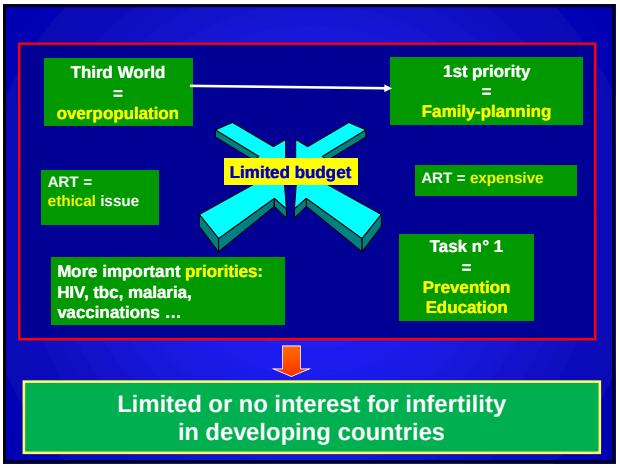
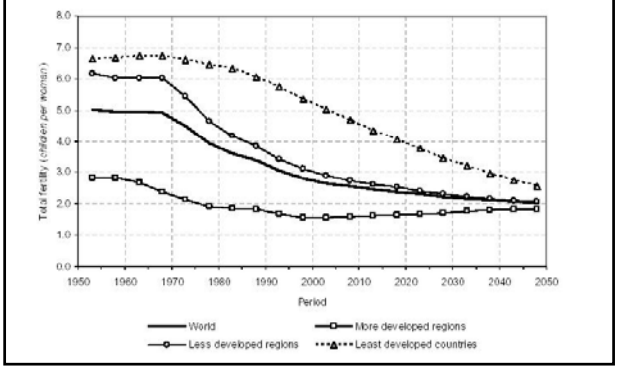
Minimal monitoring / Minimal stimulation as a means of increasing access to ART in developing countries

Willem Ombelet
Genk Institute for Fertility Technology

Maribor, 27-02-09

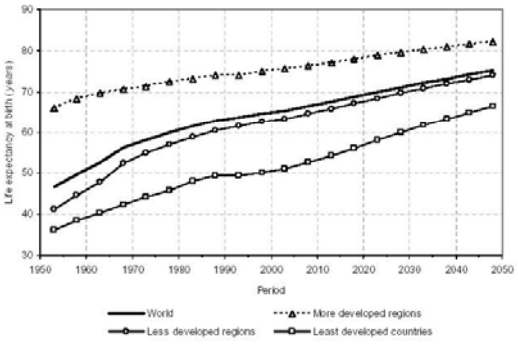


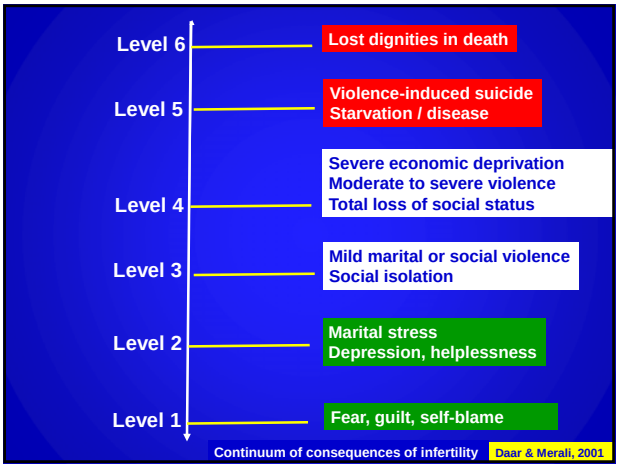
Fertility rate (FR) - Replacement level = 2.1



Global life expectance in developing countries

2000-2005: 51 yrs → 2045-2050: 67 yrs





Arusha Expert Meeting 2007

37 participants

Speakers: 22 countries /// 5 continents
Clinicians, embryologists, researchers
Ethics, sociology, health economics
Politician
President of the African Patient network
Representative from the industry
2 journalists (ESHRE, Nature)

