# 일차성 무월경

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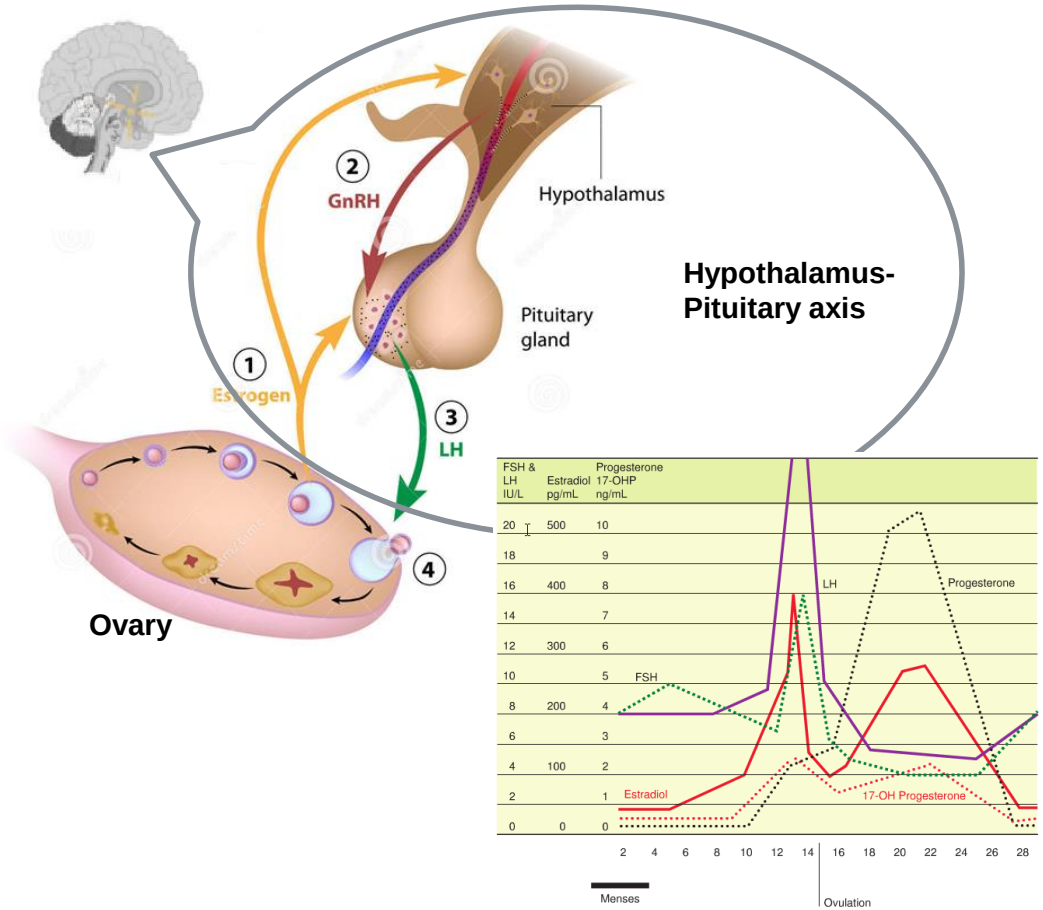
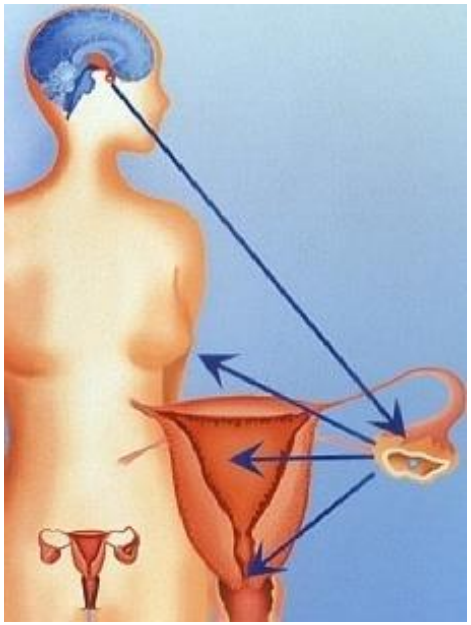
# For a normal period,

- We need an ovulation cycle and an intact female genital organ (Uterus & vagina, external genitalia).



# No period until…

- 15YO, 중3 여학생, 아직 초경이 없어요.

- Primary amenorrhea:
  - Absence of menarche by age 15 years
  - Absence of menarche by age 13 years without no visible development of secondary sexual characteristics.

- Absent secondary sexual characteristics = Never been exposed to Estrogen!

