

Assisted Reproductive Technology

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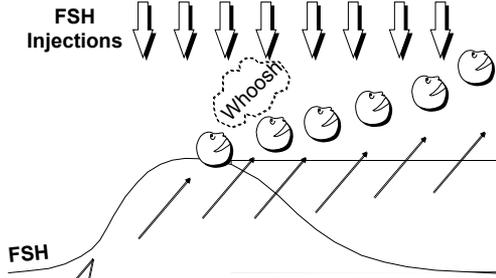
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Wolfson Medical Center,
Holon, Israel**

- ❖ Gonadotropin preparations
- ❖ GnRH-a administration protocols
- ❖ GnRH-a antagonists
- ❖ Results: SART data

Possibilities of ovarian stimulation in assisted reproduction

- clomiphene citrate
- gonadotrophins
 - human menopausal gonadotrophin (HMG)
 - urinary follicle stimulating hormone (FSH)
 - recombinant FSH, LH
- GnRH agonists
 - long protocol
 - short protocol
 - ultrashort protocol
- GnRH antagonists
 - single dose protocol
 - multiple dose protocol

Multiple Follicular Development: Extension in the Period of FSH Elevation



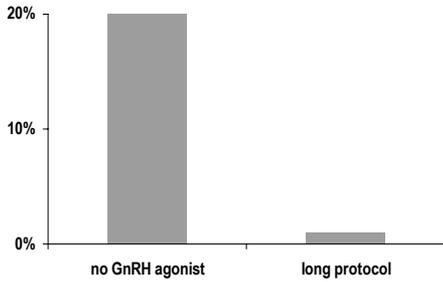
Those antral follicles which coincide with the extended period of elevated FSH can enter the final stages of follicular growth

The Importance of Retrieving Multiple Oocytes in ART

- More embryos to choose between for transfer results in higher pregnancy rate
 - better chance of picking the ‘best’ (UK HFEA Data, 1998)
- Embryos for freezing and replaced in a natural cycle (increase overall PR)
 - Subsequent chance of pregnancy without stimulation, (Howard Jones, Hum Reprod 1997)

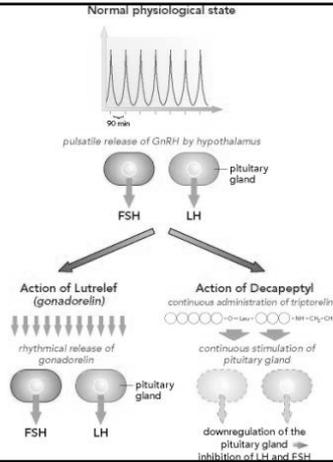
Action, structure and use of GnRH agonists and antagonist

