  - Barriers to care include:
    - Cost
    - Social obstructions
    - Psychological obstructions
    - Physical access to care
  - Low cost options seen as a major step toward broadening access to care in the US and abroad

Introduction

- Suggested low cost approaches include:
  - Mild Ovarian Stimulation IVF
  - Natural/Modified Natural Cycle IVF
  - Vaginal Incubation (Invocell)
  - IVM

Mild Ovarian Stimulation

Definition:

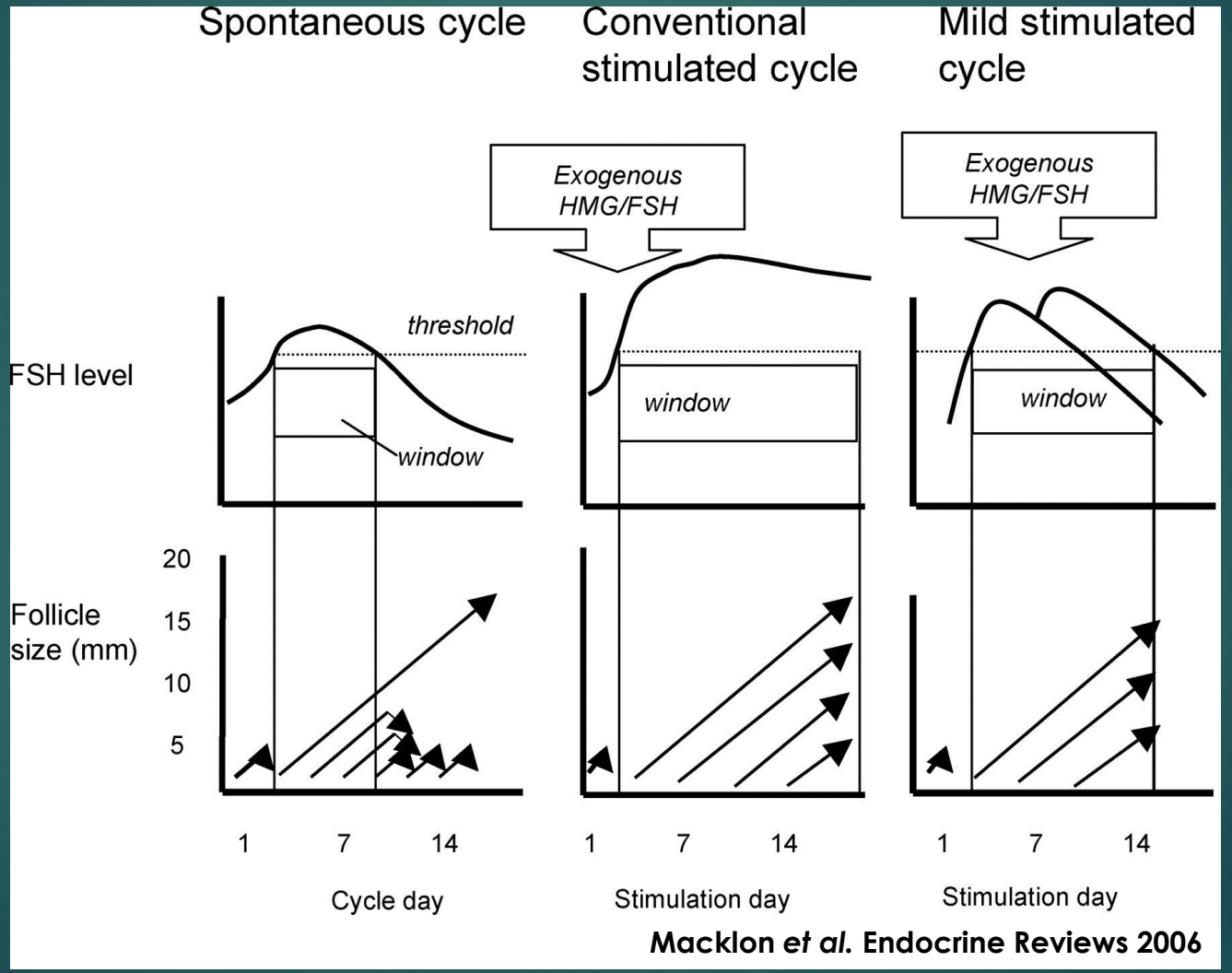
The administration of low doses (fewer days) of exogenous gonadotrophins in GnRH antagonist co-treated cycles, and/or oral compounds (like anti-estrogens, or aromatase inhibitors) for ovarian stimulation for IVF, aiming to limit the number of oocytes obtained to less than eight.

