Fertility Evaluation for the Generalist

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Fertility Evaluation for the Generalist

DISCLOSURES: Ferring and Natera- Clinical Research

LEARNING OBJECTIVES: At the conclusion of this presentation, participants should be able to:

1. Discuss the basic infertility evaluation

2. Initiate age-based testing

3. Understand initial treatment plans

4. Counsel patients about assisted reproduction and when to refer

THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER.

There Aren't Enough Babies, Alarming the Whole World

Falling birthrates bring economic, social, political implications

BY GREG IP AND JANET ADAMY

The world is at a startling demographic milestone. Sometime soon, the global fertility rate will drop below the point needed to keep population constant. It may have already happened.

Fertility is falling almost everywhere, for women across all levels of income, education and labor-force participation. Some estimates now put the number of babies each woman has over her lifetime below the global replacement rate of about 2.2. The falling birthrates come with huge implications for the way people live, how economies grow and the standings of the world's superpowers.

The baby bust is happening so quickly and so widely that it's taken many by surprise. In high-income nations, fertility fell below replacement in the 1970s, and took a leg down during the pandemic. It's dropping in devel-

Wall Street Journal May 13, 2024

Total Fertility Rates by Country 1980-2020

THE WALL STREET JOURNAL.

Total fertility rates

U.S. MEXICO INDIA CHINA SOUTH KOREA HUNGARY JAPAN
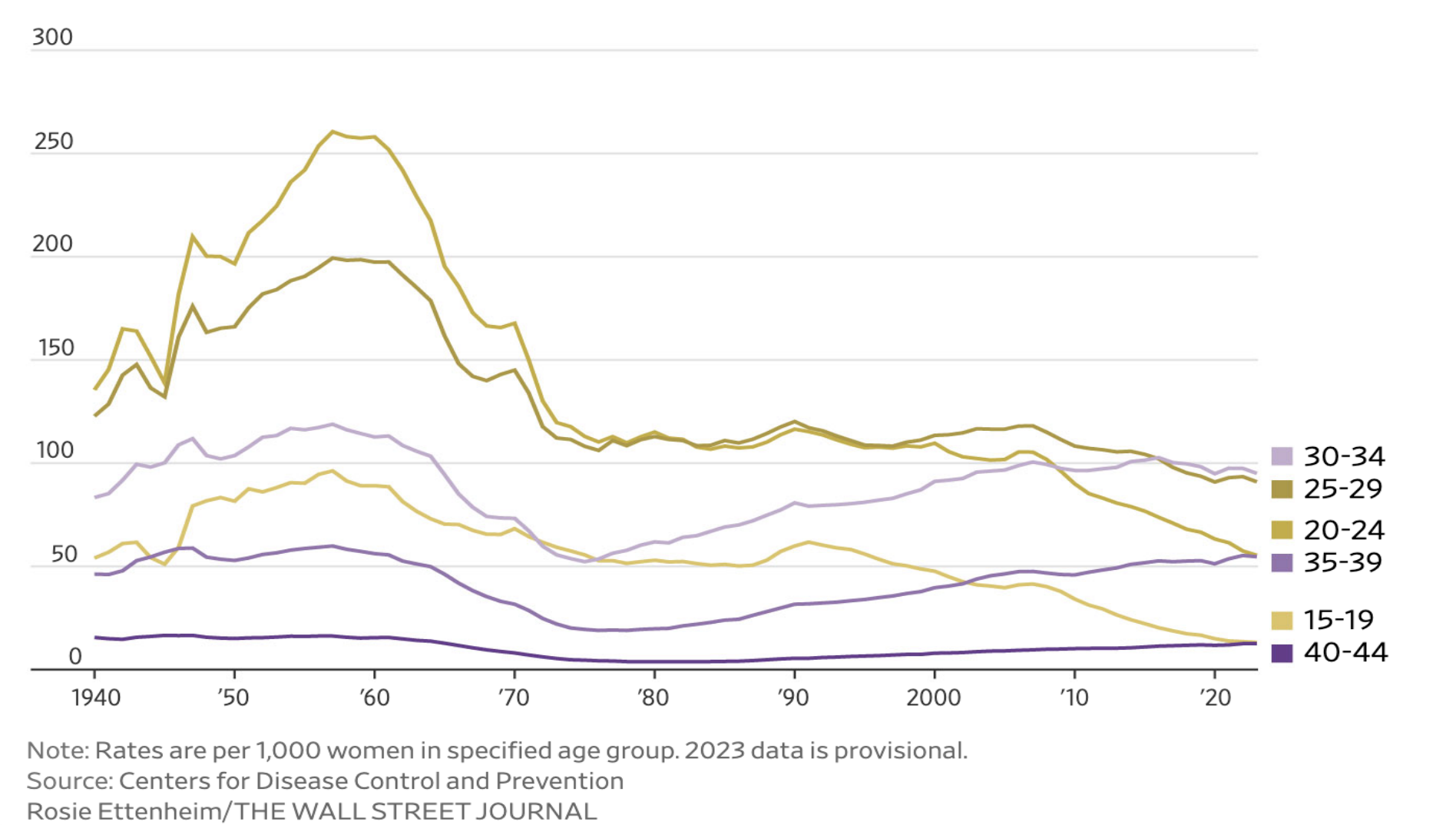
1980 '90 2000 '10 '20
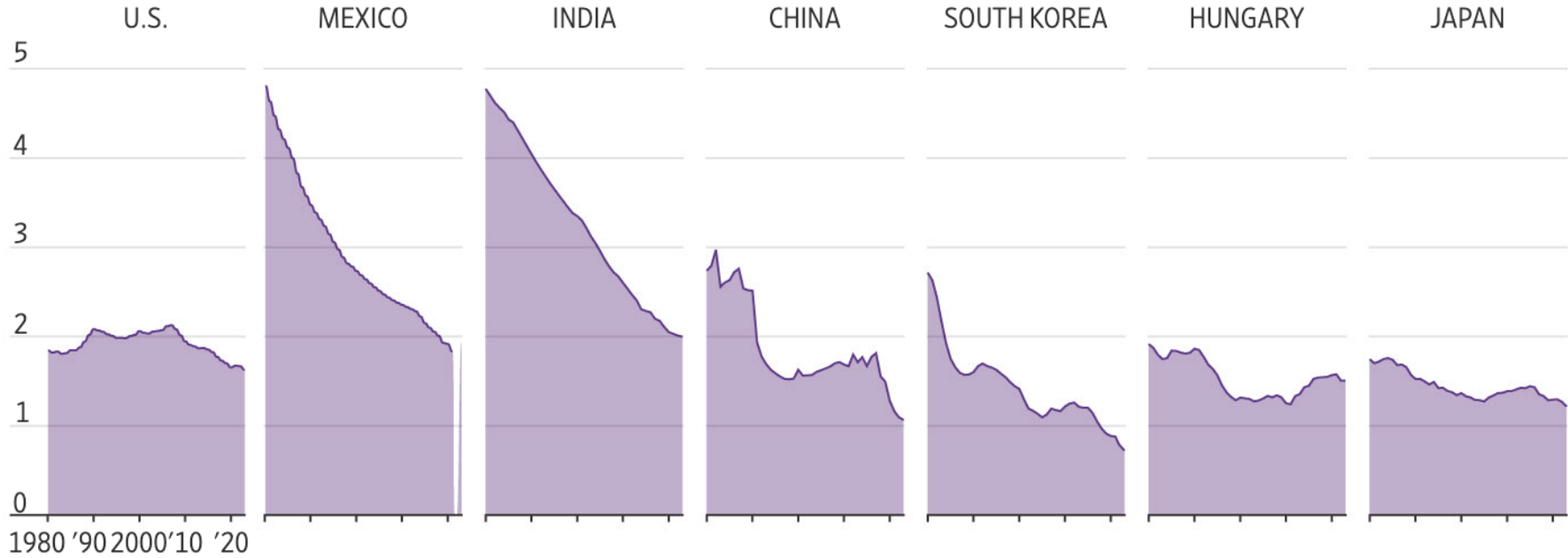
Sources: United Nations; U.S. Centers for Disease Control; national estimates compiled by Jesús Fernández-Villaverde
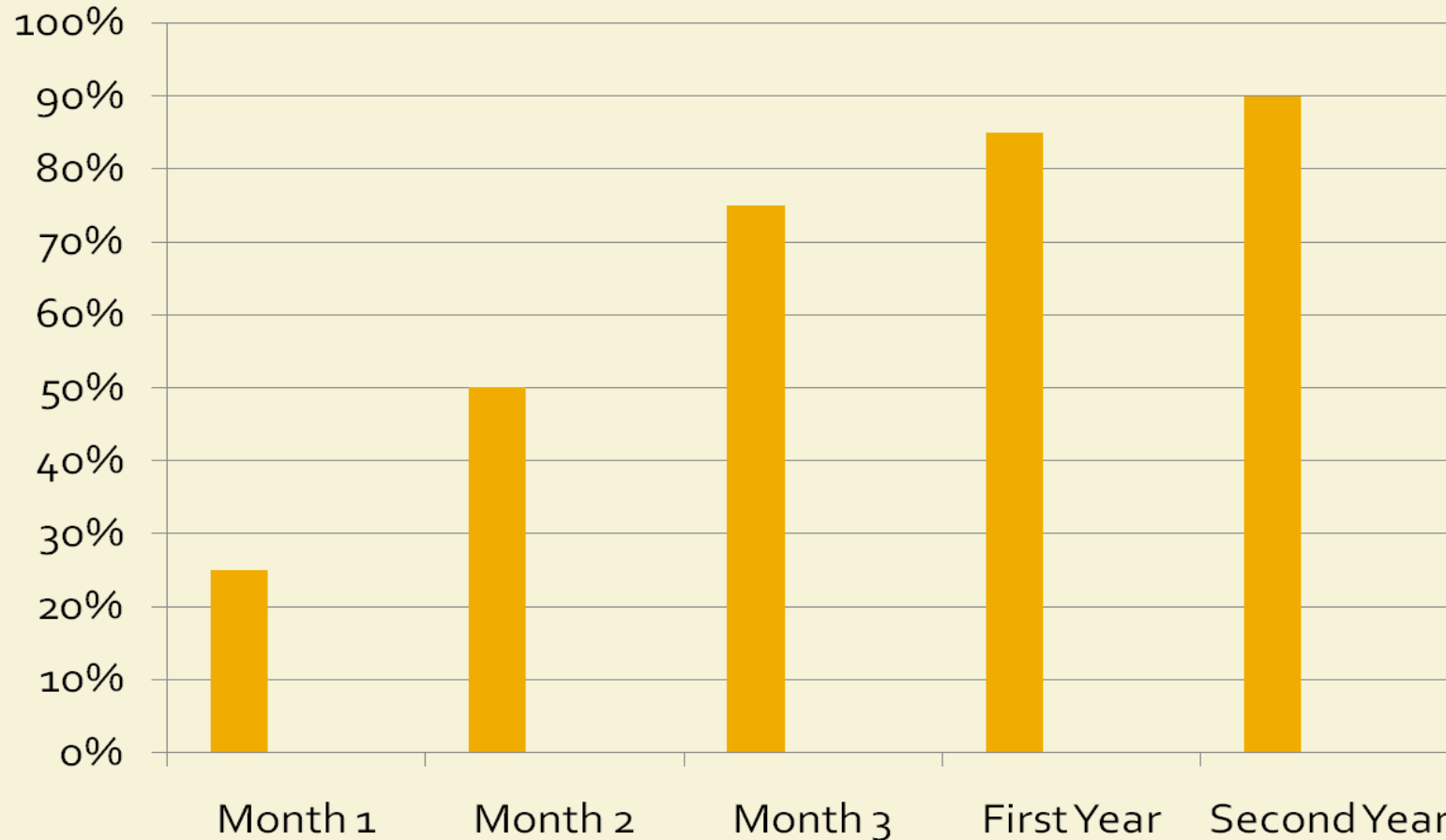Rosie Ettenheim/THE WALL STREET JOURNAL