Reduction of cancellation rates due to LH surges by use of GnRH agonists

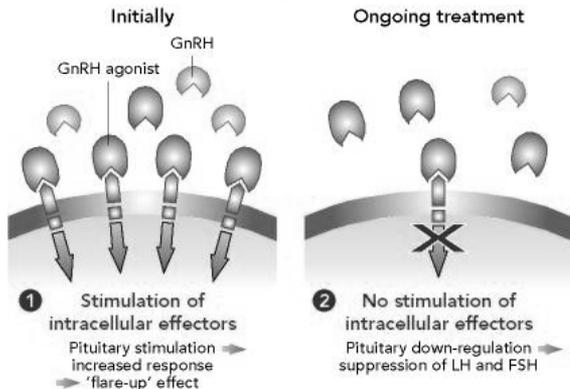


Balen, 2001

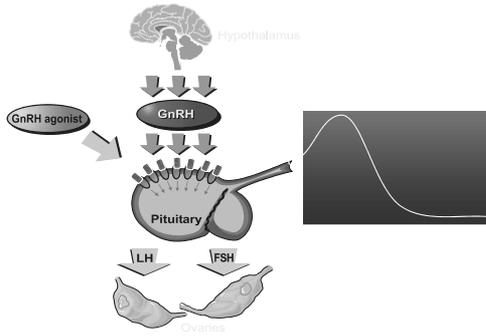
Action of GnRH and its agonist



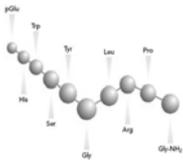
Pituitary downregulation



Mechanism of action GnRH agonist



Structure of GnRH



1 2 3 4 5 6 7 8 9 10

pyro (Glu) – His – Trp – Ser – Tyr – Gly – Leu – Arg – Pro – Gly –

activation of the
GnRH receptor

regulation
of GnRH
receptor
affinity

regulation of
biologic activity

Structure of GnRH agonists

modifications of natural GnRH
to have GnRH agonistic properties

1 2 3 4 5 6 7 8 9 10

pyro (Glu) – His – Trp – Ser – Tyr – Gly – Leu – Arg – Pro – Gly –

activation of the
GnRH receptor

regulation
of GnRH
receptor
affinity

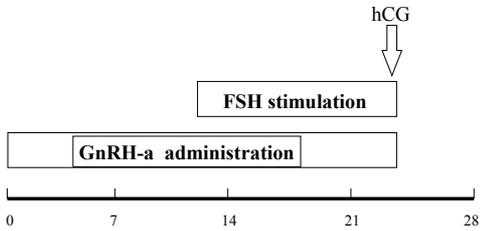
regulation of
biologic activity

Table 1. The structure of GnRH and GnRH agonistic analogues

Compound						6 th position					10 th position
Amino Acid (No)	1	2	3	4	5	6	7	8	9	10	
Native GnRH	Glu	His	Trp	Ser	Tyr	Gly	Leu	Arg	Pro	Gly-NH ₂	
Nonapeptides											
Leuprolide						Leu				NH ₂	
Buserelin						Ser(O ^t Bu)				NH ₂	
Goserelin						Ser(O ^t Bu)				AzaGlyNH ₂	
Histrelin						DHis(Bzl)				AzaGlyNH ₂	
Decapeptides											
Nafarelin						2Nal				GlyNH ₂	
Triptorelin						Trp				GlyNH ₂	

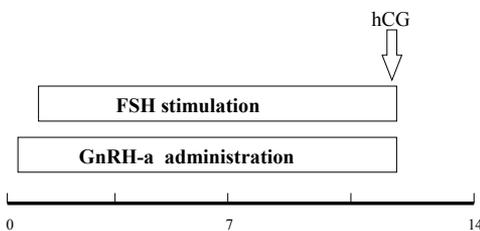
The long protocol of GnRH-a administration

- Suppression of endogenous gonadotropin secretion prior to stimulation



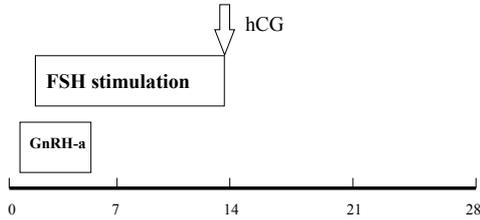
The short protocol of GnRH-a administration

- Initial stimulatory effect of GnRH-a on pituitary gonadotropin release ('flare-up effect')



The ultra-short protocol of GnRH-a administration

- Initial stimulatory effect of GnRH-a on pituitary gonadotropin release ('flare-up' effect)



The use of GnRH-a in ART: superiority of the long protocol

Meta-analysis of randomized or quasi-randomized trials

2,061 cycles comparing the long and short protocol

Combined OR for conception and birth after IVF:

1.26 (95% CI= 1.01-1.56) p=0.036



- ❖ Absolute treatment effect - 3.6%
- ❖ Relative treatment effect - 18.8%

Daya, 1997

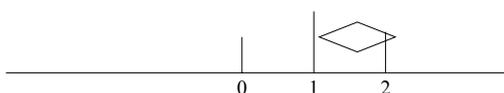
The use of GnRH-a in ART: superiority of the long protocol

- Meta-analysis of randomized or quasi-randomized trials

- 648 cycles comparing the long and ultra-short protocol

- Combined OR for conception and birth after IVF:

