Inter-hospital ENDOCRINE Conference
A 23-yr-old woman presented with epigastric pain and primary amenorrhea



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14 Dec 2018

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Topics to review

- Primary Amenorrhea
- Disorder of Sex Development (DSD)
- DSD status in Thailand
- MRKH syndrome
- Candidate genes pathway in this case

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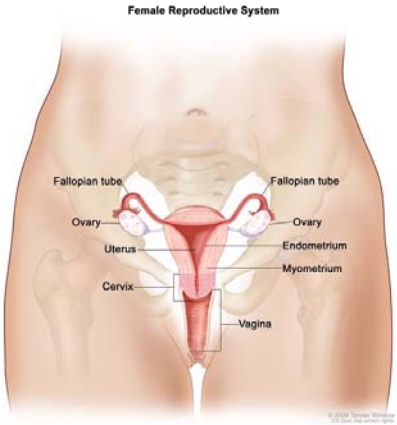
Amenorrhea: Back to the basic



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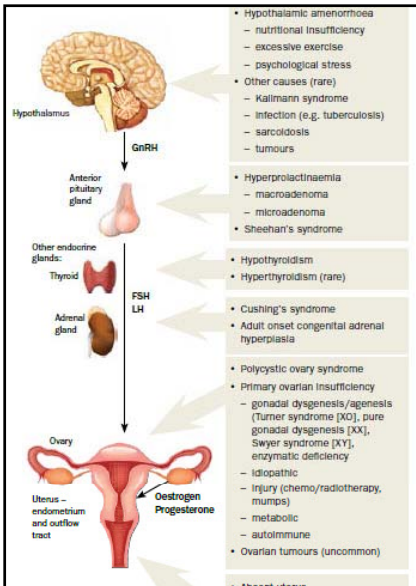

- Hypothalamic amenorrhoea
  - nutritional insufficiency
  - excessive exercise
  - psychological stress
- Other causes (rare)
  - Kallmann syndrome
  - infection (e.g. tuberculosis)
  - sarcoidosis
  - tumours
- Hyperprolactinaemia
  - macroadenoma
  - microadenoma
- Sheehan's syndrome
- Hypothyroidism
- Hyperthyroidism (rare)
- Cushing's syndrome
- Adult onset congenital adrenal hyperplasia
- Polycystic ovary syndrome
- Primary ovarian insufficiency
  - gonadal dysgenesis/agenesis (Turner syndrome [XO], pure gonadal dysgenesis [XX], Swyer syndrome [XY], enzymatic deficiency
  - idiopathic
  - injury (chemo/radiotherapy, mumps)
  - metabolic
  - autoimmune
- Ovarian tumours (uncommon)
- Absent uterus
  - Müllerian agenesis
  - complete androgen insensitivity (XY)
- Cervical or vaginal agenesis
- Asherman's syndrome
- Endometrial aplasia or hypoplasia (congenital)

Compartment-based approach in amenorrhea

1) Outflow tract (Uterus/Vagina)
2) Disorder of Ovary
3) Disorder of Pituitary
4) Disorder of Hypothalamus

Fertil Steril 2008;90(suppl 5): S219-S225.

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Primary amenorrhea

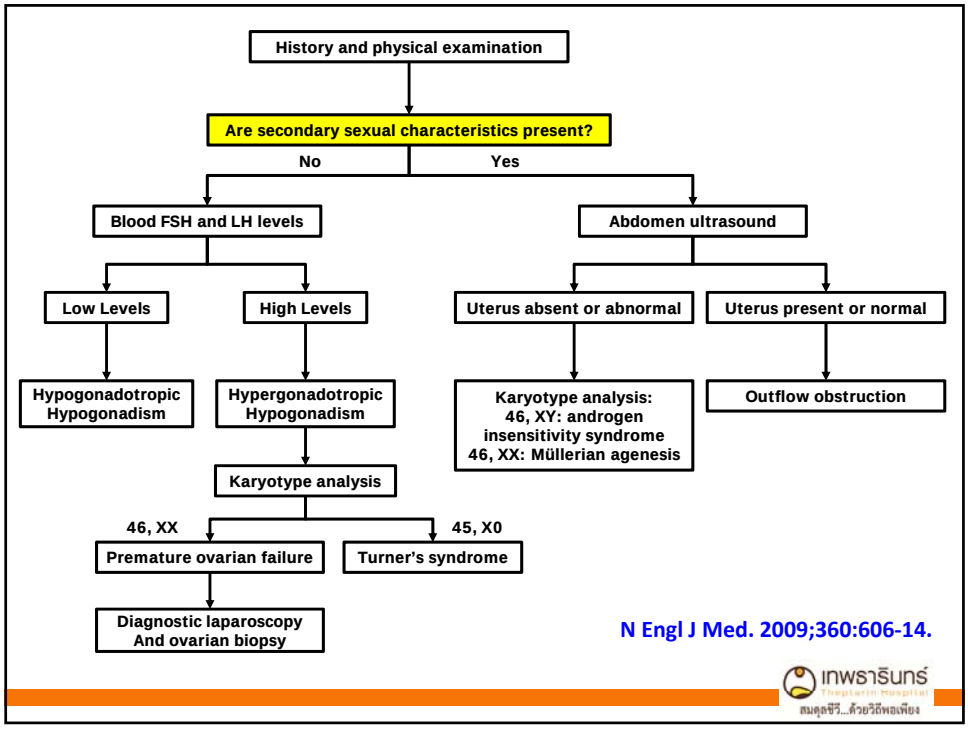
- **Primary amenorrhea is defined as**
  - **Absence of menses by 14 years of age in the absence of growth or development of secondary sexual characteristics *OR***
  - **Absence of menses by 16 years of age regardless of the presence of normal growth and development including secondary sexual characteristics.**

Evaluation in Primary Amenorrhea

- **Presence or absence of the uterus in patients with primary amenorrhea**
- **Breast development is an excellent marker for ovarian estrogen production**
- **Karyotype analysis and sex hormones should be evaluated in all cases of primary amenorrhea**

Progesterone challenge test traditionally used to use in confirmation of functional anatomy and adequate estrogenization. However, this testing is relatively unreliable in evaluation of estrogen status.