US Birthrate of 1.6 Falls Below Replacement of 2.2

1950 | '60 | '70 | '80 | '90 | 2000 | '10 | '20

2023
2.15

U.S. ○ **1.62**

South Korea ○ **0.72**

Some estimates now put the number of babies each woman has **below the global replacement rate** of about 2.2. **The U.S.** long ago passed that level. **South Korea's rate**, the world's lowest, was once unimaginable.

Wall Street Journal May 13, 2024
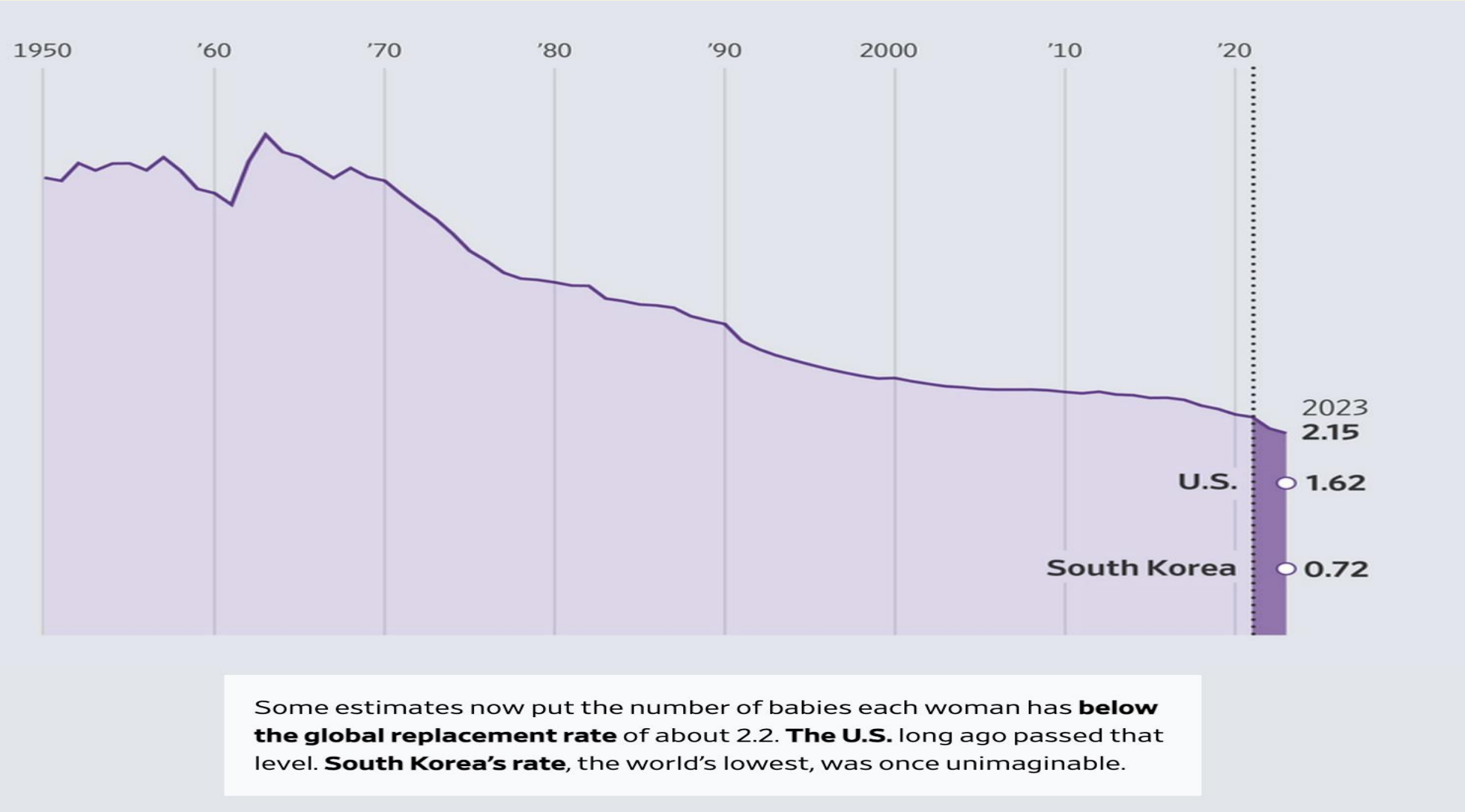
Birthrates by Age Group in the US

Note: Rates are per 1,000 women in specified age group. 2023 data is provisional.
Source: Centers for Disease Control and Prevention
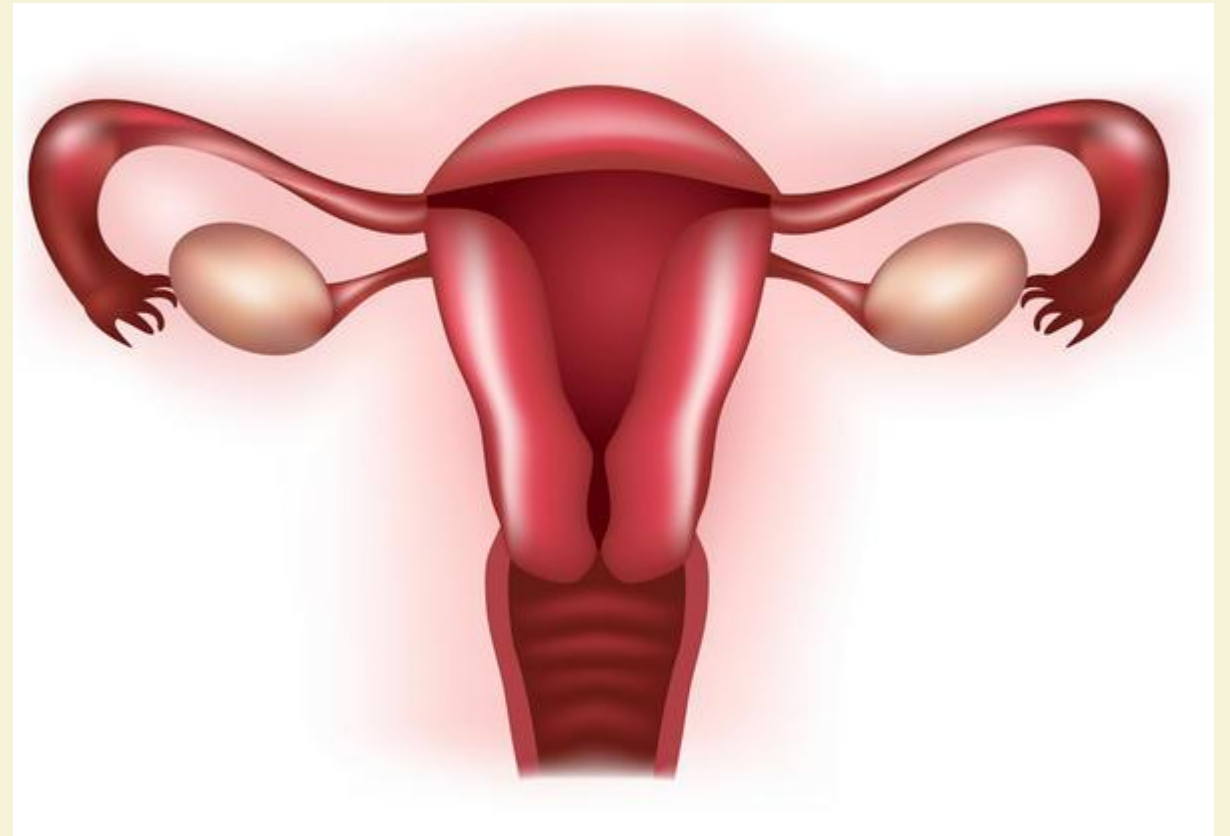Rosie Ettenheim/THE WALL STREET JOURNAL

Normal Pregnancy Rates in Newly Married Couples

Requirements to achieve Natural Heterosexual pregnancy

1. Patent fallopian tubes
2. Source of viable sperm
3. Normal uterus
4. Ovulated oocytes
5. Intercourse

Primary Management of Infertility

- Identify risk factors

    (Age, menstrual history, STD, prior surgery, Tobacco, alcohol, obesity, radiation, toxins, sexual function, prior pregnancies)

- Perform essential investigations

    (HSG, Semen analysis, documented ovulation)

- Counsel couple

    (age, years of trying)

- Initiate treatment or refer

Define and Identify Infertility Patients

Unprotected intercourse without contraception and without conception

AGE OF FEMALE	WHEN TO START EVALUATION
< 35 years	After one year of trying
35 to < 40 years	After 6 months of trying
40 or more years	Immediately

Most people diagnosed with infertility are in reality "Subfertile"

ASRM Definition of Infertility Oct. 2023

Infertility is a disease, condition, or status characterized by any of the following:

- The inability to achieve a successful pregnancy based on a patient's medical, sexual, and reproductive history, age, physical findings, diagnostic testing, or any combination of those factors. (New 2023)

- The need for medical intervention, including, but not limited to, the use of donor gametes or donor embryos I order to achieve a successful pregnancy either as an individual or with a partner. (New 2023)

- In patients having regular, unprotected intercourse and without any known etiology for either partner suggestive of impaired reproductive ability, evaluation should be initiated at 12 months when the female partner is under 35 years of age and at 6 months when the female partner is 35 years of age or older.

