Prof. Abha Majumdar

Director, Center of IVF and Human Reproduction
Sir Ganga Ram Hospital, New Delhi, INDIA

‘**President’s Medal**’ for best medical graduate 1970-75
‘Dr. B.C Roy’s award’ 1999 for outstanding contribution towards medicine
‘Vikas Ratan Award’ 2002 by Nations economic development & growth society
‘**Chitsa Ratan Award**’ 2007 by International Study Circle
‘Life time Medical excellence award’ Obs & Gyne by Hippocrates foundation 2014
‘Abdul Kalam gold medal’ by Global Economic Progress & Research Association 2015
Course director for post doctoral **Fellowship in Reproductive Medicine** by NBE since 2007, by IFS in ART since 2014, by ISAR in embryology 2015, and by FOGSI for basic & advanced infertility training since 2008.
Member of Editorial board of ‘**IVF Worldwide’, P**eer reviewer for ‘**Journal of Human Reproductive Sciences’,** Member of advisory board for ‘**Journal of Fertility Science & Research’** and consultant advisor for queries to **NDTV.com**

Past President of the Indian Fertility Society (IFS); 2008-10
Field of interest: Infertility, ART, Reproductive endocrinology, Endoscopic surgery for pelvic resurrection.

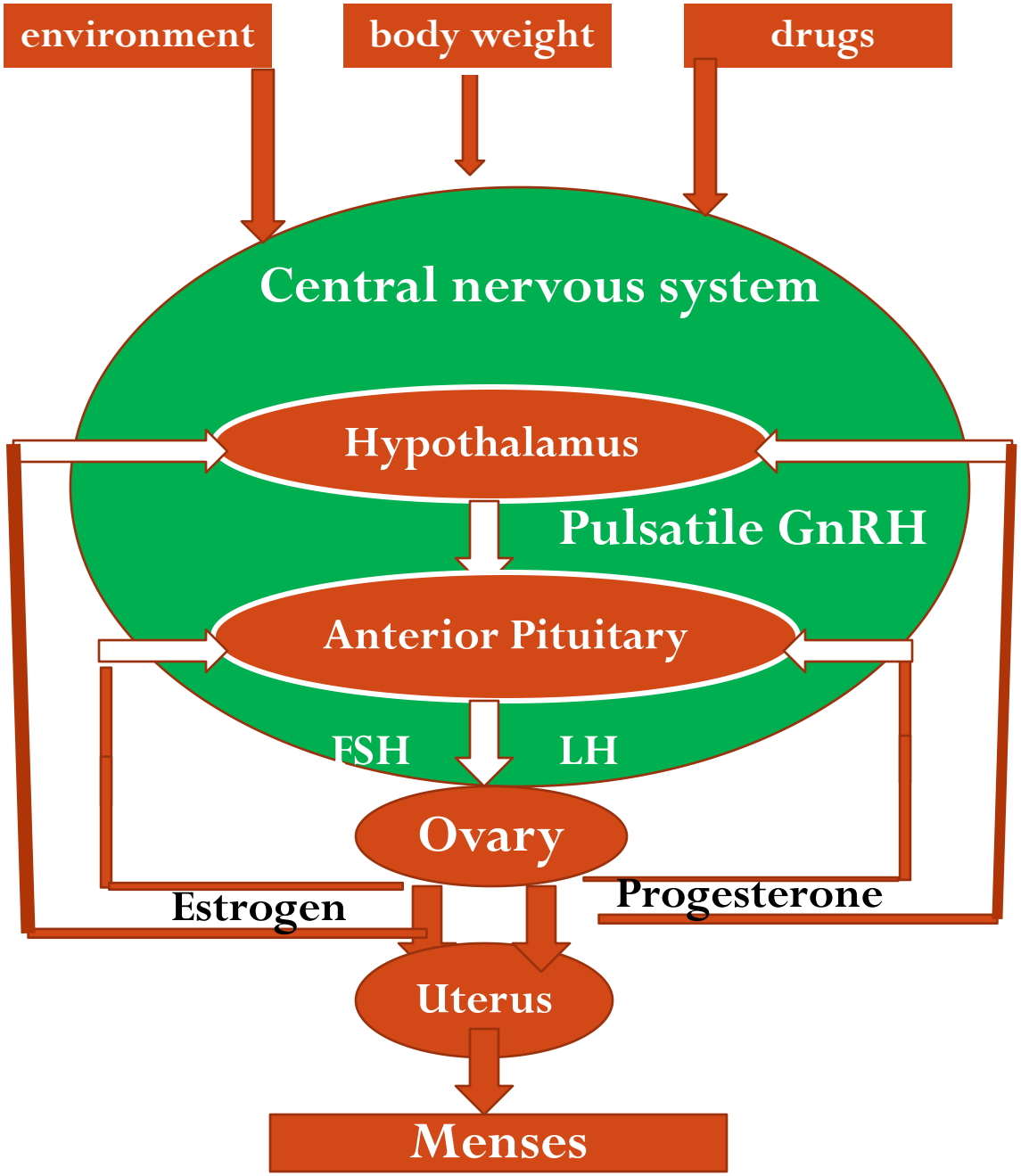
Evaluation of Amenorrhea

Prof. Abha Majumdar

Director and Head

Centre of IVF and Human Reproduction,

Sir Ganga Ram Hospital


environment
body weight
drugs
Central nervous system
Hypothalamus
Pulsatile GnRH
Anterior Pituitary
FSH
LH
Ovary
Estrogen
Progesterone
Uterus
Menses

Amenorrhea

Primary amenorrhea

- **Failure to menstruate by**
- age 15 with secondary sexual characters
- or
- by age 13 without secondary sexual character

Secondary amenorrhea

- **Cessation of menses for**
- interval of three previous cycle
- or
- 6 months in absence of pregnancy

The passage to reveal menstruation is obstructed or absent

UTERO-VAGINAL

The endocrine organ responsible for menstruation failed

OVARY

The stimulus to the endocrine gland (ovary) is absent

PIT-HYPOTHALAMUS

Obstruction to menstruation

Imperforate hymen

Transverse vaginal septum

Vagino-cervical agenesis

Mullerian agenesis

Endometrial hypoplasia or aplasia

Intrauterine synechia

Make a passage if the endometrium is functional

Gonadal agenesis
46XX

Gonadal dysgenesis
46XY

Gonadal agenesis
45XO

Premature ovarian failure

Enzymatic deficiency/ FSH-LH receptor resistance/ mutation

Gonad (ovary not functioning