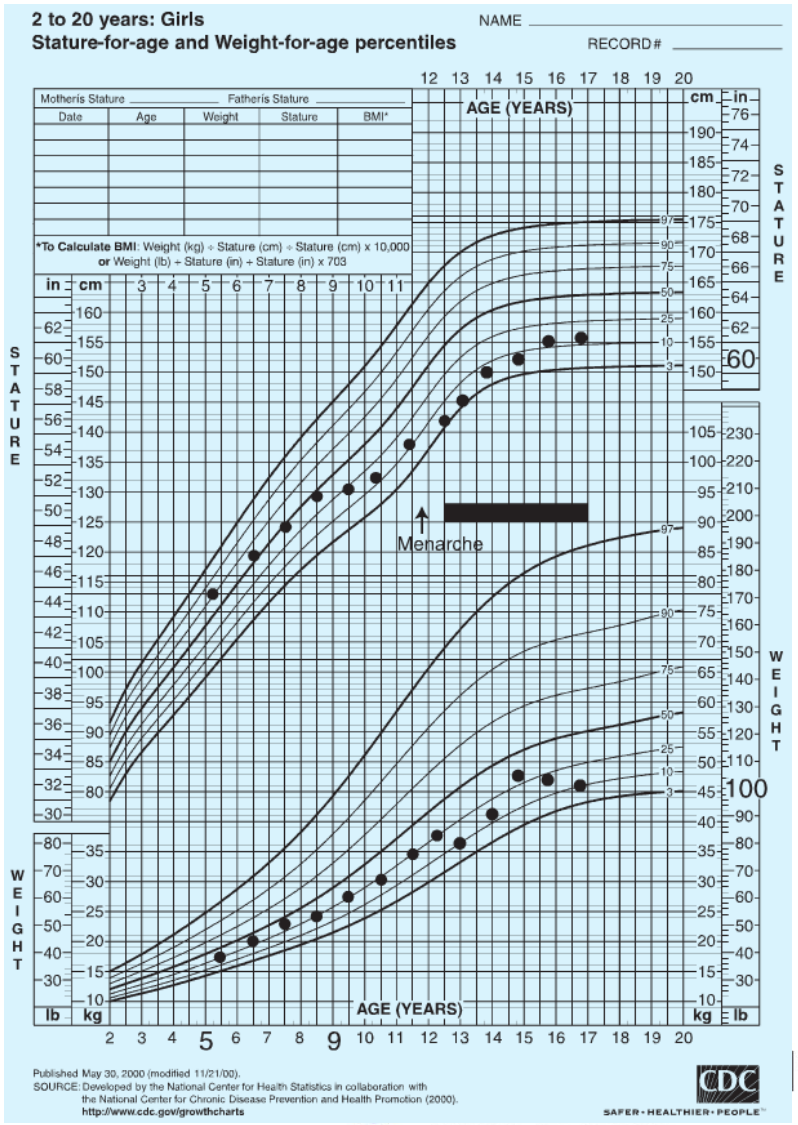
# DDX. Delayed puberty

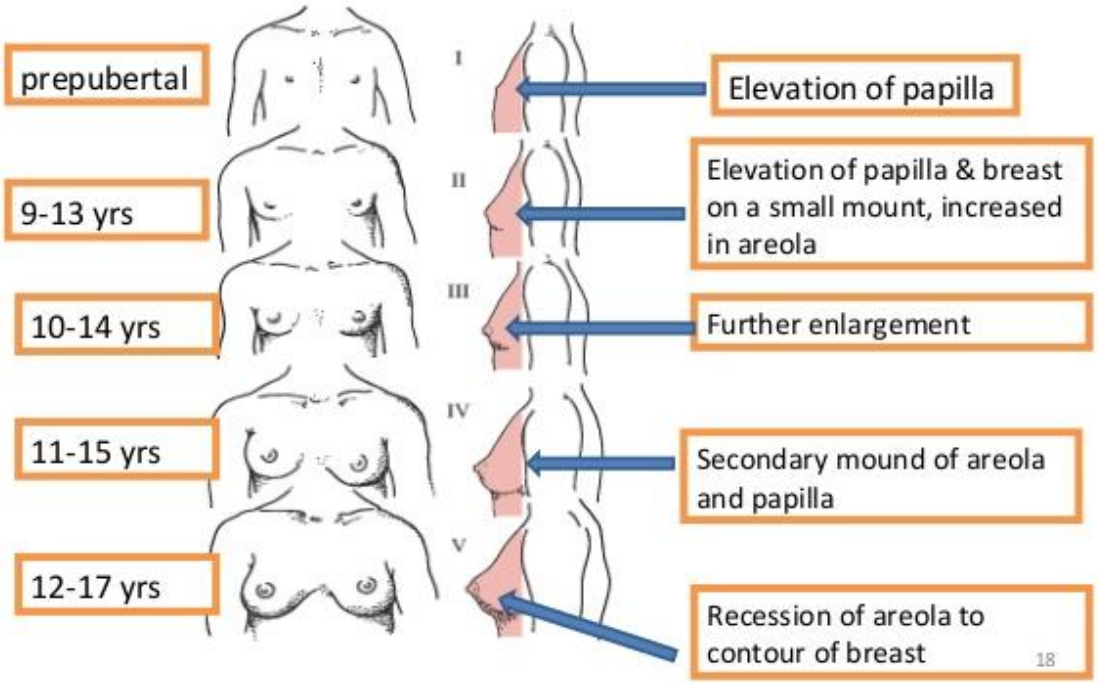
- Not experienced ANY pubertal development of the age of 13 years old: more than 2 standard deviations beyond the normal age of initiating puberty.
  - Debilitating chronic disease, ballet, competitive endurance sport such as track or gymnastics → full work up may postponed until age 14 years.

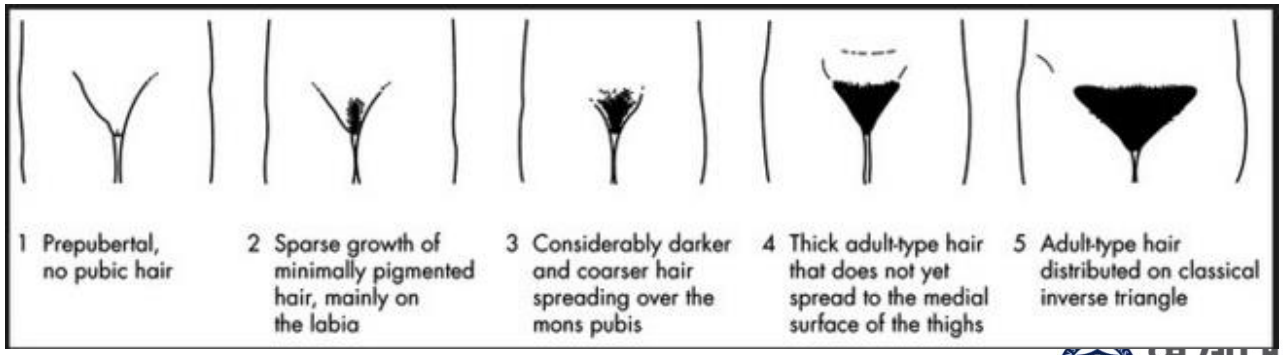
- Assessment
  - Prepubertal growth rate 2-2.5 inches/year (5-6cm/year)
  - Height, weight, BMI, Tanner staging (breast, pubic hair)
    - ✓SMR 2 -> f/u next 3-6 months
  - External genitalia: sign of estrogen effect, clitoromegaly, exclude congenital anomaly

