Infertility in Developing Countries:

Scope, Burden, Solutions

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What is the importance of having children in your community?

Biology Recap to understand Infertility

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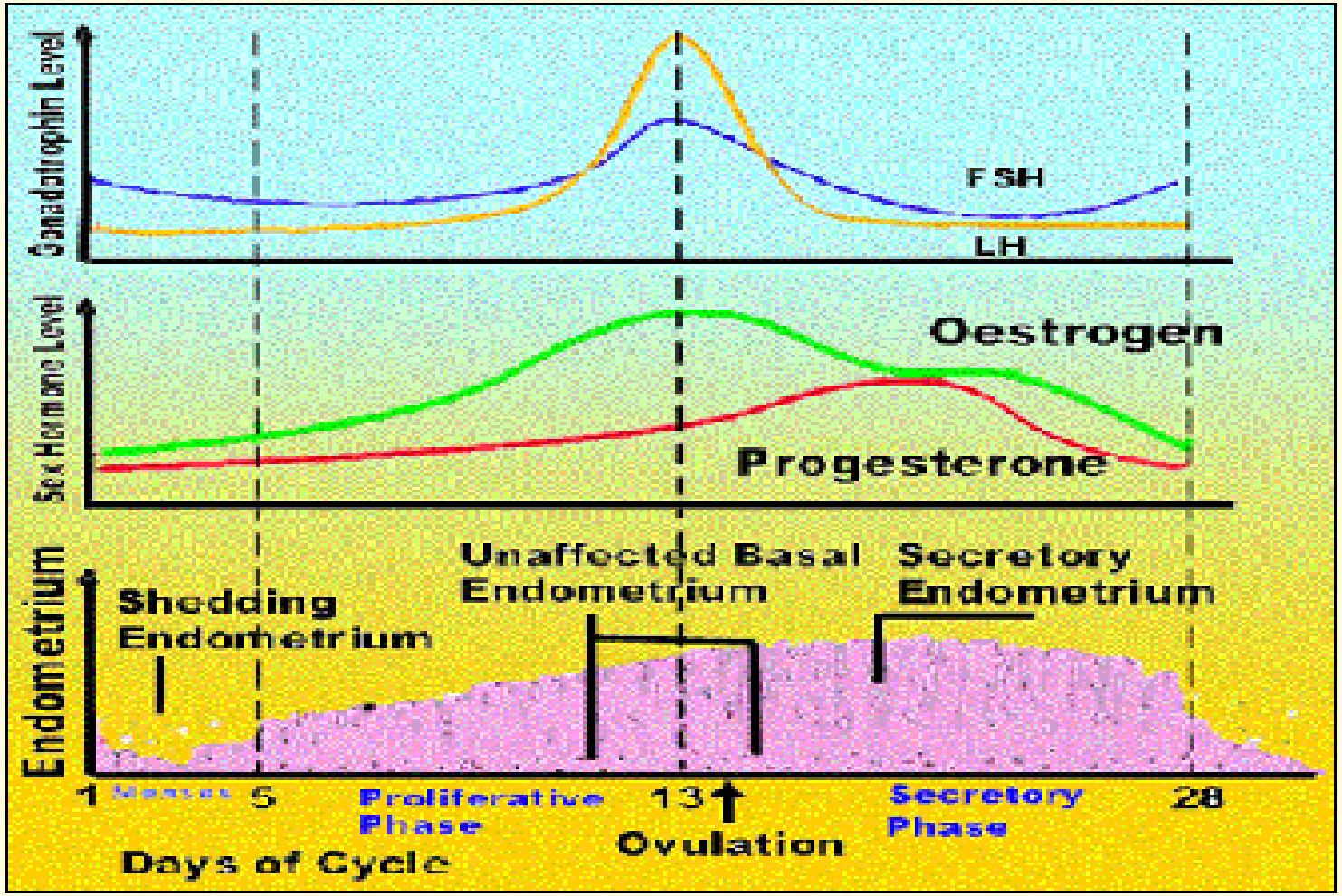
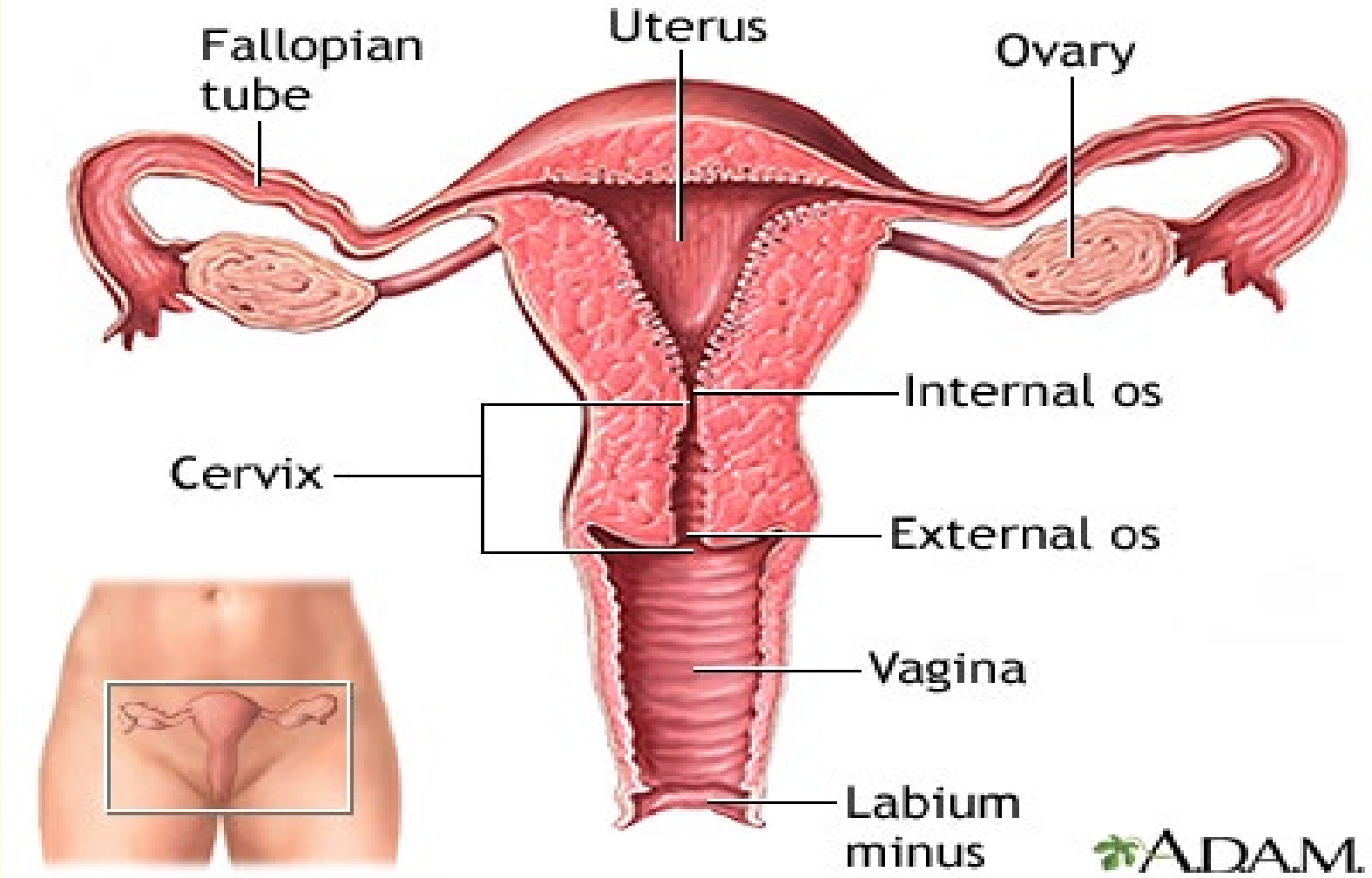
Definitions

- **Childlessness** – in/voluntary
- **Fertility** = ability to produce healthy offspring
  = birthrate: live births/ 1000 population per year
- **Infertility** = Inability to conceive a viable pregnancy and carry it to term, after regular intercourse for one year
  - Primary infertility – never pregnant
  - Secondary infertility – pregnant before

