THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

“59 Year-old Woman with Osteoporosis ”

Dr. Dickens does not have any relevant financial relationships with any commercial interests.

ENDORAMA:
59 Year-old Woman with Osteoporosis

Laura Dickens

February 9, 2017

Objectives

- Review the differential diagnosis and evaluation of primary amenorrhea
- Review the recommendations for estrogen replacement in females with hypogonadism and consequences of inadequate replacement.
- Discuss the effects of diet-induced weight loss on bone loss

Chief complaint

59 year old woman presents for evaluation of osteoporosis

HPI

- DEXA done for routine screening in 7/2015 showed osteoporosis
  - L1-L4 spinal T score -3.1
  - Total hip T score -1.7
- No history of fracture
- Adult height 5’5”, current height 5’5”
- Treated with Risedronate for about nine months, currently tolerating well with no adverse effects

Additional History

Past Medical History:

- Ovarian cancer (age 18) – treated with surgery and radiation
- Colon cancer x2 (age 35, 45) – treated with surgery x2, 5-FU and FOLFOX chemotherapy
- HTN
- Obesity *

Past Surgical History: Hysterectomy and BSO (age 18), sigmoid resection for colon cancer (age 35), right hemicolectomy for second colon cancer (age 45)

Additional History

Family History: Hip fracture in her mother around age 80, no known diagnosis of osteoporosis. Breast cancer in paternal cousin, colon cancer in paternal cousin. No family history of kidney stones.

Social Hx: Married, three adopted children. No tobacco, rare ETOH, no drugs

Medications:

- Aspirin 81mg daily
- Vitamin D3 1000 IU daily
- Losartan 25mg daily
- Phentermine-topiramate (Qsymia) 7.5-46mg daily
- Risedronate 150mg once monthly

Physical exam

VITALS: Temp 37.1, BP 134/90, HR 70, BMI 27.7

Constitutional: She appears well-developed and well-nourished. No distress.

HENT: Normocephalic and atraumatic. EOM are normal. Pupils are equal, round, and reactive to light. No scleral icterus.

Neck: Normal range of motion. Neck supple. No thyromegaly present.

Cardiovascular: Normal rate and regular rhythm. No murmur heard.

Pulmonary/Chest: Breath sounds normal. No respiratory distress. She has no rales (clear to auscultation). Normally developed breasts.

Abdominal: Well healed midline vertical incision. Soft. Bowel sounds are normal. She exhibits no distension and no mass. There is no tenderness.

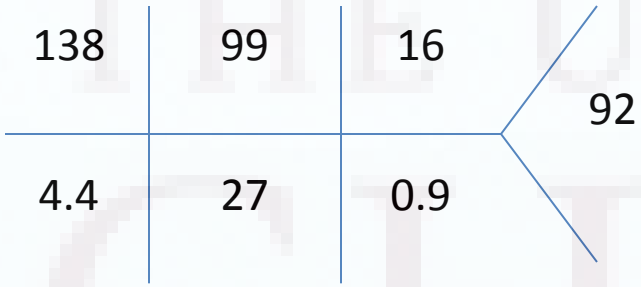
Musculoskeletal: Normal range of motion. She exhibits no edema and no tenderness. Kyphosis at the thoracolumbar junction

Neurological: She is alert. She has normal reflexes. No cranial nerve deficit. Coordination and gait are normal.

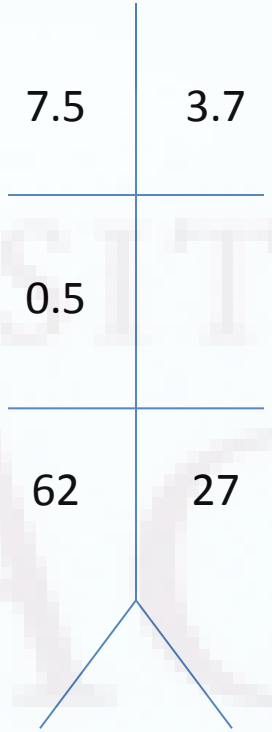
Skin: Skin is warm and dry. No rash noted. No erythema.

Psychiatric: She has a normal mood and affect. Her behavior is normal. Judgment normal.

Labs



Ca 9.7



25OH vitamin D = 33
PTH 41
GGT 93 (H)

Red flags: Osteoporosis risk factors

1. Estrogen deficiency?
2. Weight loss
3. Parental history of hip fracture

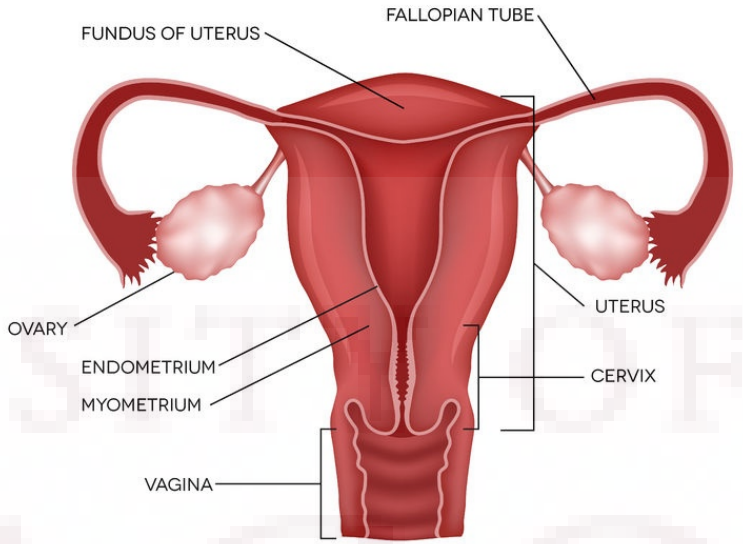
Pubertal and Gynecologic History

- Normal female external genitalia
- Patient recalls breast and pubic hair development at around age 12, similar to peers
- Growth normal, ultimately adult height normal
- Never underwent menarche
- At age 17 was evaluated for primary amenorrhea, found to have an “ovarian cyst”, and surgical removal was recommended

Ovarian Cancer History

- After surgery she was told they found ovarian cancer and “underdeveloped female organs”. She was told the surgeons “removed everything”
- Transferred care to UCMC, underwent additional exploratory surgery and radiation treatment for ovarian cancer
- On estrogen for one year, stopped due to concern about cancer risk

Primary Amenorrhea



- Definition:
  - Failure to menstruate by age 15 with normal secondary sexual characteristics
  - Failure to menstruate within 5 years of breast development if that occurs before age 10
  - *Age 13 with absent secondary sexual characteristics and no menses

Fertil Steril. 2008 Nov;90(5 Suppl):S219-25.
Image: https://www.endocrineweb.com/endocrinology/overview-ovaries

Differential Diagnosis of Primary Amenorrhea

Table 1. Major Causes of Amenorrhea

Outflow tract
- Congenital
  - Complete androgen resistance
  - Imperforate hymen
  - Müllerian agenesis
  - Transverse vaginal septum
- Acquired
  - Asherman syndrome (intrauterine synechiae)
  - Cervical stenosis

Primary ovarian insufficiency
- Congenital
  - Gonadal dysgenesis (other than Turner syndrome)
  - Turner syndrome or variant
- Acquired
  - Autoimmune destruction
  - Chemotherapy or radiation

Pituitary
- Autoimmune disease
- Cocaine
- Cushing syndrome
- Empty sella syndrome
- Hyperprolactinemia
- Infiltrative disease (e.g., sarcoidosis)
- Medications
  - Antidepressants
  - Antihistamines
  - Antihypertensives
  - Antipsychotics
  - Opiates
- Other pituitary or central nervous system tumor
- Prolactinoma
- Sheehan syndrome

Hypothalamic
- Eating disorder
- Functional (overall energy deficit)
- Gonadotropin deficiency (e.g., Kallmann syndrome)
- Infection (e.g., meningitis, tuberculosis, syphilis)
- Malabsorption
- Rapid weight loss (any cause)
- Stress
- Traumatic brain injury
- Tumor

Other endocrine gland disorders
- Adrenal disease
- Adult-onset adrenal hyperplasia
- Androgen-secreting tumor
- Chronic disease
- Constitutional delay of puberty
- Cushing syndrome
- Ovarian tumors (androgen producing)
- Polycystic ovary syndrome (multifactorial)
- Thyroid disease