Fauser *et al*. Human Reproduction 2010

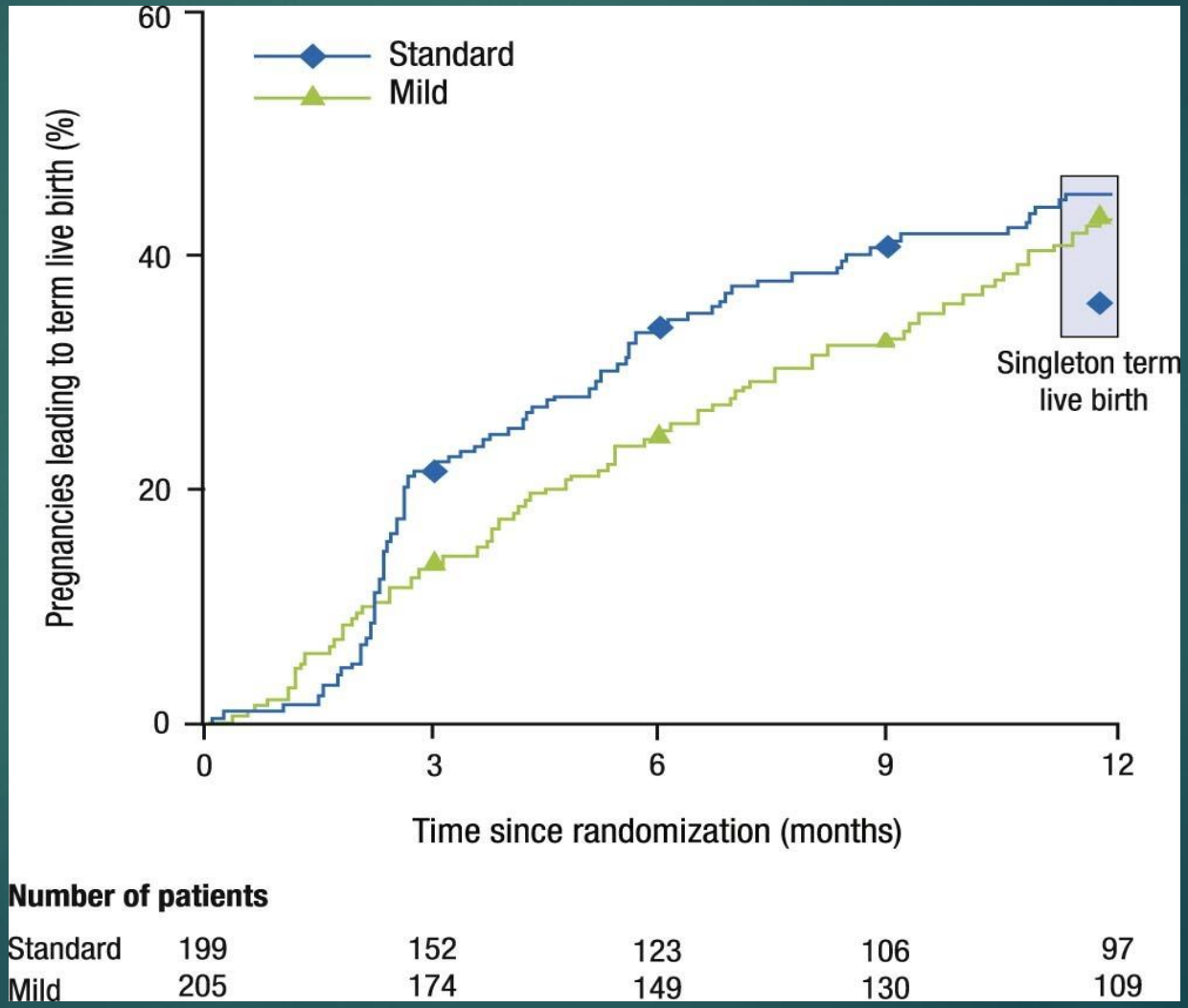
Mild Ovarian Stimulation

- Rationale
  - Decreased use of gonadotropins versus conventional COH-IVF (≤150 IU/day, Fewer days of stimulation)
  - Works best with GNRH antagonist protocols to prevent premature ovulation
  - Decreased monitoring
  - Decreased demand on lab (in theory)

Stimulation Approach



Cumulative Pregnancy Rate After 12 Months



Steward, *et al.* Fertility and Sterility, 2014

Advantages/Disadvantages

Advantages

- Similar live birth rate/cycle
- Reduced complexity
- Easier on patient
- Lower patient drop-out rate
- Lower cost
- Improved embryo quality

Disavantages

- Lower pregnancy rates/cycle
- Still require expensive medication
- Higher cancellation rates
- Fewer embryos to cryopreserve
- May result in higher overall costs when multiple cycles are required for success

Laboratory Concerns

- Prep not significantly different from conventional COH-IVF
- Hyper stimulation and excessive response risk not eliminated
- Perceived reduction in laboratory workload and income per cycle may lead to decreased support for staffing
- Greater pressure place on lab staff relative to outcomes
- Impact on SART/CDC statistics– a cycle is a cycle

Natural/Modified Natural Cycle IVF

Definitions:

Natural Cycle IVF (NCIVF) – a completely natural cycle in which the patients endogenous hormones and follicular growth is monitored until the retrieval of a mature oocyte can be attempted.