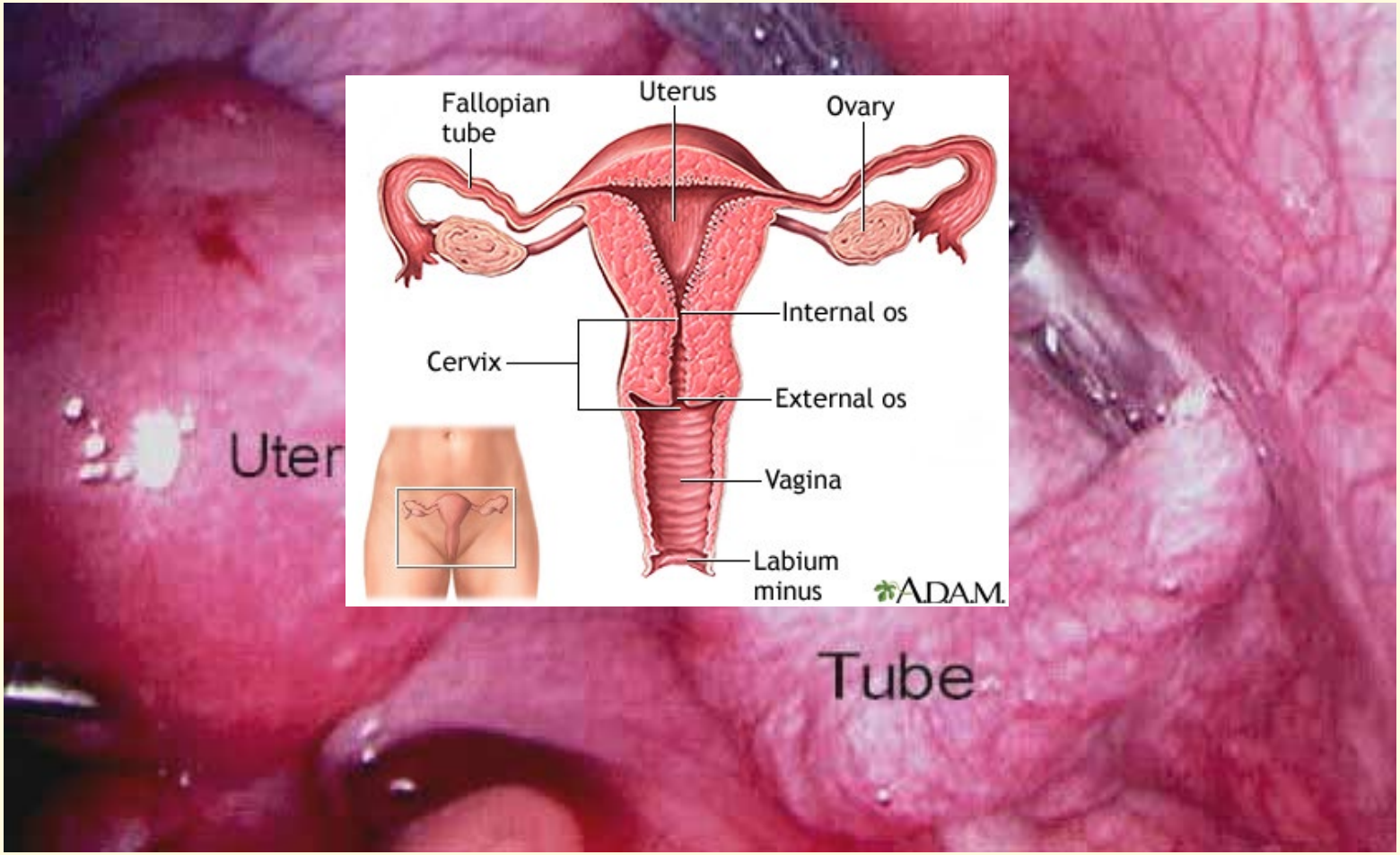
The Software - Hormones



The Hardware



Laparoscopic View of Lower Abdomen



Pop Quiz:

After one year of regular unprotected vaginal sex in a heterosexual couple, what is their chance to become pregnant?

30%	60%
90%	100%

Probability of pregnancy in couples with normal fertility

Month	Monthly probability	Cumulative probability
1	0.2	0.20
2	0.2	0.36
3	0.2	0.49
4	0.2	0.59
5	0.2	0.67
6	0.2	0.74
7	0.2	0.79
8	0.2	0.83
9	0.2	0.86
10	0.2	0.89
11	0.2	0.91
12	0.2	0.93

Biological realities and limits of the reproductive system

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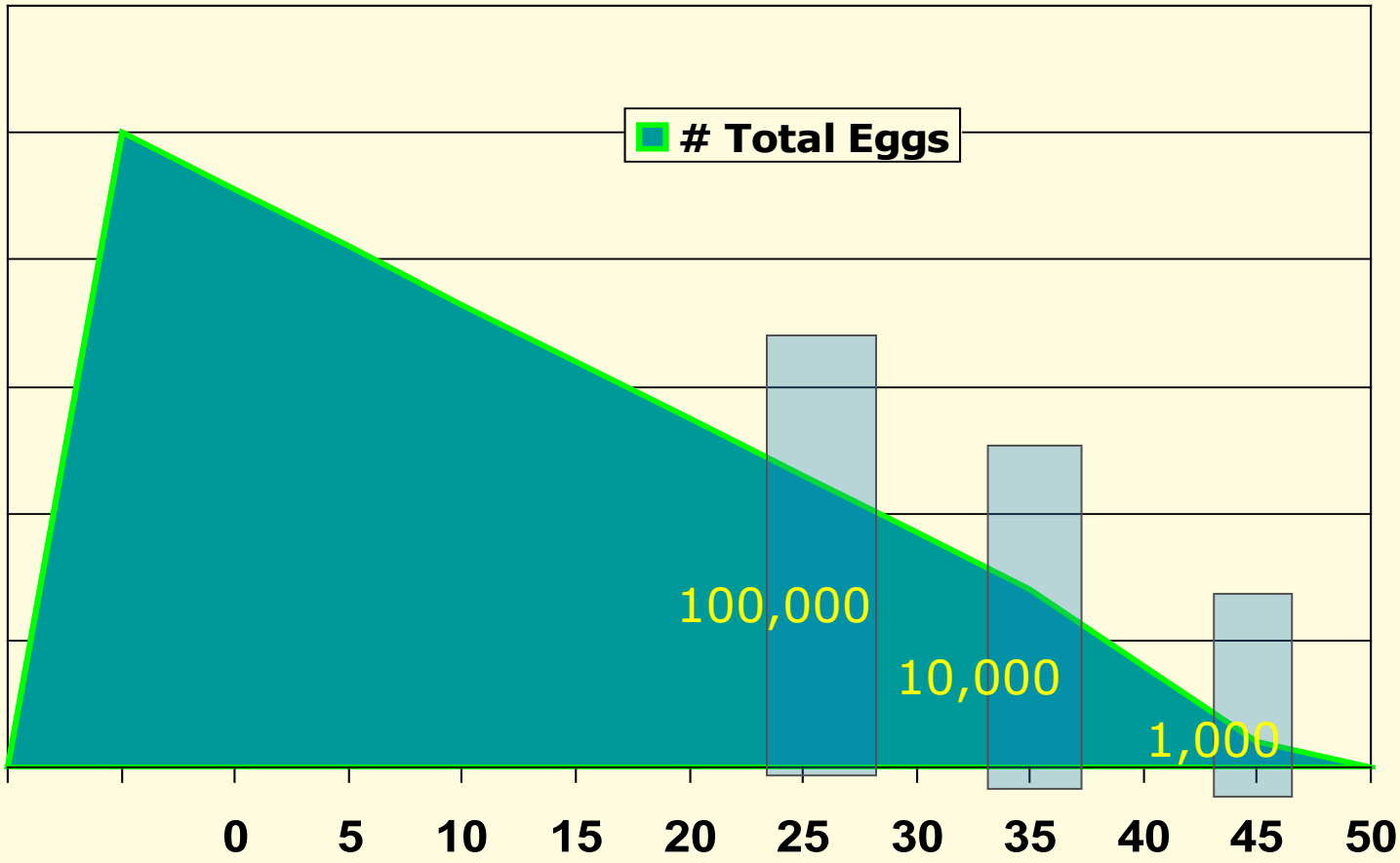
Biological clock of infertility - Ovarian reserve

In utero- 20 weeks	6 – 7 million oogonia
At birth	2 – 3 million oogonia
By puberty	300,000 oogonia
Each cycle	30 – 50 oocytes battle to become dominant follicle
> Age 30	Rapid follicular loss due to increased oocyte recruitment in order to maximize chance for healthy follicle

Naturally diminishing egg supply = Ovarian Reserve



Pop Quiz:

How are the causes of infertility distributed between men and women?