Suggested raodmap

1. To establish Working Groups (with responsible coordinator)
2. To start feasability studies (working groups)
3. If phase 2 is succesful: start centres with affordable ART treatment
4. Development fully equipped fertility centres (centres of excellence)
5. Development of more centres (supervision: centres of excellence)

4 Working Groups (WG)

- The one-day diagnostic phase R Campo
- Ovarian stimulation for IUI & IVF/ICSI N Andersen
- Laboratory phase for IUI & IVF/ICSI J Van Blerkom
- Fundraising H Sallam

5 Study Groups (SG)

- Reproductive health education, prevention & awareness G Serour
- Burden of disease & cost-effectiveness D Habbema
- Training courses I Cooke
- Intravaginal // intrauterine culturing R Frydman
- Differences in ethics / law / religion / level of care F van Balen

Developing countries & infertility

Concerning diagnosis & treatment

Make it

SIMPLE
EFFICIENT
SAFE
AFFORDABLE

Developing countries & infertility

Health Care Centres

Family planning
Mother care
Infertility diagnosis
Infertility treatment

IUI versus IVF // ICSI
Unexplained and moderate male factor subfertility

IVF // ICSI versus 3 x IUI

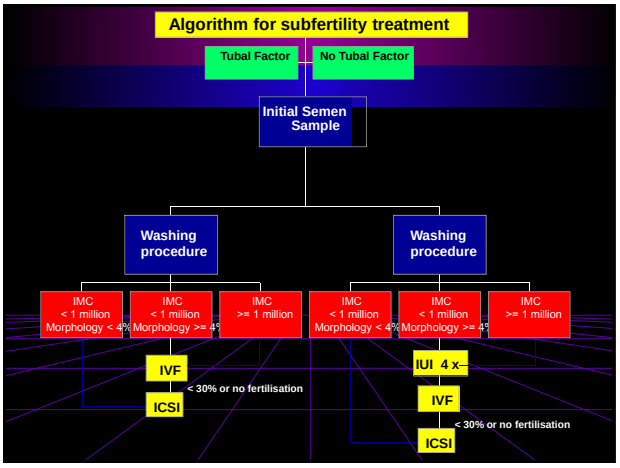

THE LANCET

13 Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility
A J Goverde and others

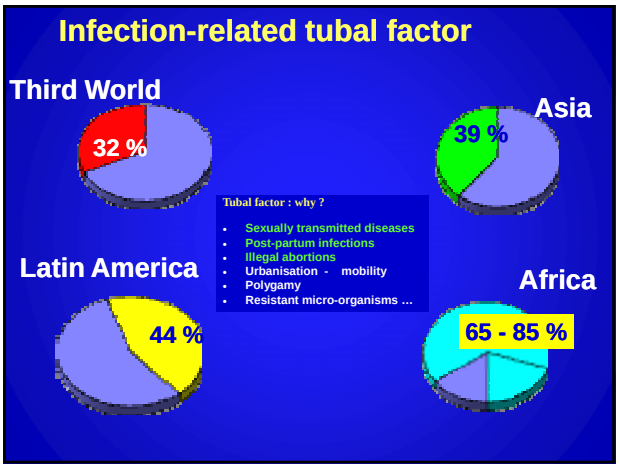
Philips et al., Hum Reprod 15, 95, 2000
Stone et al., AJOG, 180, 1522, 1999
Garceau et al., Hum Reprod 17, 3090, 2002

Cost-benefit

Procedure	Cost per delivery (USD)	
	Guzick et al	Van Voorhis et al
CC-IUI	11 905	7 808
hMG-IUI	19 203	10 282
IVF	54 217	43 138



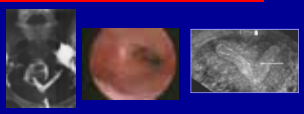
Infection-related tubal factor



Developing countries and infertility
Diagnostic phase

History
Clinical examination
Hystero-salpingography
Vaginal ultrasound
(hysteroscopy)
Blood sample // cervical smear

History
Clinical examination
Semen examination
Blood sample



One-day clinic

NEW DEBATE

Coming soon to your clinic: patient-friendly ART

Guido Pennings[1,3] and Willem Ombelet[2]