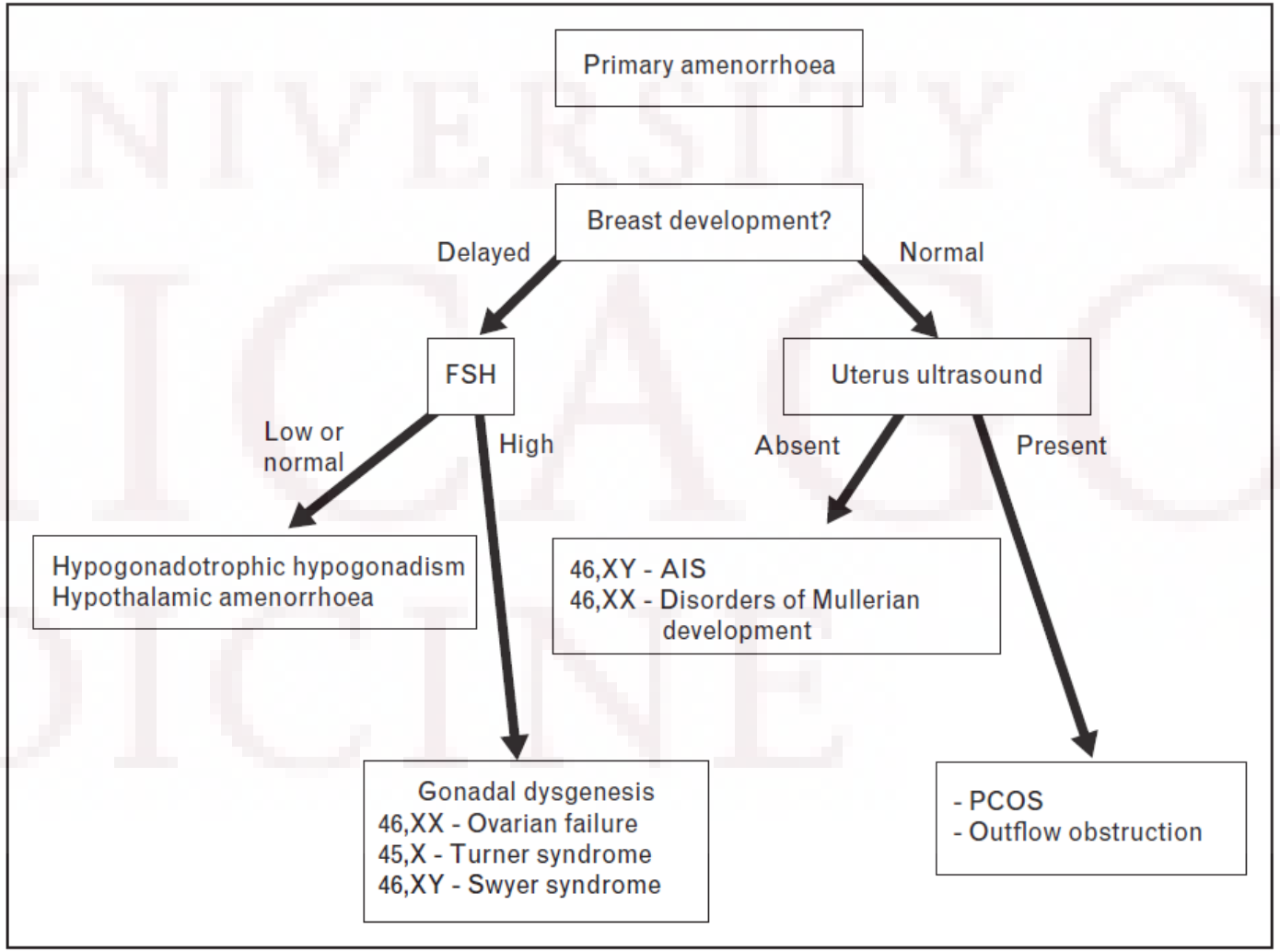
Physiologic
- Breastfeeding
- Contraception
- Exogenous androgens
- Menopause
- Pregnancy

Information from references 1, 2, and 4 through 11.

Klein et al. Am Fam Physician. 2013 Jun 1;87(11):781-8.

Primary Amenorrhea Evaluation

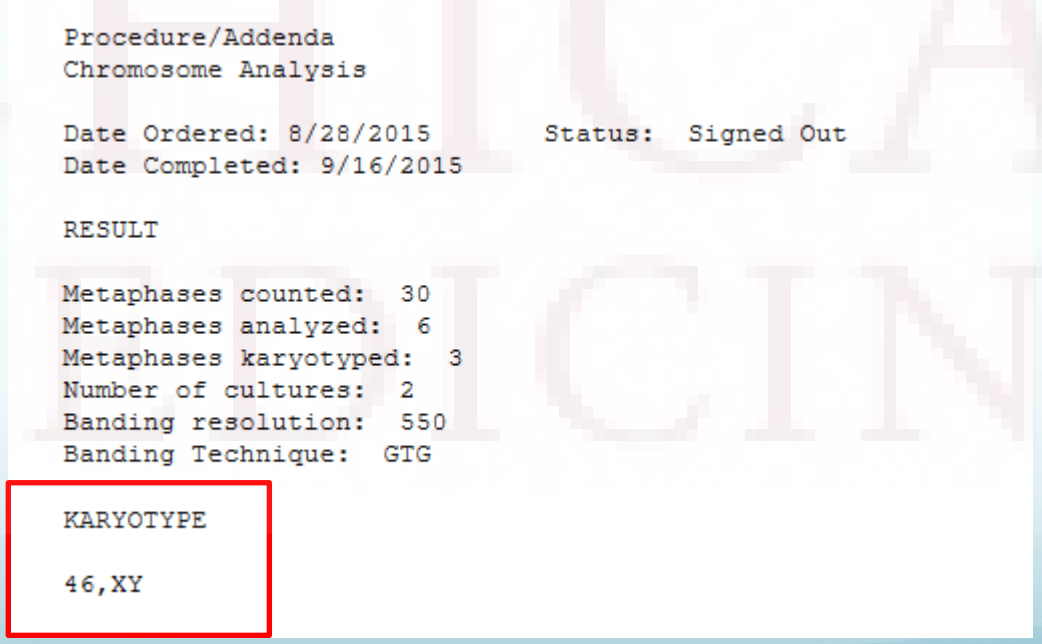
- Evaluation:
  - Physical exam – abnormal in 15% of primary amenorrhea
  - Labs – pregnancy test, prolactin, TSH, FSH
  - Ultrasound



King et al. Curr Opin Endocrinol Diabetes Obes. 2014 Dec;21(6):504-10.

More history…

- After being diagnosed with two separate colon cancers (age 35 and 45) patient was referred to the Cancer Risk Clinic for genetic testing



Procedure/Addenda
Chromosome Analysis

Date Ordered: 8/28/2015 Status: Signed Out
Date Completed: 9/16/2015

RESULT

Metaphases counted: 30
Metaphases analyzed: 6
Metaphases karyotyped: 3
Number of cultures: 2
Banding resolution: 550
Banding Technique: GTG