Menstruation by HRT
Pregnancy by donor oocyte

Hypo-thalmic pituitary deficiency / Hypo-gonadotropic hypo-gonadism

Kallmann Syndrome

Infections craniopharyngioma, hamartoma

prolactinomas, pituitary tumors

Stress, exercise, nutrition related

Menstruation by HRT
Ovulation induction by gonadotropins

Other Endocrine Gland Disorders

- Adrenal – Adult onset CAH, Cushings syndrome → PCOS like anovulation
- Thyroid – Hypo/hyperthyroidism → Oligo-ovulatory
- Ovarian tumours – granulosa cell– theca cell, brenners, cystic teratomas → Ovulatory dysfunction
- SOL – empty sella, arterial aneurysm → Hypo- hypo secondary to hyperprolactinemia
- Necrosis – Sheehan syndrome or infiltrative -Sarcoidosis, hemo-chromatosis → pan hypo-pituitarism or Hypo- hypo
- Multifactorial – Polycystic ovary syndrome → Oligo or amenorrhea

Commonest Causes

Secondary Amenorrhea

- Hypothalamic- pit
- PCOS & chronic anouvlation

60%

- Hyperprolactinemia (13%)
- Ovarian Failure (12%)

Primary Amenorrhea

- Hypothamic-pit (30%)
- Gonadal agenesis (40%)
- Gonadal dysgenesis(9%)
- Mullerian agenesis (10%)
- Constitutional delay (10%)

The Practice Committee of ASRM. Fertil Steril, 2008 . 90(3)

Primary Amenorrhea: History

Findings	Association
Incomplete stages of puberty (axillary and pubic hair, breasts)	Ovarian or pituitary failure Chromosomal abnormality
Completion of stages of puberty	Obstruction in passage or RKHS or pre-pubertal genital tuberculosis
Family history of delayed puberty?	Constitutional delay of puberty
Less height relative to family members?	Turner's syndrome
Symptoms of virilization?	Ovarian or adrenal tumor
Recent stress? Change in weight, diet, or exercise? Ballet dancers, athletes	Functional hypothalamic amenorrhea
Headaches, visual field defects, fatigue	Hypothalamic-pituitary disease

Secondary Amenorrhea: History

Findings	Association
Recent stress? Change in weight, diet, or exercise? Chronic illness?	Functional hypothalamic amenorrhea
Acne, hirsutism, striae, central obesity, skin pigmentation or deepening voice?	PCOS/ Cushing's disease Ovarian or adrenal tumor
Medications / galactorrhea	Hyperprolactinemia
Symptoms of estrogen deficiency (hot flashes, vaginal dryness, decreased libido, or poor sleep)?	Premature ovarian failure
History of obstetrical catastrophe, severe bleeding, D&C, endometritis, infection?	Sheehan's syndrome Asherman's syndrome