1.47 (95% CI= 1.02-2.12) p=0.039

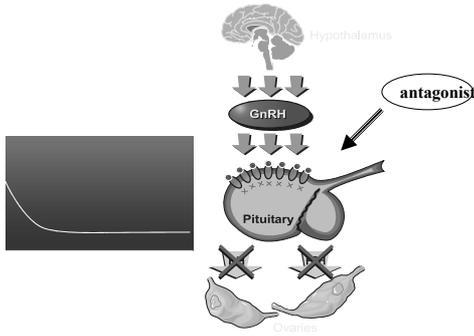


- ❖ Absolute treatment effect - 6.7%
- ❖ Relative treatment effect - 32.6%

Daya, 1997

Mechanism of action: Antagonists

Prevention of premature LH surge



Structure Compared with LHRH

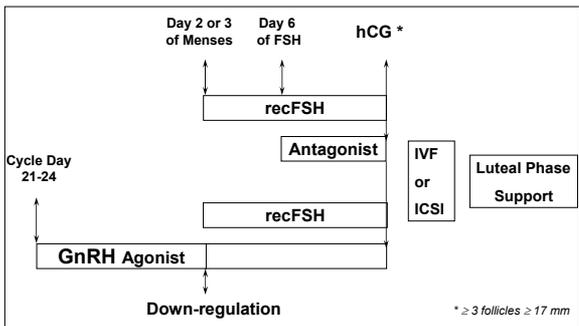
Cetrorelix



LHRH



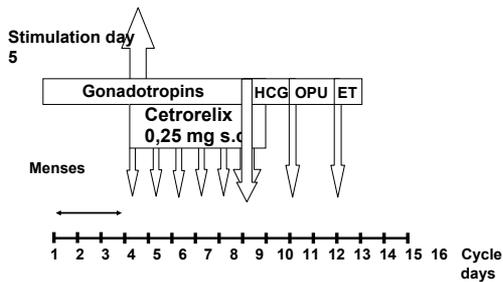
Treatment Regimens



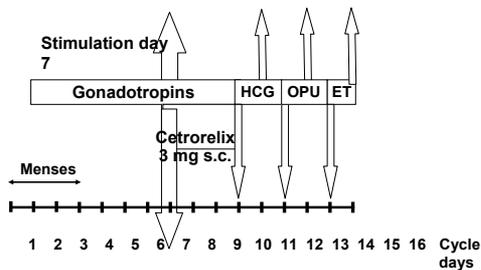
Two possible antagonist protocols

- Multiple dose protocol
- Single dose protocol

The Cetrotide 0.25 mg multiple dose protocol



The Cetrotide 3 mg single dose protocol



GnRH Antagonists in Assisted Conception

Cochrane Systematic Review

Al-Inany and Aboulghar. Hum Reprod ,2002

GnRH antagonist : 1211 subjects
GnRH agonist: 585 subjects

Total **1796** subjects

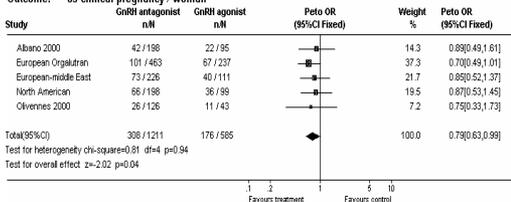
Al-Inany and Aboulghar. Hum Reprod ,2002

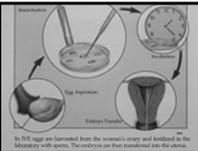
Clinical Pregnancy per woman

Pregnancy rate was significantly lower in the antagonist group
OR 0.79 (95% C.I.,0.63-0.99)

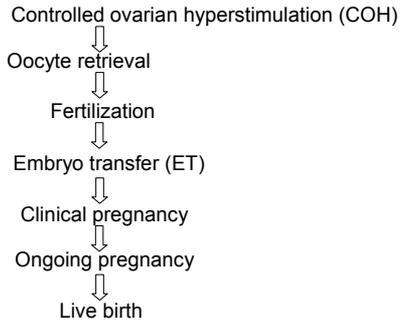
Comparison: 03 Pregnancy outcome

Outcome: 03 clinical pregnancy / woman

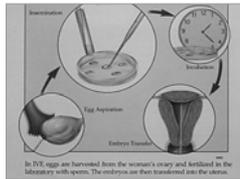
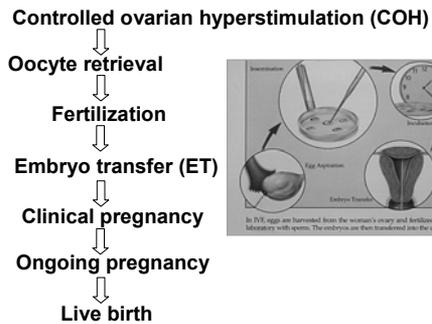