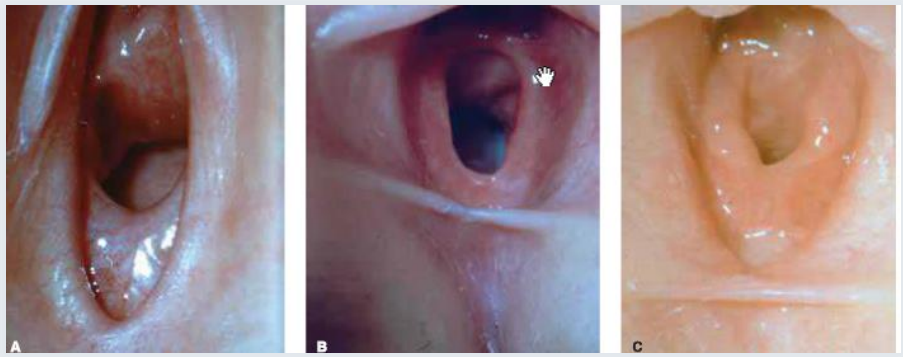
# Assessment

- **Physical examination**
  - Growth charts: weight, height
    - ✓ Recent weight loss
    - ✓ Low body fat
  - Sexual maturity rating (SMR)
    - ✓ Tanner staging of breast
    - ✓ Tanner staging of pubic hair








crescentric angular rebundant

- Pelvic examination
  - ✓External genitalia
  - a. Clitoromegaly
    - Clitoral index (width*length, mm)
      larger than 15mm$^2$ (newborn), 21mm$^2$(adult)
    - Width 3-4mm, length 4-5mm
  - b. Hymen opening
  - c. Vagina: Estrogen effect on vaginal mucosa

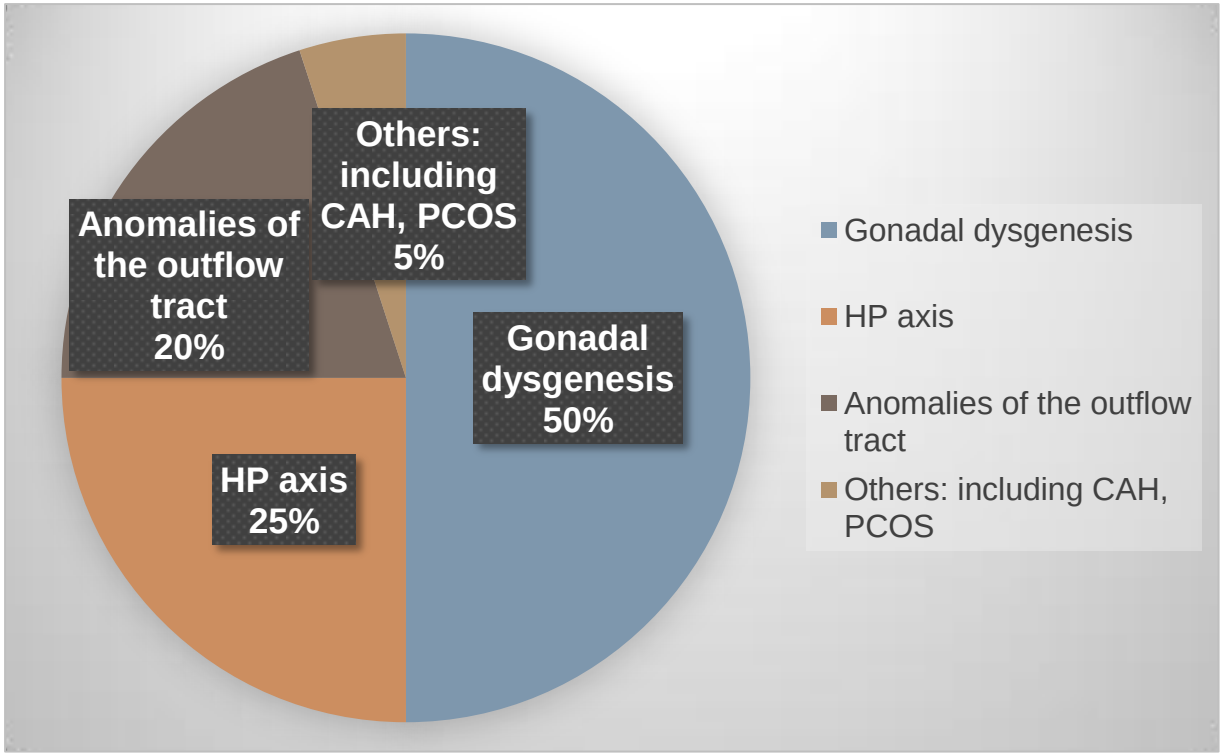
    Reddened, thin mucosa/ Pink, moist vaginal mucosa

    Vaginal patency- saline moistened cotton tipped swab

# Etiologies


| Hypothalamus | Pituitary gland | Thyroid gland | Adrenal gland | Ovaries | Uterus | Gential tract |
|---|---|---|---|---|---|---|
| Chronic disease | Idiopathic hypopituitarism | Hypo or Hyperthyroidism | CAH | Gonadal dysgenesis | Synechiae | Cervical agenesis |
| Familial delay | Tumor | | Cushing disease | Ovarian insufficiency | Agenesis | Vaginal agenesis |
| Stress, psychiatric illness | Hemochromatosis | | Addison disease | Autoimmune oophoritis | Pregnancy | Transverse septum |
| Competitive athletics | Infarction | | Tumor | PCOS | | Imperforate hymen |
| Eating disorders | Irradiation | | | Tumor | | |
| Obestiy | Surgery | | | BSO | | |
| Kallmann syndrome | | | | Irradiation | | |
| Durgs | | | | | | |
| Irradiations, tumor | | | | | | |

- Causes of primary amenorrhea




*Marsh CA et al., Obstet Gynecol Surv 69(10): 603-612*

# Anomalies of the outflow tract

- The genital tract is formed from the midline fusion of the paired Mullerian ducts (uterus, cervix, upper vagina).