Modified Natural Cycle IVF (MNCIVF) – A natural cycle supplemented with antagonists to prevent ovulation and sufficient FSH to counteract the drop in pituitary gonadotropins, similar to mild stimulation, but with the goal of obtaining a single mature oocyte.

OR

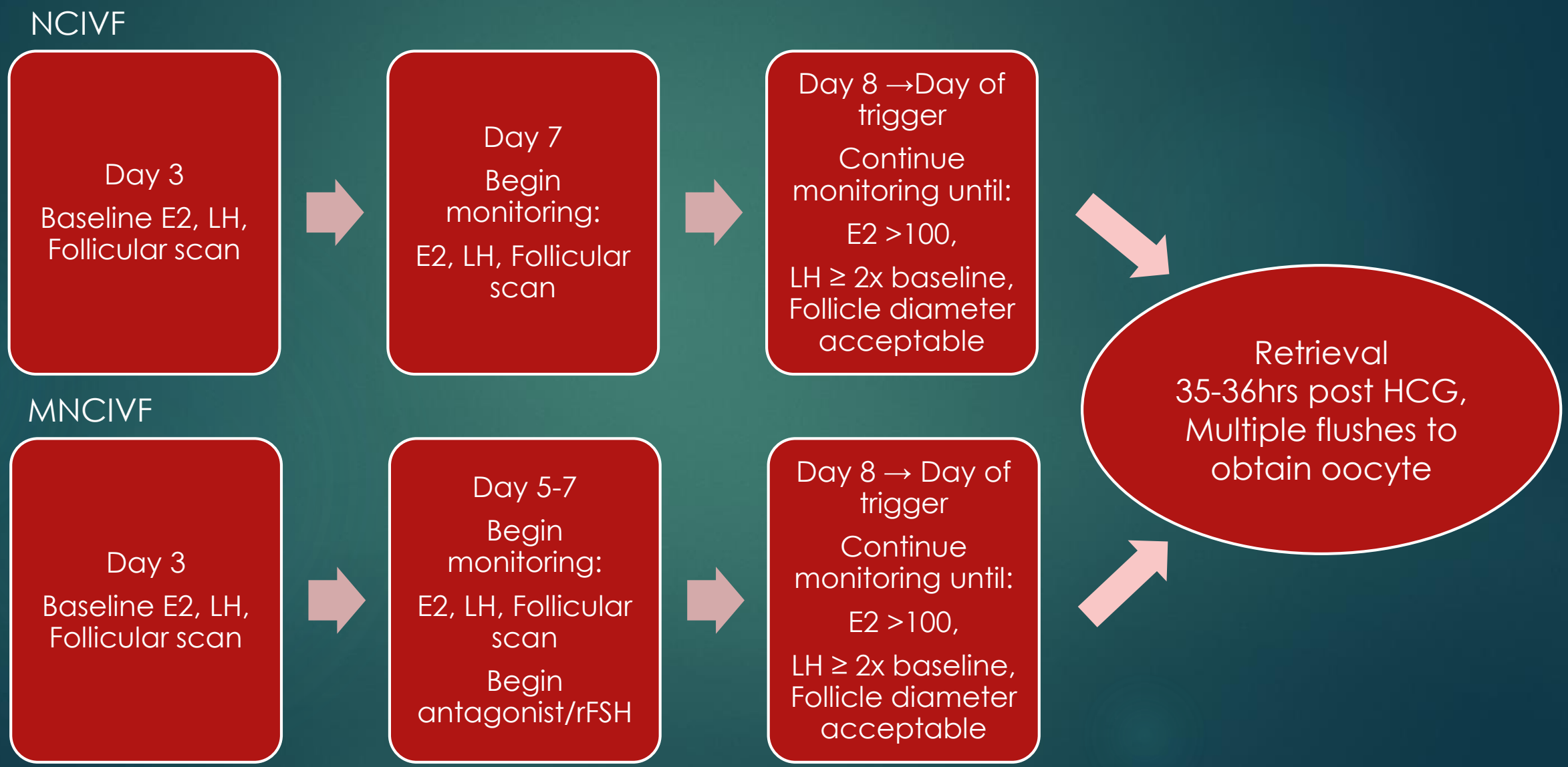
-A natural cycle supplemented with clomiphene citrate with the intent of retrieving 1 or more mature oocytes.