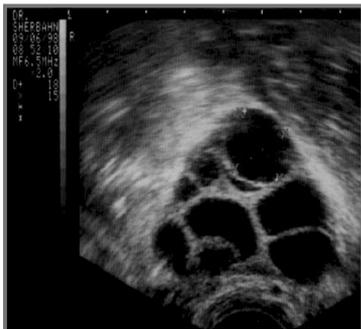


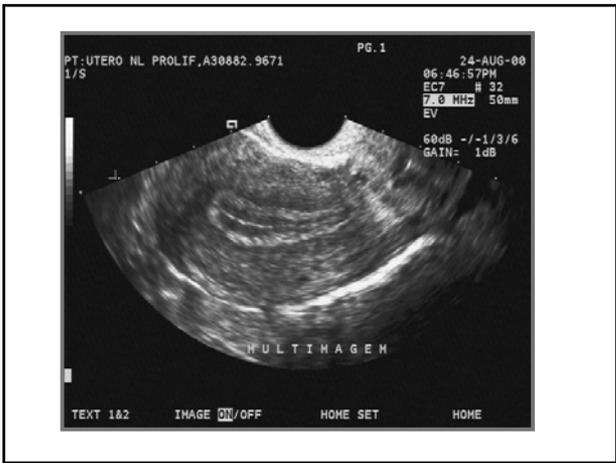
Stages of IVF

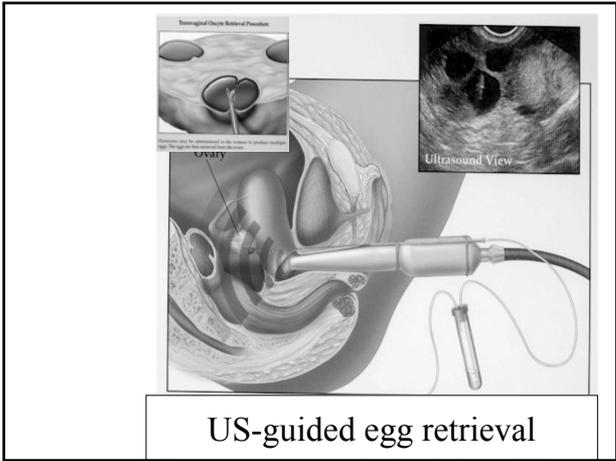


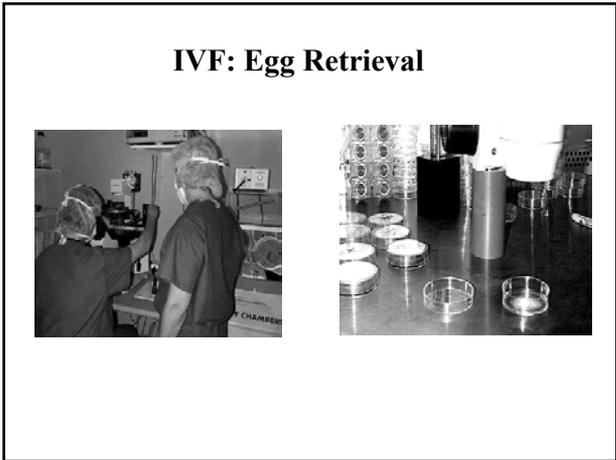
Phases in IVF

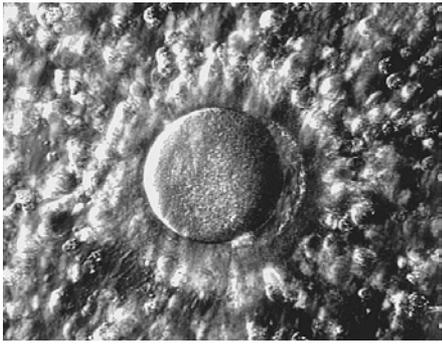










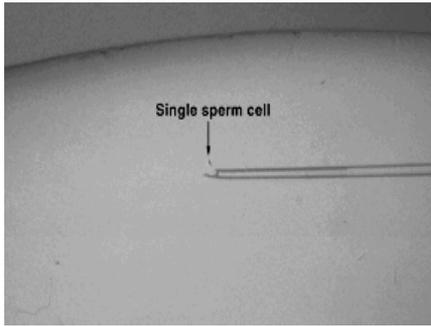




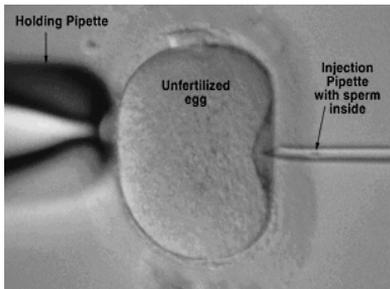
Intracytoplasmic sperm injection (ICSI)



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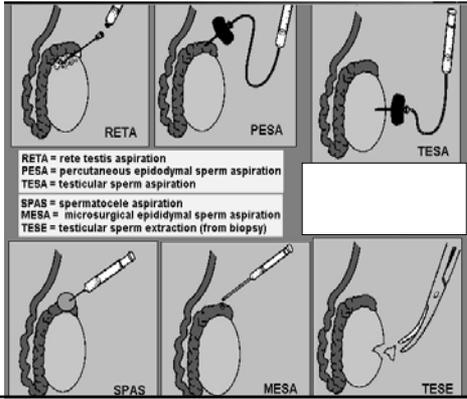