*Vertical fusion of the developing ductal system with the invaginating urogenital sinus forms the lower vagina and introitus.*

- Anomalies of the outflow tract
  - Any of the structures from the uterus down to the hymenal ring.
  - Intact hypothalamic-pituitary-gonadal axis, normal pubertal development (breast, pubic hair)
  - Sx: Cyclic pain during the onset of the puberty

- Imperforate hymen
- Transvaginal septum
- Mullerian agenesis
- Androgen insensitivity syndrome (AIS)
- 5α reductase deficiency

- Mullerian agenesis (MRKH syndrome) vs. Androgen insensitivity (AIS)

| | MRKH syndrome | AIS |
|---|---|---|
| Uterus | Absent | Absent |
| Vagina | Blind pouch-absent | Blind pouch-absent |
| Breast | Normal female | Normal female |
| Pubic hair | Yes | No |
| Karyotype | 46, XX | 46, XY |
| Testosterone | Normal female | Normal male |
| Gonadotropin | LH/FSH normal | LH/FSH normal |

# Case

- 12세 6개월
- 1주일 간 지속된 LLQ pain으로 local 소아과 경유, r/o left ovarian mass로 ER 내원.

  - Abdomen pelvis CT

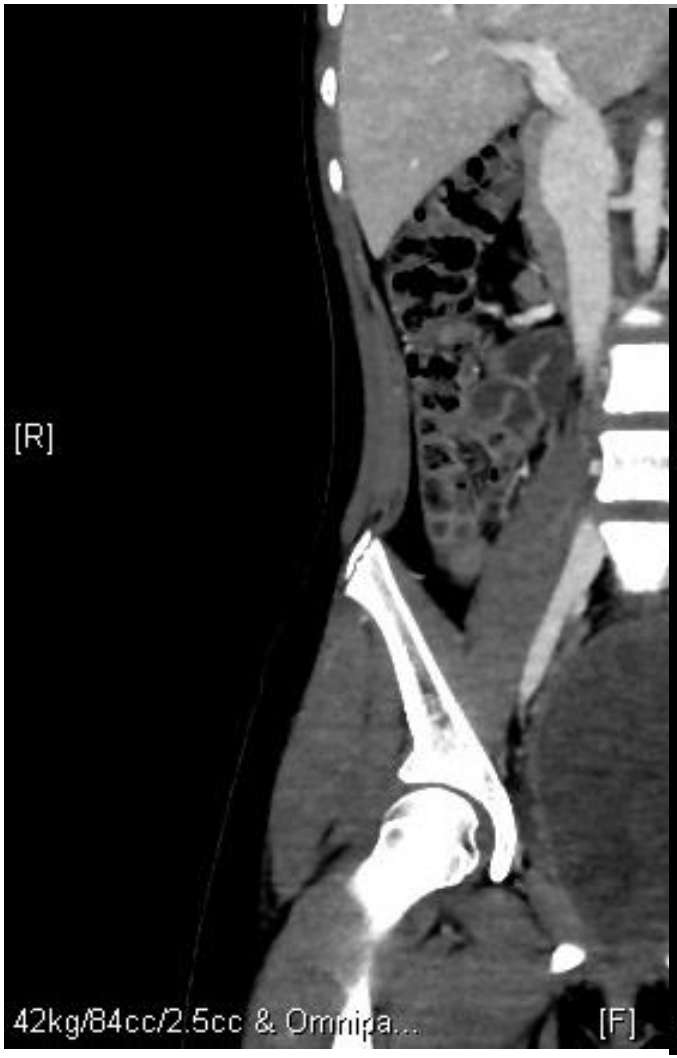
  High attenuating fluid filled distension of uterus and vagina.

  Urinary bladder is anteriorly displaced.

  IMP: Hematometrocolpos, R/O imperforate hymen.

  - Physical exam: bulging hymenal membrane, labial fusion partially.

- IMP: Imperforate hymen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42kg/84cc/2.5cc & Omnipa...
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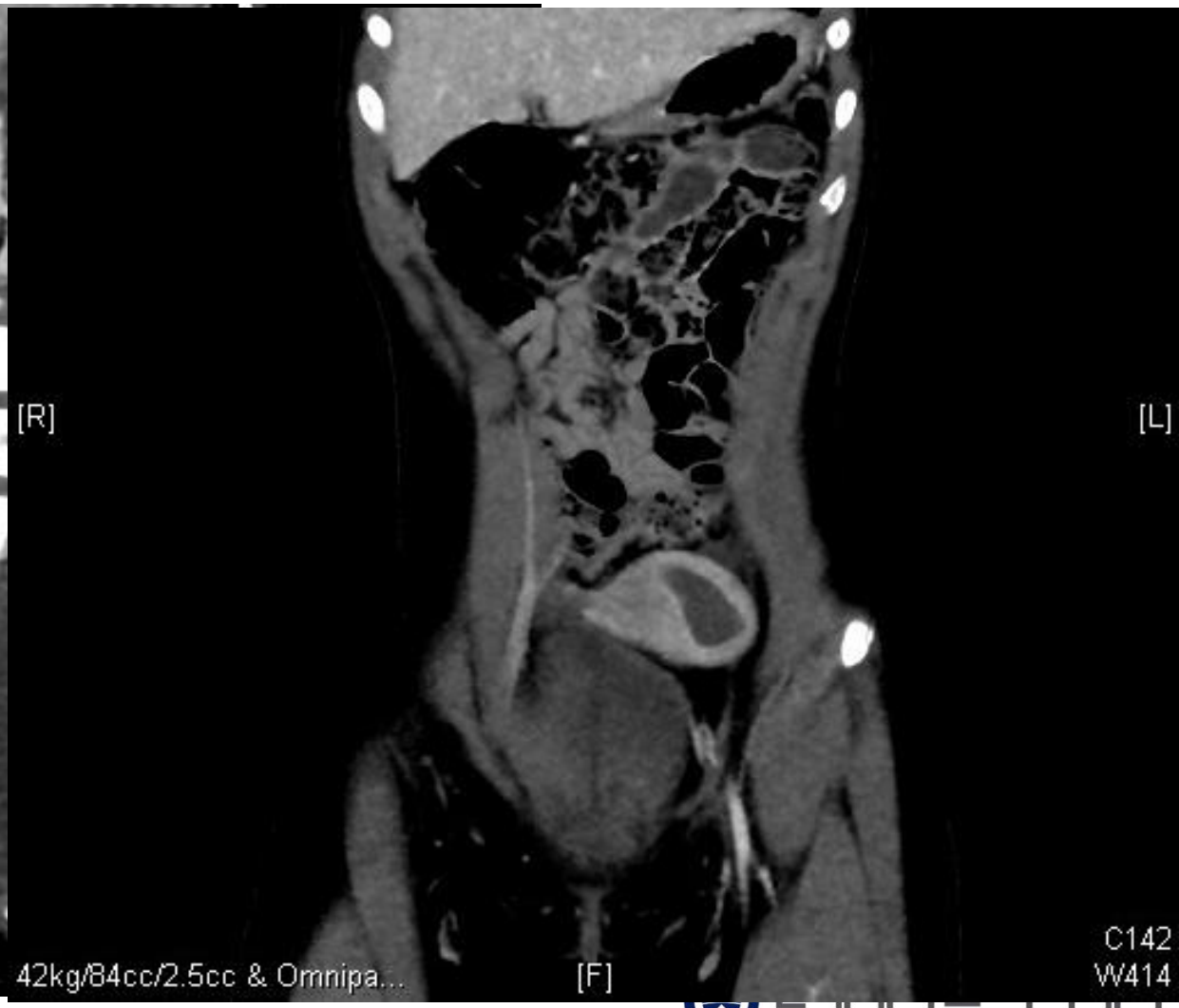
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# Case