Causes of Infertility

- Male Factors (1/3)
  - Poorly functioning and/or few sperm
- Female Factors (1/3)
  - Ovulatory problems
  - Tubal Problems
  - Uterine Problems
  - "Hostile" Peritoneal Environment
- Combined or Unknown Factors (1/3)
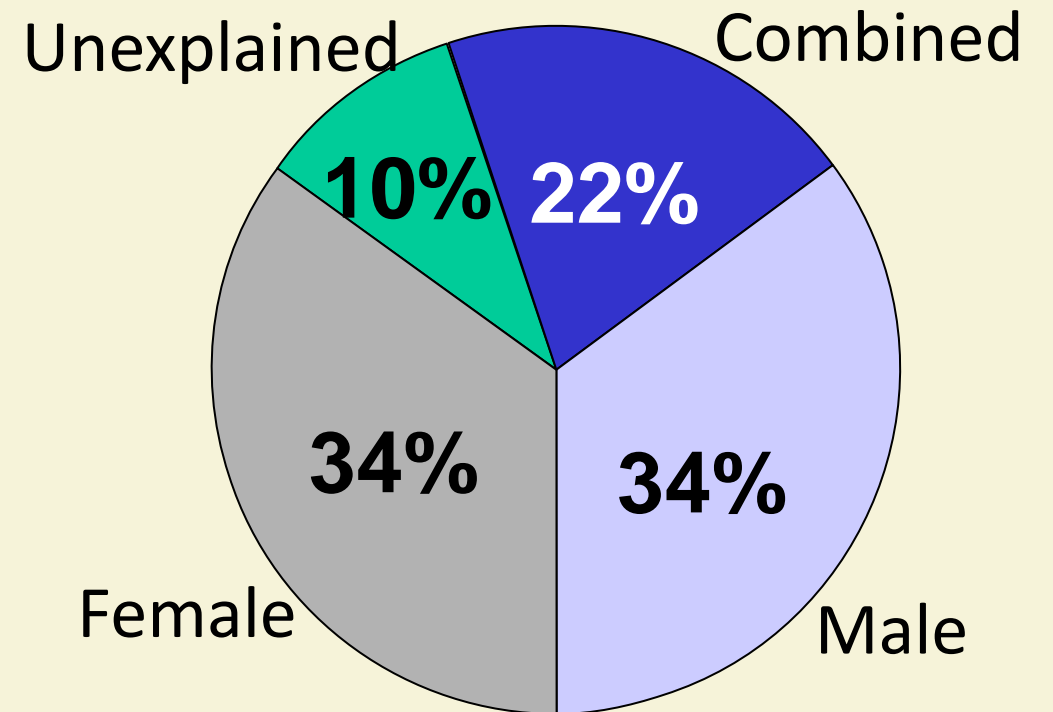
Causes of Female Infertility: Ovulation Disorders

Ovulatory Dysfunction

– Polycystic Ovaries (PCOS)

  "obese, amenorrhea, hirsute"

– Hyperprolactinemia

– Hypothyroidism

– Idiopathic Hypothalamic (IHH)

- Premature ovarian failure (POF)

Decreased Ovarian Reserve

-Advanced age of the female

- Prior chemo and/or radiation therapy

- Prior surgery on the ovary

- Turner mosaic, Fragile X premutation

- Smith-Lemli-Opitz syndrome

- FSH > 10 miu/ml, AMH < 1 ng/ml

-Antral (2-9 mm)follicles < 8

ACOG. Infertility work up for the women's health specialist. 2019
ASRM. Fertility evaluation of infertile women. 2021

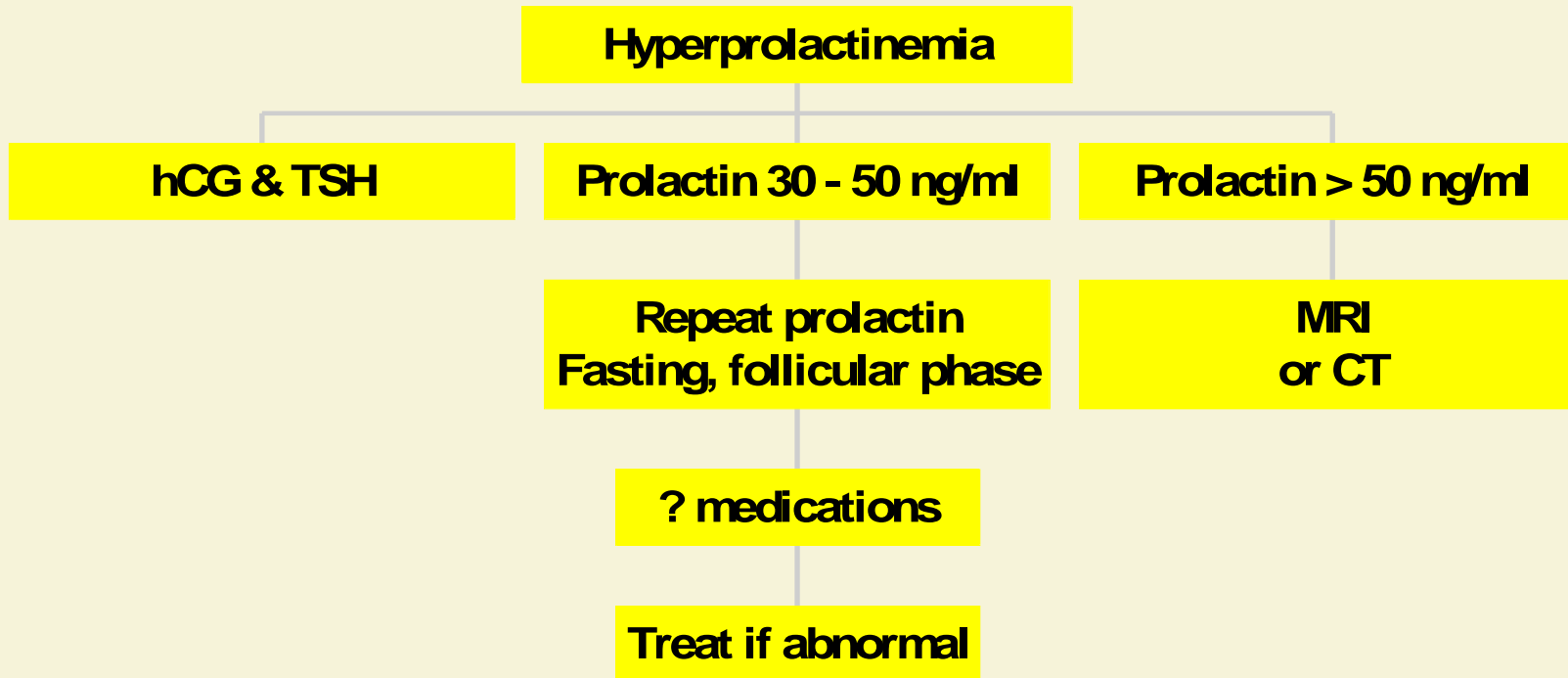# Tests to aid in the Evaluation of Ovulatory Disorders

- **Normal Ovulatory Function**
  - --Normal menstrual cycle (26-34 days)
  - --Positive urinary LH surge at midcycle
    - Cycle day 21 Progesterone: > 10 ng/ml
    - Cycle Day 3 FSH: <10 mIU/L
    - Cycle Day 3 Estradiol: < 60 pg/ml
    - Any cycle day AMH: 1.5 to 4.0 ng/ml
    - TSH: 1.0 to 2.5 mIU/ml
    - Prolactin: < 25 ng/ml
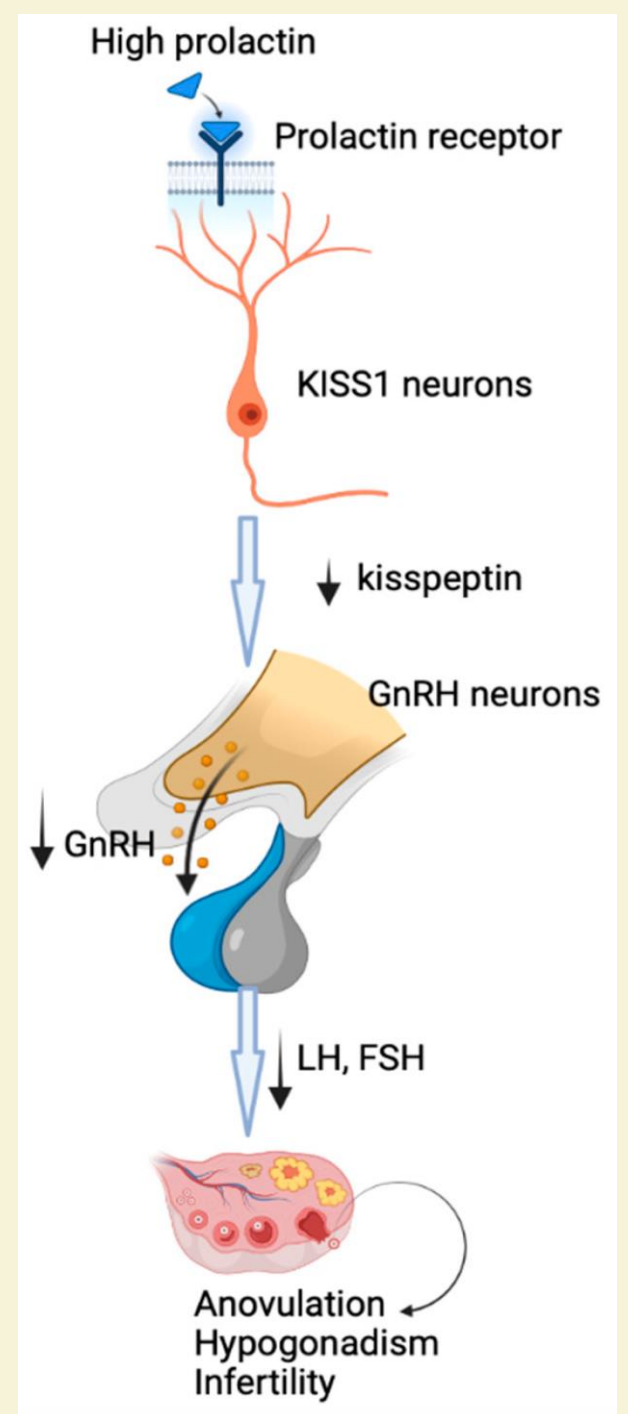   - 25-OH Vitamin D3: > 30 ng/ml
    - HgbA1c: < 5.7%
    - BMI < 30

Fertility Treatments to Induce Ovulation

- Use Clomiphene 50 mg cycle days 3 to 7 ($30.00/5)
- Use Letrazole of 2.5 mg cycle days 3 to 7 ($2.00/5)
- For PCOS patients (with elevated HgbA1c)