[1]Bioethics Institute Ghent, Ghent University, Blandijnberg 2, 9000 Gent, Belgium, [2]Gent Institute for Fertility Treatment, Department of Obstetrics and Gynaecology, Gent, Belgium

[3]Correspondence address. Tel./Fax: 0032 16 629 767; E-mail: guido.pennings@ugent.be

The current practice in medically assisted reproduction is still too exclusively focused on effectiveness and success rates. This has a number of considerable, and more importantly, avoidable drawbacks. Single embryo transfer was an important move away from this model to include safety and welfare of mother and child. Patient-friendly ART goes one big step further. It is composed of a mix of four criteria: cost-effectiveness, equity of access, minimal risk for mother and child and minimal burden for patients. All four components have a strong normative ethical basis: cost-effectiveness relies on the optimal use of community resources to maximize well-being; equity of access is based on justice, minimal risk is founded on the fundamental non-maleficence rule and minimal burden is largely based on the autonomy principle. The inclusion of the four criteria in decision-making about treatment would express these values in clinical practice.

Keywords: patient-friendly IVF, cost-effectiveness, ethics, risk, psychology

ART in developing countries

- Cost – effectiveness
- Access
  - High costs ⇒ concerns about equity
  - Private versus public
- Risk minimisation
- Burden minimisation

Income /// health care costs in DC

country	Daily income % < 1 $	Daily income % < 2 $	Health care % of GNP	Health care % out of pocket
Tanzania	90 %	58 %	4 %	83 %
India	80 %	35 %	5 %	94 %
Indonesia	52 %	8 %	3 %	75 %
China	47 %	16 %	5 %	86 %
Brazil	21 %	8 %	9 %	64 %

ART in DC: Cost – effectiveness

- IVF = effective but expensive
- Low-cost IVF possible ?
- How cheap is cheap enough ?
- Competition with preventable mortality at low cost
  - Malaria, HIV, diarrheal diseases etc
- Other options: ↓ burden of disease, AID, orphans ..

ART in developing countries

- Cost – effectiveness
- Access
  - High costs ⇒ concerns about equity
  - Private versus public
- Risk minimisation
- Burden minimisation

Risk minimisation

⇓ risk for multiples
⇓ risk for OHSS
⇓ risk for thrombosis

↓

Natural cycle / minimal stimulation

Prevention of multiples !!!

- Foetal death
- Foetal morbidity
- Perinatal mortality
- Perinatal morbidity
- Maternal death
- Maternal morbidity
- Economical impact
- Psychological impact
- ...

AIM
=
The delivery of a single healthy child

Risks for the patient & **Risks for the children**

- **STIMULATION**
  - OHSS → Thrombosis
  - Oncogenic risk
- **PICK-UP**
  - bleeding
  - infection
- **PREGNANCY**
  - OHSS
  - torsion
  - ectopic
  - heterotopic
  - cornual
  - Bleeding/miscarriage
  - multiples

Risk factors

- Young age
- Low body weight
- PCO or PCO-like patients
- GnRH agonists
- Use of hCG for luteal support
- High number of resting follicles (« necklace »)
- Size and number of mature follicules
- History of OHSS
- High E2 levels

Prevention of OHSS / thrombo-embolic complications (TEC)

- Mild stimulation protocols (no long agonist schemes!)
- Low starting dose FSH or clomiphene-citrate
- Lower estradiol levels / lower follicle numbers
  -> less risk for OHSS and TEC

Natural cycle IVF

- Complication rate (MPR & OHSS) : almost zero
- Couples: less time consuming
- Couples: less physically and emotionally demanding
- Much cheaper

Low risk, low cost, but **... less effective**

Natural cycle IVF
systematic review – 1800 cycles

- ET per cycle: 45.5 %
- Ongoing pregnancy rate per cycle: 7.2 %
- Ongoing pregnancy rate per transfer: 15.8 %

Reason: premature LH rise / ovulation

→ need for randomized controlled trials

Pelinck et al., HR Update, 8, 129, 2002

Clomiphene citrate in IVF // ICSI

Review literature

CC alone // CC-FSH // CC-antag // CC-HCG ..