- 18세
- 1' amenorrhea
  - Ht 160cm, Wt 52kg
  - Physical exam:
    - ✓ pubic hair: tanner 5
    - ✓ breast: tanner 5
    - ✓ vagina & hymen-> 환자 협조 안되어 swab 확인 못함.
    - ✓ clitoris<5mm
  - Blood tests:
    - ✓Karyotyping> 46,XX
    - ✓AMH> 8.42(ng/mL)
    - ✓LH/FSH/E2> 5.86/5.5/53 (mIU/mL, pg/mL)
    - ✓T/SHBG/FTI> 54.5/51.6/3.7 (ng/dL, nmol/L, %)
    - ✓DHEA-S/17-OHP> 270/146 (mcg/dL, ng/mL)

- Pelvis MRI:

◆ Both ovaries are noted in anterior aspect of bilateral pelvic cavity.

Small cystic lesion with internal T1 high lesion and some diffusion restriction at Lt ovary (2.0x2.7cm), probably small hemorrhagic cyst.

◆ In addition, two well-defined oval shaped lesions (about 3 cm) are demonstrated adjacent to the bilateral ovaries, probably testes.

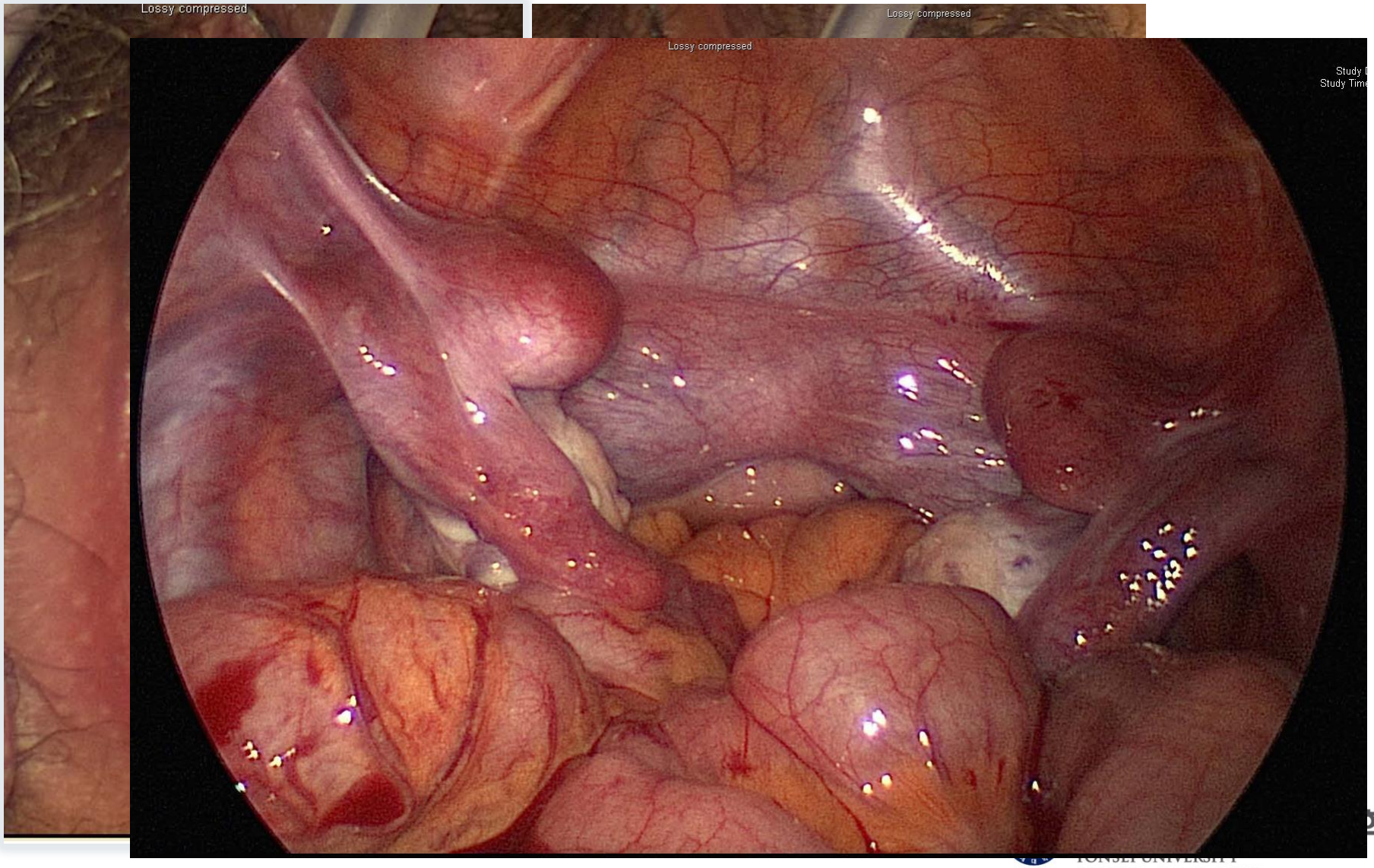
◆ No definite enhancing mass within the testis.

Bladder, urethra와 rectum 사이에 fat만 관찰되며, vagina 입구 같은 것은 의심되나 definite uterus로 보이는 구조물은 구분되어 보이지 않음.