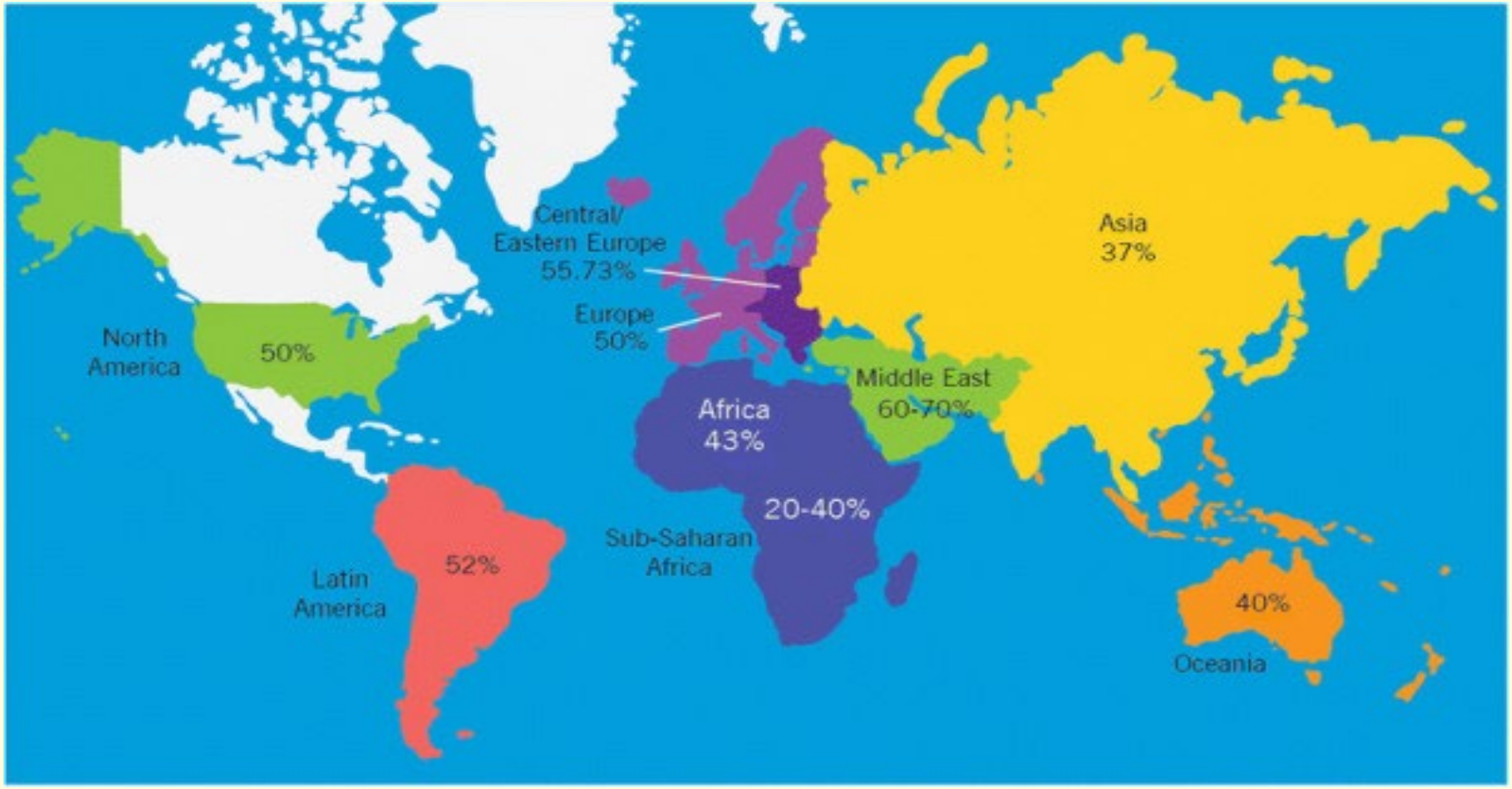
use ANNOTATE function

50 / 50 %	10 / 90 %
90 / 10 %	35 / 65 %

Causes of Infertility

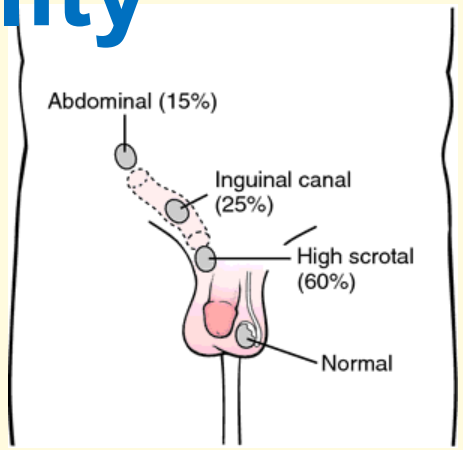
male	35 %
female	65 %
ovulatory	15 %
tubal	35 %
unexplained	10 %
other	5 %

% of infertility due to male factor



Agarwal. A unique view on male infertility around the globe. Reproductive Biology and Endocrinology 13(1):37 · April 2015

Reasons for Male Infertility



- **Congenital factors**
  - Cryptorchidism - testes don't descend to scrotum
  - Genetic abnormalities impeding sperm production
- **Acquired factors**
  - Testicular trauma or torsion
  - Varicocele (40%) – mass of varicose veins in the spermatic cord
  - Postinflammatory (mumps orchitis, epididymitis)
  - Exogenous (Chemotherapy, medication, pesticides exposure, radiation, heat)
- **Idiopathic risk factors**
  - Smoking, alcohol, recreational drugs, obesity, psychological stress, dietary factors, environmental exposure to toxins such as pesticides and heavy metals, advanced age

Understanding the cross-talk between mediators of infertility and COVID-19

Prem Rajak[a,*], Sumedha Roy[b], Moumita Dutta[c], Sayanti Podder[d], Saurabh Sarkar[e], Abhratanu Ganguly[f], Moutushi Mandi[g], Salma Khatun[h]

Table 1
Reported cases demonstrating impacts of COVID-19 on reproductive health of patients.

No. of cases studied	Gender	Impacts on reproductive health
01	Male	Bilateral orchitis (scrotal erythema, testicular pain)
10	Male	Decreased sperm quality
01	Male	Orchiepididymitis with lymphocytopenia and elevated C-reactive protein
01	Male	Ischemia-related priapism
01	Male	Testicular pain
06	Male	Interstitial edema, congestion, red blood cell exudation in testes, and epididymides; thinning of seminiferous tubules; oligozoospermia
05	Male	Numerous degenerated germ cells; altered transcriptome
11	Male	Sertoli cells with swelling, vacuolation and cytoplasmic rarefaction; reduced number of Leydig cells
50	Female	Decreased menstrual volume; cycle prolongation.
04	Female	Hypoxemia-related fetal distress during pregnancy.
05	Female	Maternal morbidity and preterm birth
27	Female	Placental injury characterized by maternal vascular malperfusion (higher retroplacental hematomas; accelerated villous maturation; distal villous hyperplasia; atherosis, fibrinoid necrosis, mural hypertrophy of membrane arterioles; vessel ectasia and persistence of intramural endovascular trophoblast)

News & Analysis

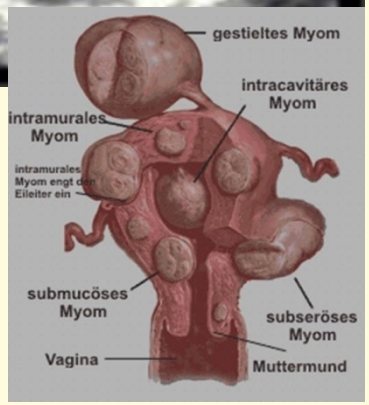
Medical News & Perspectives

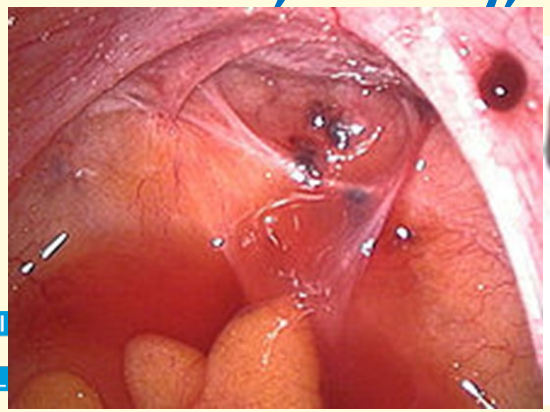
Widespread Misinformation About Infertility Continues to Create COVID-19 Vaccine Hesitancy

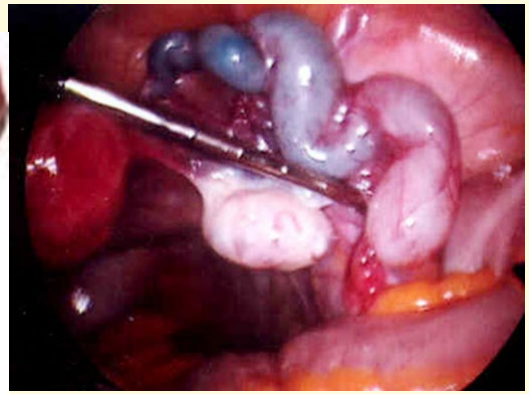
Jennifer Abbasi

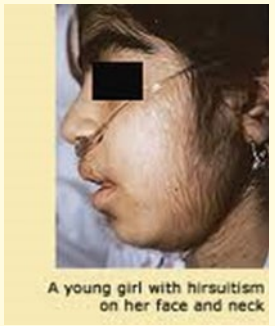
Reasons for Female Infertility

- **Ovulatory problems** – PCO
  - desynchronized follicle development/ release
  - anovulation
- **Tubal problems** - Hydrosalpinx
  - Often after STIs
- **Endocrinological** (hormonal) imbalances
- **Uterine problems** - Fibroids, polyps
- Scarring, adhesions after **endometriosis**
- **Anorexia, Obesity, Diabetes**

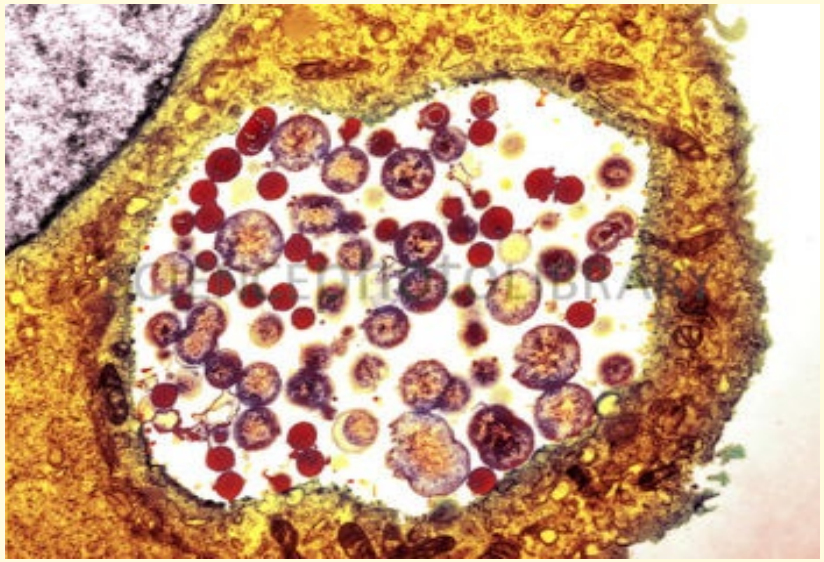


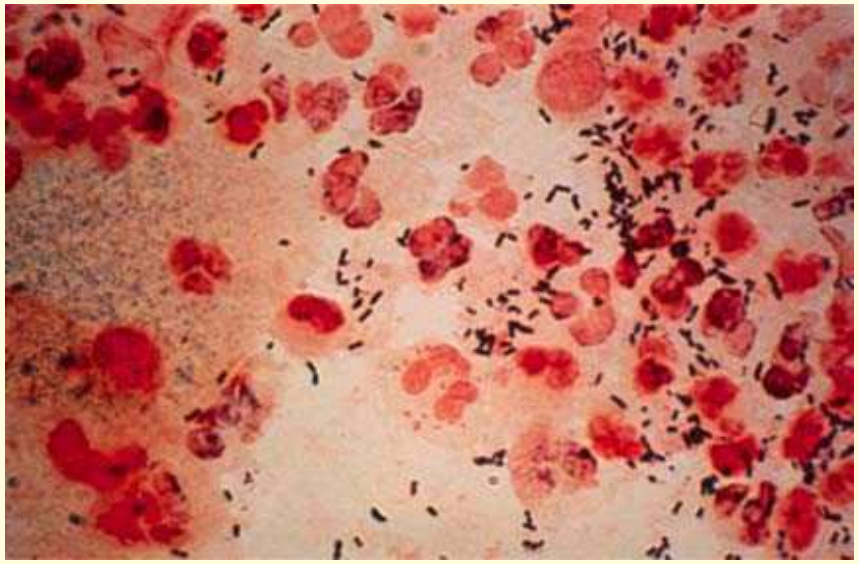






Sexually Transmitted Infections





Chlamydia trachomatis

Worldwide Cases (2008)

- **Prevalence: 105.7 million**
- **Incidence: 100.4 million**

Neisseria gonorrhea

Worldwide Cases (2008)