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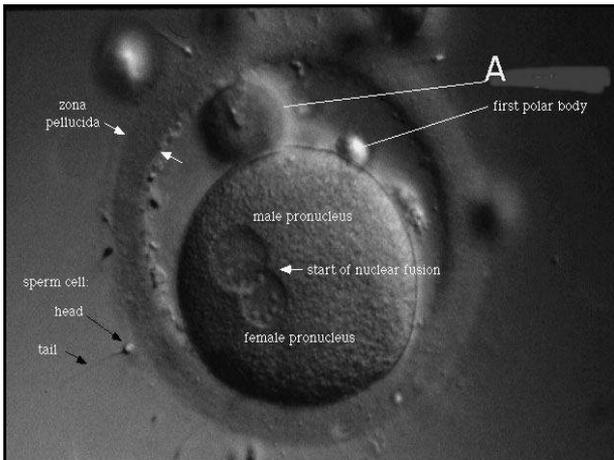


Sperm retrieval procedures



The incubator





Ideal features of embryos scored at:



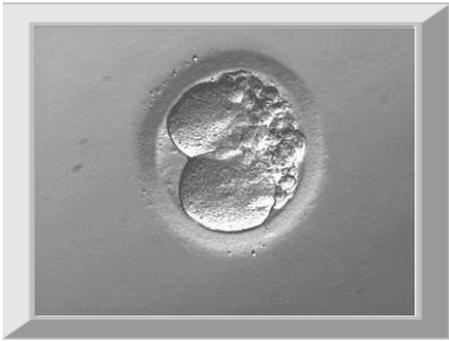
25 - 26h post insemination / injection
- embryo should be at the 2-cell stage with equal blastomeres and no fragmentation



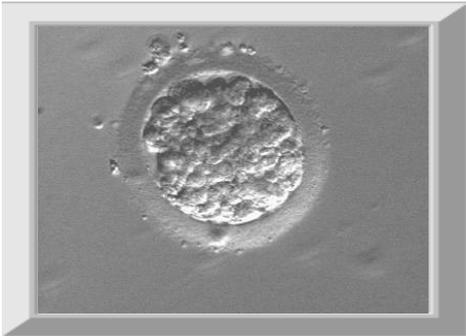
42 - 44h post insemination / injection
- embryo should have 4 or more blastomeres and less than 20% fragmentation