Imp: Bilateral ovaries and testes in both sides of pelvic cavity, without gross uterus, maybe true hermaphroditism.

- hCG stimulation test : total T 37.6 → 39.7

# IMP: MRKH syndrome



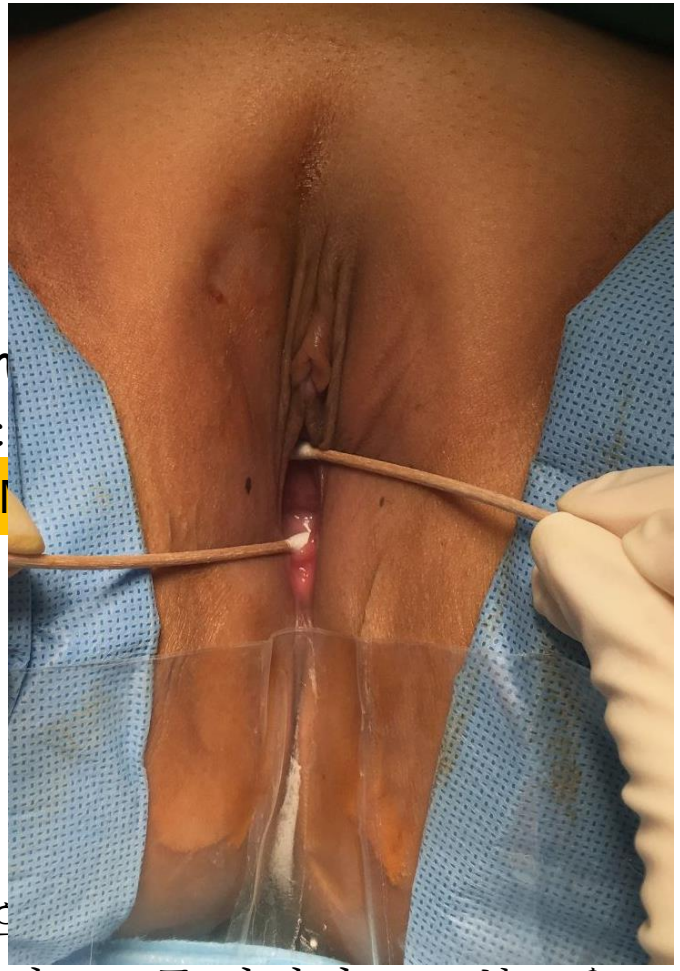
# Case

- 15세
- 1' amenorrhea, no sexual characteristics development
  - 165cm, 66kg
  - Physical exam:
    - ✓Pubic hair: Tanner 1
    - ✓Breast: Tanner 1
    - ✓External genitalia: female(?)
  - Blood tests:
    - ✓T3/fT4/TSH/Prolactin 1.46/1.27/1.79/9.6
    - ✓LH/FSH/E 44.23/100.8/8.70 (mIU/mL, pg/mL)
    - ✓T <2.5 (ng/dL)
    - ✓DHEA-S 5 (mcg/dL)
    - ✓ACTH/Cortisol 61.26/0.8
    - ✓Chol/TG/HDL/LDL 147/135/42/78

- ✓ Karyotyping: 46, XY
- Pelvis MRI:

IMP : 1. R/O streak gonads in bilateral inguin
2. No visible uterus or ovaries in pelvic

- hCG stimulation test: I
  - ✓ T <2.5
  - ✓ 5a DHT <0.02
- SRY gene positive



- Laparoscopic gonadectomy, bilateral
  - ✓ op finding: Rt side inguinal ring 아래쪽으
    가 관찰되었음. Lt 는 pedicle 이 명확치 않아 vas 를 당기며 ring 부근을 dissection 하였으며 inguinal ring 바깥에서 testis 가 복강 내로 당겨져 서 들어옴

✓Pathology

- Testis, right:

  Immature seminiferous tubules with Sertoli cell only, testis proper, see note.

  No evidence of ductal structure

- Testis, left:

  Atrophic seminiferous tubules with Sertoli cell only, testis proper

  No evidence of ductal structure

Note) 양측 gonad 모두 testis 구조가 확인되어 gonadal dysgenesis보다는 androgen insensitivity syndrome (testicular feminization syndrome)에 해당합니다.

IMP: Androgen insensitivity syndrome with leydig cell deficiency?

# Gonads

- Amenorrhea caused at the ovarian level is due to the absence of follicle capable of producing Estradiol.

- Most frequent cause of primary amenorrhea: 30-40%

- Causes
  - Incomplete or defective formation of the gonads
  - Germ cell migration and/or organization problems
  - Gonadal dysgenesis
    - ✓ Pure: 45, XO (Turner)/ 46,XX/ 46,XY (Swyer)
    - ✓ 46,XY: Testis regression syndrome, ovotestis syndrome
    - ✓ Partial: Bilateral dysgenic gonads
    - ✓ Mixed: 1 streak, 1 dysgenic gonad