KARYOTYPE

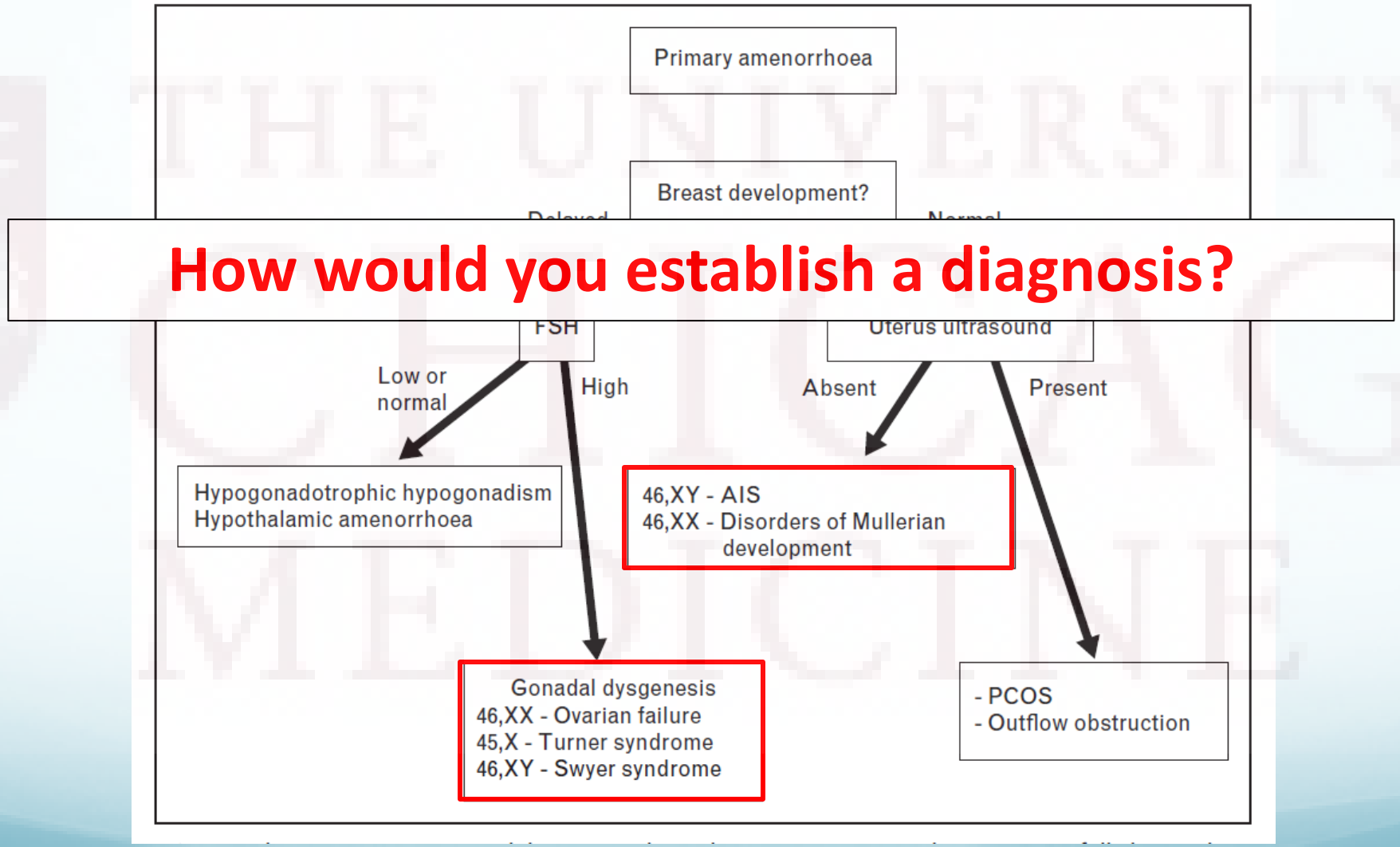
46,XY

Differential: Phenotypic female with 46XY

- 46,XY gonadal dysgenesis
- Complete androgen insensitivity syndrome
- Defect in androgen synthesis

Source: Up To Date. Causes of primary amenorrhea.

Primary Amenorrhea Evaluation



King et al. Curr Opin Endocrinol Diabetes Obes. 2014 Dec;21(6):504-10.

Additional Genetic Testing

Human Genetics Report

46,XY DSD / Complete Gonadal Dysgenesis Sequencing Panel

RESULT: c.331C>T (p.Gln111*) pathogenic sequence change identified in the SRY gene in the hemizygous state.

INTERPRETATION: This pathogenic sequence change is the likely cause of this patient's phenotype.

SUGGESTIONS:

Truncating sequence changes in SRY are typically de novo. For confirmed de novo sequence changes, the risk to this patient's father is less than 1% with each pregnancy, based on the theoretical risk of germline mosaicism.

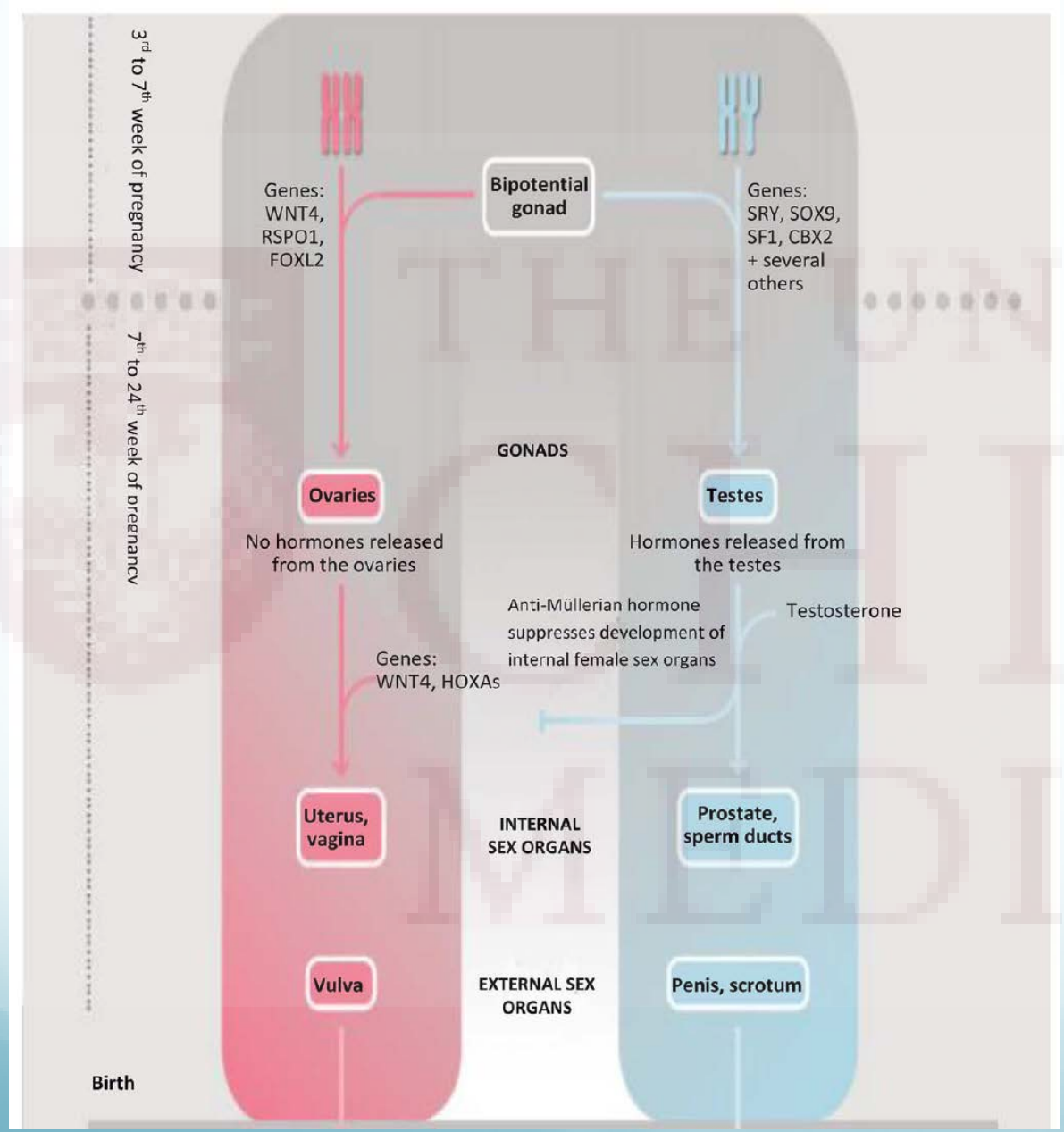
The GenomeConnect patient registry collects de-identified genetic and health information to advance knowledge of genetic variants, and is available for this patient. To learn more about this research opportunity please visit genomeconnect.org.

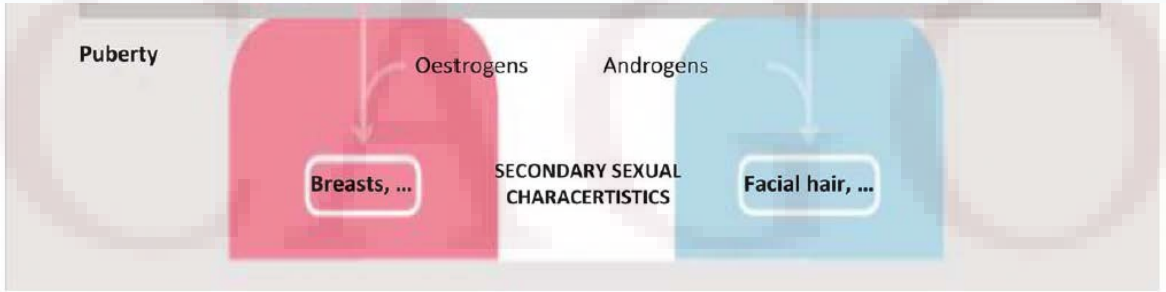
Genetic counseling is recommended to explain the implications of this result. Please call our genetic counselor with any questions regarding these results.

DETAILS: DNA sequence analysis of the SRY gene demonstrated a sequence change, c.331C>T, which results in the creation of a premature stop codon at amino acid position 111, p.Gln111*. This pathogenic sequence change is predicted to result in an abnormal transcript, which may be degraded, or may lead to the production of a truncated SRY protein with potentially abnormal function. This sequence change has not been described in patients with SRY-related disorders, however different truncating sequence changes in the same protein domain of SRY have been described in patients with 46,XY Complete Gonadal Dysgenesis (Hawkins, 1992; Giuffr8, 2004). This pathogenic sequence change is the most likely cause of this patient's phenotype.

Sequencing of all other genes included in the 46,XY DSD/CGD Sequencing panel was completed, and was normal. A list of synonymous or benign sequence changes, if identified for this patient, is available upon request. Our interpretation is based on the current understanding of the genetics of disorders of sex development.