  -Metformin ER 500 to 750 mg po daily to BID ($28.00/180)
- Vaginal progesterone supplements 3 days after LH surge
  – Vaginal suppository compounded 100 mg ($2.50/each)
  – Endometrin Micronized vaginal tablet 100 mg ($15/tablet)
  – Crinone 8% vaginal gel daily ($40/applicator)
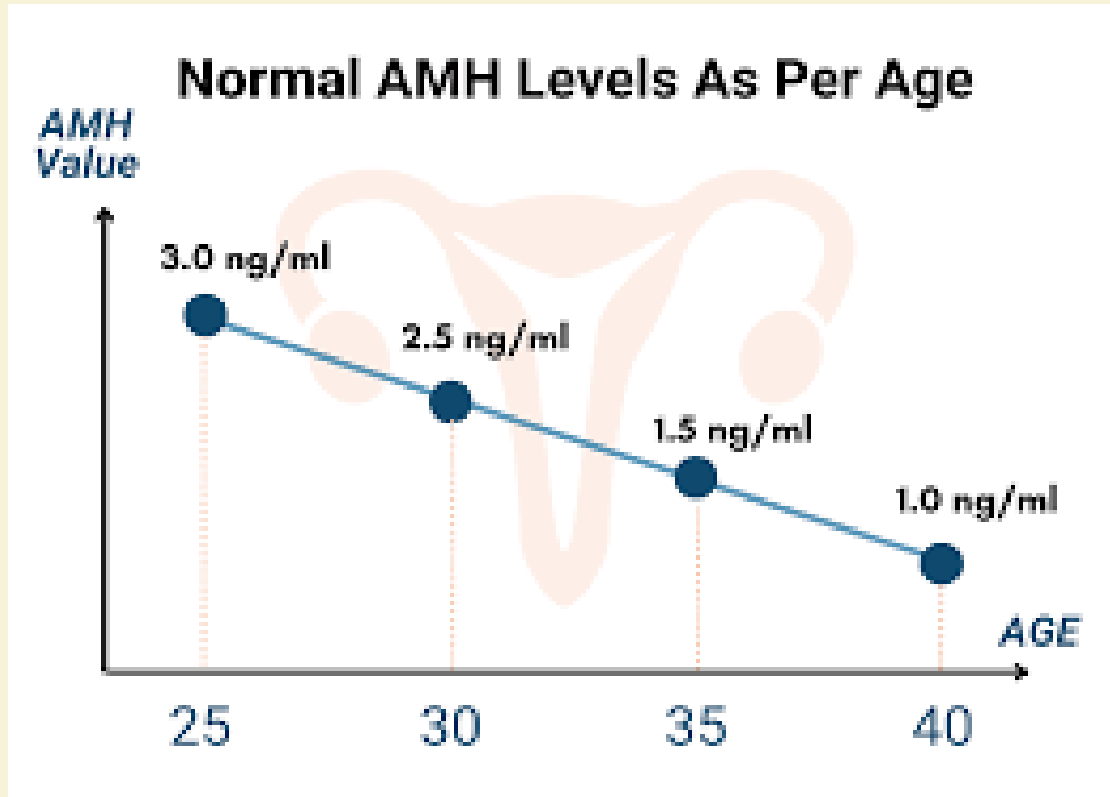 – Prometrium capsule 100 mg used vaginally-off label ($3.50/each)

Hyperprolactinemia

Hyperprolactinemia

hCG & TSH

Prolactin 30 - 50 ng/ml

Prolactin > 50 ng/ml

**Repeat prolactin
Fasting, follicular phase**

**MRI
or CT**

? medications

Treat if abnormal

- In infertile women, treat, even if mildly elevated
- Cabergoline up to 0.5 mg p0 2x/week
- Discontinue when pregnant
- Use vaginally if intolerant orally

High prolactin

Prolactin receptor

KISS1 neurons

↓ kisspeptin

GnRH neurons

↓ GnRH

↓ LH, FSH

Anovulation
Hypogonadism
Infertility

Anti Mullein Hormone (AMH) Correlates with Ovarian Reserve

Decreased AMH associated with increased age, obesity, tobacco use, endometriosis, genetic factors, chemotherapy, radiation therapy
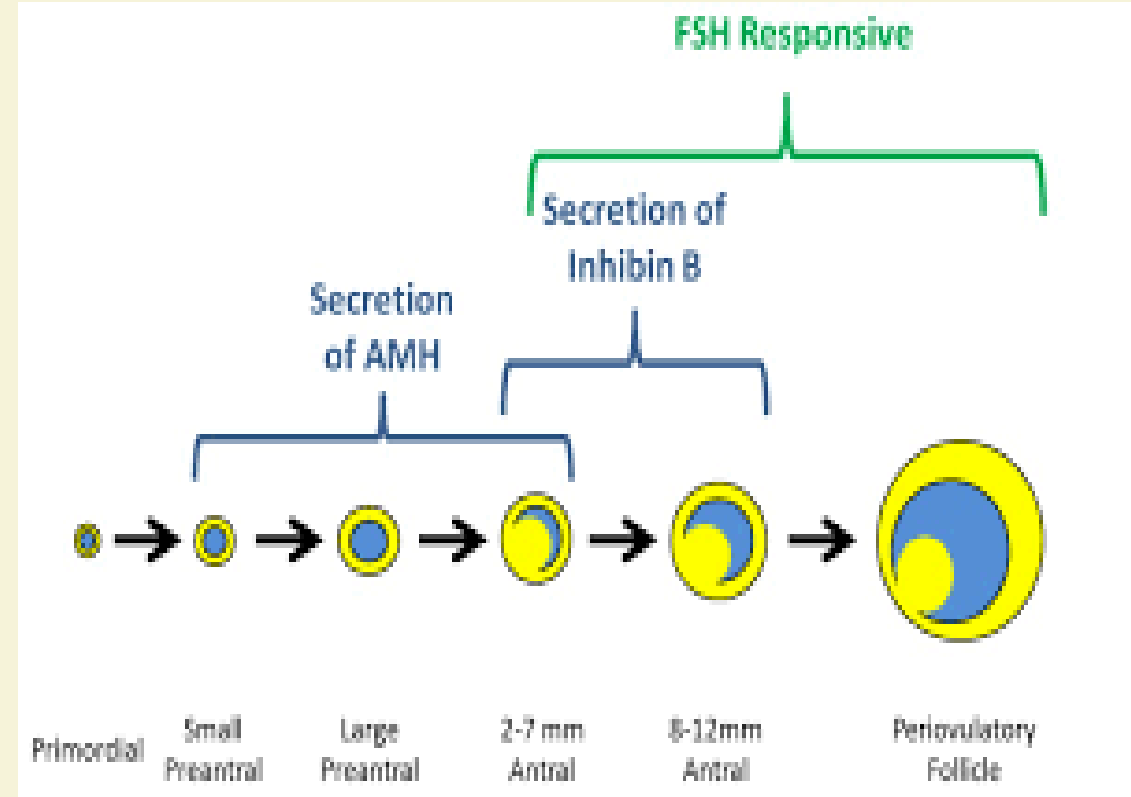
AMH is produced by the small preantral and antral Follicles (2-9mm) and correlates to the ovarian reserve

Donor Oocytes for Decreased Ovarian Function

- Uses eggs obtained through IVF from a young healthy women
- Eggs are fertilized with partner's sperm
- Embryos transferred into woman's uterus
- Expected Pregnancy rates over 60%
  - Preserves 50% genetic contribution from couple
  - Maternal experience of carrying and delivering a pregnancy preserved as well as normal breast feeding
  - Social perception no different than genetic child
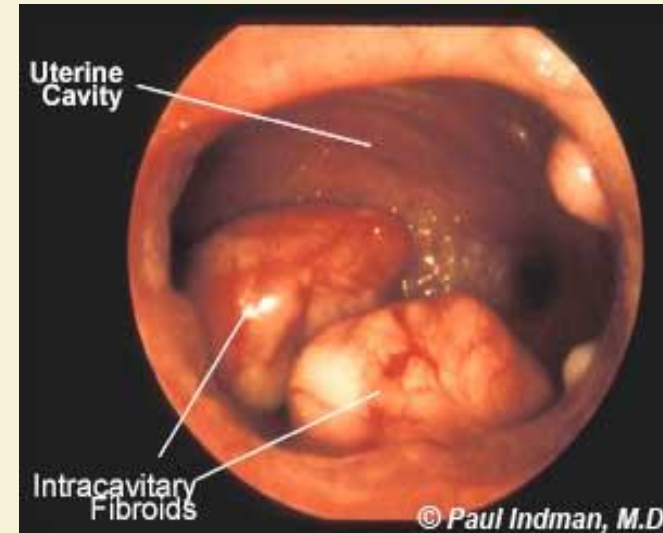
Causes of Female Infertility: Uterus and Tubes

Uterine Factors

- Fibroids
- Polyps
- Asherman's syndrome Scarring
- Endometriosis/Adenomyosis
- Congenital anomalies

Tubal Factors

- Hydrosalpinges
- Blocked or damaged tubes
- Prior infection
- Prior surgery

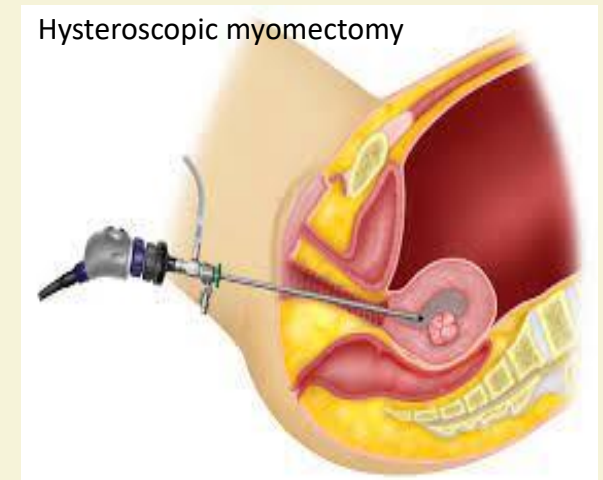# Fertility treatments: Anatomic Abnormalities