Controversy – The use of HCG as a trigger is a contested point in the US with respect to categorizing a cycle as NCIVF or MNCIVF.

Natural/Modified Natural Cycle IVF

- Rationale
  - "Natural" approach
  - No risk of OHSS
  - Reduced drug and supply costs
  - Back to back cycles are possible

Approach


NCIVF
Day 3
Baseline E2, LH, Follicular scan
Day 7
Begin monitoring:
E2, LH, Follicular scan
Day 8 →Day of trigger
Continue monitoring until:
E2 >100,
LH ≥ 2x baseline, Follicle diameter acceptable
MNCIVF
Day 3
Baseline E2, LH, Follicular scan
Day 5-7
Begin monitoring:
E2, LH, Follicular scan
Begin antagonist/rFSH
Day 8 → Day of trigger
Continue monitoring until:
E2 >100,
LH ≥ 2x baseline, Follicle diameter acceptable
Retrieval
35-36hrs post HCG, Multiple flushes to obtain oocyte

Natural Cycle IVF

- Considerations:
  - Patient must have regular ovulatory cycles
  - High cancelation rate relative to stimulate cycles
  - Trigger at smaller follicular size (≥15mm versus ≥18mm) to avoid premature ovulation
  - Multiple flushes may be required to retrieve oocyte (aspiration needle selection critical)
  - ICSI versus IVF
  - Day 3 verus Day 5 ET

History

- 1977: Steptoe and Edwards second attempt at NCIVF resulted in pregnancy and the subsequent live birth of Louise Brown (July 25, 1978)
- Bourne Hall reported reasonable success using NCIVF
- Other clinics unable to replicate this success, resorting to clomiphene/gonadoptropin stimulate cycles
- Greater oocyte yield/control of cycle has lead to the dominance of stimulated IVF throughout the world
- NCIVF still widely practiced in Europe
- 2015: ASRM encourages the exploration of NCIVF as a low cost option

Early NCIVF

Table 1 Early attempts at natural cycle *in vitro* fertilization with laparoscopic retrieval (modified from Lenton et al.[15])

	England[13]	Australia[16]	United States[17]
Laparoscopies	35	107	41
Cycles with eggs (%)	29/35 (83%)	62/107 (57.9%)	19/41 (46.3%)
Eggs fertilized (%)	24/25 (96%)	31/66 (47%)	9/15 (60%)
Pregnancy rate/embryo transfer (%)	6/24 (25%)	0	0

	Lenton (2007)	Tomazevic (2007)	Phillips (2007)	Pelinck (2008)	Kadoch (2008)	Schimberni (2009)	Aanesen (2010)	DiMattina (2010)
Cycles	775	397	NA	1048	255	NA	129	243
Oocyte retrievals attempted (%/cycle)	92.60%	92.70%	242	81.70%	87%	500	69%	86.80%
Successful retrieval (%/ attempt)	79.50%	82.30%	72.70%	73%	77.9%	78.10%	85.40%	88%
Fertilization ICSI or IVF	IVF	IVF	Both	IVF	Both	ICSI	Both	Both
Fertilization rate (%/oocyte)	NA	NA	73%	72.50%	NA	NA	NA	75%
Day of embryo transfer	NA	Blast	NA	D3	D2	NA	D2	Day 3 and Blast
Embryo transfer (n)	368	122	127	382	119	285	60	119
Embryo transfer (%/cycle)	47.40%	30.70%	NA	36.50%	46.70%	NA	46.50%	49%
Embryo transfer (%/OR attempt)	51.20%	33.10%	52%	44.60%	53.60%	57%	67.40%	56%
Pregnancy rate/ET (%)	14.40%	39.30%	18.90%	27.20%	18.50%	17.10%	26.70%	35%
Pregnancy rate/Retrieval attempt (%)	7.40%	13%	9.90%	12.10%	9.90%	9.60%	18%	20%
Pregnancy rate/cycle (%)	6.80%	12%	NA	9.90%	8.60%	48/?	12.40%	17%
GnRH-antagonist	N	N	Yes	Yes	Yes	No	N	N
rFSH add-back	N	N	Yes	Yes	Yes	No	N	N
Follicle size/E2 level	LH	> 16 mm; > 0.39 nmol/l	17 mm	18 mm	17 mm	≥ 16 mm	17-19 mm E2>500-750 pmol/l	≥ 15 mm
Timing (LH or hCG)	LH	hCG	hCG	hCG	hCG	hCG	HCG	hCG
Timing of retrieval (hr)	Varied	31-32	34	34	34	36	37 h	34
Type of needle (SL, DL, NA)	NA	SL	DL	SL	DL	NA	NA	SL
Flushing of follicle	NA	N	Yes	No	Yes	NA	Some	Yes
Luteal support/Type	NA	HCG 1500 D9	hCG 2500 OR+2 and OR+4 ; prog 200 mg PV tid	hCG 1500 OR+5, OR+8, OR+11	hCG, P4 supp	50 mg PIO	NONE	Prog supp 100 mg, estrace 2 mg

