

The assessment and investigation of the infertile couple

BIRUTE ZILAITIENE, MD, PHD, PROF., FECSM

DEPARTMENT OF ENDOCRINOLOGY AND INSTITUTE OF ENDOCRINOLOGY,
LITHUANIAN UNIVERSITY OF HEALTH SCIENCES, KAUNAS, LITHUANIA



JOINT MEETING OF INTERNATIONAL FEDERATION OF FERTILITY SOCIETIES & BALTIC FERTILITY SOCIETY "THE MANAGEMENT OF INFERTILITY", 21.-23.09.2018, TARTU, ESTONIA

Definition of infertility

- ▶ Infertility is “a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.”... (WHO-ICMART glossary¹).
- ▶ “Infertility is the inability of a sexually active, non-contracepting couple to achieve pregnancy in one year. The male partner can be evaluated for infertility or subfertility using a variety of clinical interventions, and also from a laboratory evaluation of semen.” (Semen manual, 5th Edition³).

Guidelines related to infertile couples assessment and investigation issued by:

- ▶ American College of Obstetricians and Gynaecologists (ACOG),
- ▶ American Society for Reproductive Medicine (ASRM) (2015)
- ▶ Canadian Fertility and Andrology Society (CFAS),
- ▶ European Society of Human Reproduction and Embryology (ESHRE) (1995)
- ▶ Human Fertilization and Embryology Authority (HFEA)
- ▶ Royal College of Obstetricians and Gynecologists (RCOG)
- ▶ World Health Organization (WHO) (guidelines 1992, manual 1993, revision initiated 2012)
- ▶ National Institute for Health and Care Excellence (NICE) guidelines (2013, latest update 2017, NICE Pathways 2018)

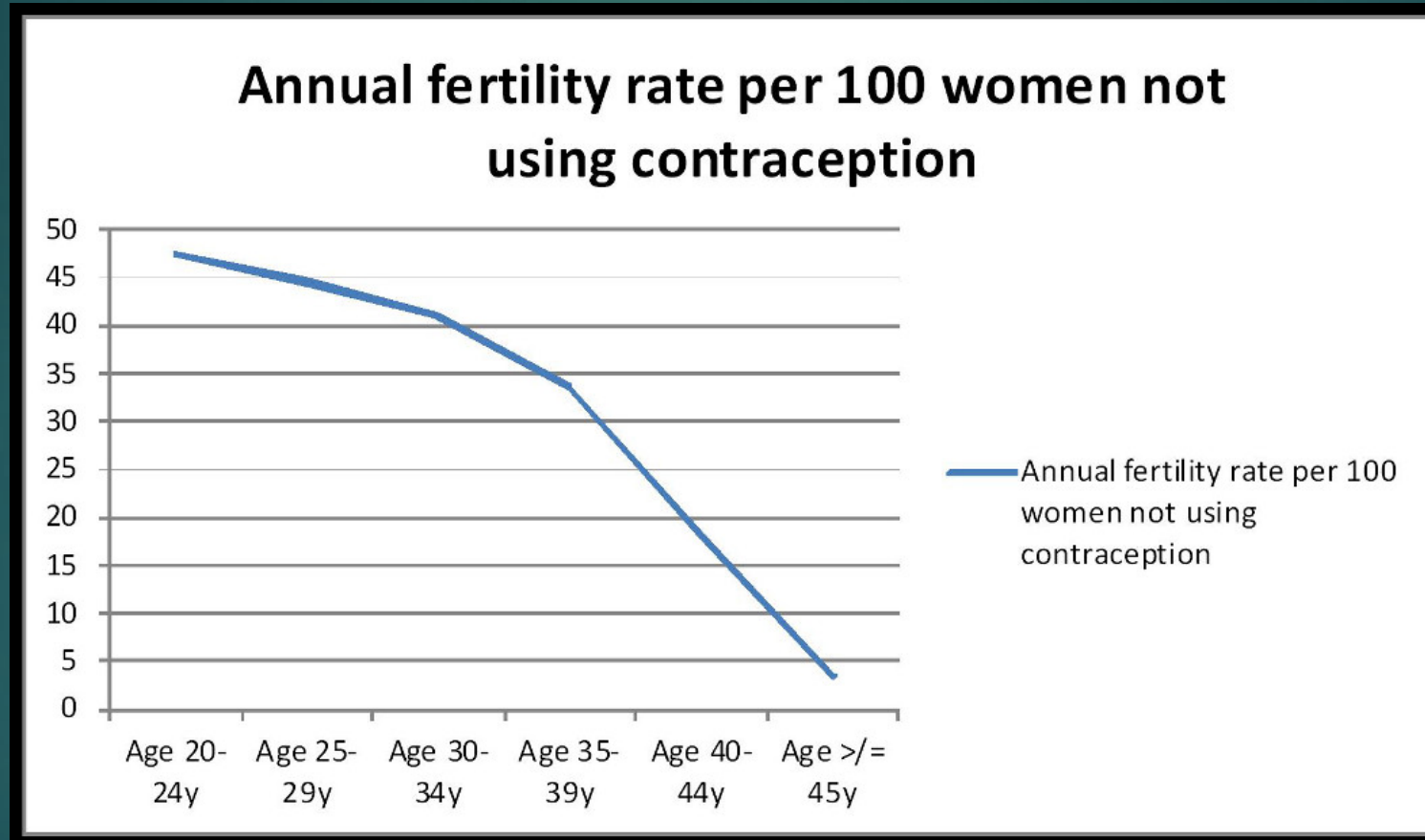
Investigation of fertility problems

Good Clinical Treatment in Assisted Reproduction - An ESHRE position paper, 2008
NICE 2017

- ▶ People who are concerned about their fertility should be informed that some **84%** of couples in the general population will conceive within **one year** if they do not use contraception and have regular sexual intercourse.
- ▶ Another **8%** will conceive in their **second year** of trying
- ▶ Additionally, they should be informed that female fertility declines with **age**.
- ▶ Women and men should also be informed about the possible negative effects of **alcohol, smoking and body weight** (overweight and underweight) on fertility, and preconceptional care should focus on assessing the **risks of treatment and pregnancy** in each individual case.
- ▶ People who are concerned about their fertility should be informed that vaginal sexual intercourse **every 2 to 3 days** optimises the chance of pregnancy