Primary Amenorrhea: Physical Examination

- Evaluation of pubertal development (height, weight) and growth chart
- Breast development (Tanner staging)
- Axillary hair growth
- Evaluation for features of Turner's syndrome

  Webbed neck, low hair line, shield chest, widely spaced nipples
- Skin for hirsutism, acne, striae, pigmentation.
- Pelvic examination- pubic hair development, clitoral size, hymnal opening, depth of vagina, presence of cervix and uterus

Secondary Amenorrhea: Physical Examination

- General
  - Evaluation of height, weight, and BMI
  - Skin for hirsutism, acne, striae, acanthosis nigricans
- Thyroid examination
- Breast for galactorrhea
- Pelvic exam
  - Size of uterus, pelvic mass
  - Vaginal dryness

Tanner Stages

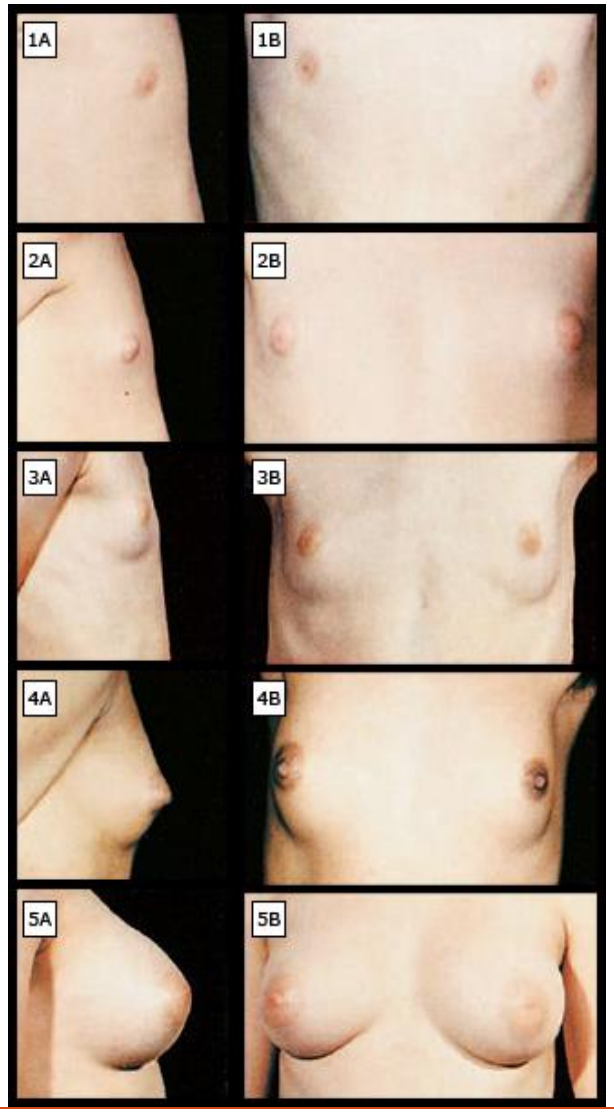
Stage 1: Prepubertal, no palpable breast tissue or pubic hair.

Stage 2: Development of breast bud; sparse, straight pubic hair.

Stage 3: Enlargement of breast; pubic hair darker, coarser, and curlier.

Stage 4: Areola and papilla project above the breast; pubic hair adult-like in appearance.

Stage 5: Recession of areola to match contour of breast; pubic hair extends to thigh.