- **Diagnosis**

  HSG

  Laparoscopy

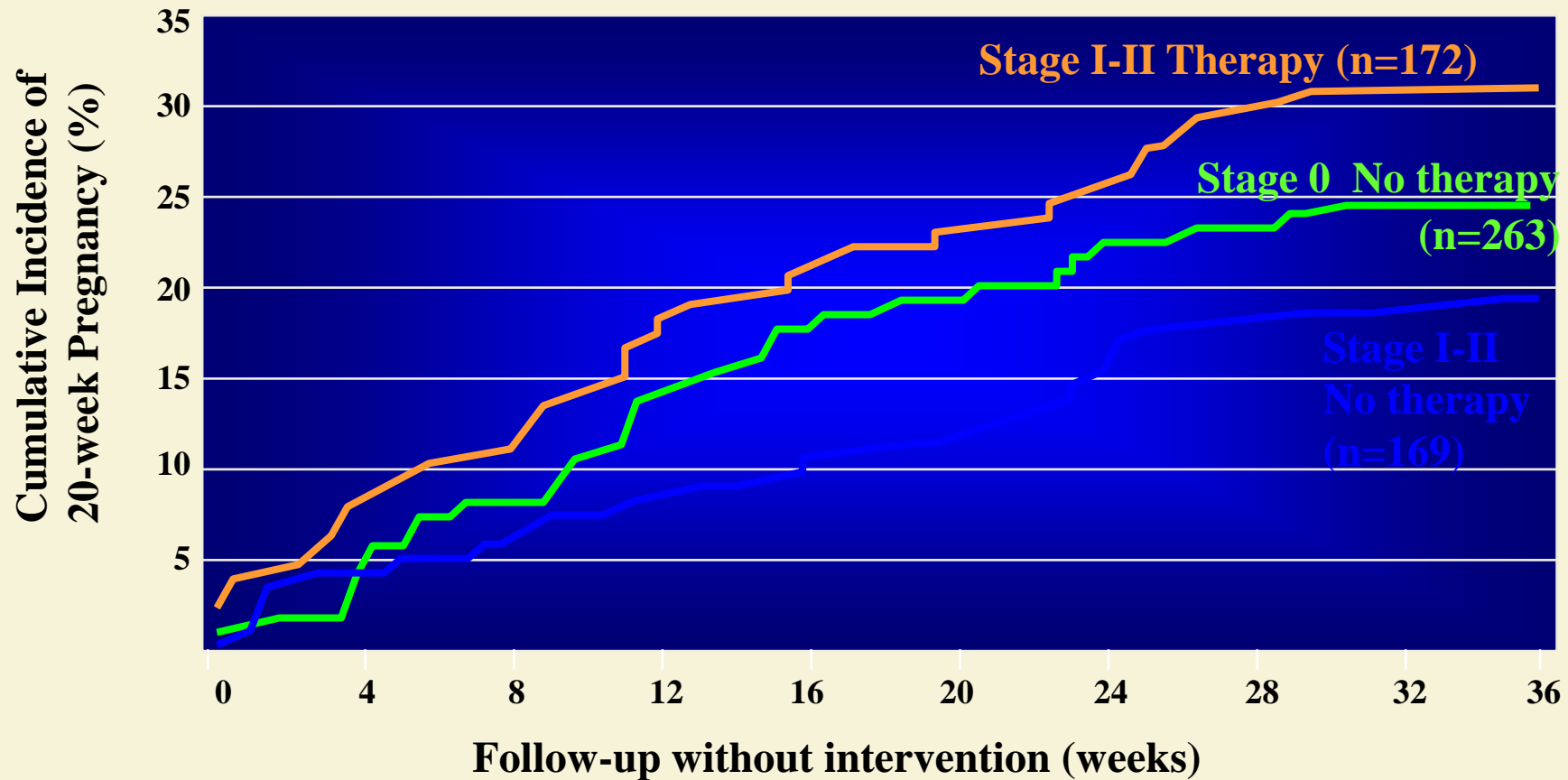 SHG

Laparoscopic Procedure

- **Surgical intervention**

  - Hysteroscopy

  - Laparoscopy

  - Open abdominal surgery

Hysteroscopic myomectomy
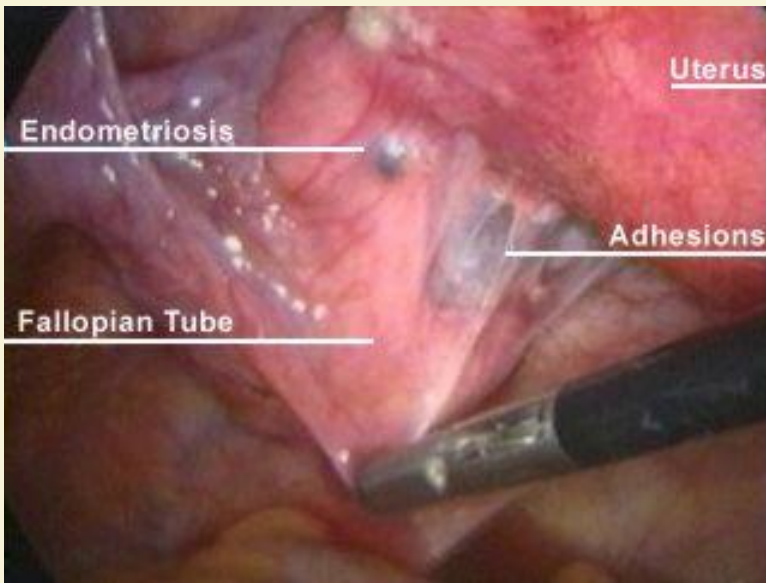
Fecundibility After Surgical Treatment of Endometriosis

ENDOCAN. Marcoux S. NEJM 1997;337:269

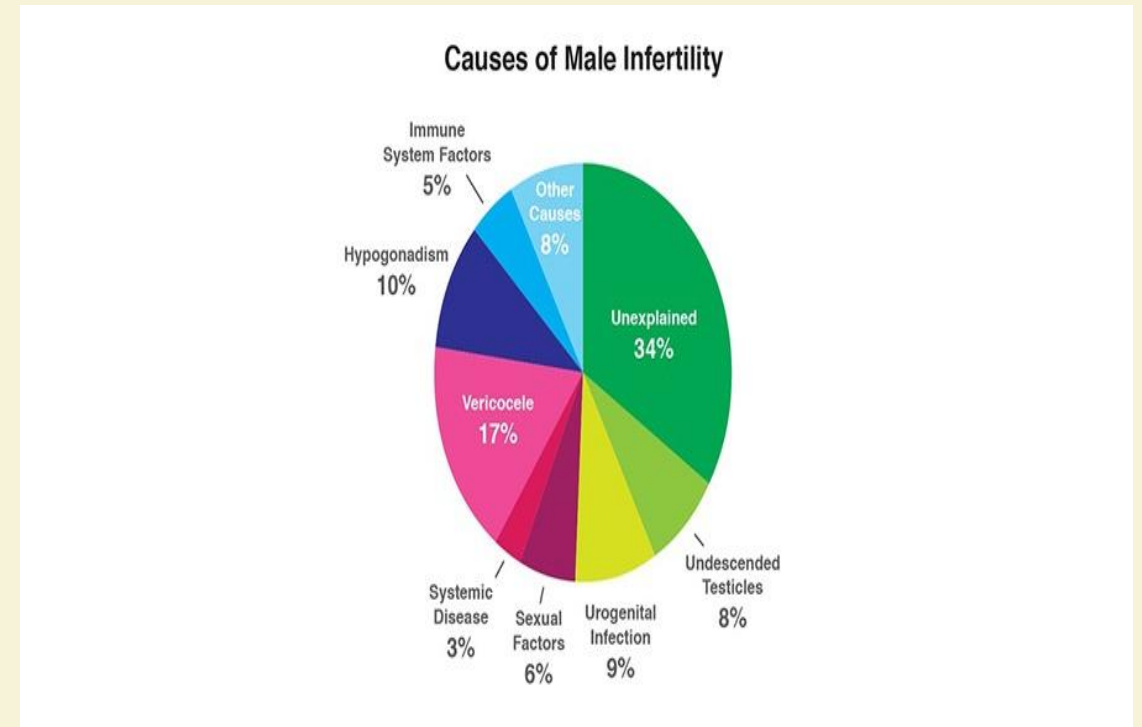# Causes of Male Factor Infertility

OBSTRUCTIVE CAUSES
  Azospermia
  Absence of the vas deferens (CFTR)
  Retrograde ejaculation
  Vasectomy

(Check for CF mutation)

NON-OBSTRUCTIVE CAUSES
  Testicular insufficiency
   Erectile dysfunction
   Oligospermia (low count)
   Asthenospermia (low motility or normal)
   Hypothalamiic

(Check FSH, LH, Testosterone, TSH, Prolactin,
Karryotype, Y-chromosome microdeletion, DNA Fragmentation)

Causes of Male Infertility

Immune System Factors 5%
Other Causes 8%
Hypogonadism 10%
Unexplained 34%
Vericocele 17%
Systemic Disease 3%
Sexual Factors 6%
Urogenital Infection 9%
Undescended Testicles 8%

Normal Sperm Parameters

Parameter	Lower reference limit
Semen volume (ml)	1.5 (1.4–1.7)
Total sperm number (10^6 per ejaculate)	39 (33–46)
Sperm concentration (10^6 per ml)	15 (12–16)
Total motility (PR + NP, %)	40 (38–42)
Progressive motility (PR, %)	32 (31–34)
Vitality (live spermatozoa, %)	58 (55–63)
Sperm morphology (normal forms, %)	4 (3.0–4.0)
Other consensus threshold values	
pH	≥7.2
Peroxidase-positive leukocytes (10^6 per ml)	<1.0

WHO 6th Edition 2021

Interpretation of Male Hormonal Profile

| Increased FSH	Increased LH	Low testosterone	Testicular failure
Increased FSH	Normal LH	Normal testosterone	Failure of Spermatogesis
Decreased FSH	Decreased LH	Low testosterone	Hypogonadotropic hypogonadism