The effect of maternal age on the average rate of pregnancy

NICE pathways, 2018

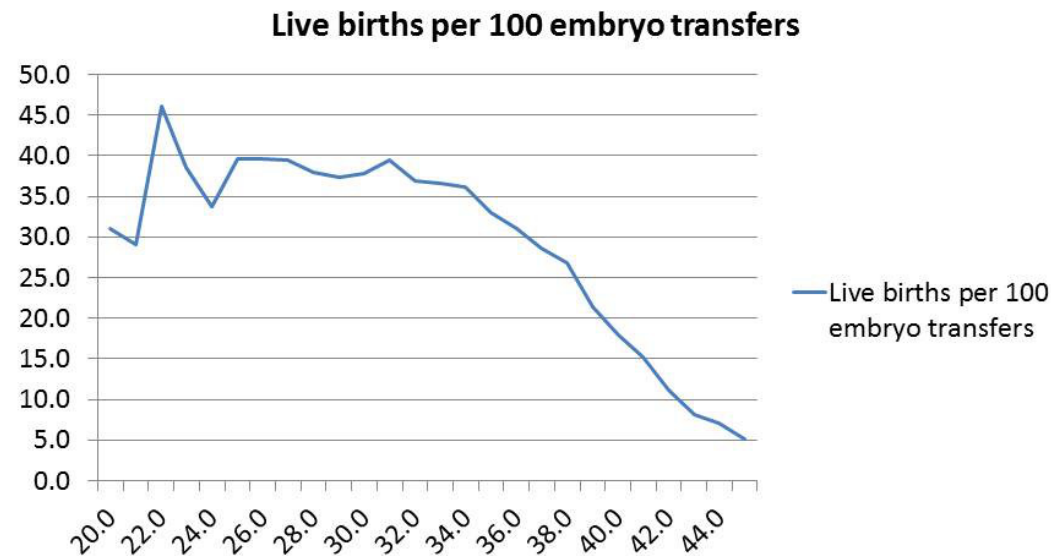


Calculated on the basis of studies in 10 different populations that did not use contraceptives (Heffner 2004, based on 2 reviews by Menken et al. 1986 and Anderson et al. 2000).

IVF success in terms of live births per 100 embryo transfers

NICE Pathways, 2018

Live birth rates per transfer by age (HFEA post-October 2007 data)



The vertical axis shows embryo transfers; the horizontal axis shows age of woman (based on all 52,996 embryo transfers using the woman's own eggs undertaken in the UK between 1 October 2007 and 30 June 2009) [HFEA, personal communication] (note: small numbers of women aged under 24 years in the HFEA database).

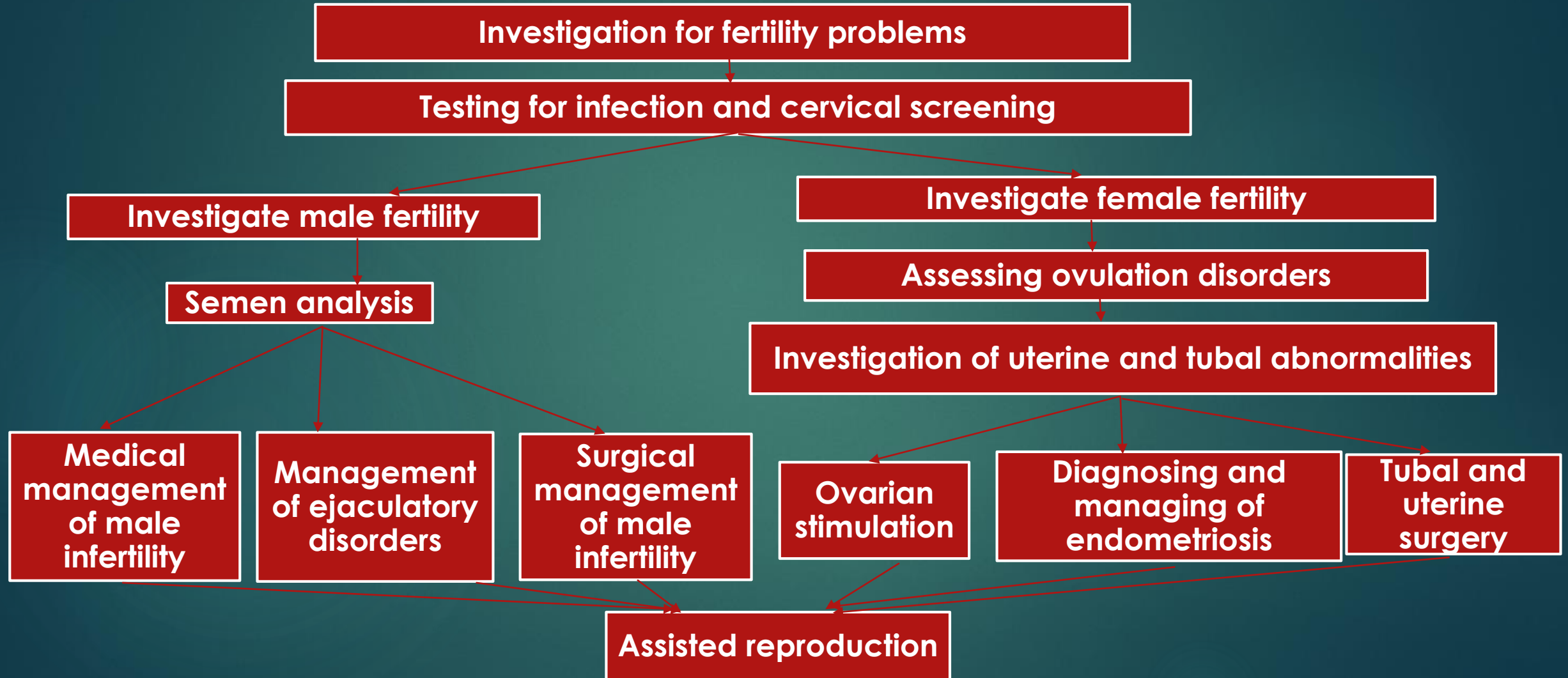
Diagnostic evaluation of infertile women

ASRM, NICE

- ▶ Women **under 35 year** of age – infertility evaluation after **1 year** of unprotected intercourse.
- ▶ Women **after 35 year** of age – infertility evaluation after **6 months** of unprotected intercourse.
- ▶ Diagnostic evaluation of infertility **immediately**:
 - ▶ Significant medical history of oligomenorrhea/amenorrhea
 - ▶ Advanced stage endometriosis (III-IV)
 - ▶ Any other condition that could limit fertility (known or suspected male subfertility)