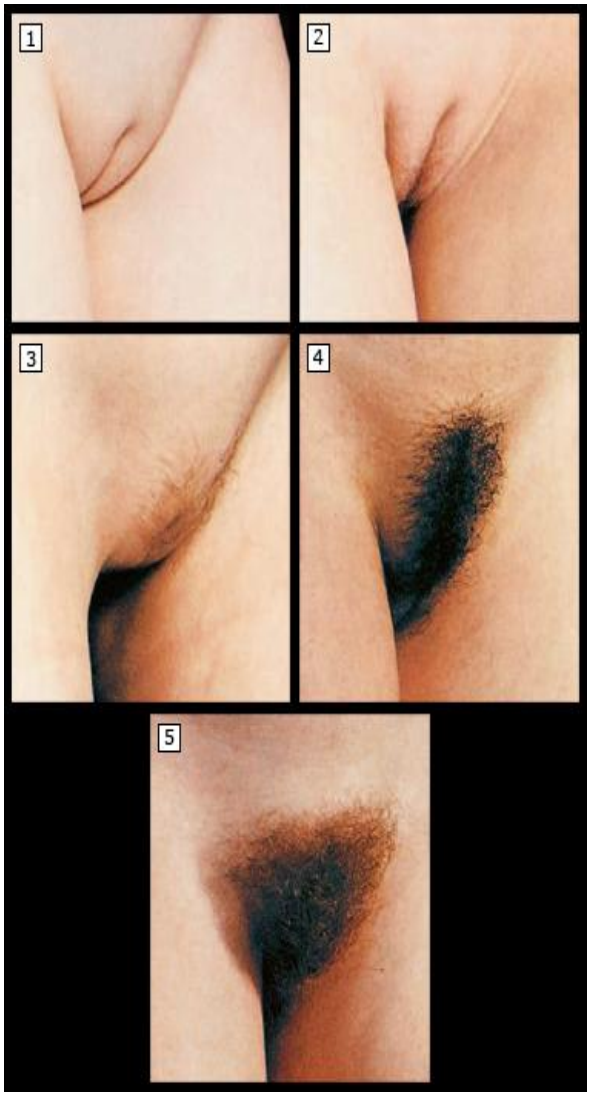


Figure from: Roede, MJ, van Wieringen, JC. Growth diagrams 1980: Netherlands third nation-wide survey. Tijdschr Soc Gezondheids 1985; 63:1. Reproduced with permission from the author.

Investigations

- *Rule out pregnancy*
- Pelvic ultrasonography for presence of uterus, ovarian volume / AFC, endometrial thickness and ovarian mass
- MRI head
- Hormonal tests :
  - Serum FSH, LH and AMH
  - Serum Prolactin
  - Thyroid function test
- Karyotype

Evaluation of Ovarian Function

Progestin Challenge Test: Withdrawal bleeding after progestin treatment implies normal circulating estrogen levels. MPA 10 mg BD X 5 days or P4 in oil250 mg i/m =Bleeding within 10days

False positive rate high - 40% women with stress, weight loss, exercise induced and 50% with early ovarian failure can have bleeding

False negative is also high- 20% of women with normal estrogen production may have no withdrawal bleeding.)

- **Estrogenic cervical mucus:** less reliable
- **Serum Estradiol concentration:** fluctuates erratically misleading
- **Endometrial thickness:** correlates well with serum E2 and progestin challenge
  - ET more than 6 mm predicts withdrawal bleeding with 95% accuracy
  - ET also identifies endometrial hyperplasia in chronic anovulation

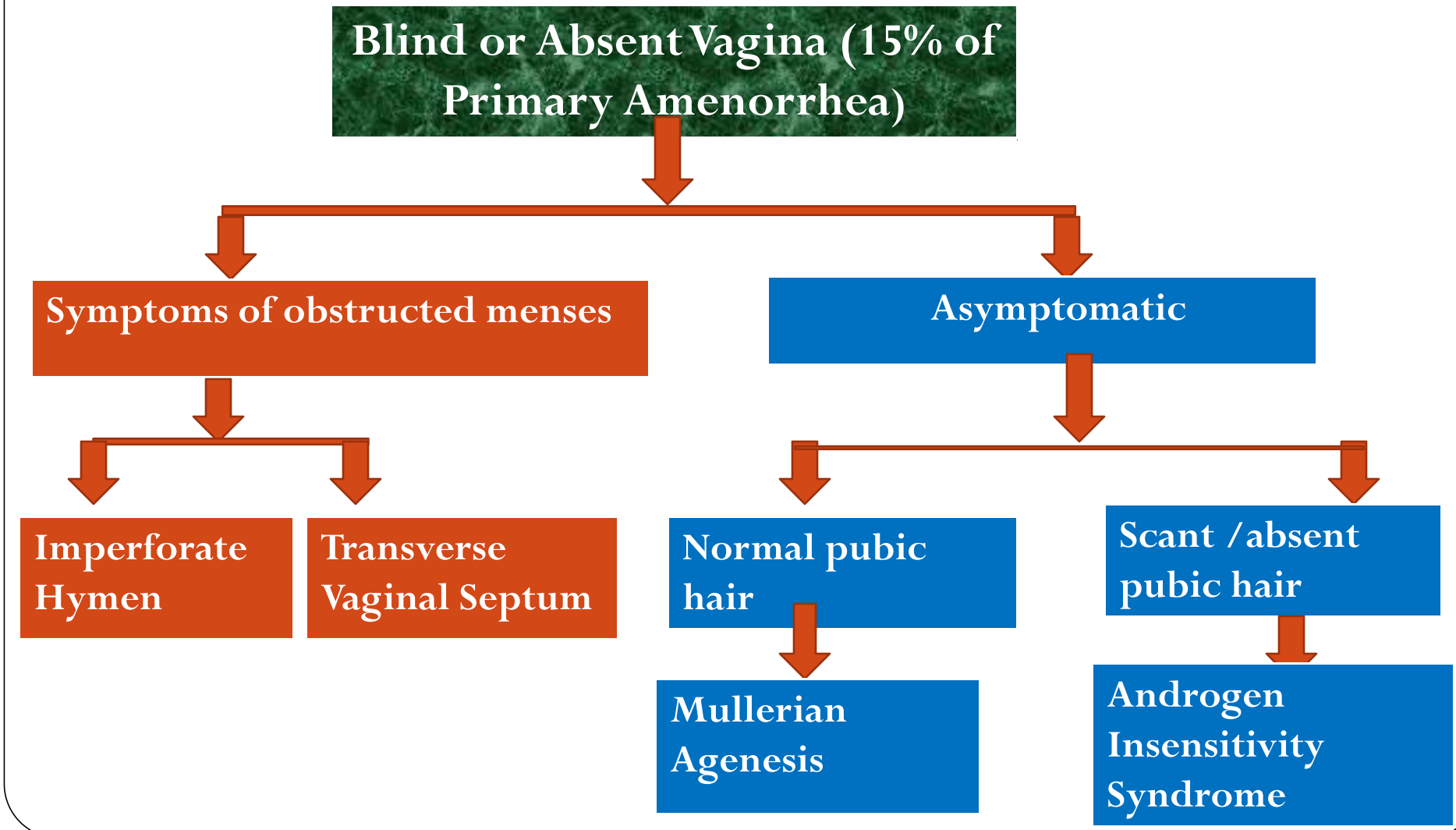
Hormones to diagnosis type of amenorrhea