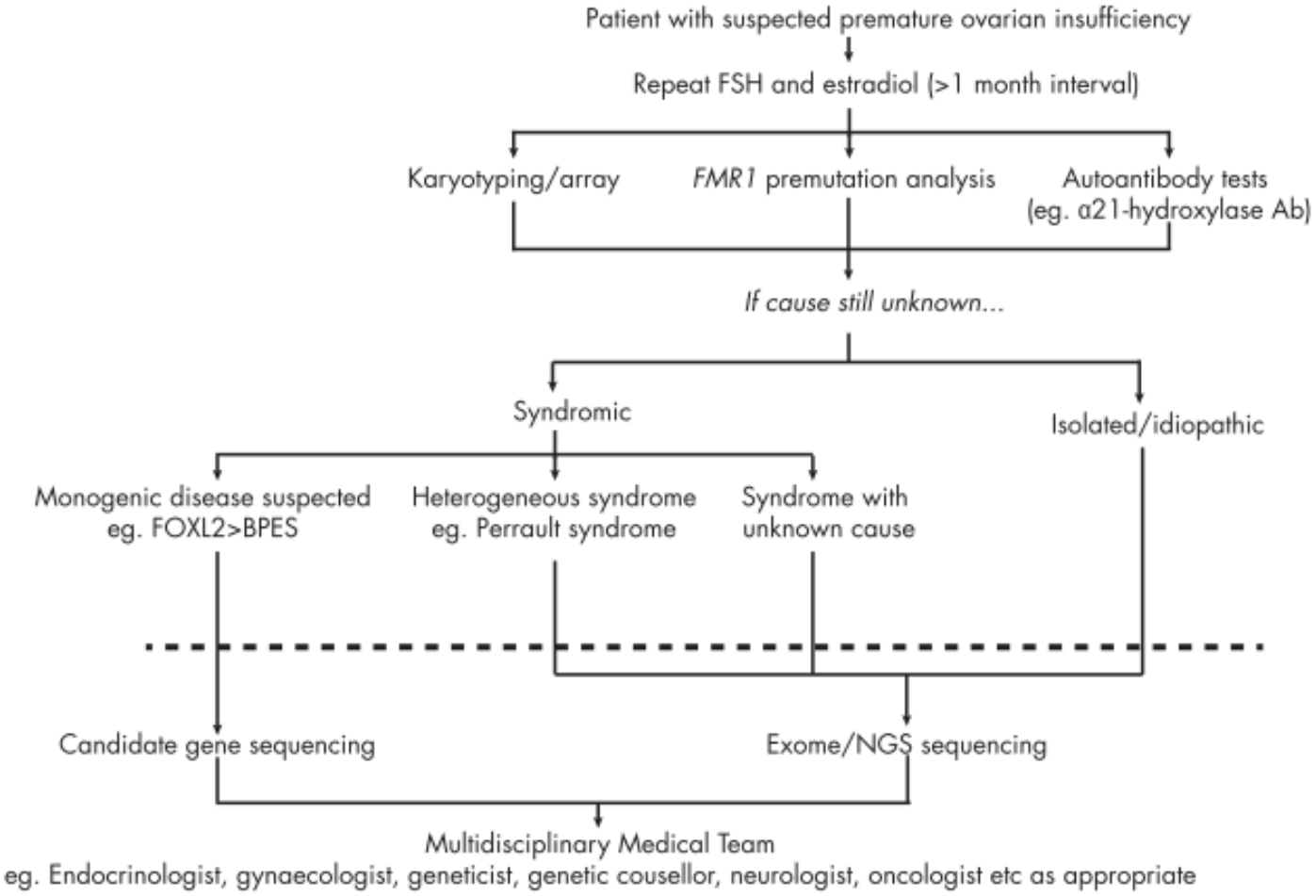
- Premature ovarian insufficiency (POI)
  ≠ Premature menopause
  - Oligo/amenorrhea for at least 4months+ FSH>25IU/L on two occasions, >4weeks apart.
  - A Retrospective cohort study, 955 Chinese women
    - ✓ Among POI, 14% presented primary amenorrhea.
    - ✓ The most severe ovarian dysfunction & more chromosomal aberrations, early onset in primary amenorrhea.

*Jiao, X. et al., 2017, J Clin Endocrinol Metab 102(7): 2281-2290.*

  - In the clinical setting: isolated POI with karyotype, FMR testing
  - Molecular diagnosis
    - ✓ WES: human POI genes

      Ex. MCM8, MCM9, STAG3, CLPP, HSD17B4, SOHLH1, SYCE1, eIF4ENIF1, RCTBT1.....

*Tucker, EJ. et al., 2016, Endocr Rev 37(6): 609-635.*




*Tucker, EJ. et al., 2016, Endocr Rev 37(6): 609-635.*

# Androgen excess

- Polycystic ovary syndrome (PCOS)
  - Adolescents with primary amenorrhea
    - ✓ Initial feature as primary amenorrhea: 1.4-14%.
    - ✓ Increased feature of the metabolic syndrome
      *Obesity, Lower HDL, higher fasting Glc, higher fasting insulin*
    - ✓ Higher androstenedione
    - ✓ More severe spectrum of a common condition
      *acanthosis nigricans, no response to progestin challenge test*

*Rachmiel M. et al., 2008, Arch Pediatr Adolesc Med **162**(6): 521-525.*

  - PCOS in adolescent
    - ✓ Menstrual patterns fairly well established 2-3 years after menarche.
    - ✓ Acne is common in adolescents.
    - ✓ Hirsutism and biochemical hyperandrogenism more specific.
    - ✓ High prevalence of metabolic risk.

*Emans SJ., Laufer MR., Pediatric and adolescent gynecology, 6th edition*

- Congenital adrenal hyperplasia (CAH)
  - Non-classic CAH, Late onset 21-Hydroxylase deficiency
  - Normal basal hormone: gonadotropins, estradiol
  - Increased level of testosterone: total T, DHEA-S, 17-OH progesterone

- Others
  - Mixed gonadal dysgenesis
  - 5α reductase deficiency
  - 17ß hydroxysteroid dehydrogenase deficiency
  - Incomplete AIS
  - Ovotestis syndrome
  - Ovarian/Adrenal tumor

# Case

- 17세
- 1' amenorrhea
  - 158cm, 73kg
  - Physical exam:
    - ✓clitoris <4mm
    - ✓hymen angular
    - ✓vaginal depth 8cm, hypoestrogenic status
    - ✓Breast: Tanner 2
    - ✓Pubic hair: Tanner 2
  - Imaging:
    - ✓ USG: small uterus (corpus volume=: 1.05x 2.83x 1.63cm3), both ovaries invisible

- Blood tests:
  - ✓TSH/PRL> 1.97/11
  - ✓LH/FSH/E2> 28.14/80.2/12 (mIU/mL, pg/mL)
  - ✓T/SHBG/FAI> 20.3/20.2/3.5 (ng/dL, nmol/L, %)
  - ✓DHEA-S> 247(mcg/dL)
  - ✓morning cortisol/IGF-1> 15.2/188.2
  - ✓AMH> <0.08 (ng/mL)
  - ✓Karyotyping: 45,X[11]/46,XX[39]

- IMP: Turner syndrome

# Case

- 14세
- 1' amenorrhea & hirsutism
  - 162cm, 78kg (BMI 30.4)
  - Pubarche 12세
  - Physical exam:
    - ✓clitoris 0.5x1cm
    - ✓Hymen: rebundant
    - ✓vagina free, 10cm depth,estrogenized mucosa
    - ✓Breast T3-4, Pubic hair T4
    - ✓Modified FG score=2+1+1+2+3+1+2+2+2= 16
  - Ultrasound: corpus volume=2.5x5.3x2.6cm3 (volume 18.4cc)