- **Prevalence: 106.1 million**
- **Incidence: 36.4 million**

Global incidence and prevalence of selected curable sexually transmitted infections - 2008, World Health Organization 2012

Global Scope and Epidemiology of Infertility

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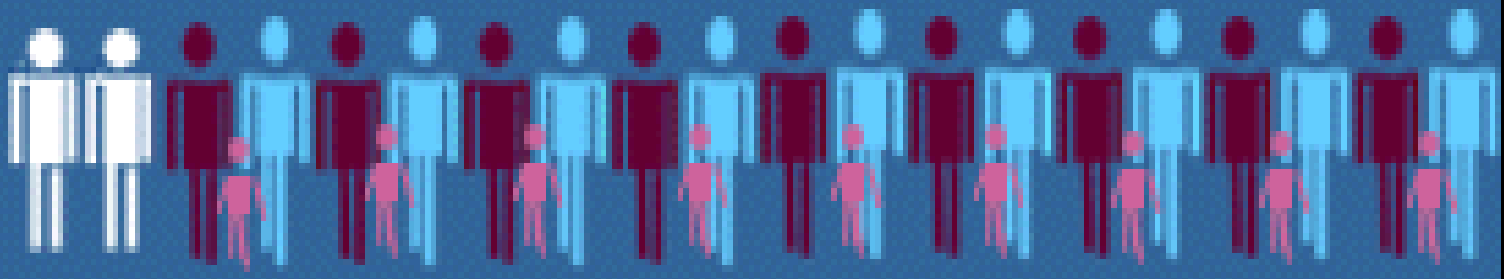
What are your experiences with fertility complications in your community?

https://www.theatlantic.com/video/index/582616/ivf-africa/ The Atlantic 2019

Scope of Infertility in the United States

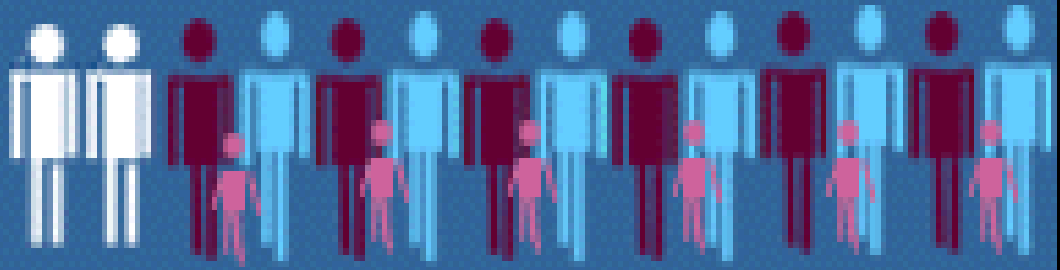
All couples

1 in 10 couples



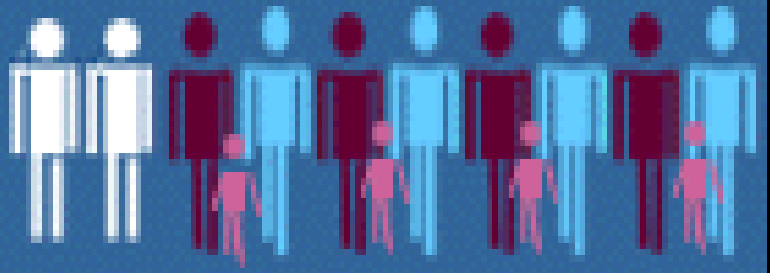
Age 30-34

1 in 7 couples



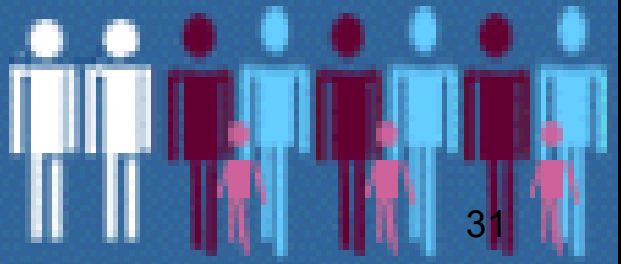
Age 35-39

1 in 5 couples

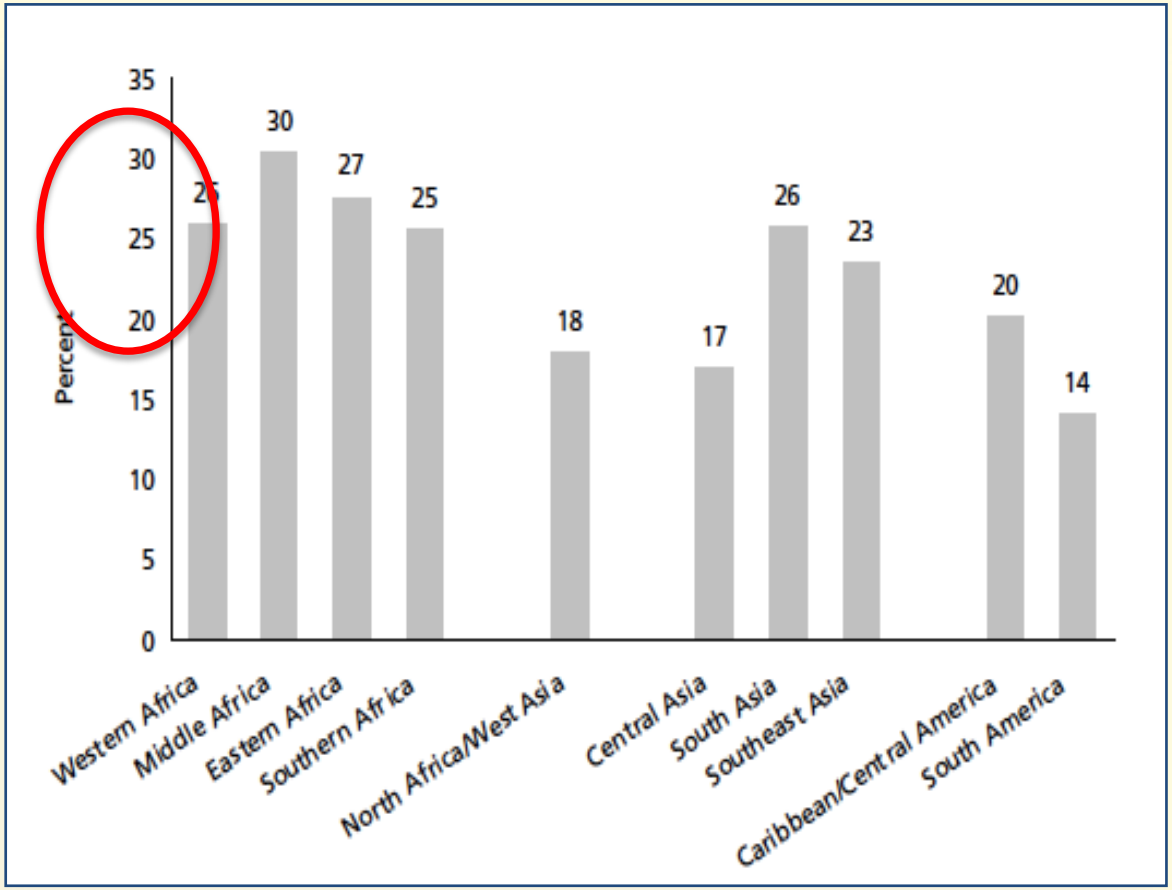


Age 40-44

1 in 4 couples



Percentage of women age 25-49 with secondary infertility



Source: DHS Comparative Reports 9. Infecundity, Infertility and Childlessness in Developing Countries. 2004

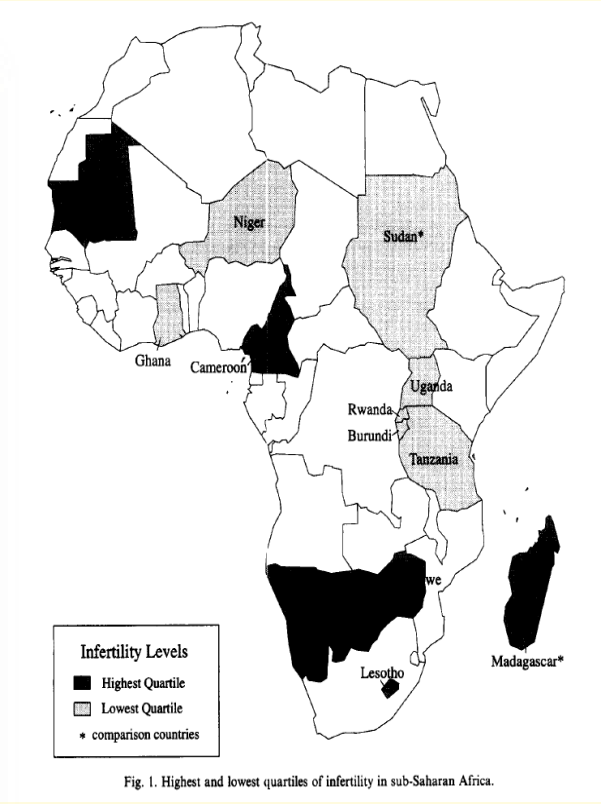


Fig. 1. Highest and lowest quartiles of infertility in sub-Saharan Africa.

ERICKSEN, K. and BRUNETTE, T. *Patterns and predictors of infertility among African women: a cross-national survey of twenty-seven nations.* Soc Sci Med, 42 (2): 209-20. 1996.