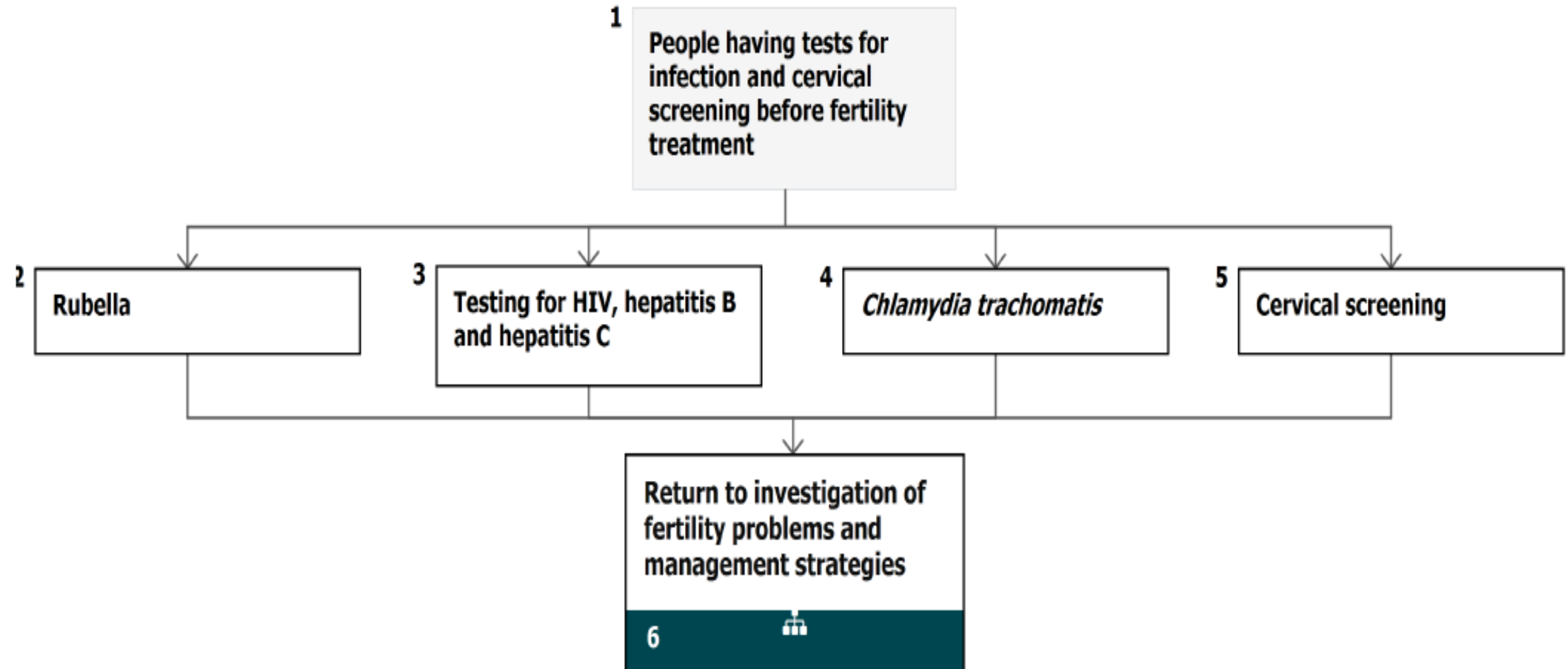
Investigation for fertility problems

NICE pathways, 2018



Testing for infection and cervical screening

NICE Pathways, 2018



Male fertility assessment: semen analysis

- ▶ The results of semen analysis conducted as part of an initial assessment should be compared with the following WHO 2010 reference values:
 - ▶ semen volume: **1.5 ml** or more
 - ▶ pH: 7.2 or more
 - ▶ sperm concentration: **15 million spermatozoa per ml** or more
 - ▶ total sperm number: **39 million spermatozoa per ejaculate** or more
 - ▶ total motility (percentage of progressive motility and non-progressive motility): **40% or more**
 - ▶ motile **32%** or more with progressive motility
 - ▶ vitality: 58% or more live spermatozoa
 - ▶ sperm morphology (percentage of normal forms): **4% or more**

Male fertility assessment: semen analysis

NICE Pathways, 2018

- ▶ If the result of the first semen analysis is abnormal, a repeat confirmatory test should be offered.
- ▶ Repeat confirmatory tests should ideally be undertaken **3 months after the initial analysis** to allow time for the cycle of spermatozoa formation to be completed.
- ▶ However, if a gross spermatozoa deficiency (azoospermia or severe oligozoospermia) has been detected the repeat test should be undertaken as soon as possible.

Sperm morphology, motility, and concentration in fertile and infertile men

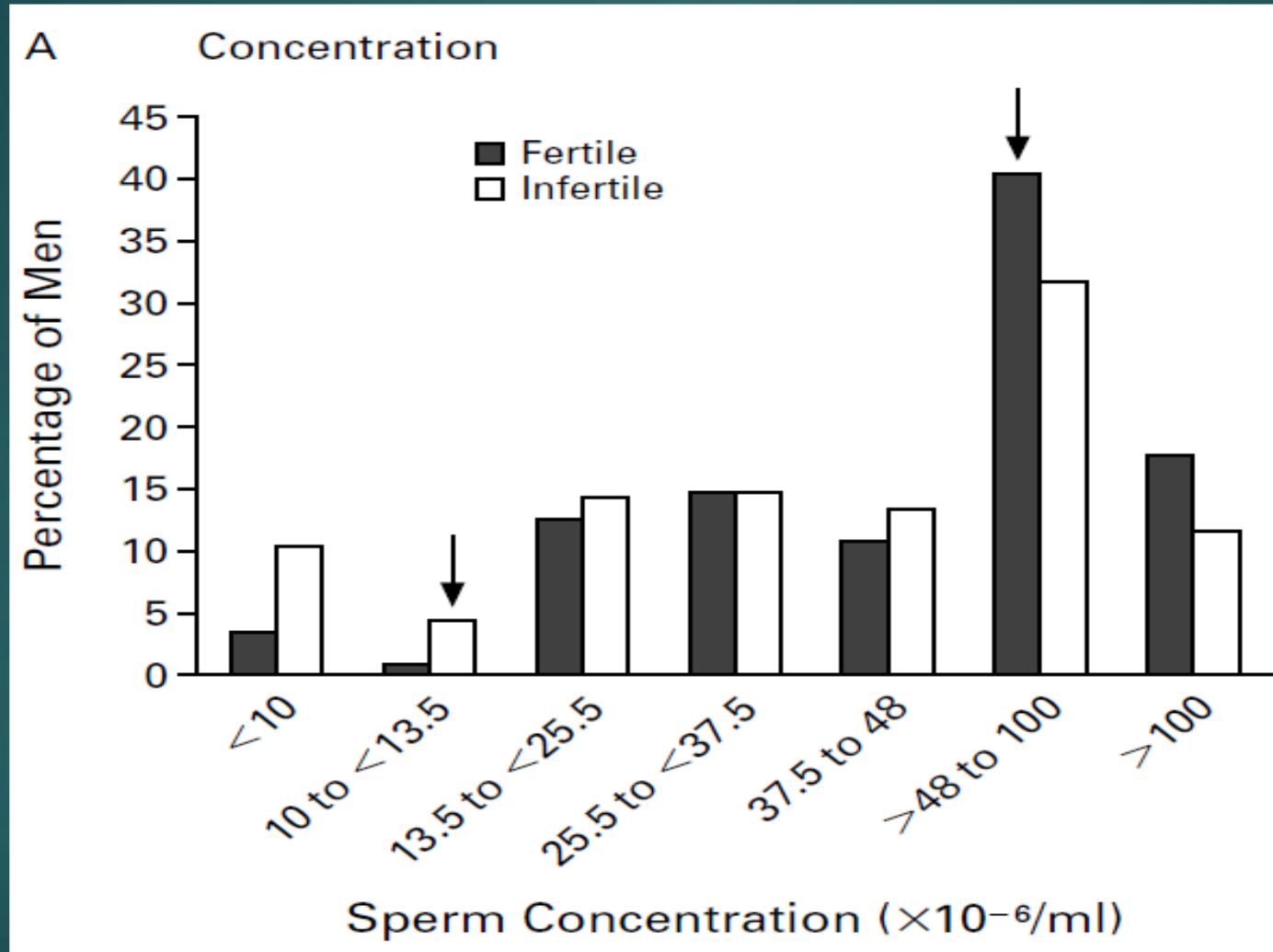
(Guzick DS et al. N Engl J Med 2001;345:1388-1393)