D2: day 2; D3: day 3; E2: estradiol; ET: embryo transfer; GnRH: gonadotropin-releasing hormone; hCG: human chorionic gonadotropin; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilization; LH: luteinizing hormone; NA: not available; OR: oocyte retrievals; rFSH: recombinant follicle stimulating hormone

Laboratory Concerns

- 1 oocyte = Greater pressure per cycle
- Prep can be greatly simplified
- Faster retrievals = faster OR turnaround
- Perceived reduction in laboratory workload and income per cycle may lead to decreased support for staffing
- Impact on SART/CDC statistics – slowly improving with new sorting methods

Advantages/Disadvantages

Advantages

- Similar implantation rate
- Reduced complexity
- Easier on patient
- Lower patient drop-out rate
- Lower cost

Disavantages

- Lower pregnancy rates/cycle
- Higher cancellation rates
- Rare to have supernumerary embryos to cryopreserve
- May result in higher overall costs when multiple cycles are required for success

INVOCell

INVO bioscience

INVOCell

- Mild, natural cycle, or modified natural cycle IVF protocol
- Vaginal incubation

History

- Technique pioneered in 1985 as a means of controlling CO_2 and O_2 instability
- Pregnancy rates similar to traditional IVF
- Proposed as a means of bringing IVF to developing countries
- 2008 INVOcell device introduced
- Currently used in clinics throughout the world
- Rapidly growing use in the US

Preliminary results

Initial results of INVO using the prototype device			
Number of publications	Countries	Number of INVO cycles	Clinical pregnancy rate/cycle (%
9	Austria, France, Germany, Japan, Netherland, UK, USA	815	19.6

Results of the prelaunch clinical trial using the INVOcell			
		Clinical pregnancy	
Groups	Cleavage rate (%)	per cycle	Rate per transfer
Group 1			
≤ 10 Oocytes retrieved	52.2	31.80% (7/22)	38.90% (7/18)
Group 2			
≥10 Oocytes retrieved	48.9	11.70% (7/60)	13.50% (7/52)
Total	49.9	17.10% (14/82)	17.10% (14/82)

Z.P. Nagy et al. (eds.), Practical Manual of In Vitro Fertilization: Advanced Methods and Novel Devices, Springer Science+Business Media, LLC 2012

Method

- Load inner chamber with medium containing 30,000 motile sperm/ml
  - Standard bicarbonate buffered culture media
- Place ≤10 oocytes into inner chamber
- Seal chamber and place in outer shell
- Outer shell is placed in diaphragm and inserted into the patients vagina by clinician

Method

- Vaginal incubation lasts 2-3 days (some current clinics are experimenting with blastocyst culture)
- Device is removed and a specialized holding block allows embryos to be graded prior to opening inner chamber
- Embryos are selected for transfer, removed, and rapidly loaded for ET in the absence of a CO_2 incubator
- Remaining embryos may be cryopreserved