Am Fam Physician 2013;87:781-8.



N Engl J Med. 2009;360:606-14.

46,XX conditions that present with abnormal development at puberty

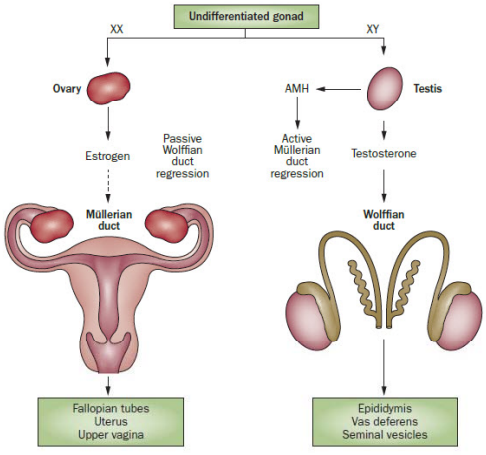
Condition	Breast/pubic hair development	Menstruation	Distinguishing feature
46,XX gonadal dysgenesis	–	–	↑ FSH & LH, ↓ E2. FSH receptor gene mutation
17α hydroxylase deficiency	–	–	Hypertension, hypokalaemia. ↑mineralocorticoids, ↓ cortisol and sex steroids. Mutation in *CYP17*
Steroidogenic factor-1 deficiency	+/–	Primary amenorrhoea or premature ovarian failure	Mutation in *NR5A1*
Mullerian duct agenesis	+	–	Normal hormone levels, anatomical anomaly seen on imaging. *WNT4* mutations in some cases

J.M. Hutson et al. (eds.), Disorders of Sex Development, Springer-Verlag Berlin Heidelberg 2012, page 53-60.

Disorder of Sex Development (DSD)

The most difficult/complex area in ENDO

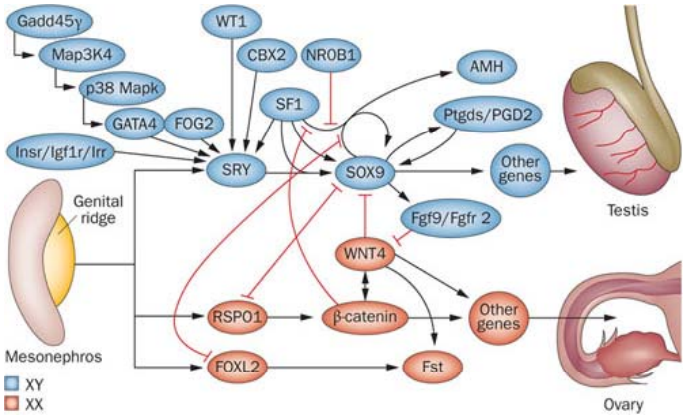
Sex determination and sexual differentiation of the internal genital ducts



Anti-Mullerian hormone (AMH)

Nat Rev Endocrinol 2014;10:476-87.

Genetic pathways of sex determination



At 6–8 wks post-conception in human fetal development, upregulated expression of *SRY in the bipotential gonad promotes testis determination, whereas activation of WNT4 and RSPO1 signalling promotes ovary determination*

Genetic pathways of sex determination

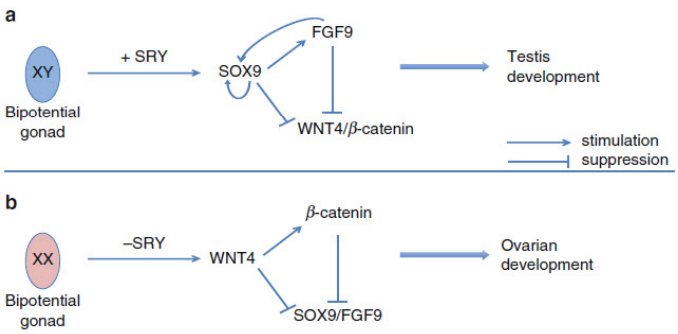
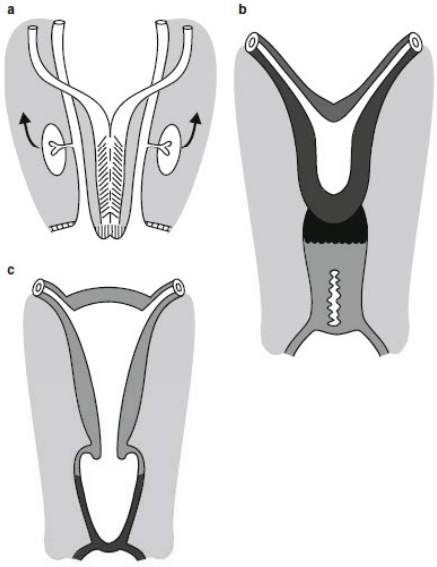


Fig. 1.1 Antagonistic pathways involved in gonad differentiation. (a) In XY individuals *SRY* is transiently expressed in the bipotential gonad. This initiates an increase in *SOX9* expression, which in turn stimulates FGF9. Both FGF9 and *SOX9* act together in a positive feedback loop, which suppresses WNT4 and leads to the establishment of the testis-specific pathway. (b) In the absence of *SRY* in XX individuals, WNT4 and β-catenin suppress the SOX9/FGF9 positive feedback loop, allowing the ovarian-specific pathway to progress

J.M. Hutson et al. (eds.), Disorders of Sex Development, Springer-Verlag Berlin Heidelberg 2012, page 1-9.