- ▶ Infertile couples in which the female partners had normal results on fertility evaluation were recruited at nine centers in the United States.
 - ▶ All of these couples had been unable to conceive for at least 12 months.
 - ▶ The mean duration of infertility was 43 months.
 - ▶ The women were required to have regular menstrual cycles, a normal hysterosalpingogram, normal results on laparoscopy, and a luteal-phase endometrial biopsy specimen that was histologically consistent with menstrual dating.

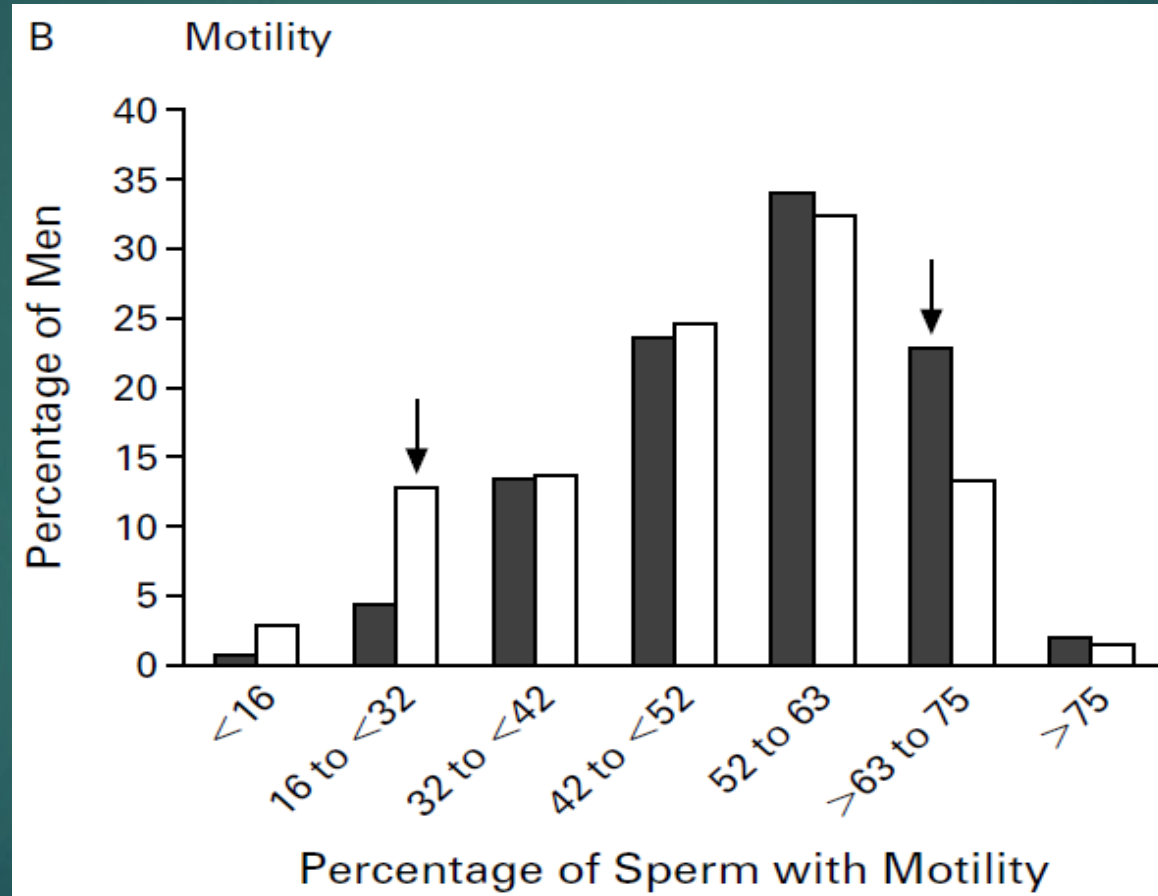
Fertile men (controls) were recruited from prenatal classes at the same hospitals.

Two semen specimens from each of the male partners in 765 infertile couples and 696 fertile couples were evaluated.

Percentage of men from infertile and fertile couples with values in the subfertile, indeterminate, and fertile ranges for sperm concentration



Percentage of men from infertile and fertile couples with values in the subfertile, indeterminate, and fertile ranges for sperm motility



Percentage of men from infertile and fertile couples with values in the subfertile, indeterminate, and fertile ranges for sperm