Hypothalmic pit failure	Ovarian failure	PCOS and obstructive
• FSH low • LH low • E2 low	• FSH high • LH high • E2 low	• FSH normal • LH normal or high • E2 normal

Evaluation of specific disorders

- **Blind or Absent Vagina**
- **Sec Amenorrhea & hyperandrogenism**
- **Secondary amenorrhea & POF**
- **Hypo-gonadotropic hypogonadism**
- **Hyper-prolactinemia**

Blind or partial Vagina Evaluation



Sec Amenorrhea & hyperandrogenism: Evaluation

Ovarian disorders: PCOS, Ovarian neoplasm

Adrenal disorders: late onset congenital adrenal hyperplasia (CAH), cushing's syndrome, adrenal neoplasm

Hormone	**Level**	**Indication**
Testosterone	≤ 200 ng/dL	PCOS
	> 200 ng/dL	Evaluate for ovarian or adrenal tumor
DHEA-S	≤700 µg/dL	PCOS
	> 700 µg/dL	Evaluate for adrenal tumor
17α-hydroxy-progesterone	> 200 ng/dL	Consider ACTH stimulation test to diagnose CAH

Secondary amenorrhea & POF Evaluation

Low serum E2 and persistent high FSH

Women < 30 years karyotype to exclude turners mosaics

FMR 1 gene (Fragile X-mental retardation)

Autoimmune abnormalities (40%)
Addison's disease, Thyroid autoimmunity, type1 Diabetes, Myaesthenia Gravis and anti-adrenal

Hypogonadotropic hypogonadism: Evaluation

- **Severe weight loss** (nutritional or exercise), chronic illnesses Abnormal pattern of GnRH secretion in order to suppress reproductive function in response to stress
- **Hyper-prolactinemia**: MRI with gadolinium contrast rule out pituitary tumors and other mass lesions
- **Sheehan's syndrome**: h/o severe PPH preceding amenorrhea
- **Kallman's syndrome:** congenital GnRH deficiency