Van der Poel, 2015, Mumbai, India

Infertility in Developing Countries – the Scope

- Newer estimates from 2000s:

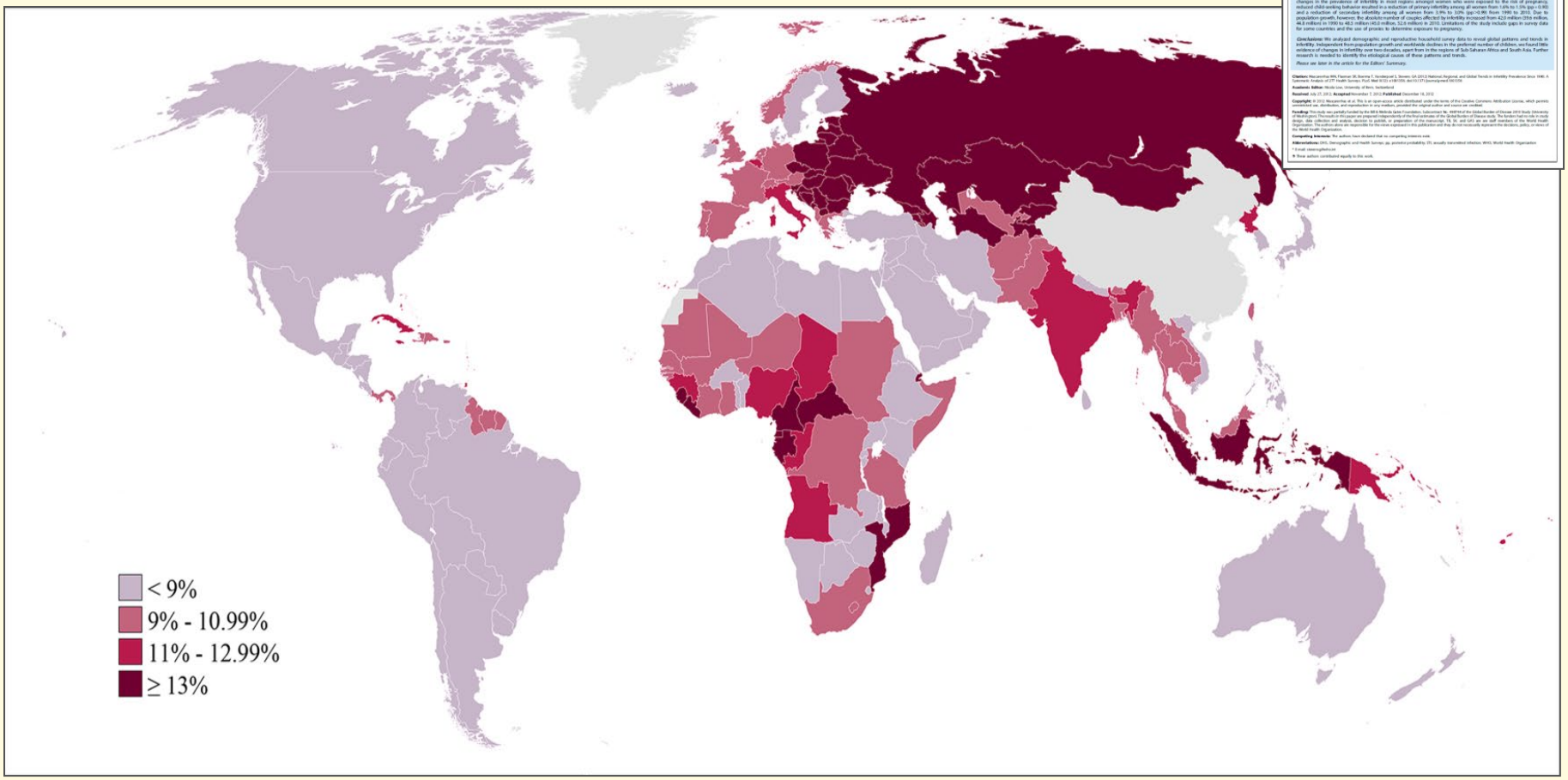
  48-186 million couples worldwide affected by primary or secondary infertility
- "Sub-Saharan Infertility Belt" expands to Southern and Western Africa
  - 10-25% of couples infertile (globally 8-12%)
  - Regional fluctuations, more prevalent in urban settings (30-40% reported)

Infertility in Developing Countries – the Scope

- Significant burden on health systems
  - 50% of couples seeking treatment
  - 10-30% of all visits in hospitals
  - Often seeking help outside the health system, e.g. traditional healers
- Some decline in infertility rates since 1970s due to antibiotic mass treatments, behavior change

Secondary infertility


National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys



WOMEN Age > **20-44; Consistent partnership without contraception,** and actively trying for a child for **5** years ***after having had one live birth.*** **Fertility surveys, mainly self-reports.**

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PLoS Med. 2012;9(12):e1001356. doi: 10.1371/journal.pmed.1001356. Epub 2012 Dec 18

Infertility in Developing Countries - Neglected in Policy

- Standard argument 1:

  "developing a medical infrastructure to diagnose and treat a non-fatal problem is a waste of health resources"

- Standard argument 2:

  "these regions should rather be concerned about hyperfertility and overpopulation"

Psychosocial Burden of Infertility

- Guilt
- Shame
- Feeling of worthlessness
- Anger, sadness, and bitterness
- Suicidal ideation
- Loneliness and social isolation

Beliefs about Infertility in some Developing Countries

- Modern Western concepts of fertility and sterility often unknown or poorly understood
- "Simultaneous logic of greedy spirits and faulty organs" (Kielmann. Barren ground. 1997)
  - Supernatural curse
    - Evil spirits and jealousy of women prevent implantation
    - Infertile women as witches with children in "another world"
    - Punishment for disobedience, deviant sexual behavior, disrespect towards ancestors
  - Lay concepts of physiological causes
    - Weak worms, unclean womb, blood does not "mix well"
  - Use of contraception would cause permanent infertility

Social Stigmatization

- Loss of social status
- Disinherited
- Risk of polygamy
- Banned from community functions
- Can be divorced, need to repay bride price, brought shame on their family
- Risk of physical violence
- Denial of proper burial rights
- Held responsible for epidemics and droughts

Women's Voices

- **"Why did you marry a thing that cannot get children?"** DYER, S., ABRAHAMS, N., HOFFMAN, M., et al. *Men leave me as I cannot have children.* Hum Reprod, 17 (6): 1663-8. 2002.
- **" If you are a woman in Sub-Saharan Africa and you don't have a child, you are worth less than a dog."** PILCHER, H. *IVF in Africa: Fertility on a shoestring.* Nature, 442 (7106): 975-977. 2006.
- **"You are a man because you have children."** DYER, S., ABRAHAMS, N., MOKOENA, N., et al. *You are a man because you have children.* Hum Reprod, 19 (4): 960-7. 2004.
- **"She will not be listened to in public."**

  PEARCE, T. O. *She will not be listened to in Public: perceptions among the Yoruba of Infertility and Childlessness in Women.* Reprod Health Matters, 7 (13): 69-79. 1999.
- **"… back home in the homelands you don't remove the bride scarf until you have a child … better to run away than to be laughed at."** DYER, S., ABRAHAMS, N., HOFFMAN, M., et al. *Men leave me as I cannot have children.* Hum Reprod, 17 (6): 1663-8. 2002.

Having Children in Developing Countries as Means for Survival

- Increased social status within society
- Power base for women's negotiation and justification of existence
- Economic security at old age
- Secure inheritance rights for women
- Continuation of the blood lineage
- Ideology of motherhood, parenthood mandated

→ **Infertility is more than a private misfortune, serious threat to gender identity and social status**

Infertility Stigma – Gender differences

- Male infertility easier to hide and "treat"
  - Impregnation within blood family
  - Men hesitate to participate in diagnostics, fear of public emasculation
- Female infertility visible – women are blamed and stigmatized
  - Public humiliation and ostracism
  - Assault, domestic violence, abandonment, suicide
  - Barred from community functions
  - Held responsible for epidemics and droughts
  - Denial of proper burial rights
- Marital infidelity by both partners to seek impregnation and assurance elsewhere

Infertility in Developing Countries – History of Action

- "fertility-infertility dialectic"
  - Concurrent high fertility and infertility rates
  - cultural emphasis on procreation leads to unprotected sex and high STI rates and high secondary infertility
- **WHO Task Force with Report in 1985**
  - Primarily secondary infertility
  - 85% by reproductive tract infections after STIs, unsafe delivery, unsafe abortions and harmful traditional practices
  - At least 50% involve male factors
  - In SSA distinctive pattern with estimated regional peaks of 30% infertility

Infertility in Developing Countries – History of Action

- **ICPD Cairo 1994:**
  - called for expansion of RH priorities
  - "prevention and appropriate treatment of infertility where feasible" in Programme of Action
- **World Health Assembly 2004 statement:**
  - "provision of high-quality services for family planning, including infertility services"

Infertility in Developing Countries – Brief History of Action

- **Beyond ICPD 2014 Report:**
  - Infertility not included anymore as explicit goal, only within general context of women's health
- **2019 Nairobi Statement of ICPD25:**
  - No specific mention of infertility
- **2021 Commission Report on ICDP25 (**"No exceptions, no exclusions: Realizing SR health, rights and justice for all"):
  - No mention of infertility

Technologies to diagnose and treat Infertility

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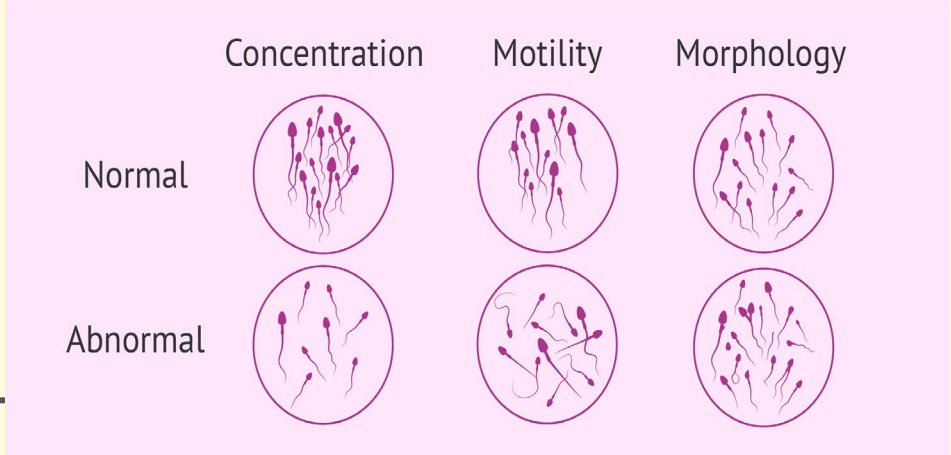
Infertility evaluation – Medical History