versus

regular stimulation protocols

long agonist
short agonist
Antagonist

or

natural cycle

The clinical significance of the retrieval of a low number of oocytes following mild ovarian stimulation for IVF: a meta-analysis

M.F.G. Verberg[1,4], M.J.C. Eijkemans[1,2], N.S. Macklon[1], E.M.E.W. Heijnen[1], E.B. Baart[1], F.P. Hohmann[1], B.C.J.M. Fauser[1] and F.J. Broekmans[1]

Mild ovarian stimulation for IVF

M.F.G. Verberg[1,4], N.S. Macklon[1], G. Nargund[2], R. Frydman[3], P. Devroey[4], F.J. Broekmans[1], and B.C.J.M. Fauser[1]

MacDougall *et al.* (1994)	Patients 38 years with >1 year of infertility, spontaneous ovulatory regular cycles and normal semen analysis	CC 100 mg, from Days 2–6, hCG when the leading follicle was 17 mm (n = 16)	Natural cycle IVF with hCG when the leading follicle was 17 mm (n = 14)	Cancellation rate 0 versus 71% Ongoing pregnancy rate 13 versus 0% (NS)
Dhont *et al.* (1995)	Patients with no previous IVF attempts. Treatment included IVF-ET, ZIFT and GIFT	OAC pretreatment, CC 100 mg for 5 Days and (150) subsequent HMG (n = 151)	OAC pretreatment, long acting GnRH agonist and (300 IU) HMG (n = 152)	Cancellation rate 20.5 versus 2.6%. Ongoing pregnancy rate 24.5 versus 38.8% (P = 0.02)
Ingerslev *et al.* (2001)	Couples with no previous IVF attempts under 35 years with ICSI indication, tubal factor or idiopathic infertility	CC 100 mg, from Days 3–7 and hCG when the leading follicle was 20 mm (68 patients, 111 cycles)	Natural cycle IVF with hCG when the leading follicle was 17 mm (64 patients, 114 cycles)	Cycles resulting in embryo transfer 53.2 versus 25.4%, Ongoing pregnancy rate (per cycle) 18.0versus 3.5% (P < 0.001)
Fiedler *et al.* (2001) (abstract)	Random selected normal cycling women	100 mg CC CD 5–9, from Day 9 additional 150 IU HMG or FSH. GnRH antagonist from Day 10 (n = 295)	100 mg CC CD 5–9, from Day 9 additional 150 IU HMG or FSH (n = 291)	Ongoing pregnancy rate 23 versus 21% (NS)
Weigert *et al.* (2002)	Women with no previous IVF cycles, between 20 and 39 years, with normal ovulatory cycles with tubal, male factor or unexplained infertility	OAC pretreatment. CC 100 mg for 5 days in combination with 225 IU of rFSH and 75 IU of rLH on alternate days (n = 154)	Long GnRH suppression and 150 IU rFSH (n = 140)	Ongoing pregnancy rate 35 versus 29% (NS)
Engel *et al.* (2003)	Healthy female partners of infertile couples, between 18 and 39 years, with regular cycle length. No more than three previous IVF cycles or basal FSH >10 IU/l	Single dose GnRH antagonist protocol. CC 100 mg CD 2–6 of 3–7, CD 6 start 150 IU rFSH (n = 5)	Single dose GnRH antagonist protocol. CC 100 mg CD 2–6 of 3–7, CD 6 start 150 IU HMG (n = 5)	Live birth rate 40 versus 20% (NS)
Lin *et al.* (2006)	Couples with male-factor infertility who were about to undergo their first ICSI cycle	CC/HMG. Cetrorelix protocol (n = 60)	buserelin long protocol (n = 60)	Pregnancy rate 41.7 versus 40% (NS)

CC-IVF versus NC-IVF

- Randomized study:
  CC 100-HCG (n=16) versus NC-HCG (n=14)
- Selected group: women < 38 years, unexplained