  -May be associated with anosmia / hyposmia

  - Family history imp- inheritance can be sex- linked or autosomal dominant

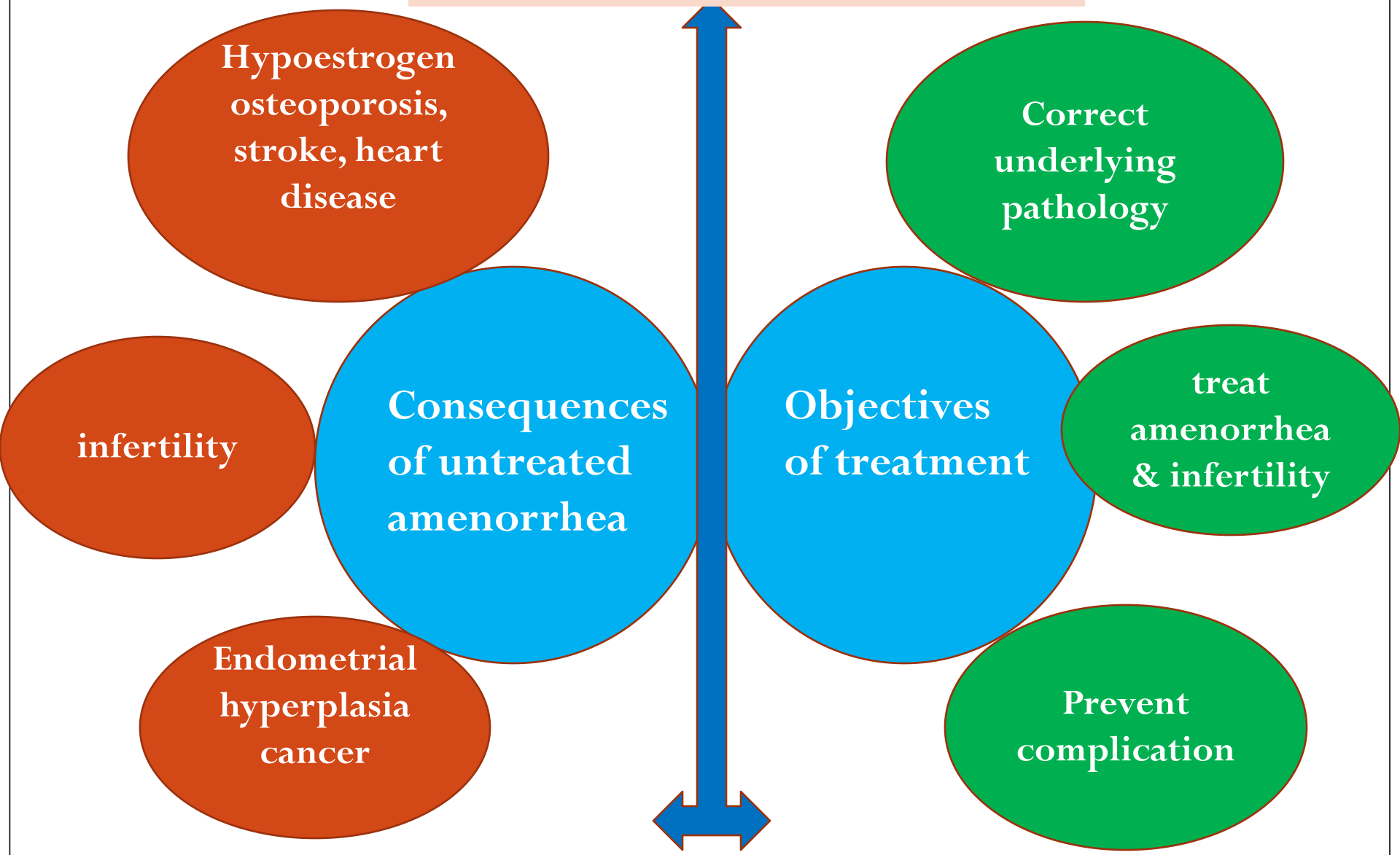
  - Normal adrenarche followed by delayed growth & puberty

Hyperprolactinemia (PRL) Evaluation

Commonest cause of secondary amenorrhea and if arises before menarche can lead to delayed puberty and primary amenorrhea

- Mildly elevated prolactin (20-50 ng/ml) repeat test.
- MRI head if serum prolactin>100ng/ml to rule out prolactinomas and other pituitary adenomas
- Hypothyroidism sometimes can lead to secondary hyperprolactinemia ; only thyroid hormone replacement is required for return of normal ovulation and menses.
- Galactorrhea only one third women with hyperPRL

Management of amenorrhea



Management

End organ failure

Gonadal agenesis (23XO)