Embryonic Gonadal Development





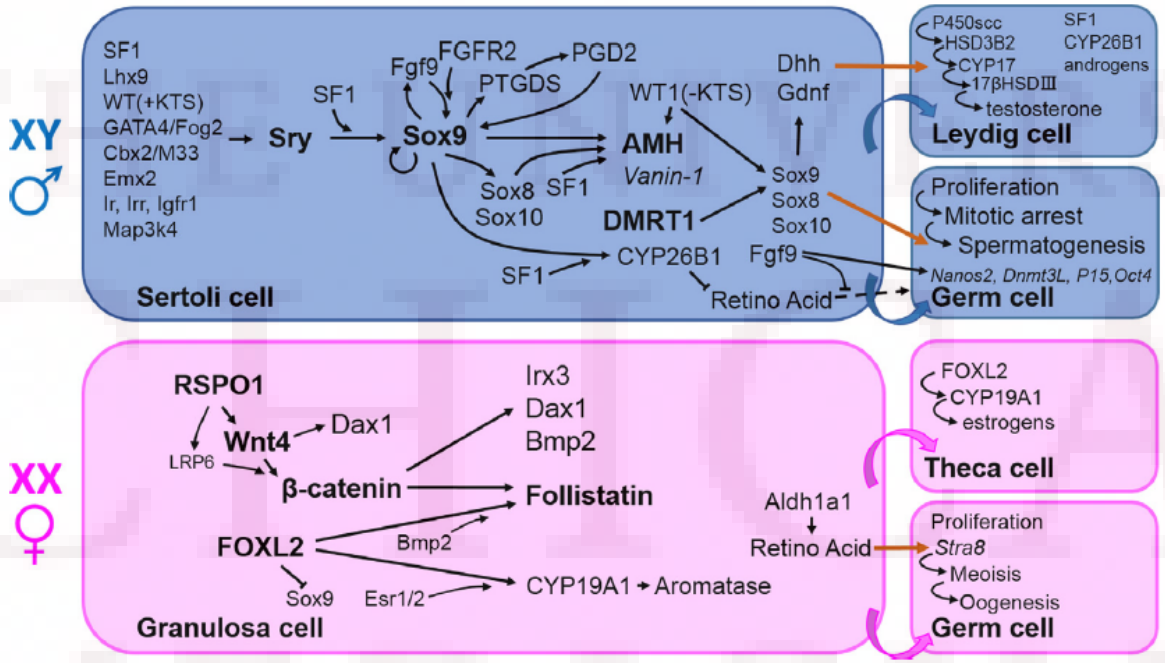
Eid et al. Birth Defects Res C Embryo Today. 2016 Dec;108(4):365-379.

Disorders/Differences of Sexual Differentiation

Genes involved in testis development			
DHH	Signaling molecule	*Dhh−/−* disruption of testis cord formation due to abnormal peritubular tissue	LOF: XY partial or complete gonadal dysgenesis
DMRT1	TXNF	*Dmrt1−/−* impaired testis development (P2) and loss of Sertoli and germ cells	Hemizygousity: XY gonadal dysgenesis
			Deletion of 9p24 (including *DMRT1*): XY gonadal dysgenesis (varying degrees)
ATRX	Chromatin remodeling	*Atrx−/−* embryonic lethal Condtional Atrx – in Sertoli cells: small testes and discontinuous tubules	Dysgenetic testis
ARX	TXNF	*Arx−/−* Leydig cell differentiation failure	Dysgenetic testis, ambiguous genitalia
GATA4	TXNF	*Gata4−/−* embryo lethality (E7–E9.5)	LOF: XY ambiguous genitalia or reduced phallus length
		Gata4 [ki] sever anomalies of testes	Deletion downstream of *GATA4* (also including *NEIL2*): XY complete gonadal dysgenesis combined with adrenal hypoplasia congenital (CAH)
MAP3K1	Kinase	[b](dependent on genetic background)	XY partial or complete gonadal dysgenesis
NR5A1	Nuclear receptor/TXNF	*Nr5a1−/−* fail to develop bi-potential gonad	Embryonic testicular regression syndrome; XY gonadal dysgenesis
			XX premature ovarian failure (POF)
NR0B1	Nuclear receptor	XY impaired testis cord formation and spermatogenesis (dependant on genetic background)	LOF/Deletions: Congenital adrenal hypoplasia (CAH)
			Duplications: XY gonadal dysgenesis with disorganized testis cords and hypogonadotropic hypogonadism
WT1	TXNF	*Wt1−/−* mice fail to develop bi-potential gonad	Denys-Drash, WAGR, and Fraiser syndromes
WWOX	Reductase	*Wwox−/− Leydig cell hypoplasia*	Dysgenetic testis
TSPYL1	Chromatin modifier	[b]	Dysgenetic testis and ambiguous genitalia
SOX9	TXNF	*Sox9−/−* XY male-to-female sex reversal	LOF: XY gonadal dysgenesis combined with campomelic dysplasia (CD)
		Deletion upstream of *Sox9*: XX female-to-male sex reversal	GOF: 46,XX DSD
		Conditional knockout: XY ovarian development	Duplications including *SOX9*: XX testicular DSD
		XX testicular development	Translocation upstream of SOX9: XY ovotesticular DSD
			Deletion upstream of SOX9: XY ovarian DSD with acampomelic campomelic dysplasia (ACD), gonadal dysgenesis, female or ambiguous external genitalia
MAMLD1	Transcriptional co-activator	b	Hypospadias
SRY	TXNF	*Sry* – XY male-to-female sex reversal	LOF: XY ovarian DSD
		Sry translocation: XX female-to-male sex reversal	GOF/Translocation: XX testicular DSD
CBX2	TXNF	Testes **0%** Ovaries **50%** Testis + 1x Ovary (NOT ovotestis) **25%** Undefined **25%** INTERNAL GENITALIA Female (Bipartite Uterus) **75%** Female + Male (Monopartite Uterus + Deferens) **25%** Male (Deferentes) **0%** EXTERNAL GENITALIA Male **16.6%** Female **33.3%** Intersex **50%** FERTILITY All animals are STERILE	-LOF XY: Ovary-like gonads with oocytes -Female external genitalia -Müllerian +
Genes involved in ovary development			
FOXL2	TXNF	*Foxl2−/−* Premature ovarian failure	BPES and premature ovarian failure (POF)
		Foxl2−/−, *Wnt4−/−* XX female-to-male sex reversal	
RSPO1	Signaling molecule	XX partial female-to-male sex reversal, similar to *Wnt4−/−* and conditional *Ctnnb1* knockout	XX testicular and ovotesticular DSD
			Duplication of 1p (including *WNT4* and *RSPO1*): XY gonadal dysgenesis (GOF)
WNT4	Signaling molecule	XX Müllerian duct agenesis, testosterone synthesis, and coelomic vessel formation	Duplication of 1p (including *WNT4* and *RSPO1*): XY gonadal dysgenesis (GOF) (male-to-female sex reversal)
			LOF: XX Müllerian duct agenesis, testosterone synthesis, and coelomic vessel formation

Eid et al. Birth Defects Res C Embryo Today. 2016 Dec;108(4):365-379.

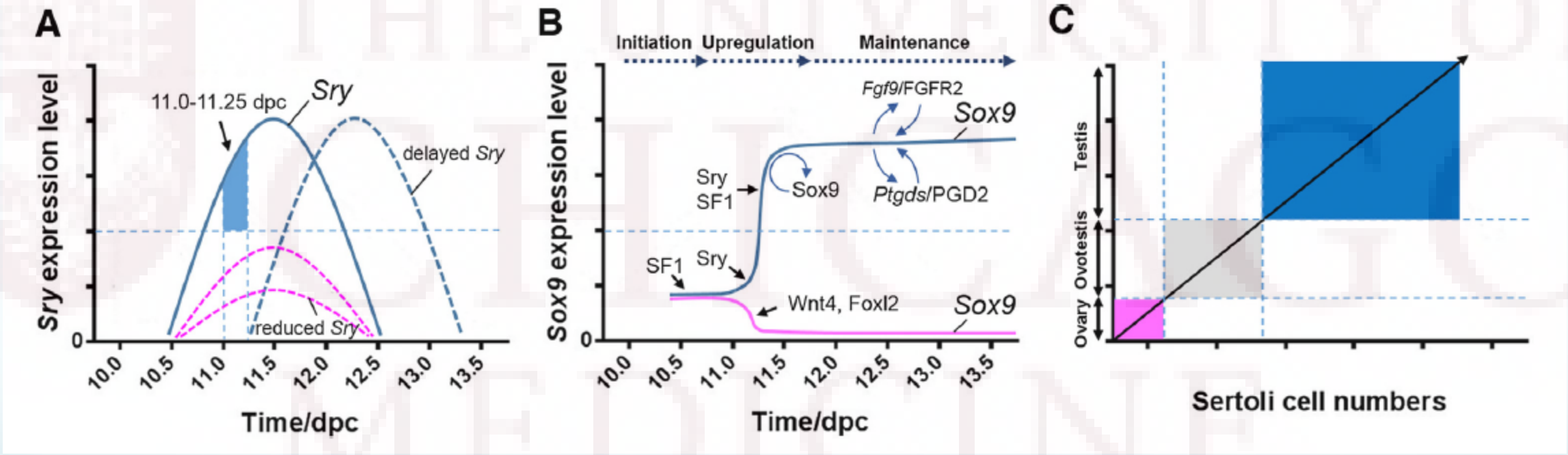
SRY gene



- Mammalian Y-chromosomal testis-determining gene
- Regulates Sox9 expression in Sertoli cell precursors to activate testis-specific genes and lead to testis determination

She et al. Semin Cell Dev Biol. 2016 Jul 29. pii: S1084-9521(16)30236-1.