	CC	NC
Cancellation rate	0 %*	71 %*
OPR / cycle	13 %*	0 %*

*** NS**

MacDougall et al., 1994, Fertil Steril, 61, 1052

CC-HMG-IVF versus long agonist-IVF

- Randomized study:
  OAC pre-treatment both groups
  CC 100-HMG (n=151) versus long protocol (n=152)
- Selected group: no previous IVF

	CC-HMG	Long agonist
Cancellation rate	20.5 %*	2.6 %*
OPR / cycle	24.5 %*	36.8 %*

***p = 0.02**

Dhont et al., 1995, HR, 10, 791

NC-IVF versus CC-IVF

- Randomized study:
  NC-ICSI (n=64) versus CC-ICSI (n=68)
- Selected group: women < 35 years, tubal factor or unexplained

	CC-ICSI	NC-ICSI
Oocyte retrieval	**81 %***	57 %*
Transfer / cycle	53 %*	25 %*
CPR / started cycle	18 %*	4 %*
CPR / transfer	34 %*	14 %*
Implantation rate	26 %	14 %
Twins	10 %	0 %

*** p < 0.05**

Ingerslev et al., Hum Reprod, 16, 696, 2001

NC-IVF versus CC-IVF

- Non-randomized study:
  long protocol-ICSI (n=116) versus CC-ICSI (n=132)
- Selected group: women < 35 years, tubal factor or unexplained

	LP-ICSI	CC-ICSI
Oocyte retrieval	96.3 %*	78.6 %*
Transfer / cycle	86.3 %*	55.1 %*
CPR / started cycle	24.2 %	16.3 %
CPR / transfer	28.0 %	29.6 %
Implantation rate	21.1 %	22.8 %
Twins	48 %	7 %

*p < 0.05

Ingerslev et al., unpublished

CC-FSH/LH versus long agonist FSH

- Randomized stydy
- Selected group: no previous IVF, nl ovulatory cycle & < 40 yrs

	CC-FSH	Long protodol
OPR / cycle	35 %*	29 %*

*p = NS

Weigert et al., 2002, Fertil Steril, 78, 34

CC-antag-HMG versus long agonist-HMG

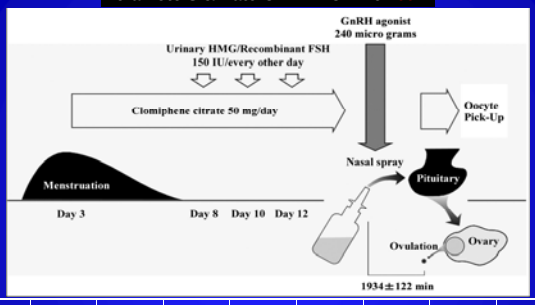
- Randomized study – n = 60 (both groups)
- Selected group: first ICSI cycle for severe male factor

	CC-antag	Long protocol
PR / cycle	41.7 %	40.0 %

*p = NS

Lin et al., 2006, Gynecol Endocrin, 22, 297

Teramoto S & Kato O: RBM Online 2007



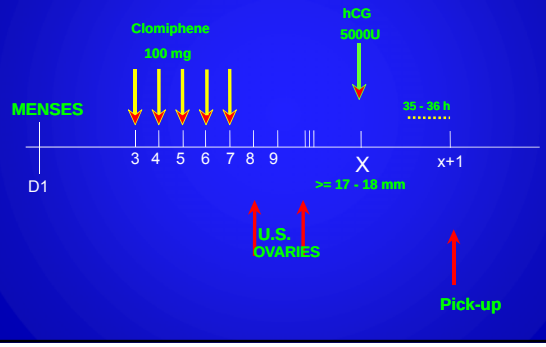
Age	27-29	30-32	33-35	36-38	39-41	42-44	45-47	Total
LBR/ Cycle (%)	14.6	13.5	10.5	7.4	3.1	1.0	0.1	5.2