Development of uterus and vagina



- Paramesonephric (Müllerian) ducts migrate to urogenital sinus, fusing with contralateral duct. Distal ends are solid.
- Contact of solid tips of paramesonephric ducts triggers proliferation of endoderm to form sino-vaginal bulb (Müllerian tubercle)

Evolution of DSD classification

- Before 2005: Unspecific and confusing terms like hermaphroditism, intersex, sex reversal, and male or female pseudohermaphroditism
- Since 2005 - Chicago consensus: 46,XY DSDs, 46,XX DSDs and sex chromosome DSDs
- In 2011, UK DSD task force proposes the initial diagnostic evaluation included AMH in 46 XY DSD
- In 2013, I-DSD registry reported 46 XY DSD → heart/CNS, 46 XX DSD → skeleton/kidneys

Pediatrics 2006;118e488-e500
Clin Endocrinol 2016;84:771-88.

Confusing and Vague Medical Terms VS. DSD

Title	Previous terminology
Disorders of sex development	Intersex
46,XY DSD	Male pseudo-hermaphrodite Under-virilised male Under-masculinised male
46,XX DSD	Female pseudo-hermaphrodite Virilised female Masculinised female
Ovo-testicular DSD	True hermaphrodite
46,XY complete gonadal dysgenesis	XY female XY sex reversal
46,XX testicular DSD	XX male XX sex reversal

Adapted from Hughes et al. (2007)

Best Pract Res Clin Endocrinol Metab 2008;22:119-34.

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Biological classification of DSD

46,XY

Disorders of gonadal development
- Ovotesticular DSD
- Complete or partial gonadal dysgenesis, monogenic forms (caused by mutations in SRY, SF1, WT1 and others)
- Syndromic forms

Disorders of androgen synthesis
- Syndromic (for example, Smith–Lemli–Opitz syndrome)
- Associated with congenital adrenal hyperplasia and early androgen biosynthesis defects (for example, mutations and/or deficiencies in StAR, P450(scc), 3β-HSD II, P450R and CYP17A1)
- Associated solely with androgen biosynthesis defects (for example, mutations and/or deficiencies in SRD5A2 and HSD17B3)
- Associated with endocrine disruption

Disorders of androgen action
- Complete and partial androgen insensitivity

Unclassified disorders
- Hypospadias of unknown genetic origin
- Epispadias
- Complex syndromic disorders

46,XX

Disorders of gonadal development
- Ovotesticular DSD
- Testicular DSD
- Syndromic forms

Disorders of androgen excess
- Congenital adrenal hyperplasia (mostly steroid 21-hydroxylase deficiency)
- Aromatase deficiency
- Luteoma
- Iatrogenic

Unclassified disorders
- Mayer–Rokitansky–Küster–Hauser syndrome
- Complex syndromic disorders

Chromosomal DSDs
- 45,X (Turner syndrome and variants)
- 45X/46,XY (mixed gonadal dysgenesis)
- 47,XXY (Klinefelter syndrome and variants)
- Other complex chromosomal rearrangements

Nat Rev Endocrinol 2014;10:520-9.

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Streak gonad as a potential of germ cell tumor in DSD

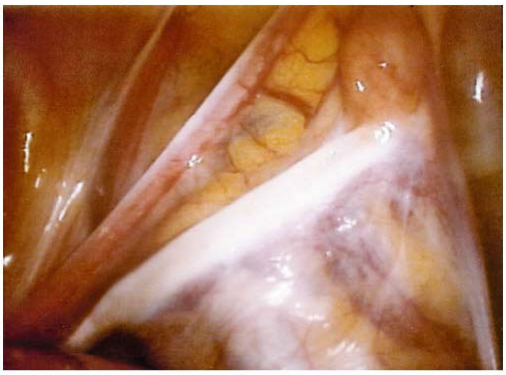


Fig. 5.1 Photo of a streak gonad taken at laparoscopy

J.M. Hutson et al. (eds.), Disorders of Sex Development, Springer-Verlag Berlin Heidelberg 2012, page 41-52.

Risk of germ cell tumors in the various categories of DSD patients

Risk group	Disorder	Malignancy risk (%)	Recommended action	Studies (*n*)	Patients (*n*)
High	GD[a] (+Y)[b] intra-abdominal	15–35	Gonadectomy[c]	12	>350
	PAIS non-scrotal	50	Gonadectomy[c]	2	24
	Frasier	60	Gonadectomy[c]	1	15
	Denys–Drash (+Y)	40	Gonadectomy[c]	1	5
Intermediate	Turner (+y)	12	Gonadectomy[c]	11	43
	17β-HSD	28	Monitor	2	7
	GD (+Y)[c]	Unknown	Biopsy[d] and irradiation?	0	0
	PAIS scrotal gonad	Unknown	Biopsy[d] and irradiation?	0	0
Low	CAIS	2	Biopsy[d] and ?	2	55
	Ovotestis DSD	3	Testis tissue removal?	3	426
	Turner (−Y)	1	None	11	557
No (?)	5α-reductase	0	Unresolved	1	3
	Leydig cell hypoplasia	0	Unresolved	2	