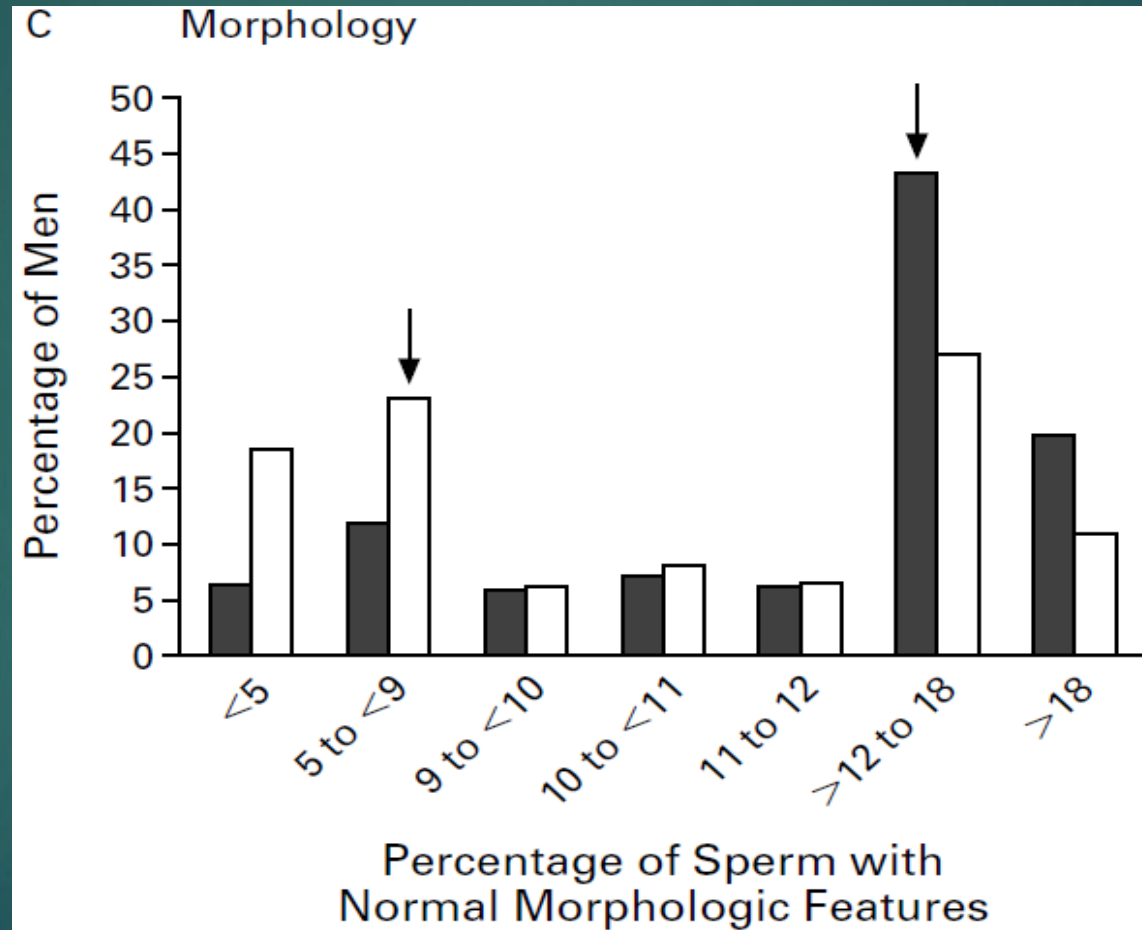


TABLE 3. ODDS RATIOS FOR INFERTILITY FOR COMBINATIONS OF SPERM MEASUREMENTS.*

MORPHOLOGIC FEATURES	SPERM MEASUREMENT RANGE		ODDS RATIO (95% CI)
	MOTILITY	CONCENTRATION	
Fertile	Fertile	Fertile	1.0
Subfertile	Fertile	Fertile	2.9 (2.2–3.7)
Fertile	Subfertile	Fertile	2.5 (1.6–4.2)
Fertile	Fertile	Subfertile	2.2 (1.3–3.6)
Subfertile	Subfertile	Fertile	7.2 (4.3–12.2)
Subfertile	Fertile	Subfertile	6.3 (3.8–10.3)
Fertile	Subfertile	Subfertile	5.5 (3.0–10.2)
Subfertile	Subfertile	Subfertile	15.8 (8.7–29.0)

Reproductive history

ASRM, 2015

- ▶ Coital frequency and timing
 - ▶ Duration of infertility and previous fertility
 - ▶ Childhood illness and developmental history
 - ▶ Systemic medical illnesses (DM, respiratory diseases)
 - ▶ Previous surgery
 - ▶ Medications and surgery
 - ▶ Sexual history
 - ▶ Gonadotoxins
-
- ▶ Evaluation in primary and secondary male infertility – the same!

Complete evaluation for male infertility

ASRM, 2015

- ▶ Performed by specialist in male reproduction
- ▶ **Indications:**
 - ▶ Abnormal reproductive history
 - ▶ Abnormal semen parameters
 - ▶ Couples with unexplained infertility
 - ▶ Couples remaining infertile after successful treatment of identified female infertility factors
- ▶ Complete medical history
- ▶ Physical examination
- ▶ Serial semen analyses
- ▶ Endocrine evaluation
- ▶ Postejaculatory urinalysis
- ▶ Ultrasonography
- ▶ Special tests on semen and sperm
- ▶ Genetic screening

Male infertility: complete medical history

ASRM, 2015

- ▶ **Reproductive history**

+

- ▶ **A complete review of systems**

- ▶ **Family reproductive history**

- ▶ **A detailed social history**

- ▶ Past and current use of anabolic steroids

- ▶ Recreational drugs

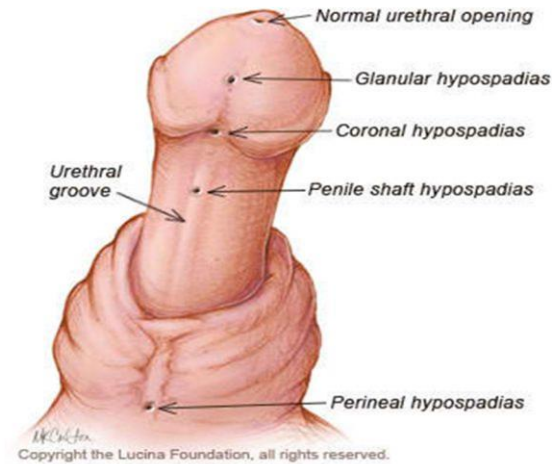
- ▶ Tobacco, alcohol

Male infertility: physical examination

ASRM 2015

- ▶ Penis, location of urethral meatus
- ▶ Palpation and measurement of testes
- ▶ Consistency and presence of both vasa and epidymides
- ▶ Secondary sex characteristics
- ▶ When indicated – digital rectal examination

Hypospadias



Prader Orchidometer



LifeCare
center

Endocrine evaluation

ASRM, 2015

- ▶ **Indications:**
 - ▶ Abnormal sperm parameters especially when sperm concentration <10 mln/ml
 - ▶ Impaired sexual function
 - ▶ Other clinical findings suggesting specific endocrinopathy
- ▶ **There is no consensus if all infertile men merit from endocrine evaluation.**
- ▶ Initial evaluation – FSH and testosterone
- ▶ When testosterone is low – second measurement of total testosterone, free testosterone, LH and prolactin measurement
- ▶ Gonadotropins – one measurement
- ▶ TSH evaluation