INVO bioscience

FIGURE 1: INNER VESSEL

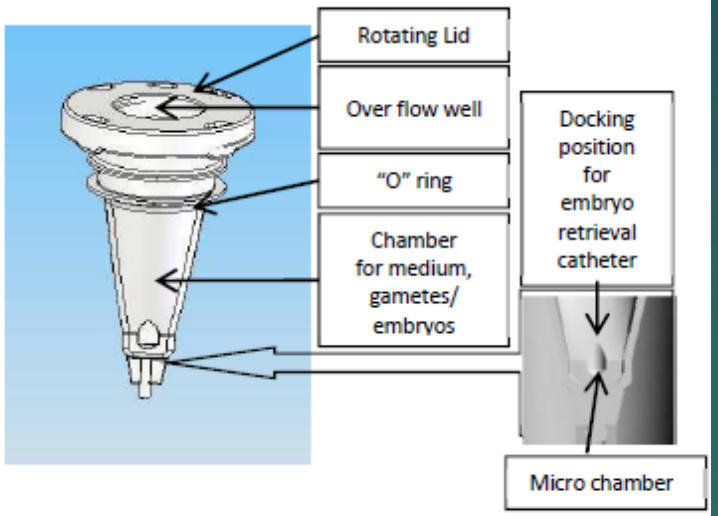
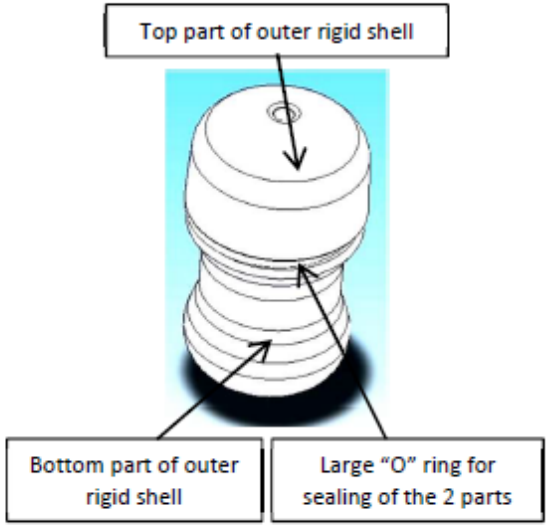


FIGURE 2: OUTER RIGID SHELL FOR CELL CULTURE CONTAINER



One package contains the inner chamber. The second package contains the top and bottom parts of the outer rigid shell.

INVO bioscience

Considerations

- No fertilization check
- CO_2 incubator greatly reduces potential failures in the process
- Presence of CO_2 incubators in developed countries may negate the logistic advantage of INVOcell

Laboratory Concerns

- Specific training required
- Prep can be simplified
- Decreased equipment demand
- Perceived reduction in laboratory workload and income per cycle may lead to decreased support for staffing
- Potential impact on SART/CDC statistics
- Growing use of ICSI and IVF insemination

Advantages/Disadvantages

Advantages

- Reports of similar pregnancy rates to tradition culture
- Reduced process complexity
- Resistance to equipment failure
- Decrease infrastructure needed
- Lower cost