CAIS complete androgen insensitivity syndrome, *17β-HSD* 17β-hydroxysteroid dehydrogenase deficiency, *PAIS* partial androgen insensitivity syndrome

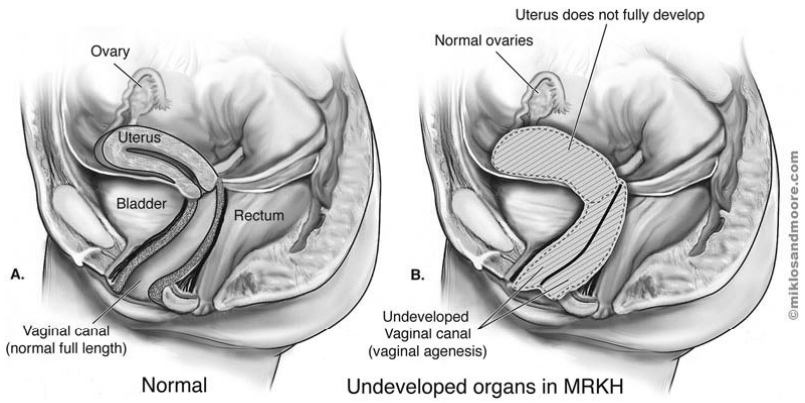
[a]Gonadal dysgenesis (including not further specified, 46XY, 46X/46XY, mixed, partial, complete)

[b]GBY region positive, including the *TSPY* gene

Best Pract Res Clin Endocrinol Metab 2007;21:480-95.

MRKH Syndrome

Mayer–Rokitansky–Kuster–Hauser (MRKH) syndrome



Mayer–Rokitansky–Kuster–Hauser (MRKH) syndrome

- Each Mullerian duct arises as an invagination of the peritoneum overlying the urogenital ridge adjacent to the cranial pole of the gonad, and the duct elongates to the cloaca caudally, using its adjacent Wolffian duct as a guide.
- Absence of the uterus and vagina might result from failure of caudal migration of the Müllerian ducts, or failure of canalization of the uterovaginal primordium.

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Mayer–Rokitansky–Kuster–Hauser (MRKH) syndrome

- MRKH Type 1 is the typical form of MRKH which only the caudal parts of the Mulerian ducts are affected and leads to congenital absence of the uterus and upper vagina but an apparently normal lower third of the vagina and external genitalia.
- MRKH type 2 (20% of all cases) has more associated anomalies, particularly renal agenesis, than does MRKHS type 1.

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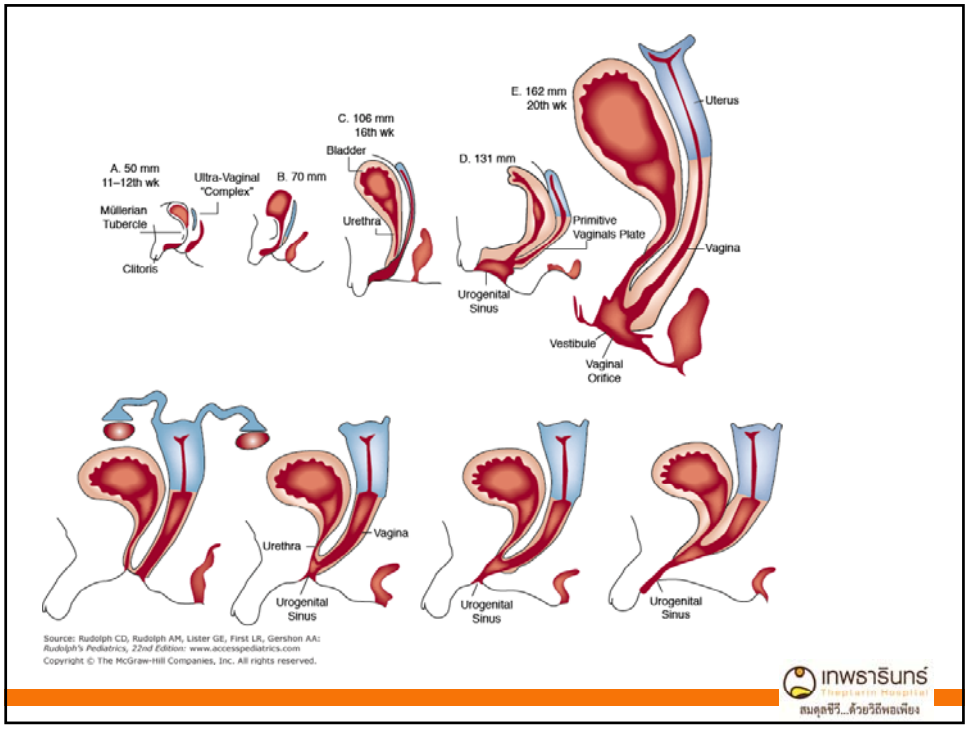


VCUAM classification	Oppelt 2012 (N = 284)	Rall 2015 (N = 346) [a]	Pan 2016 (N = 594)
Vagina			
5b			
Complete atresia	100		100
Cervix			
2b			
Bilateral atresia/aplasia	100		100
Uterus			
3			
Hypoplastic	0.7		0.2
4a			
Unilaterally rudimentary or aplastic	9.5		0.5
4b			
Bilaterally rudimentary or aplastic	84.2		98.5
Adnexae			
0			
Normal	87		96.1
1a			
Unilateral tubal malformation, ovaries normal	0.4		0.3
1b			
Bilateral tubal malformation, ovaries normal	2.5		0.2
2a			
Unilateral hypoplasia/gonadal streak	3.5		0.3
2b			
Bilateral hypoplasia/gonadal streak	0.7		0
3a			
Unilateral aplasia	2.1		0.8
3b			
Bilateral aplasia	0		0.5