Supplements and Lifestyle modification may improve some male factors

15
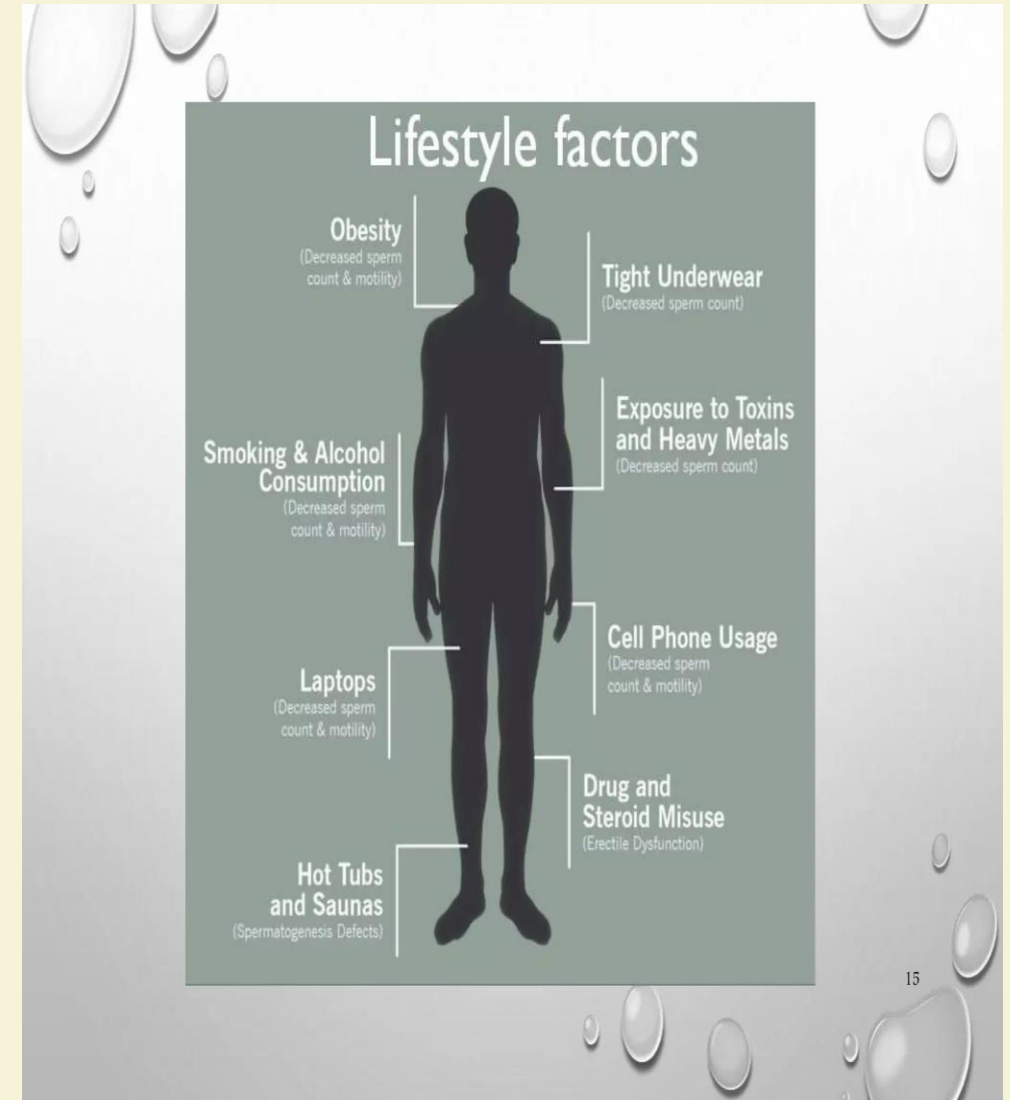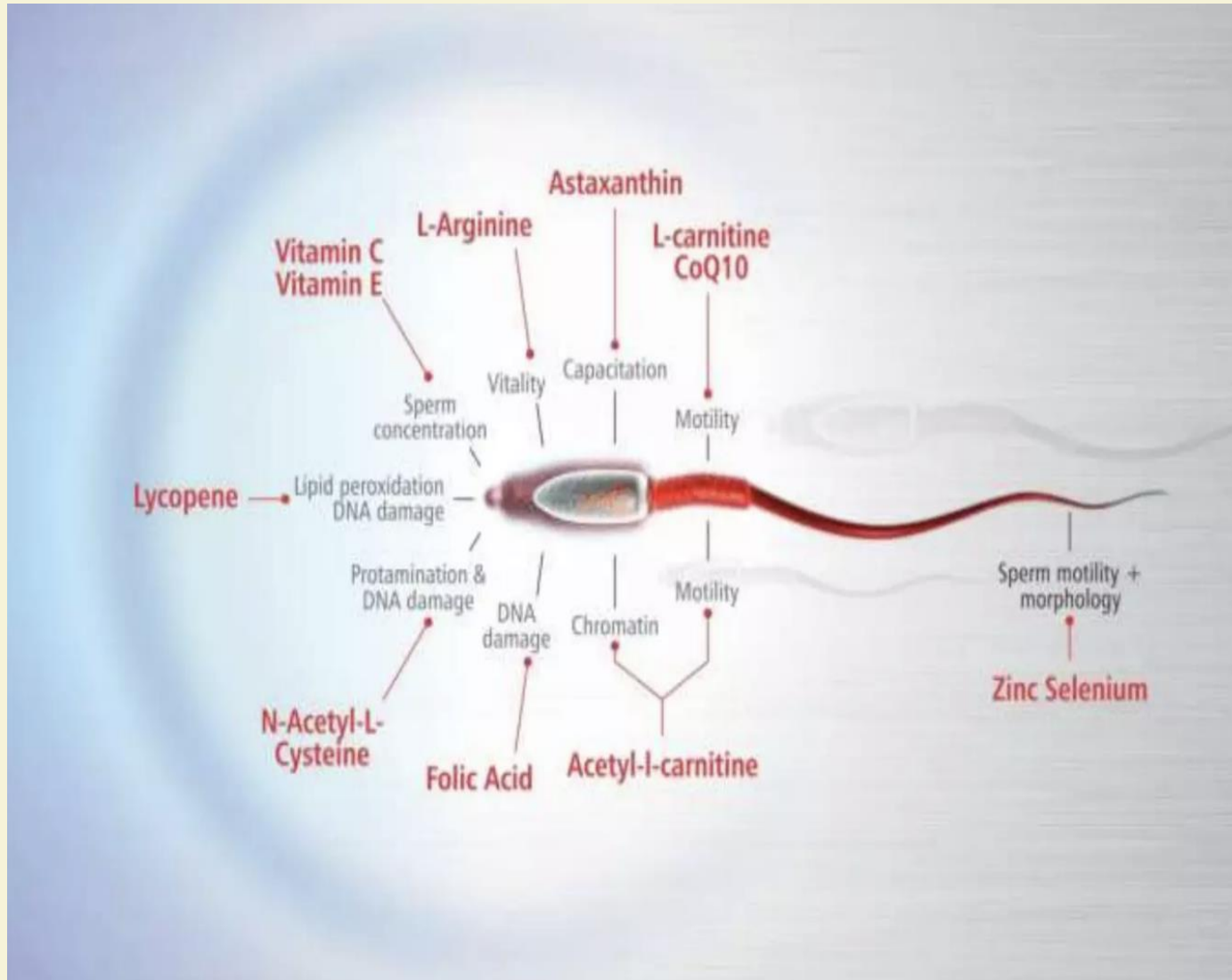
Fertility Treatments: Male + Ovulatory Factor Ovulation Induction with Intrauterine Insemination

- **Maximize every aspect of the cycle**
  - More mature eggs
  - Trigger shot to boost ovulatory signal
  - Higher concentrations of sperm
  - Sperm placed "Upstream" past cervix
  - Progesterone support
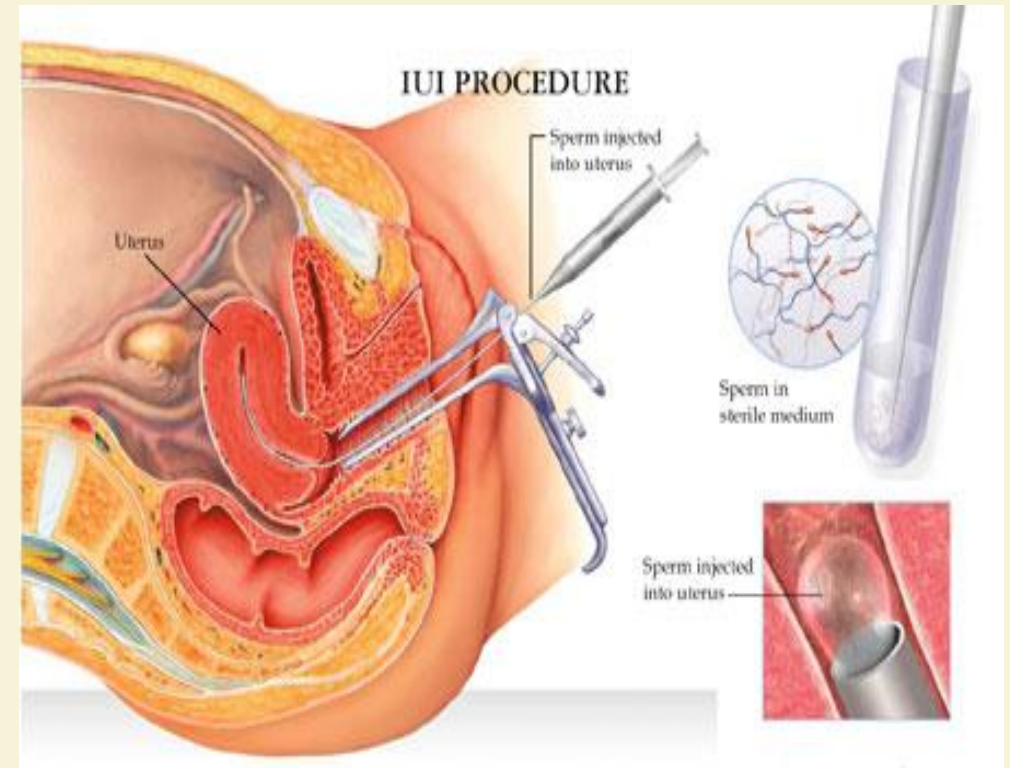
Success Rates with Ovulation Induction + IUI

IUI Success Rates Per Cycle

Age

Source: Merviel et al - Fertility and Sterility
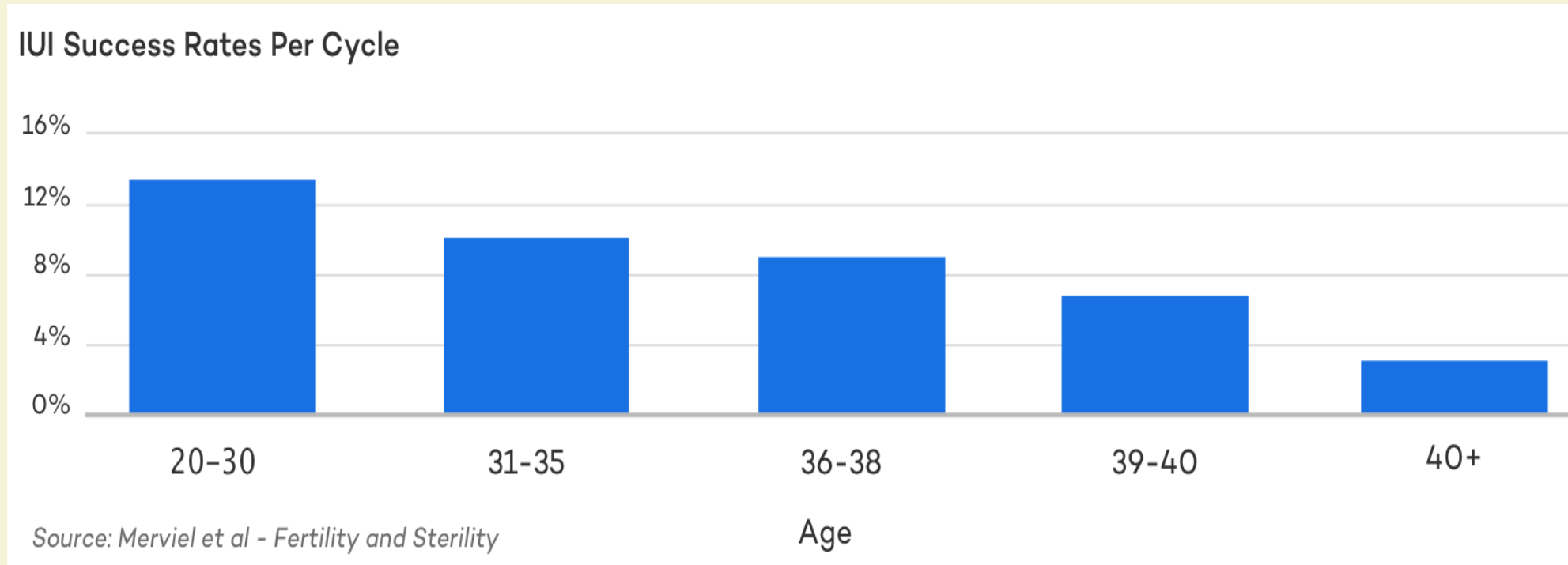
- Lower success rates with other identified causes of infertility
  - Endometriosis
  - Tubal factors
  - Abnormal semen parameters