Timing and level of Sry and Sox9 are critical



She et al. Semin Cell Dev Biol. 2016 Jul 29. pii: S1084-9521(16)30236-1.

XY Gonadal Dysgenesis – Swyer Syndrome

- Pure or complete gonadal dysgenesis
- Incidence of one in 80,000 births
- *Genetics:* 10–20% of women with Swyer syndrome have a deletion in the DNA-binding region of the SRY gene
- *Clinical presentation:* Typically presents with primary amenorrhea and delayed puberty. Phenotypically female with unambiguous female genitalia and normal Mullerian structures

King et al. Curr Opin Endocrinol Diabetes Obes. 2014 Dec;21(6):504-10.

Swyer Syndrome

- Diagnosis
  - Labs: LH, FSH, prolactin, TSH, SHBG, estradiol, testosterone, androstenedione
  - Peripheral blood karyotype
  - Sequencing of causative genes
  - Consider tumor markers: AFP, b-HCG, LDH, placental alk phos
- Imaging:
  - Transabdominal pelvis ultrasound

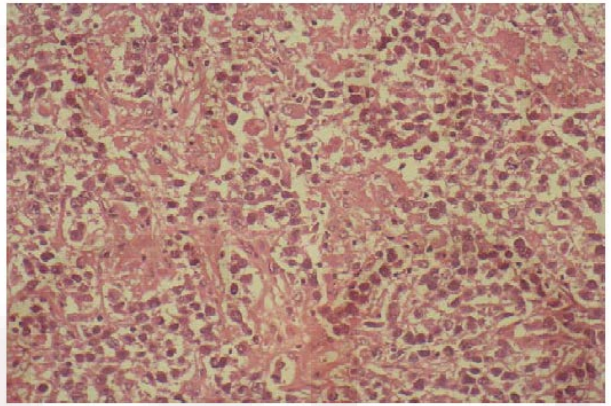


Fig. 1 Gonadoblastoma.

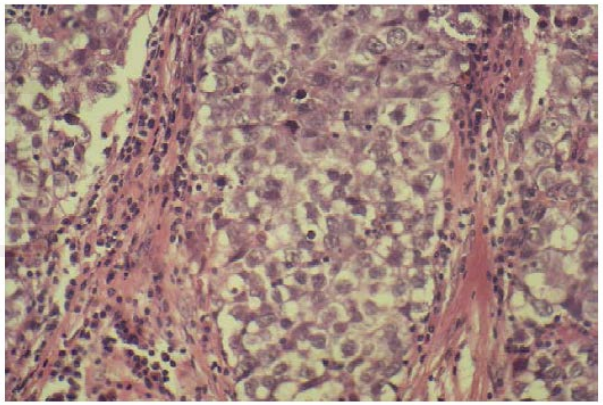


Fig. 2 Dysgerminoma.

King et al. Curr Opin Endocrinol Diabetes Obes. 2014 Dec;21(6):504-10.

Swyer Syndrome

Treatment

- Bilateral gonadectomy at the time of diagnosis
  - Risk of gonadoblastoma (benign germ cell neoplasia) 15 - 35%
  - Can be precursor to germ cell malignancy, dysgerminoma most commonly
- Hormonal treatment – to be discussed
- Fertility? Possible with egg donation by anecdotal report
- Psychosocial support

King et al. Curr Opin Endocrinol Diabetes Obes. 2014 Dec;21(6):504-10.

Outstanding questions

1. How did normal breast development occur?
2. How should estrogen replacement have been managed?

Breast development?

- Case series of 8 patients with Swyer syndrome s/p gonadectomy
- Six patients (75%) had gonadal tumors: gonadoblastoma (3), dysgerminoma (1), gonadoblastoma + dysgerminoma (2)

Table 1 Secondary sex features in patients with Swyer syndrome

Patient no.	Age (y)	Histology	B	P	Follicular apparatus
1	17	Gonadoblastoma	4	4	None
2	17	Gonadoblastoma	3	3	None
3	16	Gonadoblastoma	2	3	None
4	13	Gonadoblastoma + dysgerminoma	3	4	None
5	18	Gonadoblastoma + dysgerminoma	3	3	None
6	15	Dysgerminoma	3	4	None
7	17	Dysgenetic gonads	2	3	None
8	18	Dysgenetic gonads	1	4	None

B indicates breast according to Tanner stage; P, pubic hairs according to Tanner stage.

Zieliñska et al. J Pediatr Surg. 2007 Oct;42(10):1721-4.

Breast development?

Table 4 Hormone concentrations in patients with Swyer syndrome

Patient no.	Age (y)	Histology	FSH (mU/mL)	LH (mU/mL)	E_2 (pg/mL)	T (ng/mL)
1	17	Gonadoblastoma	64.4	66.5	40.5	
2	17	Gonadoblastoma	68.0	45.0	30.0	
3	16	Gonadoblastoma	82.4	52.1	–	5.8
4	13	Gonadoblastoma + dysgerminoma	95.5	38.0	25.0	
5	18	Gonadoblastoma + dysgerminoma	89.8	31.5	81.0	
6	15	Dysgerminoma	40.1	27.1	2.3	
7	17	Dysgenetic gonads	72.2	48.5	18.0	
8	18	Dysgenetic gonads	98.0	38.0	7.3	

FSH indicates follicle-stimulating hormone; LH, luteinizing hormone.

- Three gonadoblastomas had hormonal activity:
  - 2 estrogen-producing -> associated with higher Tanner stage breast development
  - 1 testosterone-producing -> associated with clitoromegaly

Zieliñska et al. J Pediatr Surg. 2007 Oct;42(10):1721-4.

Estrogen replacement?

- General recommendations for Swyer syndrome
  - Low dose estrogen to mimic normal puberty and breast development
  - Cyclic estrogen and progesterone throughout life until age 50
  - Estrogen therapy vital for bone mass

- What are the recommendations and evidence for other disorders with premature gonadal insufficiency (Turner's syndrome)?
- Does the diagnosis of ovarian cancer change the approach?

King et al. Curr Opin Endocrinol Diabetes Obes. 2014 Dec;21(6):504-10.

Estrogen Therapy in Turner's Syndrome

TABLE 4. Ovarian hormone replacement treatment in TS

Age (yr)	Age-specific suggestions	Comments
10–11	Monitor for spontaneous puberty by Tanner staging and FSH level	Low-dose estrogen treatment may not inhibit GH-enhanced growth in stature
12–13	If no spontaneous development and FSH elevated, begin low dose E2	Equivalent initial E2 doses: depot (im) E2, 0.2–0.4 mg/month; transdermal E2, 6.25 μg daily[a]; micronized E2, 0.25 mg daily by mouth
12.5–15	Gradually increase E2 dose over about 2 yr (*e.g.* 14, 25, 37, 50, 75, 100, 200 μg daily via patch) to adult dose	Usual adult daily dose is 100–200 μg transdermal E2, 2–4 mg micronized E2, 20 μg EE2, 1.25–2.5 mg CEE
14–16	Begin cyclic progesterone treatment after 2 yr of estrogen or when breakthrough bleeding occurs	Oral micronized progesterone best option at present; usual adult dose is 200 mg/d on d 20–30 of monthly cycle or d 100–120 of 3-month cycle
14–30	Continue full doses at least until age 30 because normally estrogen levels are highest between age 15 and 30 yr	Some women may prefer using oral or transdermal contraceptive for HRT; monitor endometrial thickness
30–50	The lowest estrogen dose providing full protection *vs.* osteoporosis is 0.625 CEE or equivalent	Monitor osteoporosis risk factors, diet, exercise; obtain BMD and begin regular screening mammography by age 45 yr
>50	Decision on estrogen use based on same considerations as for other postmenopausal women	New HRT options are appearing, and these recommendations may need updating in near future

CEE, Conjugated equine estrogens; E2, estradiol; EE2, ethinyl estradiol; HRT, hormone replacement treatment.
[a] The lowest-dose commercially available E2 transdermal patches deliver 14 and 25 μg daily; it is not established whether various means of dose fractionation (*e.g.* administering a quarter patch overnight or daily or administering whole patches for 7–10 d per month) are equivalent.

- BMD recommended at the initial visit in the adult clinic with follow up depending on results

Bondy et al. J Clin Endocrinol Metab. 2007 Jan;92(1):10-25.