Basal hormone levels in various clinical states of male partner in infertile couple

ASRM, 2015

Clinical situation	FSH	LH	Testosterone	Prolactin
Normal spermatogenesis	Normal	Normal	Normal	Normal
Hypogonadotropic hypogonadism	Low	Low	Low	Normal
Abnormal spermatogenesis	High/normal	Normal	Normal	Normal
Complete testicular failure	High	High	Normal/Low	Normal
Prolactin secreting pituitary tumor	Normal/Low	Normal/Low	Low	High

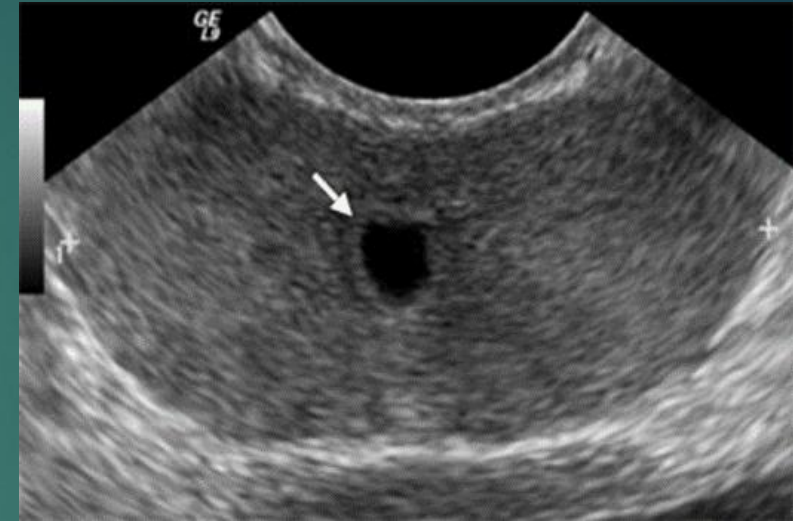
Ultrasonography in male infertility diagnostics

▶ Transrectal ultrasonography findings:

- ▶ Dilated seminal vesicles abd/or ejaculatory ducts
- ▶ Midline prostatic cysts

▶ Indications for TRUS:

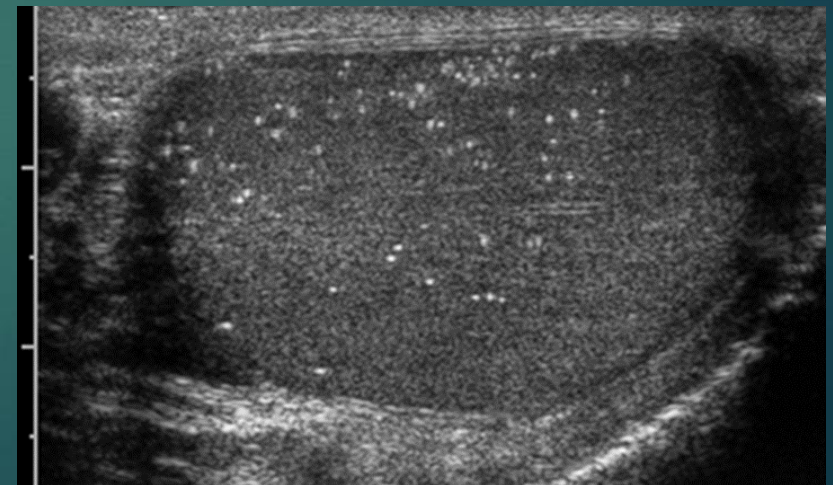
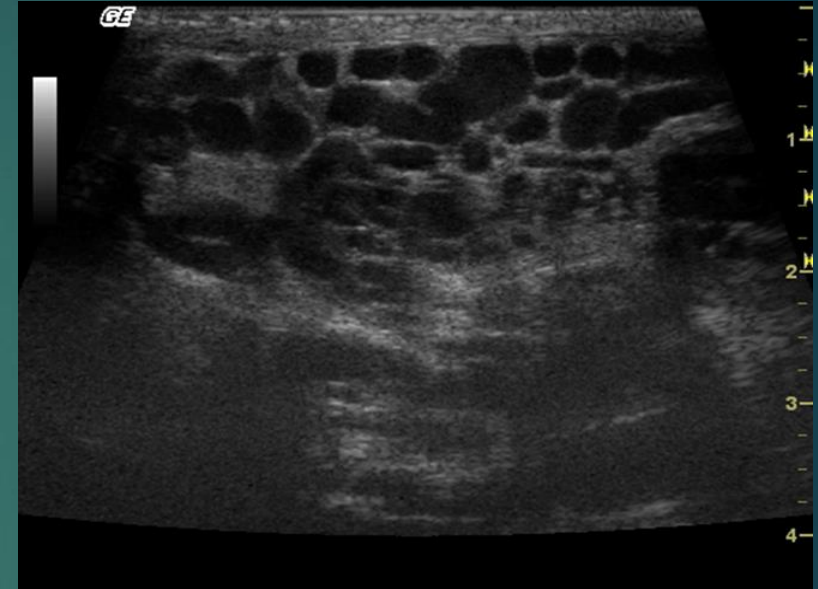
- ▶ Oligospermic patient
- ▶ Low volume ejaculate
- ▶ Palpable vasa
- ▶ Normal testicular size with normal T



Ultrasonography in male infertility diagnostics (2)

Scrotal US

- ▶ Should be considered for men presenting with **infertility and risk for testicular cancer**



Practice Committee of the American Society for Reproductive Medicine.
Diagnostic evaluation of the infertile male: a committee opinion. Fertil Steril. 2015
Mar;103(3):e18-25.

Correspondence:

Aleksander Giwercman, Department of Translational Medicine and Reproductive Medicine Centre, Lunds University and Skane University Hospital, CRC 91-10-058, Jan Waldenströms Gata 35, 21248 Malmö, Sweden.


E-mail: aleksander.giwercman@med.lu.se

*The first version was prepared by a G.M. Colpi; S. Francavilla; G. Haidl; K. Link. Subsequently, important input was given by H.M. Behre; D.G. Goulis; C. Krausz. A. Giwercman coordinated the work of the group.

The manuscript has been approved by the European Academy of Andrology (EAA) Guidelines Committee members (G. Corona, D.G. Goulis, G. Forti, H.M. Behre, M. Punab, J. Toppari, C. Krausz), EAA Executive Council (C. Krausz, D.G. Goulis, H.M. Behre, A.M. Isidori, G.R. Dohle, O. Rajmil, W. Weidner, J. Toppari, M. Simoni), EAA Center Directors and the Co-Editor-in-chief (M. Simoni).