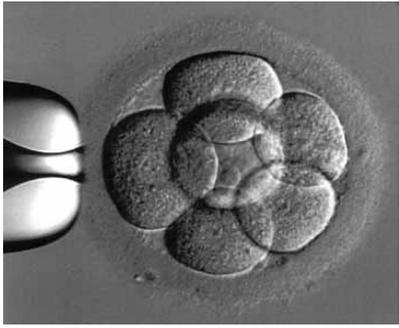
66 - 68h post insemination / injection
- embryo should have 8 or more blastomeres and less than 20% fragmentation

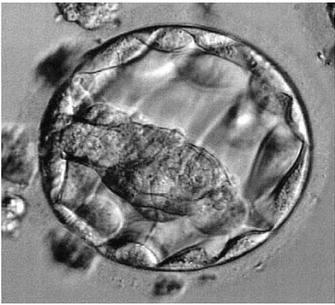


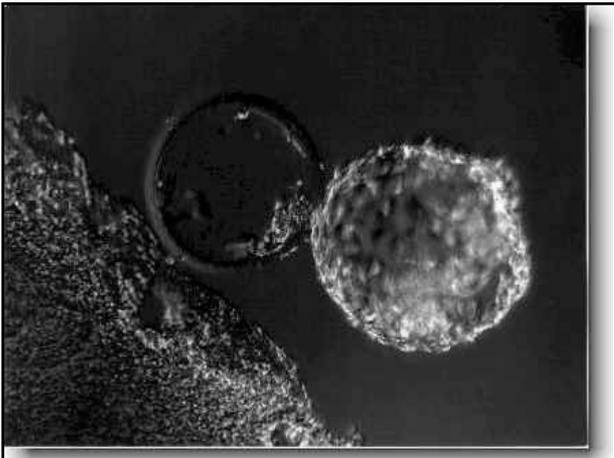
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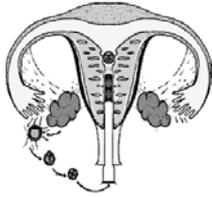
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Embryo transfer



Embryo implantation in ART

$$EI = EQ \times ER \times TE$$

EQ - embryo quality
ER - endometrial receptivity
TE - embryo transfer efficiency

Paulson et al., Am J Obstet Gynecol 1990



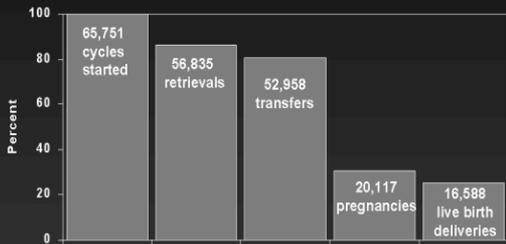
Histology of luteal phase endometrium ❖
Endometrial proteins ❖
Adhesion molecules ❖
Endometrial pinopods ❖
Sonographic quality of the uterus ❖
Hormonal milieu ❖

Data Reported 1999

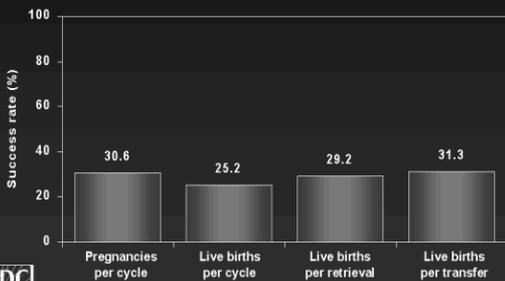
- 370 clinics reported
 - 29 clinics in operation in 1999 did not report.
- 86,822 cycles reported
 - 65,751 fresh, nondonor
 - 12,005 frozen, nondonor
 - 6,554 fresh, donor
 - 2,512 frozen, donor



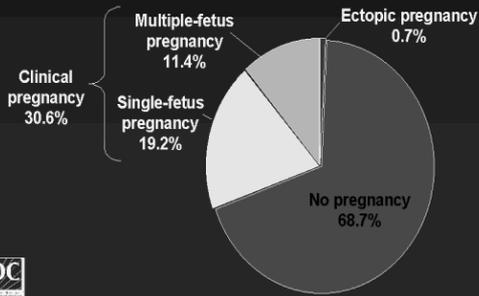
Outcome of ART Cycles Using Fresh, Nondonor Eggs or Embryos, by Stage, 1999