- Length of trial period
- Duration of infertility
- Coital frequency

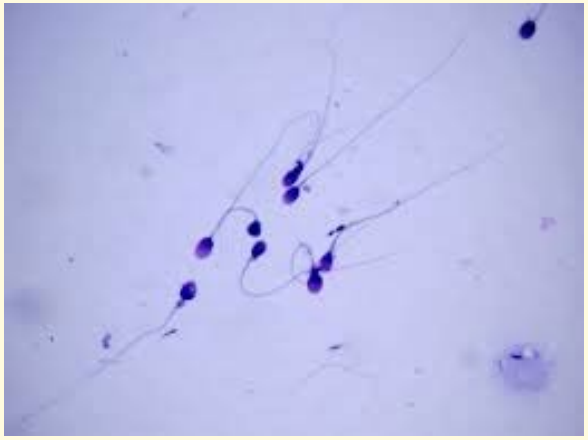
- Thorough gynecologic history (cycle, dyspareunia, cramps, pelvic pain), prior pelvic infections
- Current medical / surgical problems
- Medication list (including over-the-counter and herbs)

- Prior pregnancies from either partner
- Family history of miscarriages
- Use of contraception
- Tobacco and alcohol history

Male Factor – Semen Analysis



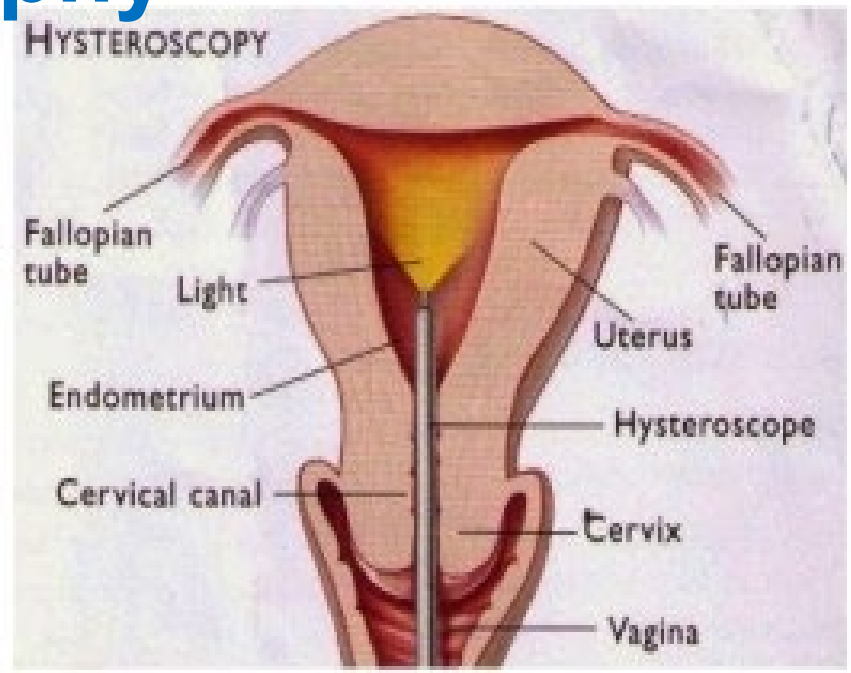
Criteria	Should be:
volume	> 2 ml
sperm concentration	> 20 million / ml
motility	> 50 % with forward progression
morphology	> 30 % normal forms
pH	> 7

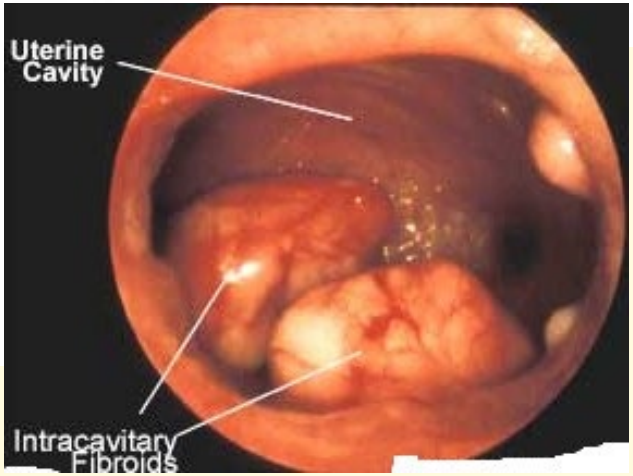


Sperm quality decreases above age 40

Hysteroscopy and Hysterosalpingography

Figure 9. Septate uterus.





Assisted Reproductive Technologies (ART) - Definition

- **infertility treatments designed to**
  - increase number of eggs and/or sperm,
  - bring them closer together
  - circumvent blockage

- **resulting in improved probability of conception**

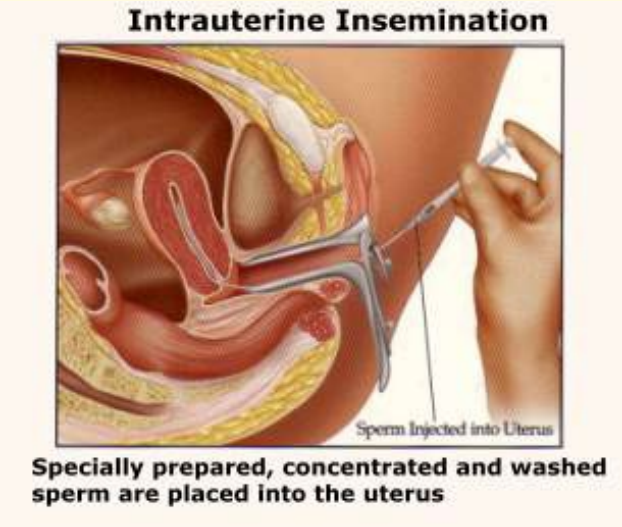
Ovulation Induction

- Best choice for ovulation disorders
- Low cost options with clomiphene citrate
- Follicle stimulating hormone FSH
- Human chorionic gonadotropin (beta HCG)

→**Hormonal stimulation of ovulation to achieve super-induction (multiple follicles ripe at once), good success rate**

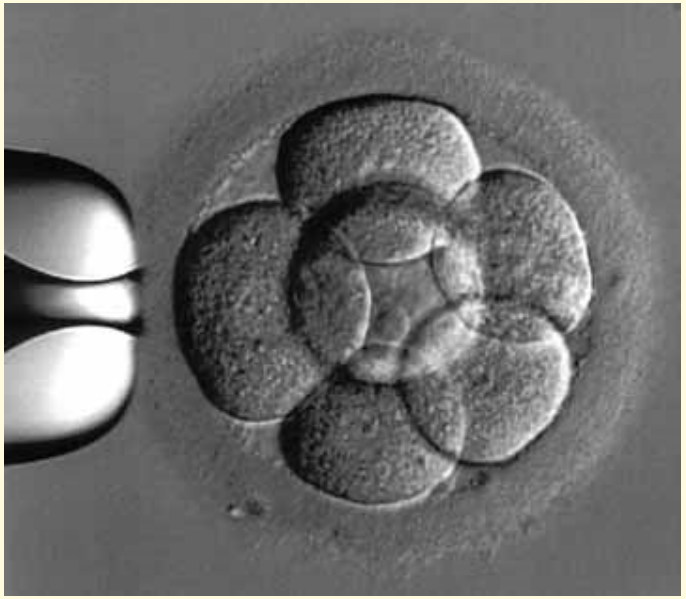
Intrauterine Insemination (IUI)

- best choice for couples with sperm disorders
- Fresh or frozen semen samples
- sperm or semen injected directly into uterus
- homologic insemination versus heterologic insemination (with donated sperm)
- For HIV discordant couples: Sperm washing to separate sperm from infectious seminal fluid