European Academy of Andrology guideline

Management of oligo-astheno-teratozoospermia

¹G. M. Colpi, ²S. Francavilla, ³G. Haidl, ⁴K. Link, ⁵H. M. Behre, ⁶D. G. Goulis, ⁷C. Krausz and ^{4,*} A. Giwercman 

¹Department of Andrology and IVF, San Carlo Clinic, Paderno-Dugnano/Milano, Italy, ²Department of Life, Health and Environmental Sciences, University of L' Aquila, L' Aquila, Italy, ³Department of Dermatology/Andrology Unit, University of Bonn, Bonn, Germany, ⁴Department of Translational Medicine and Reproductive Medicine Centre, Lunds University and Skane University Hospital, Malmö, Sweden, ⁵Center for Reproductive Medicine and Andrology, University Hospital, Martin Luther University Halle-Wittenberg, Halle, Germany, ⁶Unit of Reproductive Endocrinology, 1st Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece, and ⁷Department of Experimental and Clinical Biomedical Sciences 'Mario Serio', Centre of Excellence DeNothe, University of Florence, Florence, Italy

- ▶ We recommend scrotal ultrasound as part of **routine investigation of men with OAT**. In case of testicular microlithiasis, testicular biopsy should be considered although this is still a controversial issue
- ▶ Andrology. 2018 Jul;6(4):513-524

Additional sperm function tests

NICE, 2017

- ▶ Screening for **antisperm antibodies(ASA)** should not be offered because there is no evidence of effective treatment to improve fertility. [2004]
- ▶ **EAA guideline, 2018**
- ▶ **Sperm DNA integrity tests** could be applied in addition to standard semen analysis in following cases:
 - 1)When it is considered whether the couple should be referred for assisted reproduction or given additional time for trying achieving spontaneous pregnancy;
 - 2)When IUI with partner's spermatozoa is considered;
 - 3)When standard IVF or ICSI is considered.

ASRM, 2015

- ▶ **ASA** screening is not recommended if ICSI is planned. Some studies showed that ASA correlated with presence of spermatozoa in azoospermic men (obstruction).
- ▶ **DNA integrity tests.** Current evidence about relationship between DNA integrity and reproductive outcomes is limited, so routine testing is controversial. But it is important to IUI, IVF, ICSI results prediction.

Genetic tests for male partner

EAU Guidelines on Male Infertility, update 2017

Recommendations	GR
Standard karyotype analysis should be offered to all men with damaged spermatogenesis (spermatozoa < 10 million/mL) who are seeking fertility treatment by IVF.	B
Genetic counselling is mandatory in couples with a genetic abnormality found in clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	A
All men with Klinefelter's syndrome need long-term endocrine follow-up and usually require androgen replacement therapy	A
Testing for microdeletions is not necessary in men with OA	A
Men with severely damaged spermatogenesis (spermatozoa < 5 million/mL) should be advised to undergo Yq microdeletion testing for both diagnostic and prognostic purposes	A
If a man with Yq microdeletion and his partner wish to proceed with ICSI, they should be advised that microdeletions will be passed to sons, but not to daughters.	A
When a man has structural abnormalities of the vas deferens (unilateral or bilateral absence), he and his partner should be tested for CF gene mutations.	A

History: infertile women

ASRM, 2015

- ▶ **Duration of infertility** and results of previous evaluations and treatments
- ▶ **Menstrual history** (age at menarche, cycle length and characteristics, presence of polymenorrhea, onset/severity of dysmenorrhea)
- ▶ **Pregnancy history**
- ▶ Previous methods of **contraception**
- ▶ **Coital** frequency and sexual dysfunction
- ▶ **Thyroid** diseases, **galactorrhea**, **hirsutism**, pelvic pain, dyspareunia
- ▶ Previous abnormal **pap smears**, subsequent treatments
- ▶ Current **medications** and allergies
- ▶ **Family history**: birth defects, developmental delay, early menopause, reproductive problems
- ▶ Environment hazards, use of tobacco, alcohol, recreational or illicit drugs

Physical examination: infertile women

ASRM, 2015

- ▶ Weight, BMI, BP, pulse
- ▶ Thyroid evaluation
- ▶ Breast characteristics and evaluation for secretion
- ▶ Signs of androgen excess
- ▶ Vaginal or cervical abnormality, secretion, discharge
- ▶ Pelvic or abdominal tenderness, organ enlargement or masses
- ▶ Uterine size, shape, position, mobility
- ▶ Adnexal masses or tenderness
- ▶ Cul-de-sac masses, tenderness, nodularity

Diagnostic evaluation of infertile women: ovulatory function

ASRM, 2015

- ▶ Ovulatory dysfunction - 15% of infertile couples, 40 % of infertile women
- ▶ The underlying cause should be sought
- ▶ The most common causes:
 - ▶ PCOS
 - ▶ Obesity
 - ▶ Weight gain or loss, strenuous exercises
 - ▶ Thyroid dysfunction
 - ▶ Hyperprolactinemia

Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome^{†,‡}

Helena J. Teede^{1,2,3,*}, Marie L. Misso^{1,2,3}, Michael F. Costello⁴, Anuja Dokras⁵, Joop Laven⁶, Lisa Moran^{1,2,3}, Terhi Piltonen⁷, and Robert J. Norman^{1,2,8}, on behalf of the International PCOS Network[§]

The guideline was primarily funded by the Australian National Health and Medical Research Council of Australia (NHMRC) supported by a partnership with ESHRE and the American Society for Reproductive Medicine
Governance included a **six continent** international advisory and a project board, five guideline development groups, and consumer and translation committees

Ovulatory function

ASRM, 2015

▶ Clinical evaluation

- ▶ Ovulatory status: regular menstrual cycles (21-35 days), regular flow characteristics, consistent pattern of minimal symptoms,
- ▶ Anovulation – abnormal uterine bleeding, oligo/amenorrhea