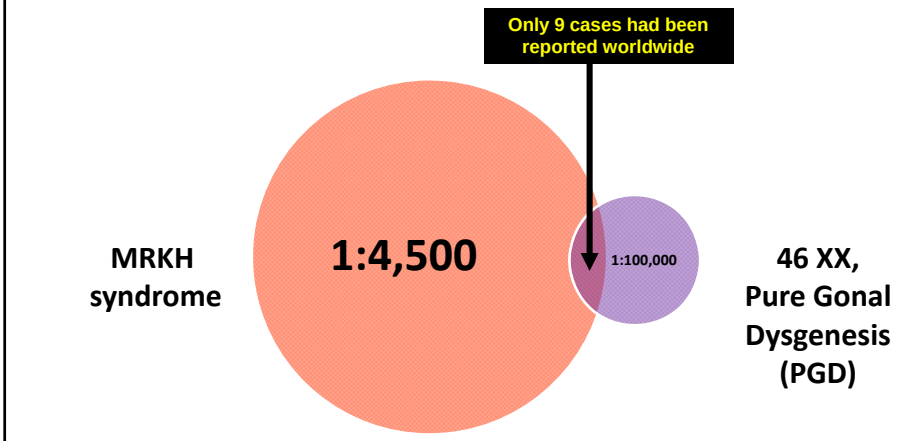
The Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome occurs in approximately 1:4,000 to 1:5,000 female live births

VCAUM (vagina, cervix, uterus, adnexae-associated malformation) classification

0.5% from 594 cases = 3 cases

Fertil Steril 2016;106:1047-8.

Coexistence of 2 rare diseases



The first reported case in 1976

An XX female with sexual infantilism, absent gonads, and lack of Müllerian ducts*

TABLE

EFFECT OF INTRAVENOUS ADMINISTRATION OF 100 μg SYNTHETIC LH-RH (Ayerst, ICI) ON SERUM LEVELS OF LH AND FSH IN PATIENT WITH ABSENT GONADS

	Time (min.)					
	0	15	30	60	120	180
LH	2650	4250	5000	5000	4875	5000
FSH	967	1275	1312	1312	1020	976

Normal response to LH–RH†

	Basal	Max
LH	127 ± 15	758 ± 170 (M ± SE)
FSH	212 ± 21	315 ± 20

* Values are expressed in ng/ml. of LER-907 (National Pituitary Agency, NIHMDD, USA).
† Taken from Zárate *et al* (1973).

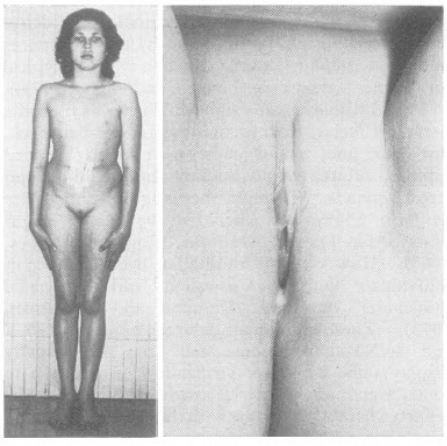


FIG. 1. FIG. 2.

FIG. 1. General appearance of the patient.
FIG. 2. The external genitalia show the normal infantile type.

J Med Genet 1976;13:68-9.

Previous reports of 46 XX PGD with MRKH

Year	Country	Age	Presentation	Associated features
Levinson 1976	Mexico	17	Primary amenorrhea	-
Oyer 1994	US	Newborn	Multiple anomalies at birth	Multiple anomalies
Gorgojo 2002	Spain	17	Primary amenorrhea	Subclinical hypothyroid
Marrakchi 2004	France	19	Primary amenorrhea	-
Bousfiha 2010	Morocco	19	Primary amenorrhea	-
Kebaili 2013	India	21	Primary amenorrhea	–
Shah 2013	India	21	Primary amenorrhea	-
Bhandari 2015	India	17	Primary amenorrhea	-
Manne 2016	India	20	Primary amenorrhea	Short stature, Scoliosis, AS

Status of DSD in THAILAND

Siriraj Intersex Care Team (Since 2006)

N = 191 from 2002-2014, only patients presented with ambiguous genitalia

Diagnosis and sex assignment of 191 DSD patients.

46,XY DSD (*N* = 163; 85.3%)	*n* (%)	M	F	46,XX DSD (*N* = 8; 4.2%)	*n* (%)	M	F	Sex chromosome DSD (*N* = 20; 10.5%)	*n* (%)	M	F
Unknown etiology	66 (40.5)	59	7	Ovotesticular DSD	5 (62.5)	3	2	MGD	13 (65.0)		
Developmental defect	59 (36.2)	58	1	Unknown etiology	2 (25.0)	0	2	45,X/46,XY	7	4	3
46,XY DSD	57	57	0	Common cloaca	1 (12.5)	0	1	45,X/46X,del(Y)	1	0	1
45,XY, rob (21:22)(q10:q10)	1	1	0					45,X/46,X,+marker	3	1	2
47,XY,+21	1	0	1					45,X/47,XYY	1	1	0
5-alpha-reductase deficiency	15 (9.2)	14	1					45,X/46,XY/47,XYY	1	0	1
Partial AIS	6 (3.7)	5	1					Ovotesticular DSD	3 (15.0)		
Complete AIS	2 (1.2)	0	2					46,XX/48,XXYY	2	1	1
MGD	5 (3.0)	5	0					46,XX/46,XY	1	1	0
46,XY DSD	4	4	0					Klinefelter syndrome 47,XXY	1 (5.0)	1	0
46,XY der(12)t(?;12)(?;q22)	1	1	0					Klinefelter syndrome variant 49,XXXXY	1 (5.0)	1	0
Testicular regression syndrome	3 (1.8)	1	2					47,XYY	1 (5.0)	1	0
Extrophy of cloaca	4 (2.5)	1	3					Developmental defect due to 46,X, inv (Y) (p11.2q11.23)	1 (5.0)	1	0
Pure gonadal dysgenesis	2 (1.2)	0	2								
Acampomelic campomelic dysplasia	1 (0.6)	0	1								

M male, F female.