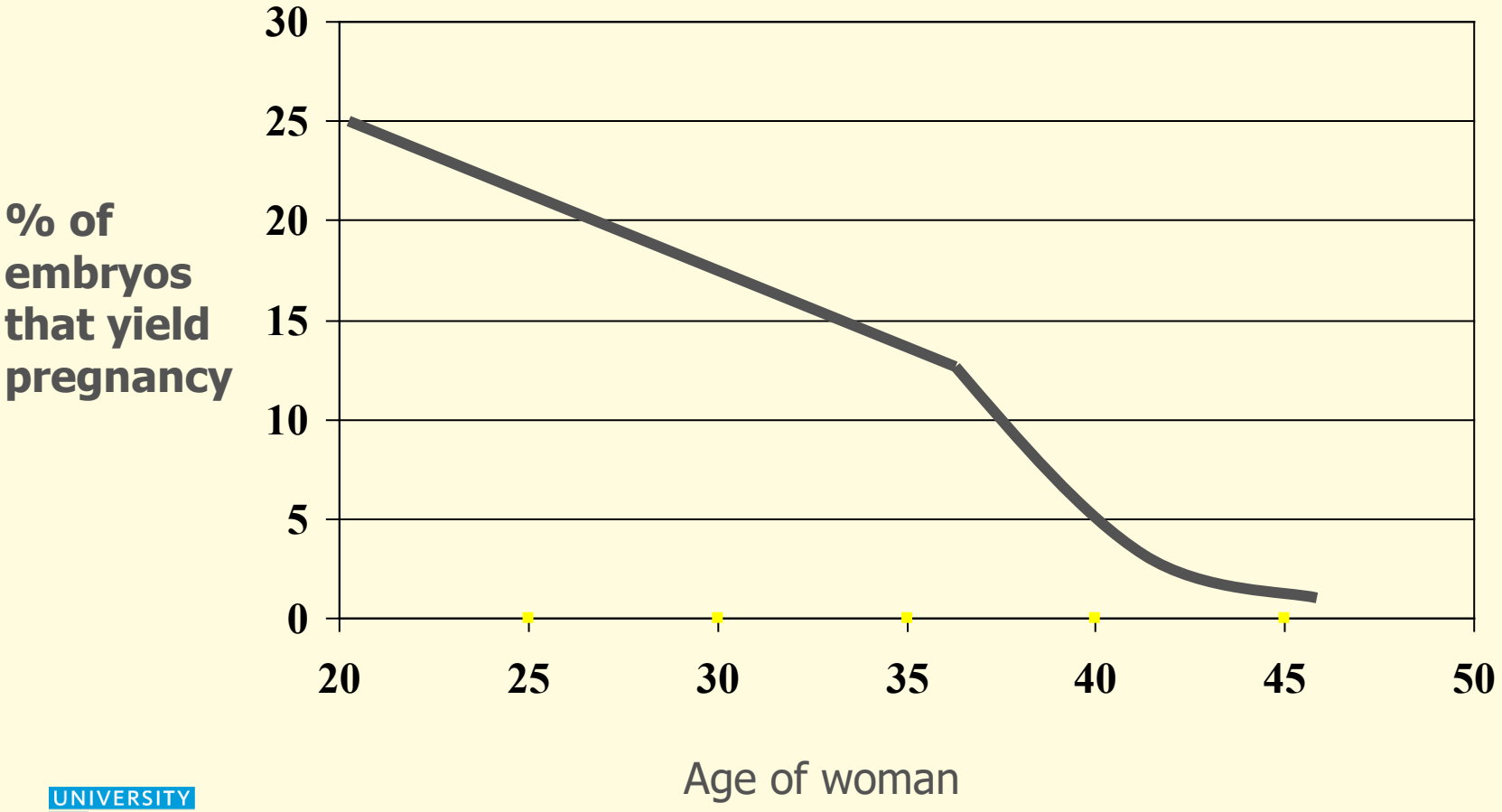


In Vitro Fertilization (IVF)

- **retrieving eggs** after stimulated ovulation ("harvest ripe eggs"), **and sperm**
- **Extracorporal mixing:** in a laboratory dish to enhance fertilization
- Transfer of **fertilized eggs** (blastocyst stadium) **back into uterus**



Decreasing embryo quality with maternal age



Kooij et al., F&S 66:769-75, 1996

Multiple Gestations and ART

- **major obstetric concern**
  - prematurity, preeclampsia, gestational diabetes, IUGR
- **major pediatric concern**
  - Preterm deliveries, low birth weight
  - Long term sequelae: learning disabilities, lung disease, physical disabilities (vision, hearing, allergies)
- **Affected by clinician practices, e.g. number of *viable* embryos transferred to maximize success rates**
  - some countries cap maximum number of implanted embryos at 3

ART and abortion restriction

- **Status of fertilized eggs (8-cell blastocyst stage)**
  - hastily prepared legislation and vague language could have unintended consequences for ART
  - IVF with uncertain legal status — unless laws that define life as beginning at fertilization clarify the status of those embryos' creation, storage and possible destruction
  - Can an embryo be defined as a life inside a pregnant person but only as potential life in a lab?
  - What about testing embryos for genetic abnormalities before IVF transfer?
  - While many US states now ban abortion, these bans will increasingly and explicitly exempt IVF.

Infertility in Developing Countries – Infrastructure

- **2000 – IVF services in 45 countries (24%),** mainly first world nations
- **2010 – IVF services in 105 countries (55%)**
  - Growth mainly in wealthier countries of the Middle East, South Asia and Latin America
  - Some catering to IVF tourism and surrogacy
- **In SSA: IVF only in 15 of 48 nations**
  - Only three with advanced infrastructure: Nigeria, South Africa, Ghana

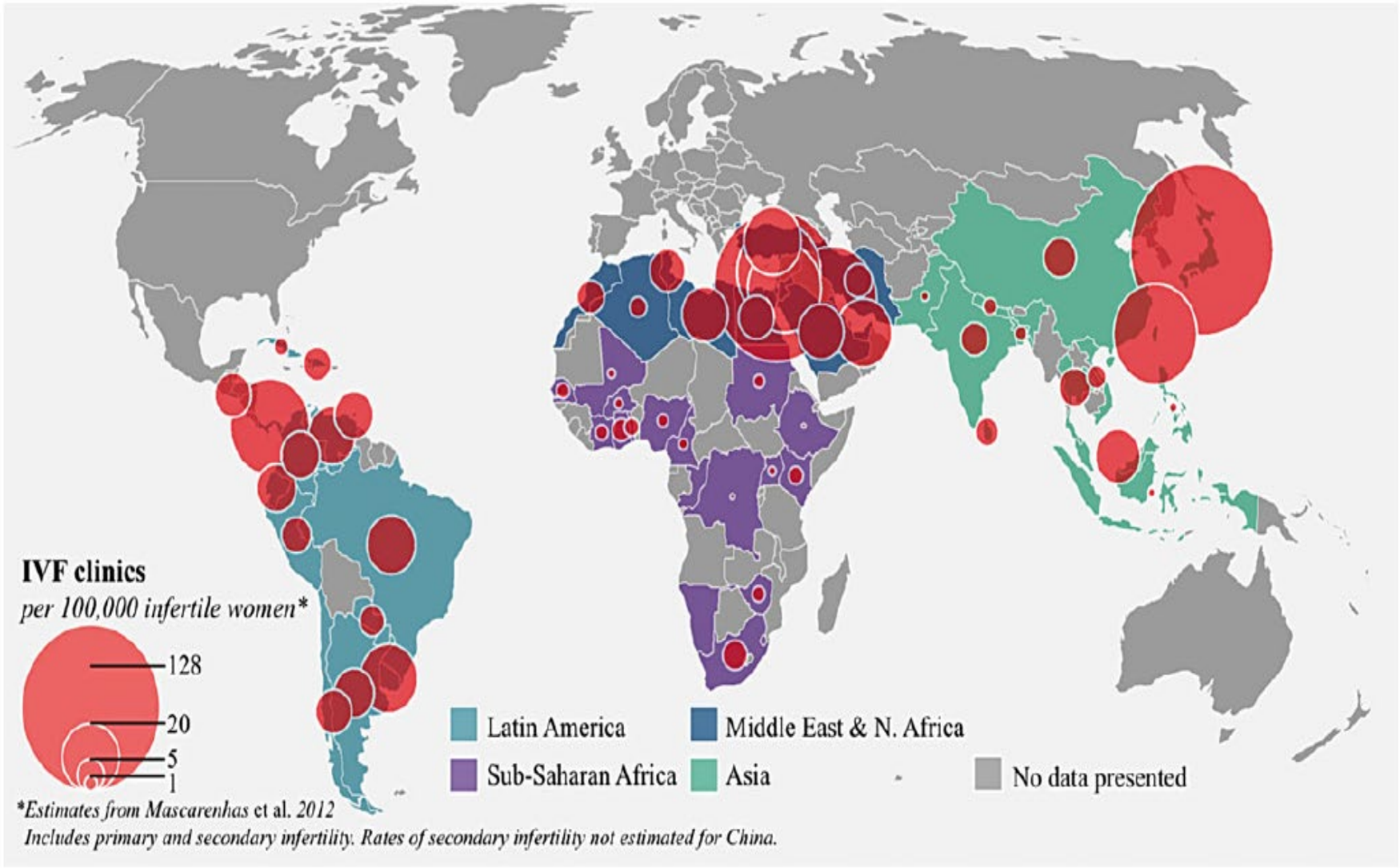


Figure 2 Comparative regional distribution of IVF clinics per estimated numbers of infertile women.

Assisted Reproductive Technologies (ART) Sub-Saharan Africa

- Overall development of medical infrastructure slow and exclusively in private clinics
- < 1% of the African population has access to ART
- African Network and Registry for ART:
  - 40 centers in 13 countries (e.g. South Africa, Nigeria, Kenya, Ghana, Mali, Uganda, Zimbabwe, Cameroon, Guinea, Senegal Sierra Leone, Togo)
- Centers often follow European or US practices and guidelines

Chiware. IVF and other ART in low- and middle-income countries. 2021

Assisted Reproductive Technologies (ART) Sub-Saharan Africa

- Examples for costs per IVF cycle:
  - No reports of state-funded ART treatments
  - 200 US$ in Uganda, 2,700 US$ in Ghana, 4,000 US$ in Kenya, 10,000 US$ in Nigeria
- Many couples incur catastrophic costs (> 40% of annual non-food health expenditures)
- Other issues:
  - Limited quality storage facilities with power generator
  - Religious concerns about fate of additional embryos
  - Common practice of transferring up to 5 embryos
  - Cultural concerns such as legitimacy of children born through IVF

Chiware. IVF and other ART in low- and middle-income countries. 2021
Asemoto. Access to Infertility Care in the developing World. 2015

Strategies for Solution in Developing Countries ?

Infertility Services: Appropriate Technology Options

- Medical History Taking and Counselling
- Simple diagnostic tests such as automated smart-phone based semen analysis
- medical help to prevent miscarriage
- Cost-effective off-patent ovulatory drugs
- Artificial insemination
- Low cost IVF

Table 1 A proposed national system for improved infertility care in resource-poor settings

Level 1 (community)	Level 2 (district hospital)	Level 3 (regional referral centers)
Village health care workers	Midwives and district health officers	Specialist consultant physicians
Education	Basic infertility workup and management	Assisted reproduction
• Reproductive physiology • Causes of infertility • Promote and optimize natural fertility • Dispel myths and stigma	• Semen analysis • Basic laboratory evaluation • HSG • Ultrasound • Ovulation induction with oral agents • Possibly IUI	• IUI • IVF/ICSI • Third-party reproduction

Abbreviations: HSG, hysterosalpingography; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization.