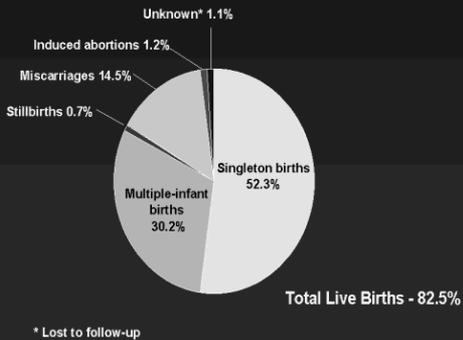
Success Rates for ART Cycles Using Fresh, Nondonor Eggs or Embryos, by Different Measures, 1999



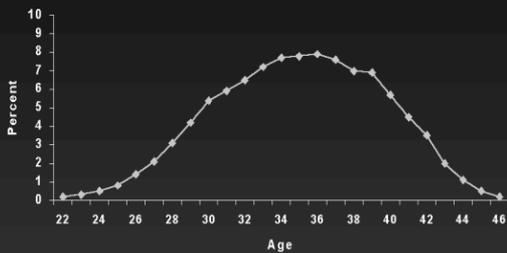
Results of ART Cycles Using Fresh, Nondonor Eggs or Embryos, 1999



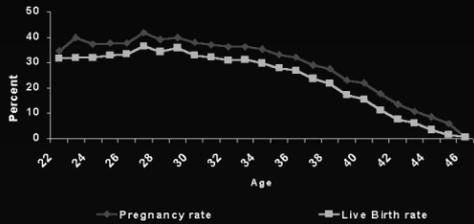
Outcomes of Pregnancies Resulting from ART Cycles Using Fresh, Nondonor Eggs or Embryos, 1999



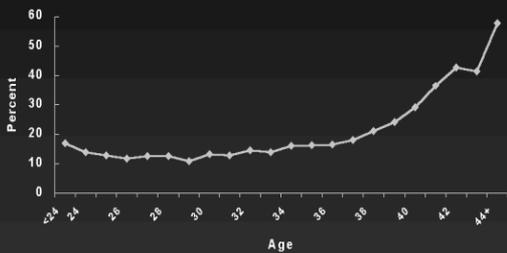
Age Distribution of Women Who Had ART Cycles Using Fresh, Nondonor Eggs or Embryos, 1999



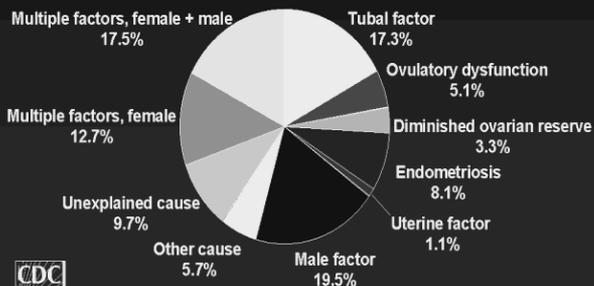
Pregnancy and Live Birth Rates for ART Cycles Using Fresh, Nondonor Eggs or Embryos, by Age of Woman, 1999



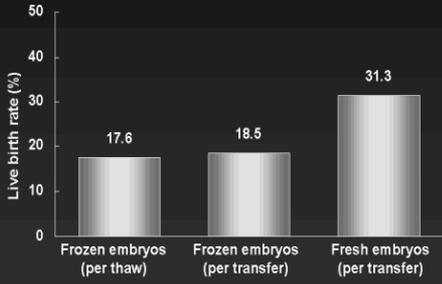
Miscarriage Rates Among Women Who Had ART Cycles Using Fresh, Nondonor Eggs or Embryos, by Age of Woman, 1999



Primary Diagnoses Among Couples Who Had ART Cycles Using Fresh, Nondonor Eggs or Embryos, 1999



Live Birth Rates for Frozen Embryos and Fresh Embryos, 1999



Live Births per Transfer for Fresh Embryos From Own and Donor Eggs, by Age of Recipient, 1999