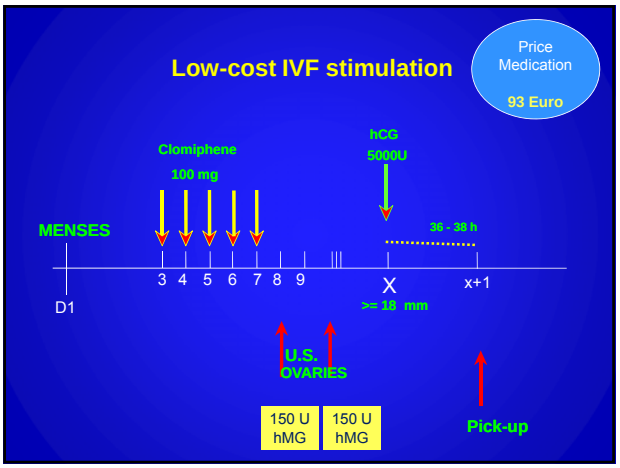
Minimal monitoring

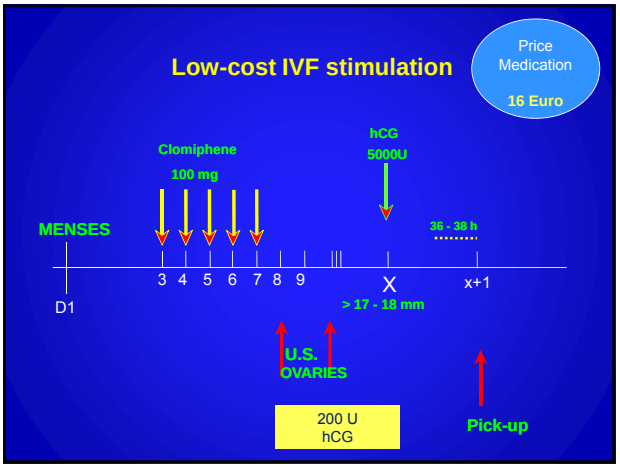
- E2 monitoring required only for those at risk of OHSS
- E2 levels did not correlate with IVF outcome
  Thomas K et al Acta Obst Gyn Scand 2002
- A single USS on day 8 or 9 reduces cost without compromising success rates
  Hurst BS et al Fertil Steril 2002
- The addition of E2 /Follicle criteria to USS in normal responders seldom changes hCG timing, does not increase pregnancy rates or risk of OHSS
  Lass A et al Fertil Steril 2003

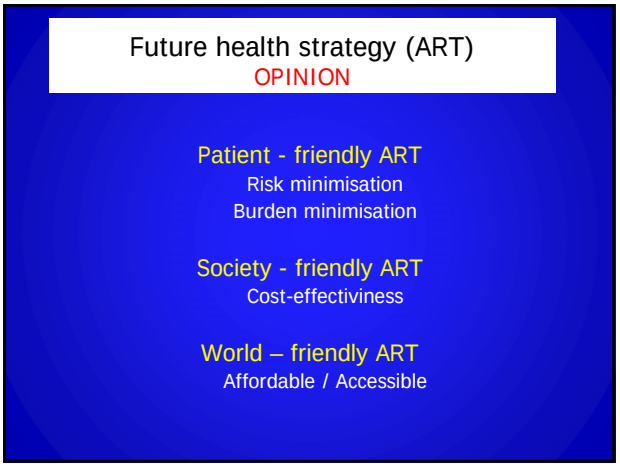
Low-cost IVF stimulation

Price Medication
13 Euro




Low-cost IVF stimulation
Price
Medication
93 Euro
Clomiphene
100 mg
hCG
5000U
MENSES
36 - 38 h
3 4 5 6 7 8 9
X
x+1
D1
>= 18 mm
U.S.
OVARIES
150 U
hMG
150 U
hMG
Pick-up


Low-cost IVF stimulation
Price
Medication
16 Euro
Clomiphene
100 mg
hCG
5000U
MENSES
36 - 38 h
3 4 5 6 7 8 9
X
x+1
D1
> 17 - 18 mm
U.S.
OVARIES
200 U
hCG
Pick-up


Future health strategy (ART)
OPINION
Patient - friendly ART
Risk minimisation
Burden minimisation
Society - friendly ART
Cost-effectiviness
World – friendly ART
Affordable / Accessible