Strategies for Solution in Developing Countries

- **Prevention of Infections**
  - Most promising, feasible and cost-effective
  - FP, safe delivery and condoms as triple protection and safeguard of fertility (prevention of infections)
- **Infertility Diagnostics & Treatment**
  - Still limited to few capital cities, expensive
  - Development of appropriate technologies necessary
  - Include traditional healers, religious leaders for medical and spiritual approaches to infertility treatment

Strategies for Solution in Developing Countries

- **Education and Destigmatization**
  - Alleviate stigma and cultural pressures that blame the victim
  - Reframing infertility as a Human Rights issue
  - Decrease pronatalist pressures in society
  - Re-define women's roles in society
  - BOTH partners need to take responsibility for infertility
  - Education about causes of infertility and possibilities for prevention

ANNEX 2E. REASONS PROVIDED BY WOMEN FOR NOT USING CONTRACEPTION

DHS	Reason for not using contraception					
	Wants more children	Opposition to use	Knows no method	Knows no source	Health concerns	Access or cost
Benin 2001	17.6	17.6	5.2	2.9	14.3	1.4
Burkina Faso 2003	17.5	13.7	3.9	5.8	10.0	3.2
Cameroon 2004	37.4	11.8	4.7	1.2	7.2	0.8
Chad 2004	19.0	18.0	19.3	7.5	4.0	0.8
Côte d'Ivoire 1998/99	39.8	17.4	8.3	4.2	4.1	0.2
Eritrea 2002	60.3	7.4	4.4	3.9	4.8	0.2
Ethiopia 2000	41.8	10.4	7.9	1.8	10.4	0.3
Ghana 2003	13.8	8.8	4.4	1.3	33.2	1.8
Guinea 1999	55.6	12.6	5.6	0.8	4.4	0.5
Kenya 2003	13.9	15.8	2.0	0.3	22.0	0.2
Madagascar 2003/2004	19.8	12.5	4.5	3.5	28.6	0.9
Malawi 2000	7.9	20.9	2.8	0.9	20.8	0.9
Mali 2001	16.3	32.9	8.2	3.2	8.8	1.2
Mauritania 2000/01	15.9	15.2	4.2	2.9	7.2	0.3
Mozambique 2003	49.4	9.1	2.9	1.2	4.3	1.0
Namibia 2000	21.0	16.1	4.1	0.3	11.0	0.9
Niger 1998	33.2	9.2	7.4	7.8	2.9	2.6
Nigeria 2003	36.1	17.7	7.3	1.2	8.6	0.3
Rwanda 2000	19.8	8.1	2.3	4.1	19.7	1.8
Senegal 1997	31.1	6.6	13.1	-	4.7	0.7
South Africa 1998	23.8	13.3	1.6	0.7	19.5	-
Tanzania 2004	15.6	22.9	1.8	1.1	28.4	0.3
Togo 1998	28.0	10.6	2.6	4.9	9.9	1.5
Uganda 2000/01	10.6	10.9	3.1	1.8	23.4	2.0
Zimbabwe 1999	9.3	8.9	0.5	-	10.2	2.7

Sources: Demographic and Health Surveys

Population Issues for the 21st century. The Role of the Worldbank. HNP 2007 Report.

Broadening Family Planning

“ … childlessness represents a neglected aspect of family planning

and narrow-minded and goal-oriented population control is likely to be unsuccessful

if it does not take into account all determinants of human reproductive failure.”

BERGSTROM,S. *Reproductive failure as a health priority in the third world.* East Afr Med J. 1992

“ Infertility is not only an issue of reproductive health,

but also a social issue that can influence marital, family and other interpersonal relationships,

particularly in settings where childbearing is highly valued and central to ideas of womanhood.”

Bourey and Murray 2021

Conclusions

- Infertility in developing countries is a problem with enormous psychosocial implications for couples.
- Need to PREVENT, improve infrastructure for diagnostics and treatment, educate , demystify and destigmatize, challenge ideology of motherhood.
- Women with no reproductive history need a productive future as respected members of their communities.

Ethical Considerations for Infertility Treatments

UNIVERSITY OF CALIFORNIA

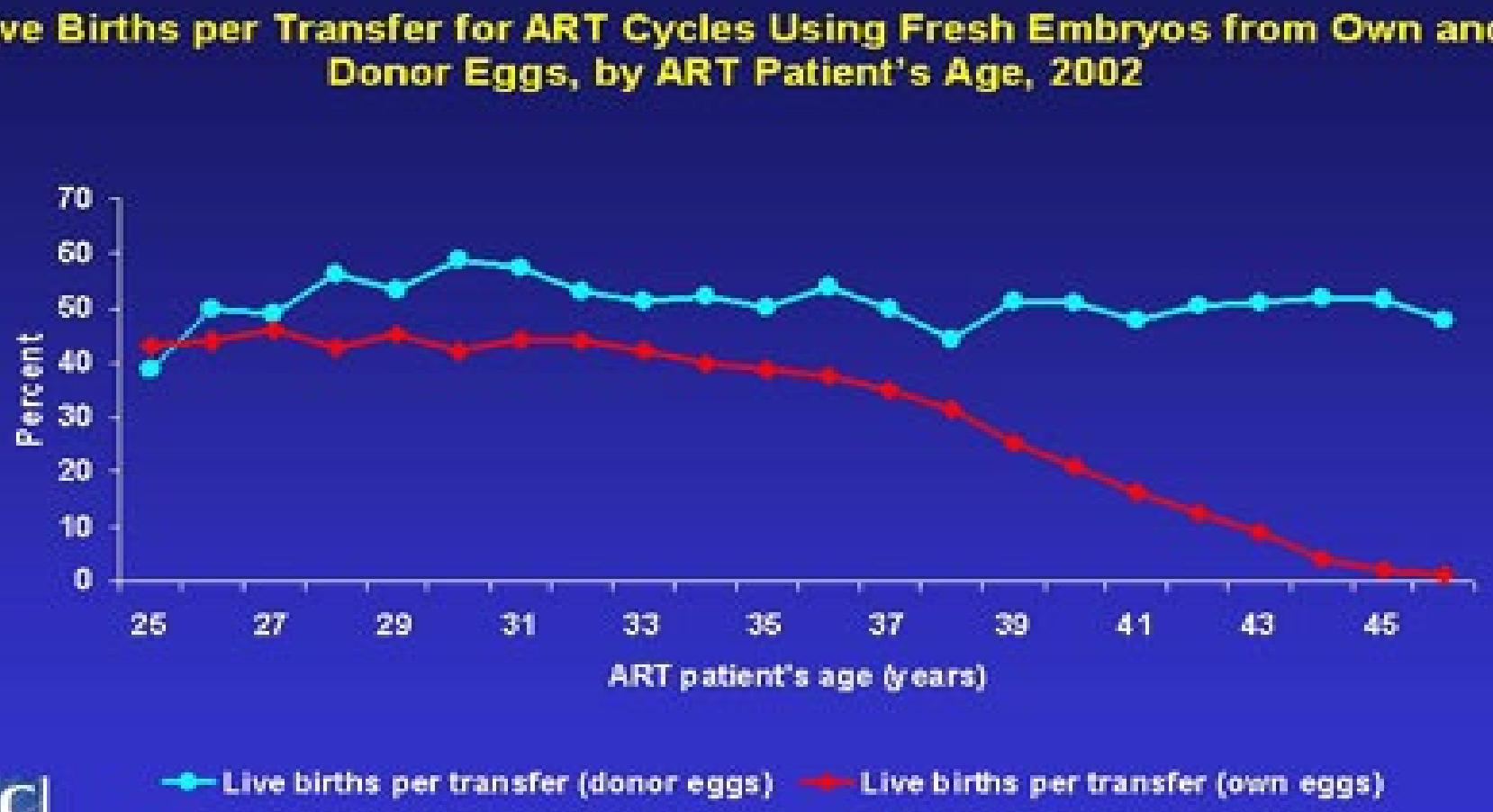
Global Health Institute

Age of the mother

- Increase in pregnancy rates of older age groups
- Risk: higher maternal and fetal morbidity and mortality
- Oocytes are limiting factors, not the uterus !

→ **Age cut-off for ART ?**
Individual right to privacy and reproductive choice?
Life expectancy raises, so why not reproductive life span ?
Man are allowed to procreate until age 100!

Life Births depend on age of eggs



CDC

Egg Donation

- young woman undergoes ovarian stimulation
- her eggs are fertilized with sperm (husband or donor)
- embryo is implanted in older woman's uterus

Surrogacy: Global Business

- woman agrees to bear the fetus for another person
- India:
  - 150 known fertility clinics, about 60% offer surrogacy
  - Surrogacy for $20,000, gestational carriers get ~$7,500
  - In 2005, the Indian Council of Medical Research laid out non-mandatory guidelines for regulation of surrogacy

→ **What are the rights of the surrogate mother ?**
What are the rights of the intentional parents ?
No – return policy ?
Monetary compensation for surrogate carrier ?

http://www.sfgate.com/local/bayarea/item/India-surrogacy-Chapter-One-23858.php

Preimplantation Genetic Diagnosis

- Eliminating embryos with serious genetic disease
- Widest choice for women at risk of having children with genetic abnormalities

→ Provision of life for children who may otherwise never be born

→ **Family balancing justified ?**
Future pressure by society, employer or insurance to undergo procedure ?
Right to life for people with disabilities ?

Cryoconservation and Left-over Embryos

- Typically, during fertility treatments, remaining fertilized eggs are frozen for future ART cycles
  - 10,000 generated per year nationally
  - No overseeing federal agency
  - Sometimes donated to infertile couples
  - Legislation often gives donors the legal rights for use or disposal

→ **Mandatory time limit or couples' instructions for use (research, donation, disposal) ?**
Legal issues about parental rights after donation?
Ethical solution for disposal ?

ART and abortion restriction

- **Status of fertilized eggs (8-cell blastocyst stage)**
  - hastily prepared legislation and vague language could have unintended consequences for ART
  - IVF with uncertain legal status — unless laws that define life as beginning at fertilization clarify the status of those embryos' creation, storage and possible destruction
  - Can an embryo be defined as a life inside a pregnant person but only as potential life in a lab?
  - What about testing embryos for genetic abnormalities before IVF transfer?
  - While many US states now ban abortion, these bans will increasingly and explicitly exempt IVF.

Sex Selection

- Motivations
  - **Sex linked genetic disorders**
    - Hemophilia, Duchenne's muscular dystrop
  - **Non-medical reasons**
    - Family "balancing"
    - Rebuild family after death of child
    - General preference for children of one sex over another for economic, cultural or social reasons

→ **Sperm Sorting**
IVF and Pre-implantation Genetic Diagnosis
Selective Abortion

Discrimination on gender basis ?
Shift in male/female ratio (e.g. India and China)