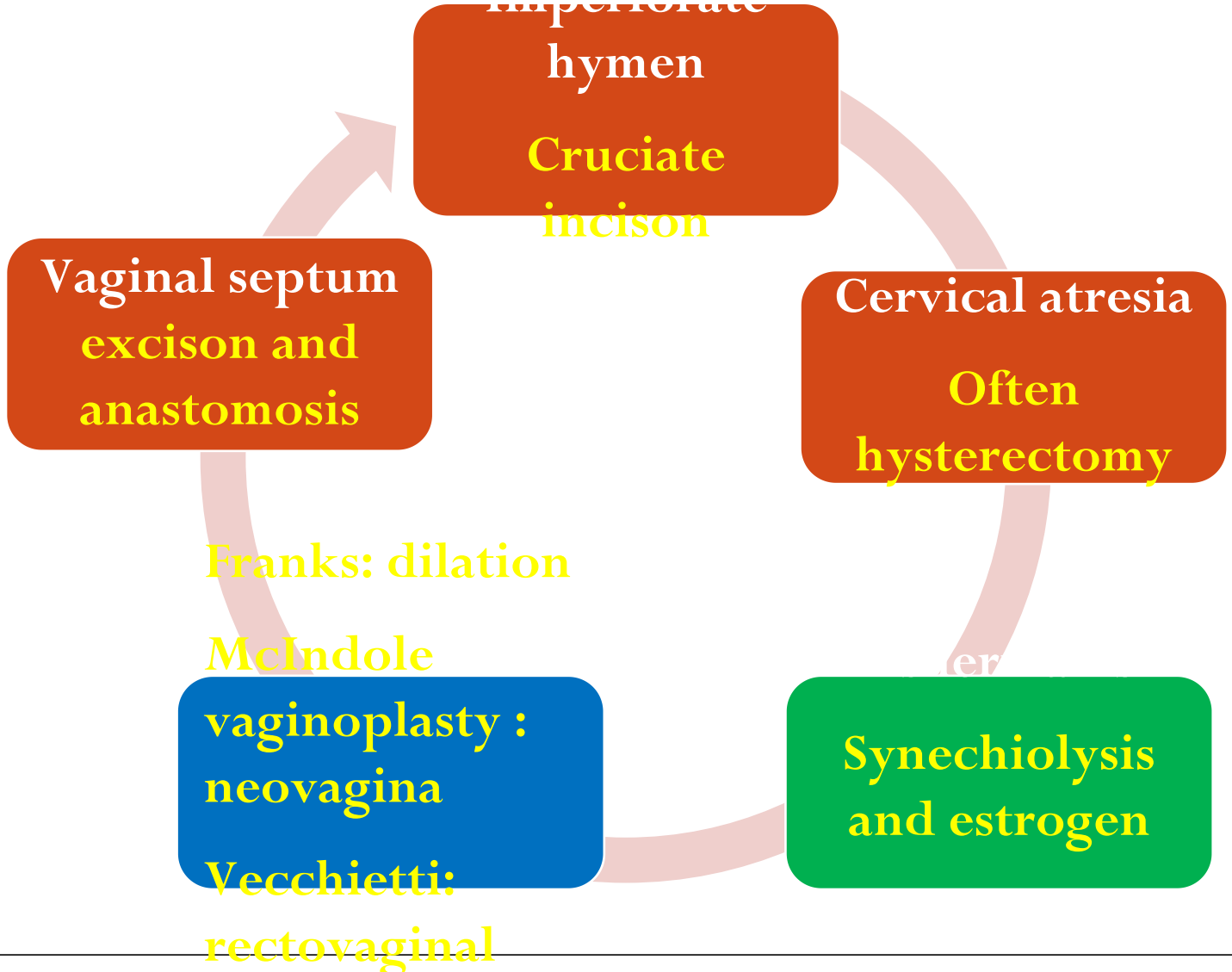
Gonadal dysgenesis (24XY)