In vitro fertilization (IVF)

Fertilization of eggs with sperm

Embryos

One Embryo transferred into uterus

Eggs Isolated
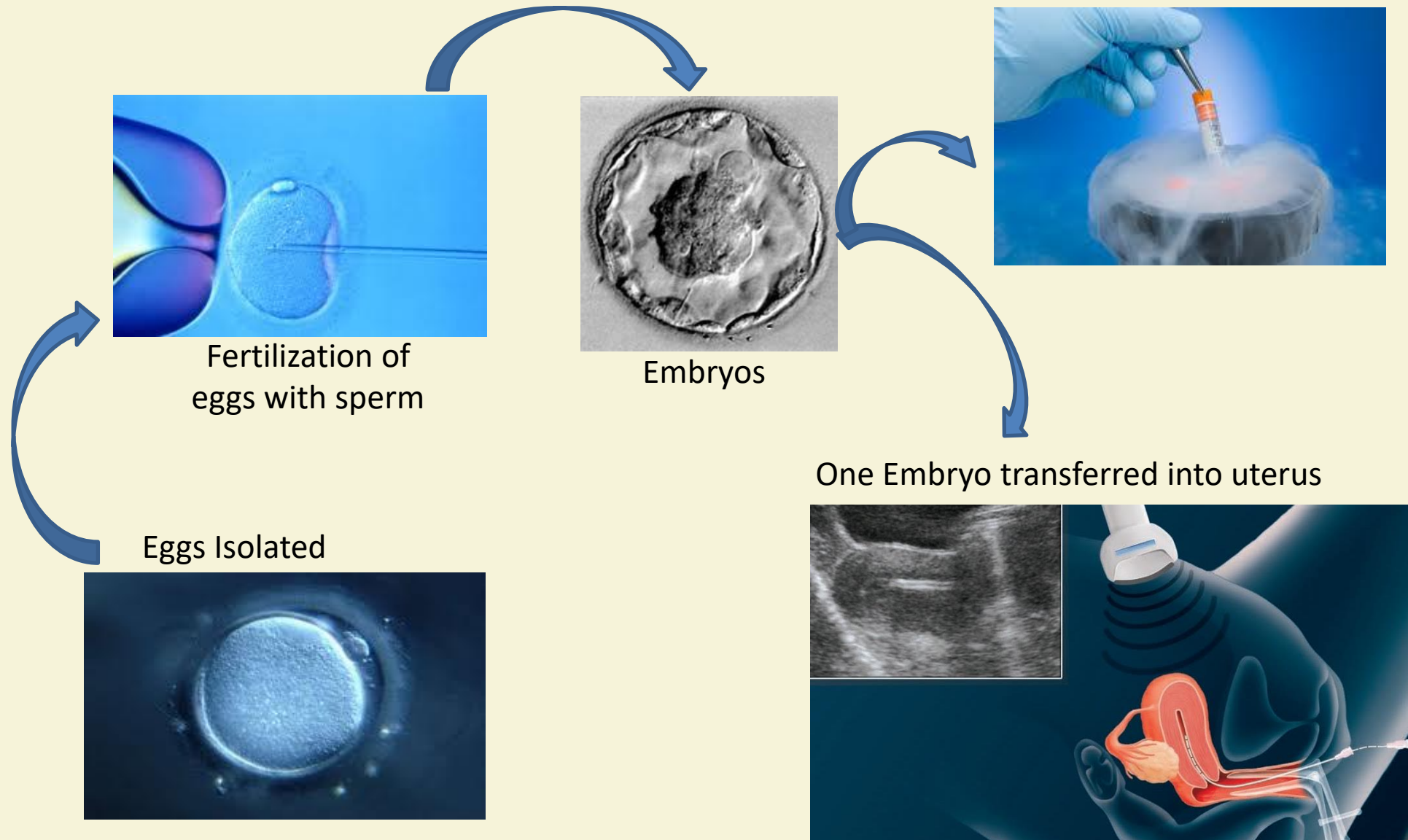
IVF accounted for 2.4% of Live births in US 2021

89,208 IVF live births in US 2021

Increased 14% since 2019

3,591,328 total live births in US in 2023

Decreased 2.0% since 2022

Top Reasons for Pursuing IVF in the US 2021

Reason	Percentage
Egg or embryo banking	40.9%
Other factor	30.0%
Male factor	27.8%
Diminished ovarian reserve	26.9%
Preimplantation genetic testing	16.6%
Ovulatory dysfunction	14.3%
Unexplained factor	10.5%
Tubal factor	10.4%
Endometriosis	6.5%
Recurrent pregnancy loss	6.3%
Uterine factor	5.8%
Gestational carrier	1.4%

Centers for Disease Control and Prevention (CDC.gov/art/reports/2021/summary)

FSH Stimulated vs Natural Egg Recruitment

20-25 Mature Eggs

1 Dominant Egg

FSH Stim for IVF

(mature eggs develop in more Follicles because of exogenous FSH stimulation)

Natural Cycle

(other follicles become atretic due to decreasing production of FSH)

20-25 "Recruited" Eggs/month

Age 30
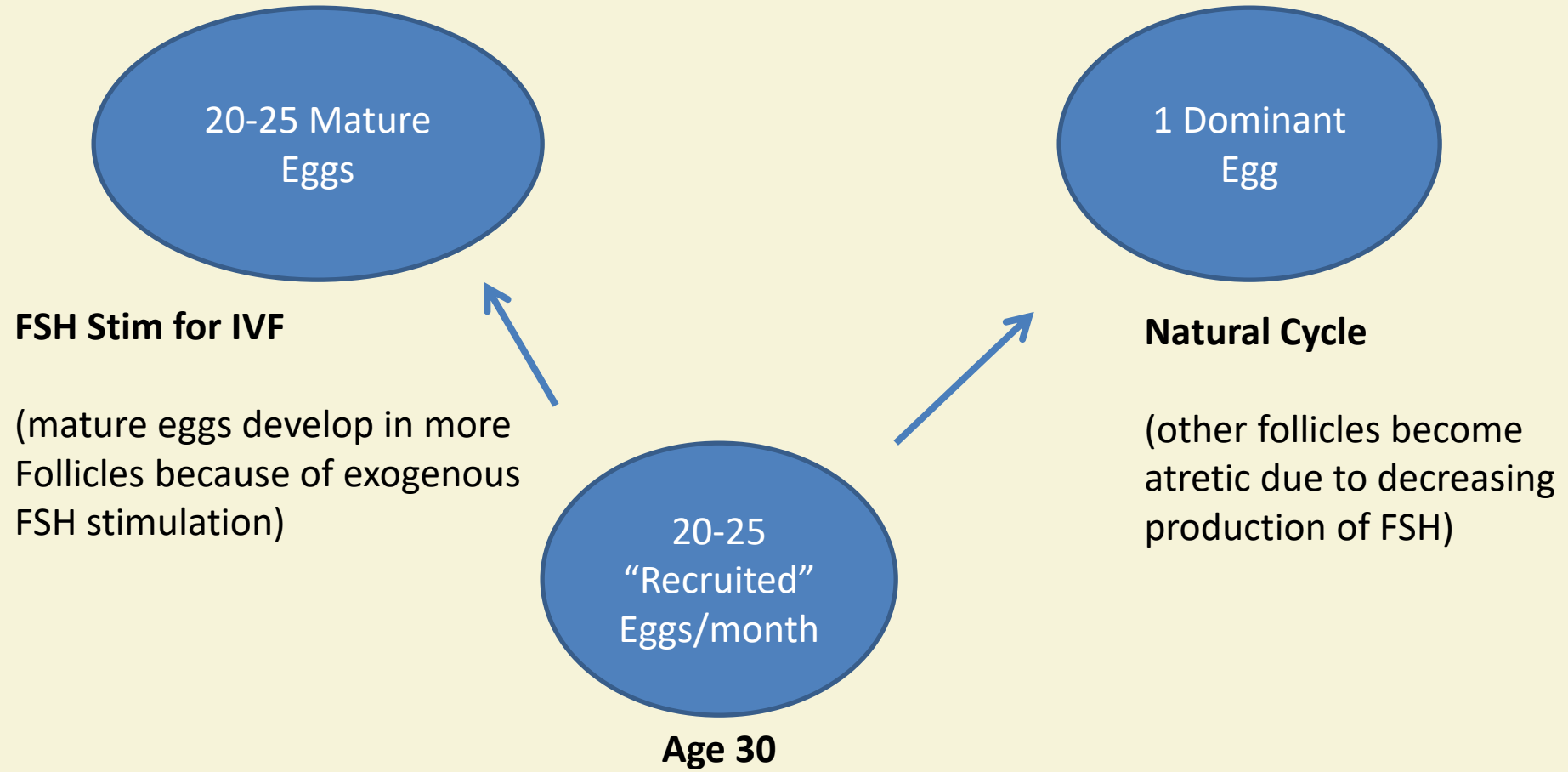
Effect of Maternal Age and Body Mass Index on Live Birth Rate after IVF

	BMI, kg/m²							
Age, y	<18.5	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	40.0-44.9	45.0-49.9	≥50
	Underweight	Normal weight	Overweight	Class I obesity	Class II obesity	Class III obesity	Morbid obesity	Super obesity
<30	65	64	59	60	50	48	40	25
30	60	63	57	59	54	48	20	20
31	61	59	57	54	46	40	30	.
32	61	58	55	53	43	44	35	22
33	45	56	52	54	44	37	43	.
34	44	51	48	42	44	40	43	.
35	47	50	44	46	42	44	38	17
36	41	43	40	42	43	39	33	.
37	39	39	38	35	38	24	33	30
38	30	32	33	30	25	20	25	21
39	10	25	27	27	28	23	11	.
40	19	20	19	21	17	12	31	.
41	6	13	15	12	19	14	7	.
42	2	11	9	11	9	11	14	.
>42	0	3	4	5	2	5	0	.