Effect of (no) ERT in Turner's Syndrome

TABLE 2. ERT AND LUMBAR SPINE BMD IN TURNER SYNDROME

Characteristic	*ERT ≥75%* (n = *34*)	*ERT <75%* (n = *16*)	p *value*
Age (years)	42 ± 1.4	42 ± 2.1	0.8
Height (cm)	144.2 ± 1.1	145.2 ± 1.9	0.6
Weight (kg)	54 (36–150)	61 (40–120)	0.23[a]
BMI (kg/m^2)	25 (18–47)	29 (20–54)	0.04[a]
Years ERT taken	25 ± 1.5	8 ± 1.6	<0.0001
Eating disorders, *n* (%)	5/34 (15)	1/16 (6)	0.37
DXA LS-AP BMD (g/cm^2)	0.91 ± 0.02	0.75 ± 0.03	<0.0001
DXA LS-AP Z-score	−0.9 ± 0.2	−1.9 ± 0.3	0.002
QCT LS BMD (mg/cm^3)	137 ± 3.8	109 ± 6.8	0.0005
QCT LS Z-score	−0.6 ± 0.2	−2 ± 0.3	0.0001
Diagnosis of osteoporosis, *n* (%)[b]	0/34 (0)	6/16 (38)	0.0004

[a]Rank-sum test.

[b]The diagnosis of osteoporosis according to WHO criteria (T-score ≤ −2.5 SDs) is based on DXA data. DXA, however, is an areal method that tends to underestimate BMD in small people. Therefore, we corrected the measured areal BMD values for body surface area as previously described[8] and then calculated T-scores using the corrected areal BMD and normative data from the manufacturer.

Hanton et al. J Womens Health (Larchmt). 2003 Dec;12(10):971-7.

Estrogen Therapy in Ovarian Cancer Survivors

- RCT in 1999 randomized patients with invasive epithelial carcinoma to estrogen replacement (ERT) or no ERT
- Compliance was good
- No difference in disease free or overall survival

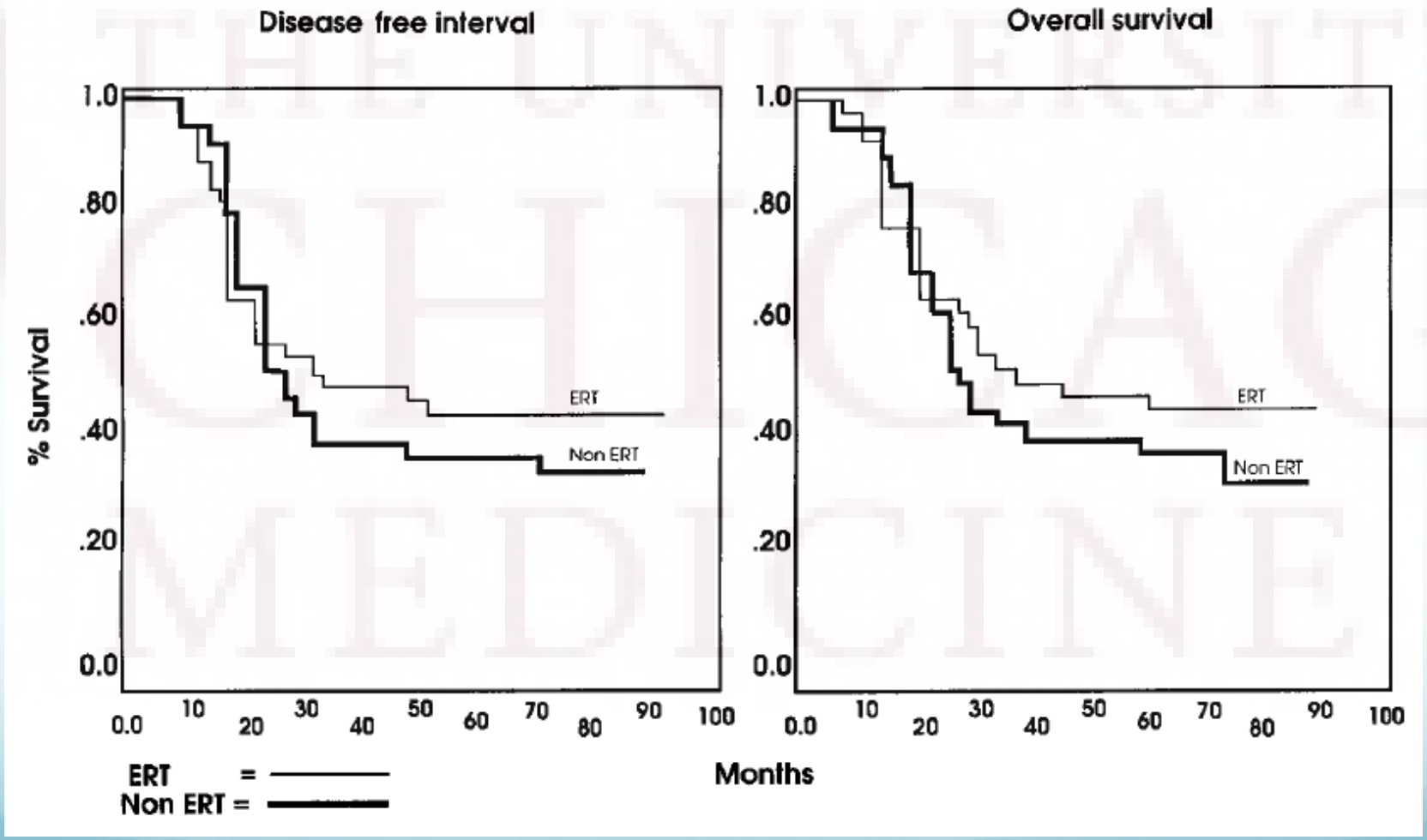
TABLE 2
Occurrence of Relapses According to Stage, Differentiation, and Debulking Surgery

	No. (%) of patients		
	ERT	Non-ERT	*P* value
Stage			
I	1 (14%)	2 (22%)	
II	2 (22%)	1 (25%)	
III	25 (66%)	33 (72%)	N.S.
IV	4 (80%)	5 (71%)	N.S.
Differentiation			
Well differentiated	7 (22%)	8 (19.5%)	N.S.
Moderately	9 (28%)	8 (19.5%)	N.S.
Poorly	16 (50%)	25 (61%)	N.S.
Surgery			
Optimal	19 (43%)	22 (48%)	N.S.
Suboptimal	13 (86%)	19 (95%)	N.S.

ERT: estrogen replacement therapy; N.S.: not significant.

Guidozzi et al. Cancer. 1999 Sep 15;86(6):1013-8.

Estrogen Therapy in Ovarian Cancer Survivors



Guidozzi et al. Cancer. 1999 Sep 15;86(6):1013-8.

In summary

- Hindsight is 20/20
- Patient would have benefitted from ERT, or at least further discussion about risks and benefits
- BMD should have been evaluated sooner

Psychosocial impact of diagnosis

- Patient was informed of her diagnosis by a genetic counselor over the phone
- She had many questions…
  - Was I supposed to be a man?
  - What do I tell my husband?
- Counseling recommended

Any experiences with delayed diagnosis of DSD?

Back to the reason for her visit – Osteoporosis

Additional labs

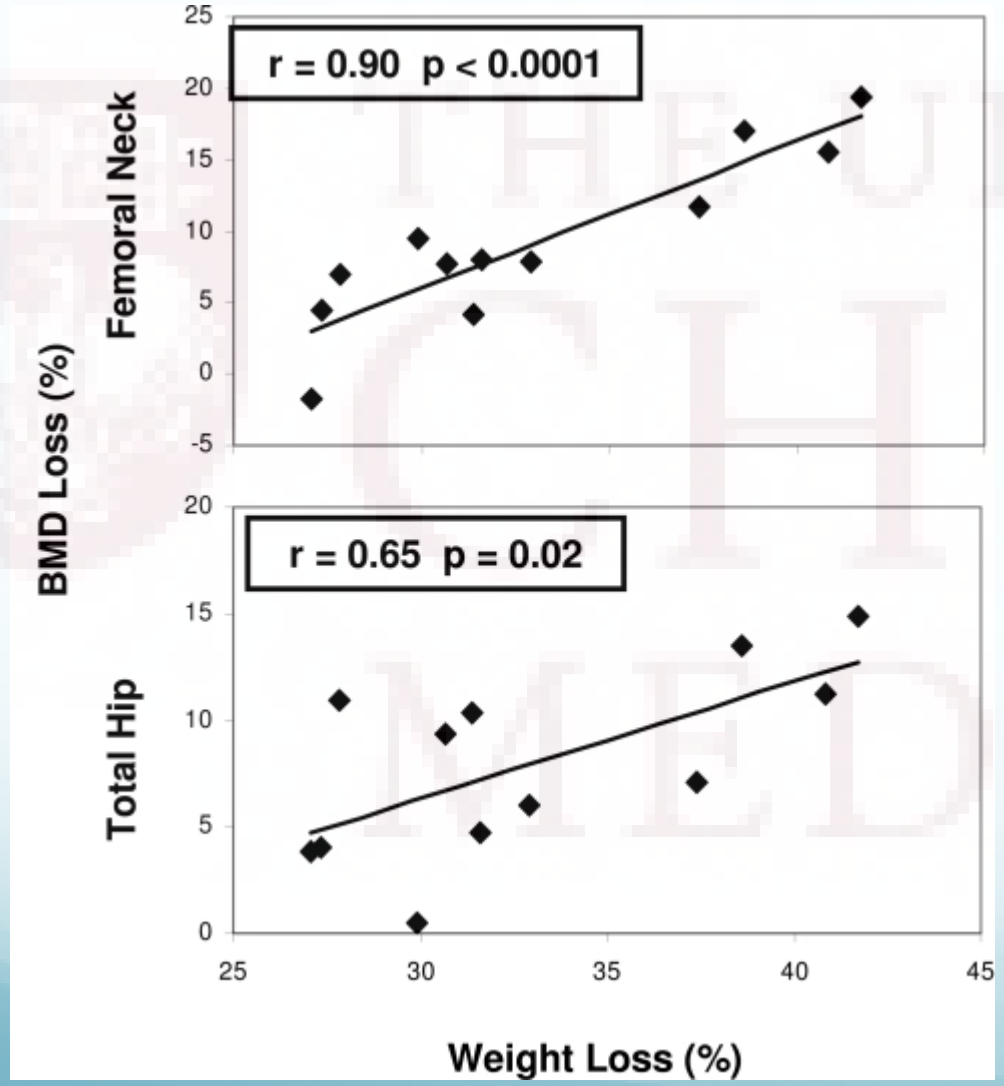
- Estradiol <10
- Testosterone
  - Free = 1
  - Total = 12
- BSAP 21