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Southeast Asian J Trop Med Public Health 2017;48(Suppl 2):120-31.

Siriraj Intersex Care Team (Since 2006)

N = 191 from 2002-2014, only patients presented with ambiguous genitalia

As for the 46,XX DSD group, if the female patients with CAH were excluded, the most common diagnosis was ovotesticular DSD (62.5%); however, if they were included, the most common diagnosis would be CAH at 81%, similar to previous studies (Thyen *et al*, 2006; Mazen *et al*, 2008; Erdogan *et al*, 2011). In our study, all patients in the 46,XX DSD group were initially reared as females before their first visit, and were also assigned as females by the physicians.

46,XX DSD (*N* = 8; 4.2%)	*n* (%)	M	F
Ovotesticular DSD	5 (62.5)	3	2
Unknown etiology	2 (25.0)	0	2
Common cloaca	1 (12.5)	0	1

Southeast Asian J Trop Med Public Health 2017;48(Suppl 2):120-31.

Only 3 studies of DSD reports in Thai patients

Study		Nimkarn *et al*	Thyen *et al*	Mazen *et al*	Erdogan *et al*	Jaruratanasirikul and Engchuan	This study
Year		2002	2006	2008	2011	2014	2017
Country		Thailand	Germany	Egypt	Turkey	Thailand	Thailand
Number of patients		104[a]	80[b]	208	95	117	225[a]
Overall prevalence	46,XY DSD	46.2%	51.3%	65.9%	47.0%	17.1%	72.4%
	46,XX DSD	51.9%	28.8%	28.0%	25.0%	29.9%	18.7%
	Sex chromosome DSD	1.9%	12.5%[c]	0.96%	27.0%	53.0%	8.9%
Etiology in each classification	46,XY DSD	Suspected AIS or 5-alpha reductase deficiency 45.8%	AIS 31.7%	Suspected defect in androgen synthesis or action 60.0%[d]	Defect in androgen action 44.4%	Gonadal dysgenesis 35.0% Complete AIS 30.0%	Unknown 40.5% Developmental defect 36.2% 5-alpha reductase deficiency 9.2% AIS 4.9%
	46,XX DSD	CAH 96.3%	CAH 52.2%	CAH 75.4%	CAH 66.7%	CAH 88.6%	CAH 81.0% Ovotesticular DSD 11.9%
	Sex chromosome DSD	Ovotesticular DSD 100%	MGD 40.0%	MGD 100%	TS 80.7%	TS 69.4%	MGD 65.0% Ovotesticular DSD 15.0%

[a] Originally classified as true hermaphroditism, female pseudohermaphroditism, and male pseudohermaphroditism (Nimkarn *et al*, 2002).

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Southeast Asian J Trop Med Public Health 2017;48(Suppl 2):120-31.

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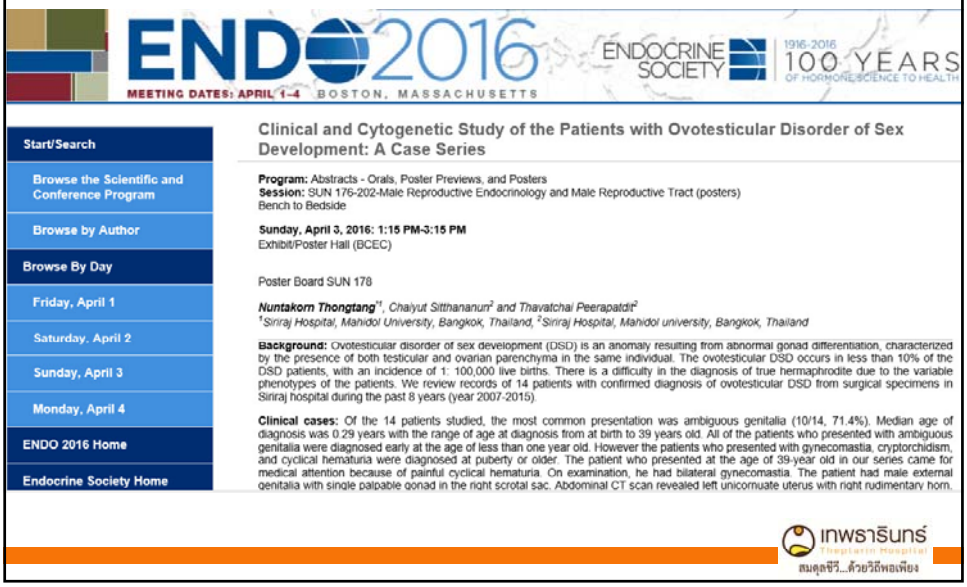
Ovotesticular DSD in 14 Thai patients