Color legend: 65, 55, 45, 35, 25, 15, 5

Cumulative likelihood of live birth (%) on the basis of maternal age and BMI among 51,959 first fresh IVF cycles that started in 2014 + 16,067 frozen embryo cycles between 2014 and 2015, representing data from >90% of IVF cycles in the United States and Puerto Rico. Note that cumulative live birth refers to the live birth rate after both fresh and frozen transfers of embryos derived from the first fresh IVF stimulation and retrieval. BMI = body mass index; IVF = in vitro fertilization. (From Goldman et al. [74]. Reprinted by permission of the publisher.)

*Practice Committee of the American Society for Reproductive Medicine*asrm@asrm.org. Obesity and reproduction. Fertil Steril 2021.*

Live Births 2021 IVF at Fertility Associates of Memphis

PATIENT'S OWN EGGS
LIVE BIRTHS PER NEW PATIENT

| Age of woman	< 35	35 - 37	38 - 40
Number of patients	155	67	42
Singleton Births	**58.7 %**	**47.8 %**	**23.8 %**
Live Births	61.3 %	50.7 %	23.8 %
(Confidence Range)	(53.6 - 69.0)	(38.8 - 62.7)	(10.9 - 36.7)
Singleton (percentage of live births)	95.8 %	94.1 %	10/10
Twins (percentage of live births)	4.2 %	5.9 %	0/10
Triplets or more (percentage of live births)	0 %	0 %	0/10
Term	83.2 %	76.5 %	9/10
Pre-term	13.7 %	23.5 %	1/10
Very pre-term	3.2 %	0 %	0/10

Unexplained Infertility

If woman is younger than 30 years old,

- try empiric clomiphene or letrazole for 3 - 4 months
- 75-90% ovulate – check progesterone
- 8-10% twins, 0.5% triplets
- 85% of pregnancies occur in first 3 ovulatory months
- 75% of pregnancies occur at 100mg or lower
- Do not:
  - use supplemental estrogen until after LH surge
  - arbitrary use of hCG for ovulation triggering

Fertility Preservation: Egg Freezing

(Best before age 35 with good AMH)

Egg retrieval

Ovarian stimulation

Egg isolation and
cryopreservation
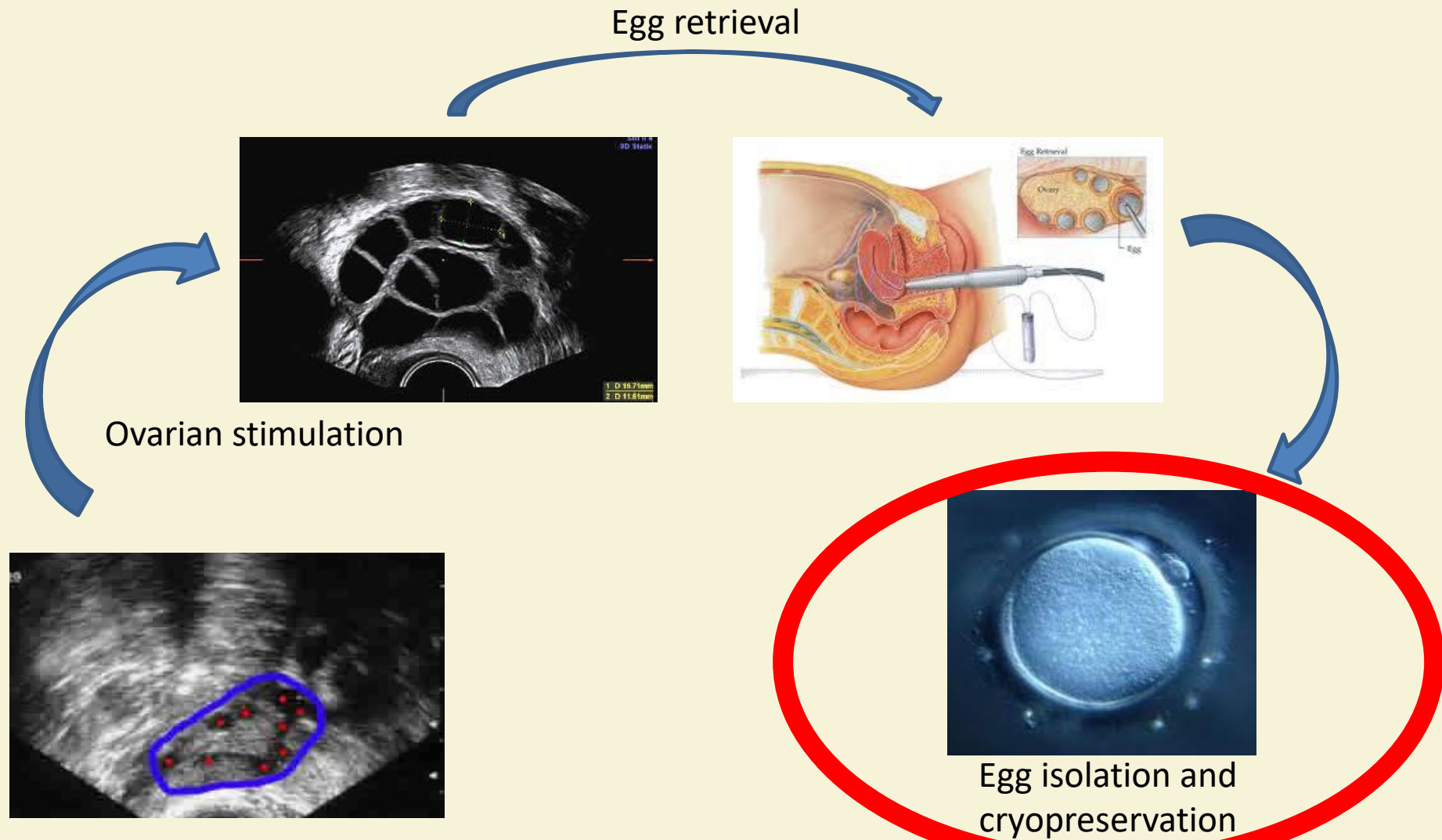
When to Refer Your Patient- Depends on You

- Female age greater than 35
- Patient of any age with low AMH (<1.0 to 1.5)
- Patient of any age with day 3 FSH > 10
- Abnormal semen analysis
- Infertility of multiple etiology
- Young patient with infertility of more than 24 months
- No success after 4 to 6 months of ovulation induction
- Patient frustration or expectation level is high

Summary: Algorithm for the Evaluation of Infertility
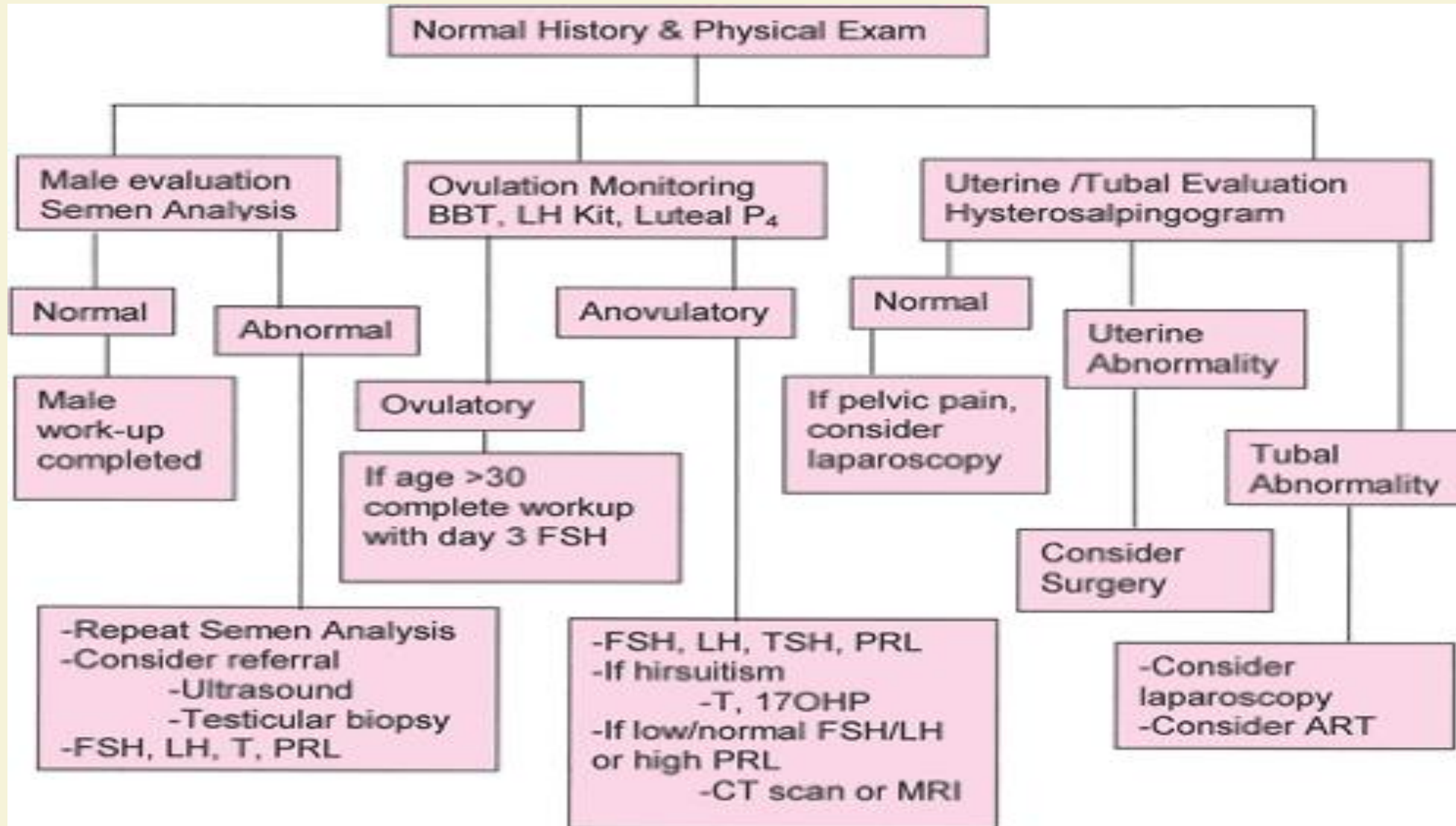
Infertility for the Generalist

Thank you!

Questions?