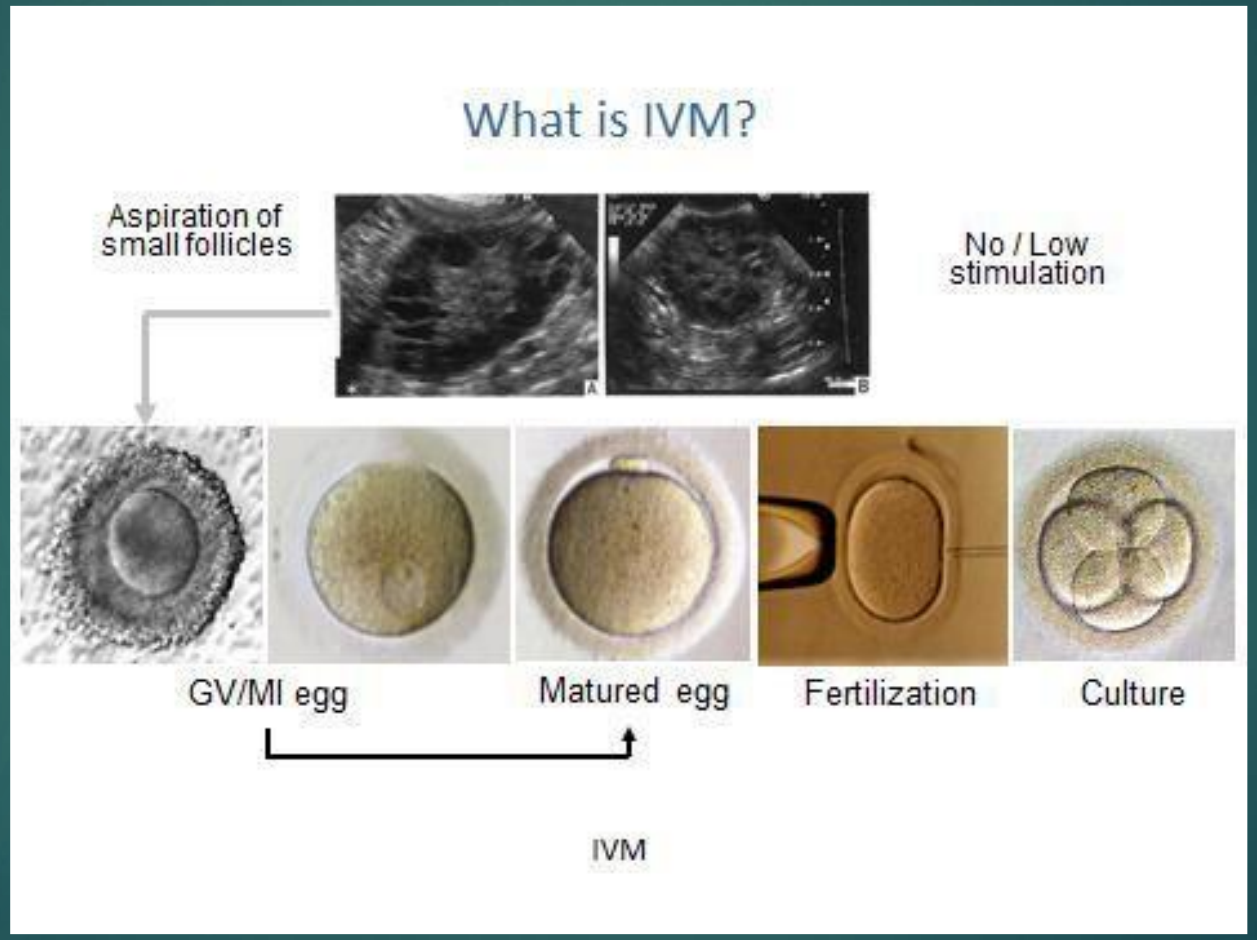
Disadvantages

- No fertilization check
- Cannot verify development until day of ET
- Uncomfortable for some patients
- Cost benefit in existing US lab unclear

in vitro Maturation (IVM)

- Definition (ASRM): maturation in culture of immature oocytes after their recovery from follicles which may or may not have been exposed to FSH, but were not exposed to either LH or hCG prior to retrieval to induce meiotic resumption

in vitro Maturation (IVM)