PCOS

POF

Hypo-hypo and hyperprolactinemia

End organ Failure

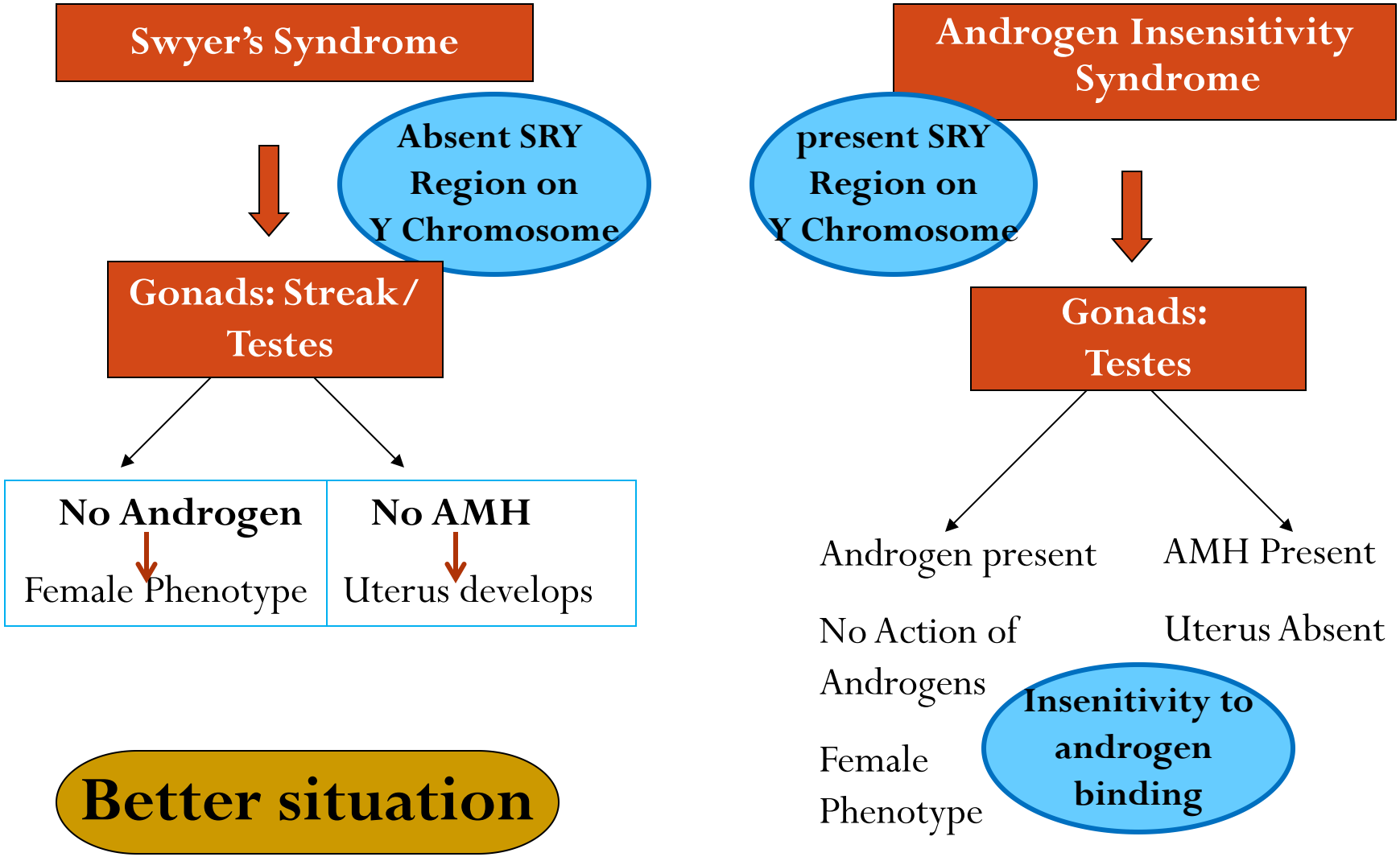


Gonadal agenesis **Turner syndrome** (45,X)

- Commonest form of amenorrhea confirmed by karyotype. High FSH low E2
- Present with primary amenorrhea but mosaics can present with POF
- Associated medical problems should be evaluated: Echo-cardiography, renal USG, audiometry, LFT, KFT, thyroid profile, lipid profile & sugar
- Estrogen therapy must be started after 12 years and before 15 years so that growth and adult height can be attained
- Estrogen started at low dose (0.25 – 0.5mg micronized estadiol) and increased gradually every 6 months till sexual maturation
- After 1-2 years of estrogen treatment progestin is added to get withdrawal bleeding

-

Gonadal dysgenesis: XY Females



Management gonadal dysgenesis

AIS

*Creation of neovagina

*Gonadectomy after puberty

*Estrogen replacement

*[illegible]

Swyers

*Vagina present

*Gonadectomy as soon as diagnosed

*Estrogen replacement

*Oocyte donation

Management of POF

Defined as hypergonadotropic hypogonadism and amenorrhea before the age of 40 years

- Estrogen replacement therapy: conjugated equine estrogens 0.625mg-1.25mg or transdermal 0.1mg/24hrs either cyclic or continuous with progestogen
- OCP's
- Calcium & Vit D supplement and exercise to protect bones.
- Pregnancy by oocyte donation

HRT should continue up to 50 years

Management of PCOS with amenorrhea

- *Lifestyle modification if overweight : Diet and exercise*
- Periodic treatment with progestin to induce cyclic menses and protect against endometrial hyperplasia

  Tab MPA 10 mg BD for 5 to 7 days every month or alternate months
- Either desiring contraception or with acne & hirsuitism: OCP
- Desiring fertility ovulation induction:

  CC/letrozole/ tamoxifen/gonadotropins.

Management of Hypo- Hypo/hyper PRL

Anorexia nervosa: behavioral and nutritional therapy with antidepressants. Return of menses with weight gain. Stressful conditions leading to amenorrhea: remove stress if possible.

- Fertility possible by ovulation induction with gonadotropins containing FSH and LH both
- Dopamine agonists (cabergoline and bromocriptine) restores menses and ovulation in 2-3 months in hyperprolactinemia.
- Women with amenorrhea and hypoestrogenic symptoms, not willing for fertility can be managed with HRT.

To conclude...

- *A thorough history , physical examination and lab tests help in identifying underlying cause in amenorrhea*
- *Constitutional delay in primary amenorrhea should be a diagnosis of exclusion*
- *Pregnancy should be ruled out in patients with secondary amenorrhea before starting work up*
- *Treatment goals of amenorrhea should include prevention of complications such as osteoporosis, endometrial hyperplasia and heart disease; preservation of fertility; and in primary amenorrhea, progression of normal pubertal development.*