ENDO 2016 MEETING DATES: APRIL 1–4 BOSTON, MASSACHUSETTS

ENDOCRINE SOCIETY 1916-2016 100 YEARS OF HORMONE SCIENCE TO HEALTH

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Friday, April 1

Saturday, April 2

Sunday, April 3

Monday, April 4

ENDO 2016 Home

Endocrine Society Home

Clinical and Cytogenetic Study of the Patients with Ovotesticular Disorder of Sex Development: A Case Series

Program: Abstracts - Orals, Poster Previews, and Posters
Session: SUN 176-202-Male Reproductive Endocrinology and Male Reproductive Tract (posters)
Bench to Bedside

Sunday, April 3, 2016: 1:15 PM-3:15 PM
Exhibit/Poster Hall (BCEC)

Poster Board SUN 178

Nuntakorn Thongtang[1], *Chaiyut Sitthananun*[2] *and Thavatchai Peerapatdit*[2]
[1]*Siriraj Hospital, Mahidol University, Bangkok, Thailand,* [2]*Siriraj Hospital, Mahidol university, Bangkok, Thailand*

Background: Ovotesticular disorder of sex development (DSD) is an anomaly resulting from abnormal gonad differentiation, characterized by the presence of both testicular and ovarian parenchyma in the same individual. The ovotesticular DSD occurs in less than 10% of the DSD patients, with an incidence of 1: 100,000 live births. There is a difficulty in the diagnosis of true hermaphrodite due to the variable phenotypes of the patients. We review records of 14 patients with confirmed diagnosis of ovotesticular DSD from surgical specimens in Siriraj hospital during the past 8 years (year 2007-2015).

Clinical cases: Of the 14 patients studied, the most common presentation was ambiguous genitalia (10/14, 71.4%). Median age of diagnosis was 0.29 years with the range of age at diagnosis from at birth to 39 years old. All of the patients who presented with ambiguous genitalia were diagnosed early at the age of less than one year old. However the patients who presented with gynecomastia, cryptorchidism, and cyclical hematuria were diagnosed at puberty or older. The patient who presented at the age of 39-year old in our series came for medical attention because of painful cyclical hematuria. On examination, he had bilateral gynecomastia. The patient had male external genitalia with single palpable gonad in the right scrotal sac. Abdominal CT scan revealed left unicornuate uterus with right rudimentary horn.

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The largest series of 46 XX pure gonadal dysgenesis in Chinese patients

http://informahealthcare.com/gye
ISSN: 0951-3590 (print), 1473-0766 (electronic)
Gynecol Endocrinol, 2016; 32(12): 995–998

DOI: 10.1080/09513590.2016.1190820

GYNECOLOGICAL ENDOCRINOLOGY

Taylor & Francis

46 XX GONADAL DYSGENESIS

Clinical features and management of 33 patients with 46,XX pure gonadal dysgenesis

He Huang[1], Chun-Qing Wang[2], and Qin-Jie Tian[1]

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Abstract

The objective of the study is to summarize the clinical characteristics of 33 patients' cohort (46,XX pure gonadal dysgenesis, 46,XX PGD), discuss the management, and propose treatment suggestions. Patients' information, medical history, and medical records were obtained. All patients were closely followed up. At the time of diagnosis, the patients presented 19.53 ± 3.60 years old, 165 ± 6.49 cm height, breast development of Tanner stage I, and infantile female genitalia. High level of follicle-stimulating hormone (87.41 ± 21.50 mIU/mL) and LH (27.10 ± 8.47 mIU/mL) and low level of E2 (8.85 ± 6.13 pg/mL) were observed. Individualized hormone replacement therapy (HRT) was initiated after diagnosis. After 2 years of treatment, all patients had obvious breast development; the uterus showed (2.38 ± 0.60) × (1.38 ± 0.70) × (1.38 ± 0.55) cm growth. The incidence of osteopenia changed from 69.70% to 22.22% and that of osteoporosis changed from 18.18% to 0. Dysgerminoma was found in one patient. We concluded that gonadal dysgenesis in 46,XX PGD causes secondary sexual characteristic absence, tendency of taller, osteoporosis, infertility, and sexual health problems. There is minor chance of tumor occurrence for the patients. Optimal care including HRT and close follow-up are required.

Keywords

46,XX pure gonadal dysgenesis, hormone replacement therapy, hypergonadotrophins, hypogonadism, management

History

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Baseline data (N=33): Osteopenia 70%, Osteoporosis 18% Mean age at diagnosis 19.5 yrs

Table 1. Clinical characteristics of 46,XX PGD patients ($n = 33$).

Characteristics	Range	Mean ± standard deviation	Proportion
Age (years)	14–28	19.53 ± 3.60	
Height (cm)	150.0–180.0	165 ± 6.49	
Breast development (Tanner stage)			I 100% (33/33)
Pubic hair development (Tanner stage)			I 60.60% (20/33) II 36.36% (12/33) III 3.03% (1/33) IV and V 0
FSH (mIU/mL) (<10)*	47.75–130.21	87.41 ± 21.50	
LH (mIU/mL) (2.12–10.89)*	14.3–47.62	27.10 ± 8.47	
E2 (pg/mL) (27.0–122.0)*	0.0–29.0	8.85 ± 6.13	
P (ng/mL) (0.38–29.26)*	0.11–2.65	0.61 ± 0.54	
T (ng/mL) (0.10–0.75)*	0.02–0.86	0.30 ± 0.20	
Uterus length (cm)	1.3–3.3	2.28 ± 0.45	
Uterus width (cm)	1.0–2.8	1.71 ± 0.55	
Uterus thickness (cm)	0.5–2.1	1.27 ± 0.34	
BMD in the lumbar spine (L2–L4) (T-score)	−2.8—−0.78	−1.9 ± 0.75	
BMD in femural neck (T-score)	−3.8–0.2	−1.56 ± 0.97	
Osteopenia			69.70% (23/33)
Osteoporosis			18.18% (6/33)

*Reference range.