Vuong Thi Ngoc Lan, M.D., MCE, ASRM Access to Care Whitepaper, 2015

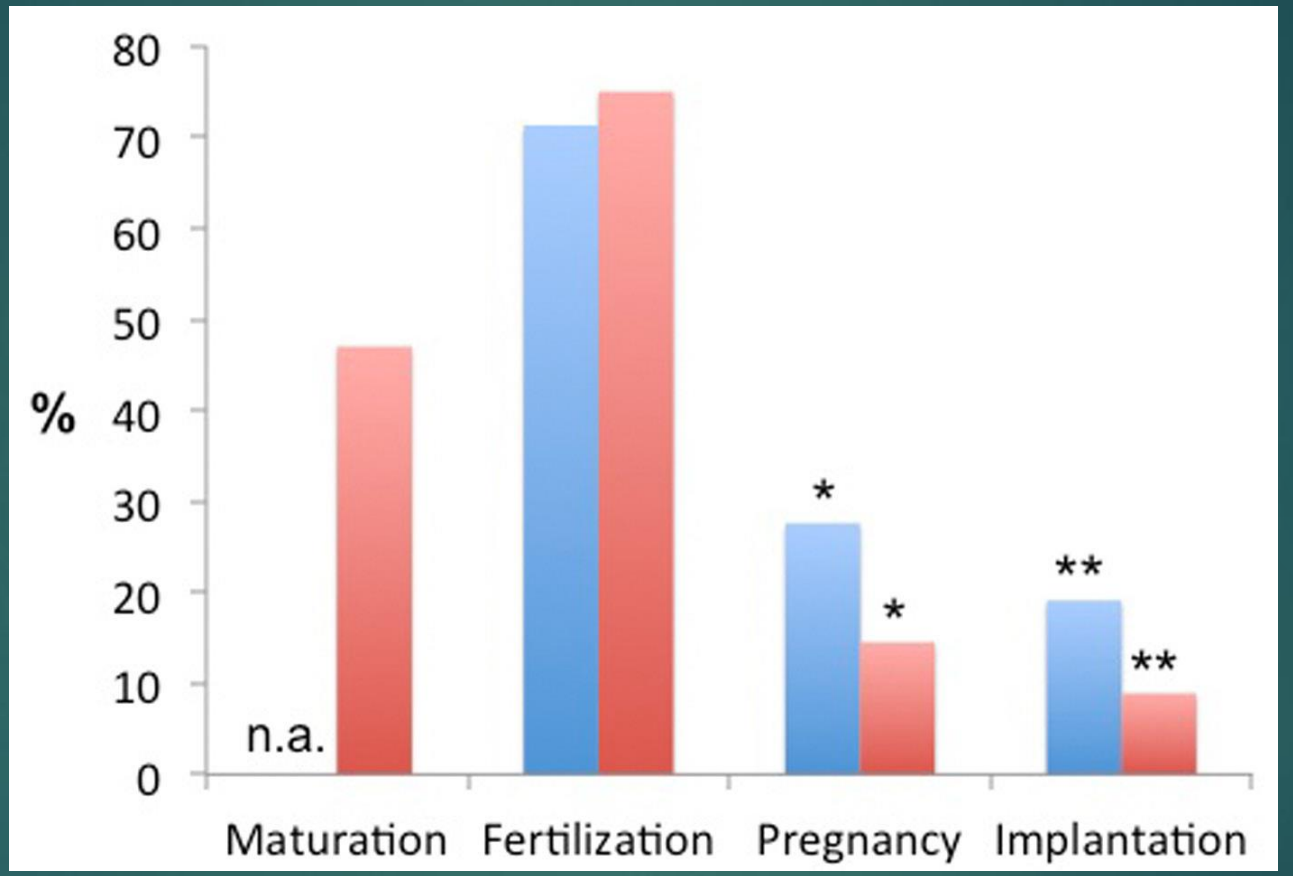
IVM History

- 1935: Pincus and Enzmann perform successful IVM on rabbit oocytes
- 1944: Culture of human oocytes for 22-28hrs prior to fertilization and cleavage (Rock and Menkin)
- 1965: First reported IVM of human oocytes (Edwards)
- 1989: First reported human birth using IVM (Cha, *et al.*)
- 1994: First treatment of PCO patients (Trounson *et al.)*

Method

- Follicles monitored in a natural or FSH supplemented cycle until they reach 10-12mm
- Aspiration of COCs followed by 30-48hrs of *in vitro* culture prior to stripping
  - Culture media may contain FSH, LH or HCG, Estradiol, serum.
  - No consensus on media enrichment
- Insemination by ICSI of MII oocytes
  - Zona Hardening concerns

Results



Maturation, fertilization and developmental competence (expressed as pregnancy and implantation rates) of human oocytes derived from invitro maturation cycles and matured invivo (blue bars) or in vitro (red bars). Percentages are cumulative frequencies. See also text for further details (Dal Canto et al., 2012). * $p < 0.0001$, ** $p < 0.0001$.

Clinical Concerns

Table 1. Reported birth outcomes after IVM

Citation (authors, ref no.)	Year	Number of included births	Obstetric and perinatal outcomes
Cha et al. [35]	2005	20 Singleton, 4 twin live births after IVM	3 Congenital anomalies (5.3%) 2 Major (omphalocele: miscarriage, hydrops fetalis: termination, normal chromosome)
Mikkelsen [39]	2005	47 Births after IVM	No specific abnormalities related to the IVM procedure One 46 XX with CCNH gene variation, inherited paternally (no clinical significance) One IUFD, induction failure, and asphyxia
Soderstrom-Anttila et al. [40]	2006	40 Singletons, 3 sets of twins	8 (19%) Minor developmental problems expressed One optical glioma Neuropsychological development within the normal range at 2 yr of age
Shu-Chi et al. [37]	2006	21 IVM births	Growth and developmental scale comparison with non IVM, no developmental delay
Buckett et al. [36]	2007	55 IVM, 217 IVF, and 160 ICSI babies compared	Risk of congenital anomalies (odd ratios) 1.42, 1.21, and 1.69, respectively
Fadini et al. [38]	2012	200 Babies born following IVM	No detected major congenital abnormalities

IVM, *in vitro* maturation; ref no., references number; IUFD, intrauterine fetal death; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection.

Chang, et al. Clinical and Experimental Reproductive Medicine, 2014

Laboratory Concerns

- Increased culture complexity
- Longer duration in laboratory
- Increased training needed to identify and isolate COCs
- Methodologies not standardized
- Potential impact on SART/CDC statistics

Advantages/Disadvantages

Advantages

- Reduced cost to patient
- Reduced risk of OHSS
- More gentle approach for patient

Disadvantages

- Clinical outcome concerns
- Increased demand on lab/cycle
- Physiologic differences between *in vivo* and *in vitro* maturation unknown
- Cost benefit to lab/clinic is unclear

Summary

Approach	Target patients	Key benefits	Drawbacks	Concerns
Mild Stim	All, OHSS	Cost, Comfort	↓embryos	Cumulative cost, OHSS?
NCIVF	Normal cycling	Cost, Comfort	1-2 embryos	Cumulative cost
INVOCell	All	Decreased Infrastructure requirements	Embryo monitoring	Actual savings?
IVM	All, OHSS, PCOS	Drug cost, Comfort	↓PR ↑demand on lab ↑clinical cost	Outcomes (perinatal concerns)

Summary

- Access to infertility care is seen as a major health issue for the 21st century, both in the US and internationally
- Multiple strategies are being refined to address this shortcoming
- No single strategy offers a complete solution.

The End

Questions?