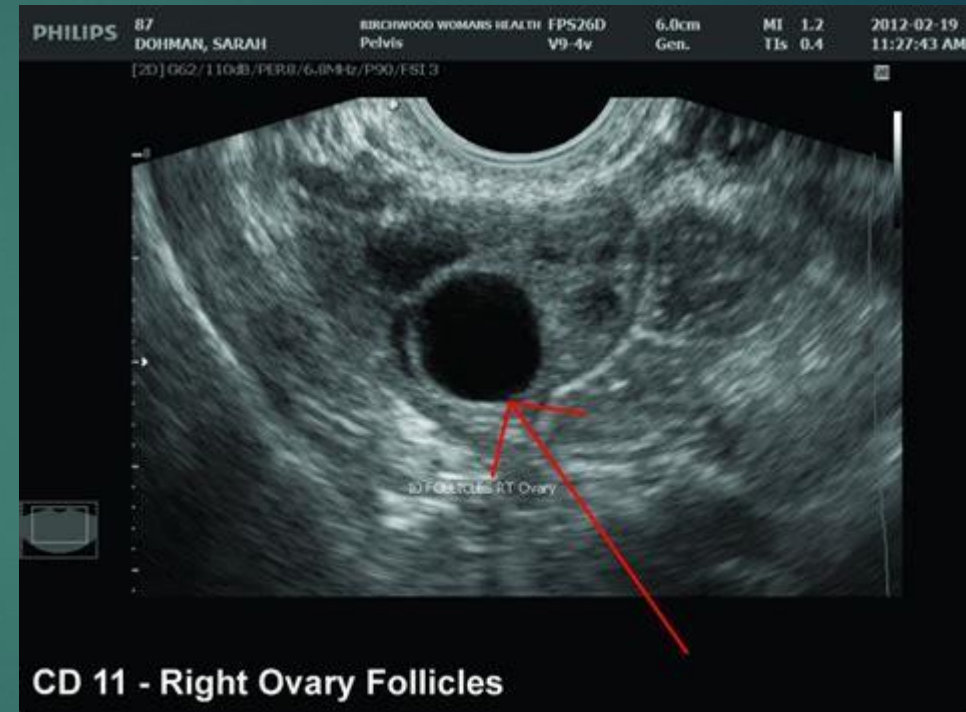
▶ Ovulation confirmation tests

- ▶ BBT – not longer preferred method for ovulation evaluation
- ▶ Progesterone – 1 week before menses $>3\text{ng/ml}$. Quality of luteal function – mid-luteal progesterone $>10\text{ ng/ml}$ (31.8 nmol/L) (Jordan J et al., 1994). Not reliable due to pulsatile progesterone secretion (Flicori M et al., 1984)

Ovulatory function

ASRM, 2015

- ▶ Transvaginal ultrasonography
- ▶ Anovulatory women
 - ▶ TSH, prolactin
 - ▶ Amenorrhea – $\text{FSH} \uparrow$, $\text{E2} \downarrow$ – ovarian failure, $\text{FSH} \downarrow \leftrightarrow$, $\text{E2} \downarrow$ – hypothalamic amenorrhea



Thyroid function in infertile women

2017 Guidelines of the American Thyroid Association
for the Diagnosis and Management of Thyroid
Disease During Pregnancy and the Postpartum

NICE, 2017

► RECOMMENDATION 16

- Evaluation of serum TSH concentration is recommended for **all women seeking care for infertility**.

- *Weak recommendation, moderate-quality evidence.*

► RECOMMENDATION 20

- Subclinically hypothyroid women undergoing IVF or ICSI should be treated with LT4. The goal of treatment is to achieve a **TSH concentration <2.5mU/L**.

- *Strong recommendation, moderate-quality evidence.*

- Women with possible fertility problems are no more likely than the general population to have thyroid disease and the **routine measurement of thyroid function should not be offered**. Estimation of thyroid function should be confined to women with symptoms of thyroid disease. [2004]

Ovarian reserve

ASRM, 2015

- ▶ **Day 3 FSH and E2 measurements.** High FSH – high predictive value for poor response to ovarian stimulation. **E2 – useful** to interpret „normal“ FSH. High E2 (60-80 ng/ml) in early follicular phase – limited evidence of poor response to gonadotropin stimulation.
- ▶ **Antral follicle count.** Sum of antral follicles (2-10 mm) in early follicular phase by US. Low count – **3-6** follicles – predicts poor response to ovarian stimulation, but does not predict pregnancy.
- ▶ **Serum AMH** concentration. Low AMH levels- <1 ng/ml – are associated to poor response to ovulation stimulation, poor embryo quality, poor pregnancy outcome in IVF.
- ▶ **Clomiphene citrate challenge** test. Replaced with newer tests.

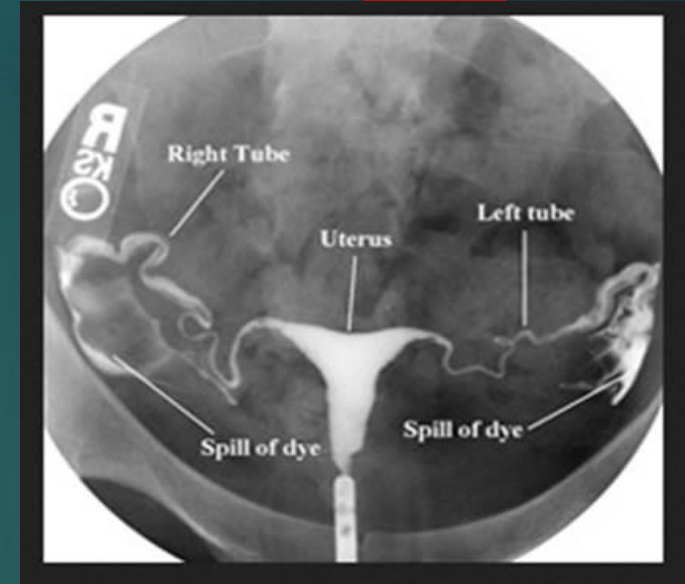
NICE 2017 (2013)

- ▶ FSH greater than 8.9 IU/l for a low response and less than 4 IU/l for a high response. **Do not use E2** to predict outcome of fertility treatment
- ▶ Total **antral follicle count** of less than or equal to **4** for a low response and greater than 16 for a high response
- ▶ **Serum AMH** of less than or equal to 5.4 pmol/l (2.4 ng/ml) for a low response and greater than or equal to 25.0 pmol/l for a high response.
- ▶ **Do not use the following tests** to predict outcome of fertility treatment: ovarian volume, ovarian blood flow, inhibin B, E2.

Investigation of tubal and uterine abnormalities

NICE, 2017

- ▶ Women who are not known to have comorbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) should be offered **hysterosalpingography** (HSG) to screen for tubal occlusion.
- ▶ Where appropriate expertise is available, screening for tubal occlusion using **hysterosalpingo-contrast-ultrasonography** should be considered
- ▶ Women who are thought to have comorbidities should be offered **laparoscopy** and dye so that tubal and other pelvic pathology can be assessed at the same time.
- ▶ **Histeroscopy** is a definite method to diagnose **intrauterine** pathology
- ▶ Costly and invasive method, can be reserved for further evaluation and treatment of abnormalities defined by less invasive methods – HSG, US



**Thank you for
your attention!**

Questions?