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Follow-up data at 2 years (N=18)
Osteopenia 22%, Osteoporosis 0%

Table 2. Follow-up of 46,XX PGD patients receiving treatment ($n = 18$).

	Initial treatment			2 Years after treatment			
Characteristics	Range	Mean ± standard deviation	Proportion	Range	Mean ± standard deviation	Proportion	Result change
Breast development (Tanner stage)			I 100% (18/18)			I and II 0 III 33.33% (6/18) IV 61.11% (11/18) V 5.56% (1/18)	
Pubic hair development (Tanner stage)			I 55.56% (10/18) II 44.44% (8/18) III, IV, and V 0			I, II, and V 0 III 1.11% (11/18) IV 38.89% (7/18)	
Uterus length (cm)	1.7–2.8	2.34 ± 0.39		3.8–5.6	4.72 ± 0.51		2.38 ± 0.60
Uterus width (cm)	1.0–2.7	1.71 ± 0.58		2.6–4.0	3.09 ± 0.36		1.38 ± 0.70
Uterus thickness (cm)	0.5–1.8	1.26 ± 0.37		2.0–3.0	2.64 ± 0.38		1.38 ± 0.55
BMD in the lumbar spine (L2–L4) (T-score)	−2.8–−0.78	−1.99 ± 0.50		−1.4–0.85	−0.20 ± 0.81		1.80 ± 0.84
BMD in femural neck (T-score)	−2.6–0.2	−1.76 ± 0.67		−0.9–0.6	−0.39 ± 0.62		1.37 ± 0.74
Osteopenia			66.67% (12/18)			22.22% (4/18)	
Osteoporosis			16.67% (3/18)			0	

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Candidate genes pathway in this case

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Genes involved in MRKH syndrome

Gene	Chromosome	Cytogenetic band	Beginning	End	Size	Orientation
WT1	11	11p13	32,409,321 bp from *pter*	32,457,176 bp from *pter*	47,856 bases	Negative filament
WNT4	1	1p36.23–p35.1	22,443,798 bp from *pter*	22,470,462 bp from *pter*	26,665 bases	Negative filament
PAX2	10	10q24	102,505,468 bp from *pter*	102,589,698 bp from *pter*	84,231 bases	Positive filament
HOXA7	7	7p15.2	27,193,335 bp from *pter*	27,196,296 bp from *pter*	2,962 bases	Negative filament
HOXA13	7	7p15.2	27,235,022 bp from *pter*	27,239,725 bp from *pter*	4,704 bases	Negative filament
LHX1	17	17q12	35,294,499 bp from *pter*	35,301,912 bp from *pter*	7,414 bases	Positive filament
HNF1B	17	17cen–q21.3	36,046,434 bp from *pter*	36,105,237 bp from *pter*	58,804 bases	Negative filament
KLHL4	X	Xq21.3	86,772,715 bp from *pter*	86,925,050 bp from *pter*	152,336 bases	Positive filament
SHOX	X	Xp22.33; Yp11.3	585,079 bp from *pter*	620,146 bp from *pter*	35,068 bases	Positive filament

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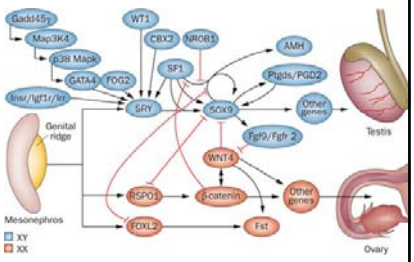
Genes involved in 46 XX pure gonadal dysgenesis

- **WNT4**
- **RSPO1,**
- **CATENIN gene defects**
- **SOX9 gene duplication**
- **FOXL2**
- **nucleoporin-107 mutations**



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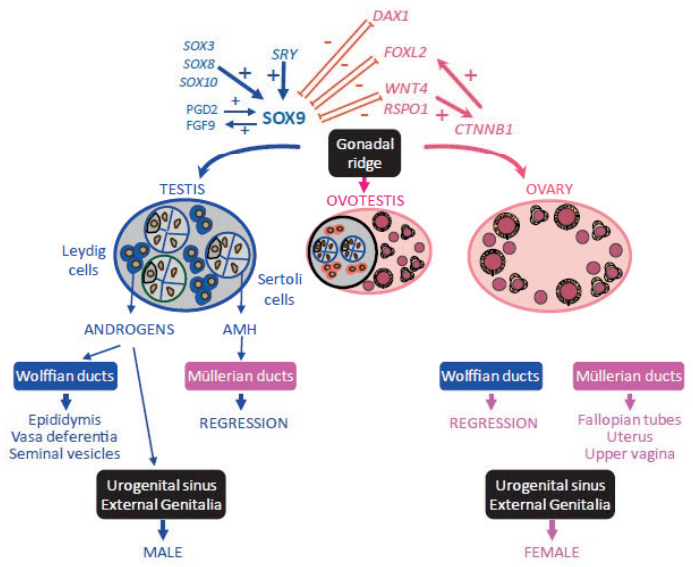

Take Home Messages

- The correct diagnosis of a child with a disorder of sex development (DSD) is crucial because impacts of long-term consequences from their initial diagnostic work-up and management could affect patients throughout lifespan.

- The management of a patient with a DSD is complex and requires skills beyond the capacity of any individual clinician.

THANK YOU FOR YOUR ATTENTION

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