Repeat DEXA

- L1-L4 spinal T score -2.7 (decreased 5.5% from 7/2015)
- Total hip T score -2.0 (decreased 6.8% from 7/2015)

Why is she still losing bone?

Bone Loss after Bariatric Surgery



- 23 patients who underwent RYGB followed for one year
- BMD, PTH, 25-OH vitamin D, osteocalcin, and urinary N-telopeptide
- Significant decreases in BMD
  - Femoral neck 9.2% decrease
  - Total hip 8.0% decrease
- Strong correlation between extent of weight loss

Fleischer et al. J Clin Endocrinol Metab. 2008 Oct;93(10):3735-40.

Diet-induced Weight Loss and Bone Loss

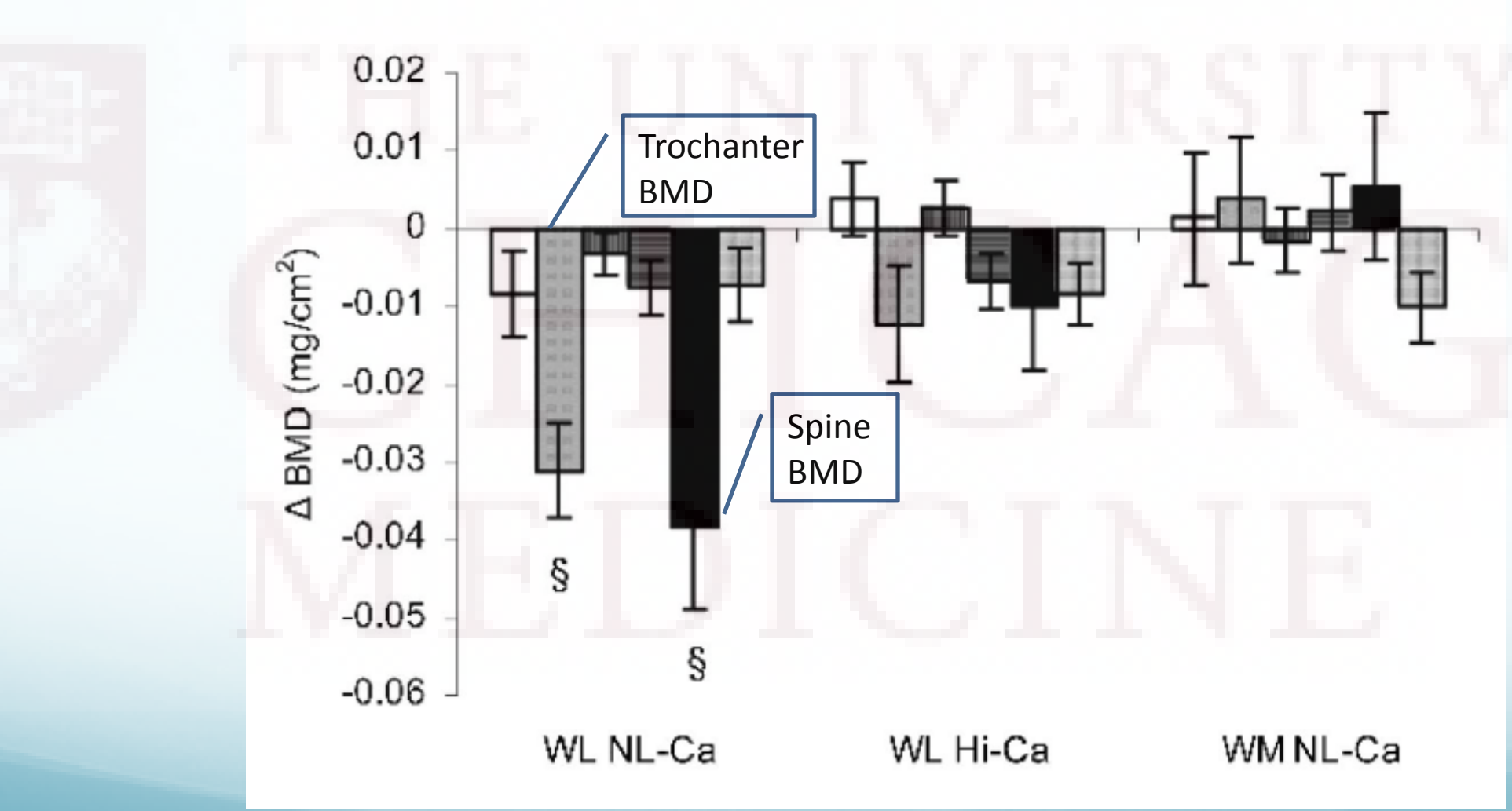
- 66 women
  - 47 weight loss (WL)
  - 19 weight maintenance (WM)
- WL group randomized to normal or high Ca intake (supp + MVI + diet)
- BMD at baseline and 6 months

Bone and Body Composition Measurements at Baseline and Percent Changes After 6 Months of WM or WL Ca Intake (NL-Ca, 1.0 g/day; Hi-Ca, 1.8 g/day)*

	WL Hi-Ca (n= 23)		WL NL-Ca (n= 24)		WM NL-Ca (n= 19)		
	Baseline	Change (%)	Baseline	Change (%)	Baseline	Change (%)	p Value§
Body weight (kg)	71.3 ± 6.4	−8.7 ± 3.9†¶	73.8 ± 6.9	−10.0 ± 3.9†¶	69.6 ± 7.8	0.6 ± 1.9	<0.0001
Lean mass (kg)	38.4 ± 4.6	−2.8 ± 4.2†	38.3 ± 2.9	−3.6 ± 3.8†	37.7 ± 3.7	−1.5 ± 3.2‡	0.2226
Fat mass (kg)	28.9 ± 4.7	−16.6 ± 8.0†¶	31.2 ± 1.7	−17.7 ± 8.7†¶	28.0 ± 4.6	4.5 ± 6.2†	<0.0001
BMD (g/cm^2)							
Femoral neck	0.82 ± 0.09	0.5 ± 2.8	0.86 ± 0.11	−0.9 ± 3.0	0.87 ± 0.13	−0.04 ± 3.9	0.3182
Trochanter	0.70 ± 0.13	−1.4 ± 5.6	0.75 ± 0.10	−4.2 ± 4.1†¶	0.74 ± 0.16	0.5 ± 5.2	0.0150
UD-radius	0.31 ± 0.04	1.0 ± 5.5	0.31 ± 0.04	−1.1 ± 4.4	0.32 ± 0.06	−0.4 ± 5.4	0.4010
1/3-radius	0.62 ± 0.08	−1.0 ± 2.9	0.64 ± 0.08	−1.2 ± 2.8†	0.62 ± 0.08	0.5 ± 3.6	0.2180
Total spine	0.97 ± 0.09	−1.0 ± 4.2	1.00 ± 0.09	−3.8 ± 5.0†¶	0.98 ± 0.12	0.6 ± 4.2	0.0088
Total body	1.10 ± 0.08	−0.8 ± 1.7†	1.12 ± 0.08	−0.7 ± 2.2	1.13 ± 0.10	−0.9 ± 1.7†	0.9271
BMC (g)							
Femoral neck	4.08 ± 0.51	1.0 ± 6.6	4.38 ± 0.76	−1.1 ± 6.8	4.34 ± 0.68	0.02 ± 5.8	0.1345
Trochanter	8.18 ± 2.38	−1.1 ± 8.1	8.98 ± 2.16	−4.8 ± 7.1†¶	8.60 ± 2.99	2.9 ± 7.1	0.0074
UD-radius	1.05 ± 0.20	2.1 ± 27.3	1.10 ± 0.20	2.2 ± 21.5	1.04 ± 0.28	19.8 ± 36.2†	0.0604
1/3-radius	1.55 ± 0.21	−3.9 ± 12.6	1.58 ± 0.21	−2.7 ± 3.0†	1.57 ± 0.26	0.7 ± 3.8	0.1582
Total body	2268 ± 320	−0.1 ± 3.5	2313 ± 248	−0.9 ± 4.3	2325 ± 407	1.2 ± 3.0	0.1877

Riedt et al. J Bone Miner Res. 2005 Mar;20(3):455-63.