    EM 4.7mm, RO- 2.67x2.19x2.37cm3(vol. 7.26ml) 2~9mm sized follicle: 24, LO- 3.65x1.96x1.98cm3(vol. 7.40ml) 2~9mm sized follicle: 28

- Blood tests:
  - ✓T/SHBG/FTI 57.9/13.1/15.3(ng/dL, nmol/L, %)
  - ✓TSH/PRL 1.31/25.8(μIU/mL, ng/mL)
  - ✓LH/FSH/E2 15.08/7.9/53(mIU/mL, pg/mL)
  - ✓DHEA-S/17-OHP 418/pending (mcg/dL, ng/mL)
  - ✓AMH pending (ng/mL)

- IMP: PCOS

# Central problems-Hypothalamus

- Hypogonadotropic hypogonadism: Low levels of gonadotropins (LH, FSH <5mIU/mL) due to central suppression of GnRH.

- Causes
  - Functional hypothalamic amenorrhea
  - Kallman syndrome
  - Craniopharyngiomas
  - Cranial radiation
  - Constitutional delay

# Central problems-Pituitary

- Rare prior to puberty, usually present with secondary amenorrhea.

- Causes
  - Hyperprolactinemia
  - Empty sella syndrome

# Case

- 16세
- 1' amenorrhea without sexual characteristics
- PHx: spina bifida, rib fusion, congenital scoliosis- Vertebral segmentational and fusion anomaly at lower T spines and L spines, with thoracolumbar scoliosis.

  - 138cm, 31kg
  - Physical exam:
    - ✓clitoris <3mm
    - ✓angular hymen
    - ✓unestrogenized mucosa
    - ✓Pubic hair T1
    - ✓Breast T1

- Blood tests:
  - ✓AMH 1.85 (ng/mL)
  - ✓Testosterone/SHBG/FTI <2.5/73.2/unable (ng/dL, nmol/L, %)
  - ✓TSH/PRL 1.57/7.1
  - ✓LH/FSH/E2 <0.2/0.5/21 (mIU/mL, pg/mL)
  - ✓IGF-1(Somatomedin-C) 213.5
  - ✓DHEA-S 51(mcg/dL)
  - ✓Combined pituitary function test> mild cortisol deficiency, gonadotropin deficiency

- Spine MRI에서 empty sella 소견 보임
- Kallman syndrome에 대한 gene study 진행함 (NGS).
- Growth hormone treatment 시작함.
- GH 치료 먼저 시작하고 pubertal induction 예정임.

- IMP: 1' amenorrhea due to Hypopituitarism
  R/O Kallman syndrome

# Case

- 16세
- 1' amenorrhea
- 3년 전 체중 감량으로 35kg까지 빠졌음.
  - 160cm, 46kg
  - Physcial exam:
    - ✓clitoris: <3mm
    - ✓hymen: angular
    - ✓pubic hair: tanner 2
    - ✓breast: tanner 3
  - Ultrasound(타병원): small uterus

- Blood test:
  - ✓TSH/PRL> 0.82/5.8(μIU/mL,ng/mL)
  - ✓LH/FSH/E2> 1.69/3.9/35(mIU/mL, pg/mL)
  - ✓T/SHBG/FAI> 28.5/57.2/1.7(ng/dL, nmol/L, %)
  - ✓DHEA-S/17-OHP> 281/96(mcg/dL, ng/mL)
  - ✓AMH> 7.41 (ng/mL)

- IMP: Functional hypothalamic amenorrhea

# Management

- Outflow obstruction
  - Surgical correction

- Patients with uterus & fully developed 2' sexual characteristics ► **Unopposed estrogen** increases the risk for EM hyperplasia & cancer.
  - Cyclic progestin/E+P or combined oral contraceptive

- Hypogonadism
  - Patients with inadequate breast development ► pubertal induction starting with low dose E. Avoid progestin until the breast develops adequately (tubular, misshapen breast).
  - Risk for **Osteoporosis**
    - ✓ Dual energy X-ray absorptiometry (DEXA)
  - Vitamin D, calcium, hormone replacement(E or E+P)

- Patients with 46,XY karyotype
  - Screening for intra-abdominal gonadal structures
  - Gonadectomy- Appropriate timing of gonadectomy
    - ✓ Gonadal dysgenesis- Early gonadectomy
      - Risk of germ cell tumor: 25-33%
      - Mixed and pure gonadal dysgenesis: total incidence of malignancy 11.1%
    - ✓Complete AIS- Postpubertal gonadectomy

      After secondary sex characteristics are fully developed.

      Around age 16-18YO.
      - Adult: malignant testicular tumor in 16% of adult patients/
      - Pediatric: malignancy rates 0.8-2.0%

*Hum Reprod. 2014;29(7):1413-19*
*Clin Endocrinol (Oxf). 2012 Jun;76(6):894-8*

- Hormone treatment
  - ✓Complete AIS

| Drug | Dose (mg) | Note |
|---|---|---|
| 17ß Estradiol | 1 | Natural form and natural binder for estrogen receptors (ERs) in humans; ineffective orally (hepatic inactivation) |
| Ethinyl estradiol | 0.01 | Synthetic analog, it binds ERs as 17β-estradiol, but it is retained for longer time; protected from hepatic inactivation |
| Conjugated estrogen | 0.3 | Not estradiol precursors; protected from hepatic inactivation, multiple estrogens |

*Bertelloni,S. et al., 2011, Horm Res Paediatr 76(6): 428-433.*

  - ✓Swyer syndrome
    - In line with other causes of female hypogonadism
    - Cycic E+P throughout life until the age of 50.
    - Despite adequate estrogen dosing, breast development may not be sufficient.

# Take home message

- 15YO girl presenting primary amenorrhea
  - Height, Weight, BMI & related history.
  - Physical examination: sexual characteristics, external genitalia.
  - Hormone labs
  - Karyotyping
  - Imaging study: USG/pelvis MRI.
  - Management: Surgical correction or Hormone treatment.
  - Further evaluations & follow up according to the cause, respectively.

감사합니다 !