Change in BMD with Weight Loss



Riedt et al. J Bone Miner Res. 2005 Mar;20(3):455-63.

Meta-Analysis: Diet-induced weight loss and BMD

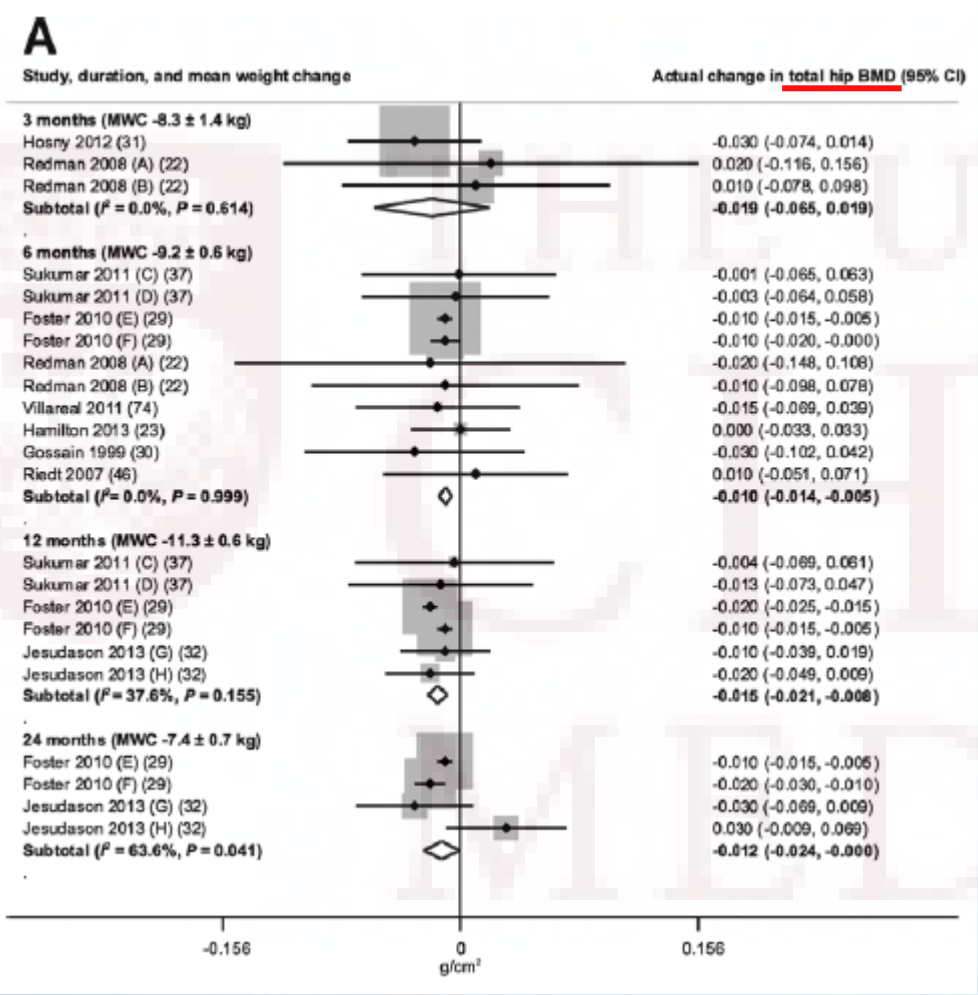
ORIGINAL ARTICLE

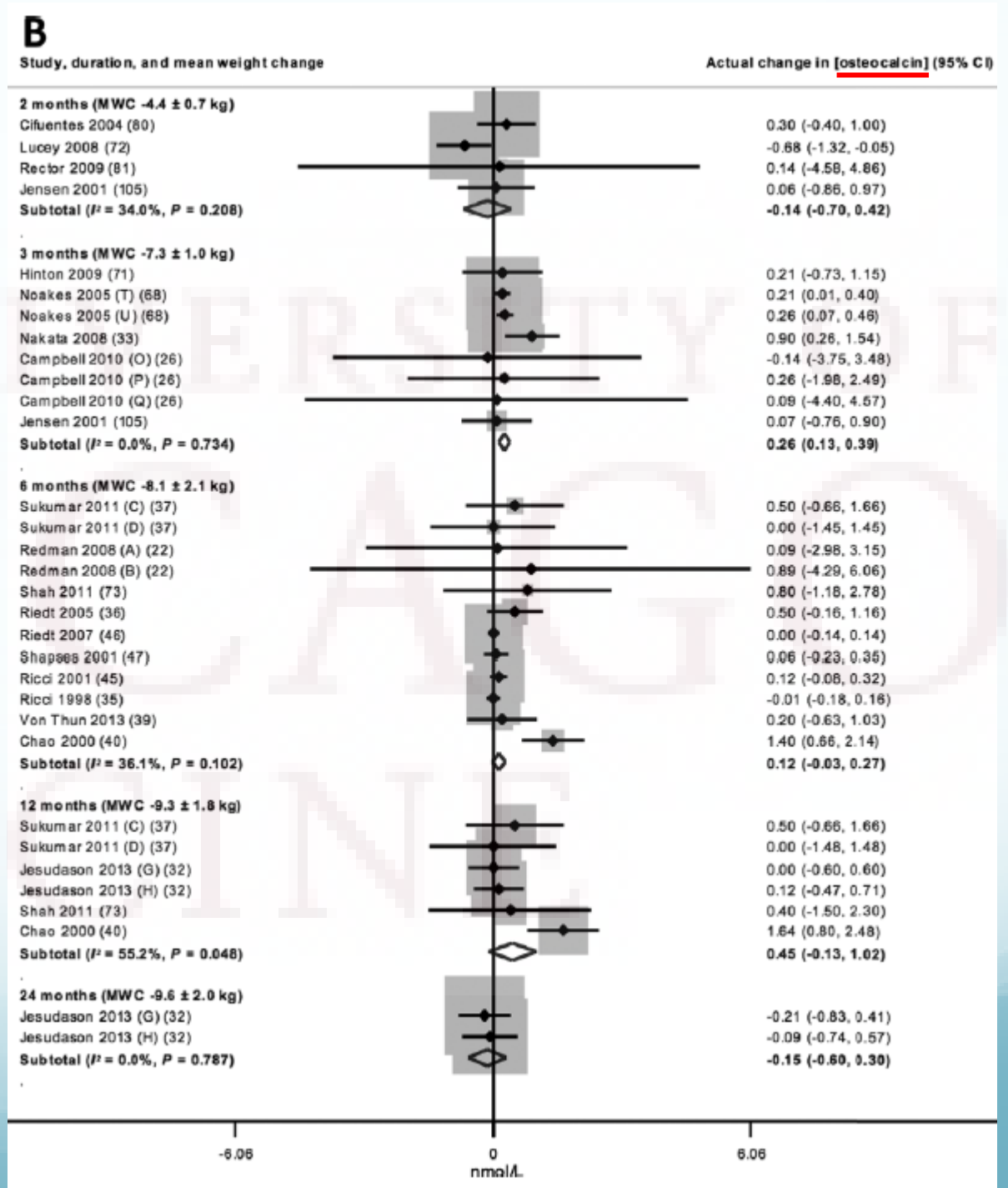
JBMR®

Does Diet-Induced Weight Loss Lead to Bone Loss in Overweight or Obese Adults? A Systematic Review and Meta-Analysis of Clinical Trials

Jessica Zibellini,[1] Radhika V Seimon,[1] Crystal MY Lee,[1] Alice A Gibson,[1] Michelle SH Hsu,[1] Sue A Shapses,[2] Tuan V Nguyen,[3,4,5] and Amanda Sainsbury[1]

- Meta-analysis of 38 publications which included healthy patients with BMI >25 undergoing dietary weight loss intervention
- Studies NOT included if involved exercise as the “primary means of eliciting weight loss” or weight loss meds
- Outcomes: BMD of total hip, lumbar spine, total body, bone turnover markers





Zibellini et al. J Bone Miner Res. 2015 Dec;30(12):2168-78.

Case Conclusion

- Switched from Risedronate to IV Zoledronic acid for more potent antiresorptive effect
- Continues follow up with weight loss clinic
- To our knowledge has not yet informed her husband about her diagnosis of 46, XY complete gonadal dysgenesis

Special Thanks

- Dr. Darrel Waggoner (Clinical Genetics)
- Jessica Stoll (Genetics Counselor)

Objectives

- Review the differential diagnosis and evaluation of primary amenorrhea
- Understand the physiology and presentation of disorders/differences of sexual development (DSD) and 46, XY Complete Gonadal Dysgenesis
- Review the recommendations for estrogen replacement in females with hypogonadism and consequences of inadequate replacement.
- Discuss the effects of diet-induced weight loss on bone loss

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