Primary Ovarian Insufficiency

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Atlantic Society Meeting
September 16th, 2017

I have no potential conflicts of interest

Lucy

14 years old

2^0 Amenorrhea

Differential Diagnosis

- Secondary Amenorrhea
  - Pregnancy
  - PCOS
  - Thyroid Disease
  - Prolactinoma
  - Hypothalamic Amenorrhea
  - Ovarian Failure
  - Asherman's **
  - Sheehan's **

Lucy

14 years old
2^0 Amenorrhea
Menarche 13yo
Normal Puberty 11yo
LMP 6/12 ago
Cycles were q28-32d
Now c/o VMS
Not sexually active
Healthy otherwise
Physical Exam
Tanner Stage IVx2
Normal Otherwise

Work up

- Pregnancy Test
- Provera Challenge
- FSH/LH/E2 ideally Day 3 but in this setting random is helpful.
- TSH
- Prolactin

BhCG –ve
PRL 12
E2 60
FSH 75
LH 55
TSH 1.23

Why have my periods stopped?

Primary Ovarian Insufficiency

- Criteria for
  - Amenorrhea for 4 months
  - FSH>40 (low estradiol) on two occasions at least a month apart.
  - Most recent ESHRE Guideline suggest over 25
  - Under the age of 40

AMH

- AMH shouldn't be used in the diagnosis of POI
- AMH levels decline before Menopause
- Patients can still have regular cycles despite having a low AMH level
- May be warranted in the assessment of AUB in adolescents with no known cause of AUB (Chaloutsou et al, 2017)

Other Considerations

- Patients may not have complete amenorrhea but FSH levels may be elevated
- Elevated E2 will falsely normalize FSH levels
  - Day labs can show elevated E2 on Day 3 with normal FSH
    - Other causes include ovarian cysts and PCOS patients can have elevated E2 levels due to peripheral conversion

Other Considerations

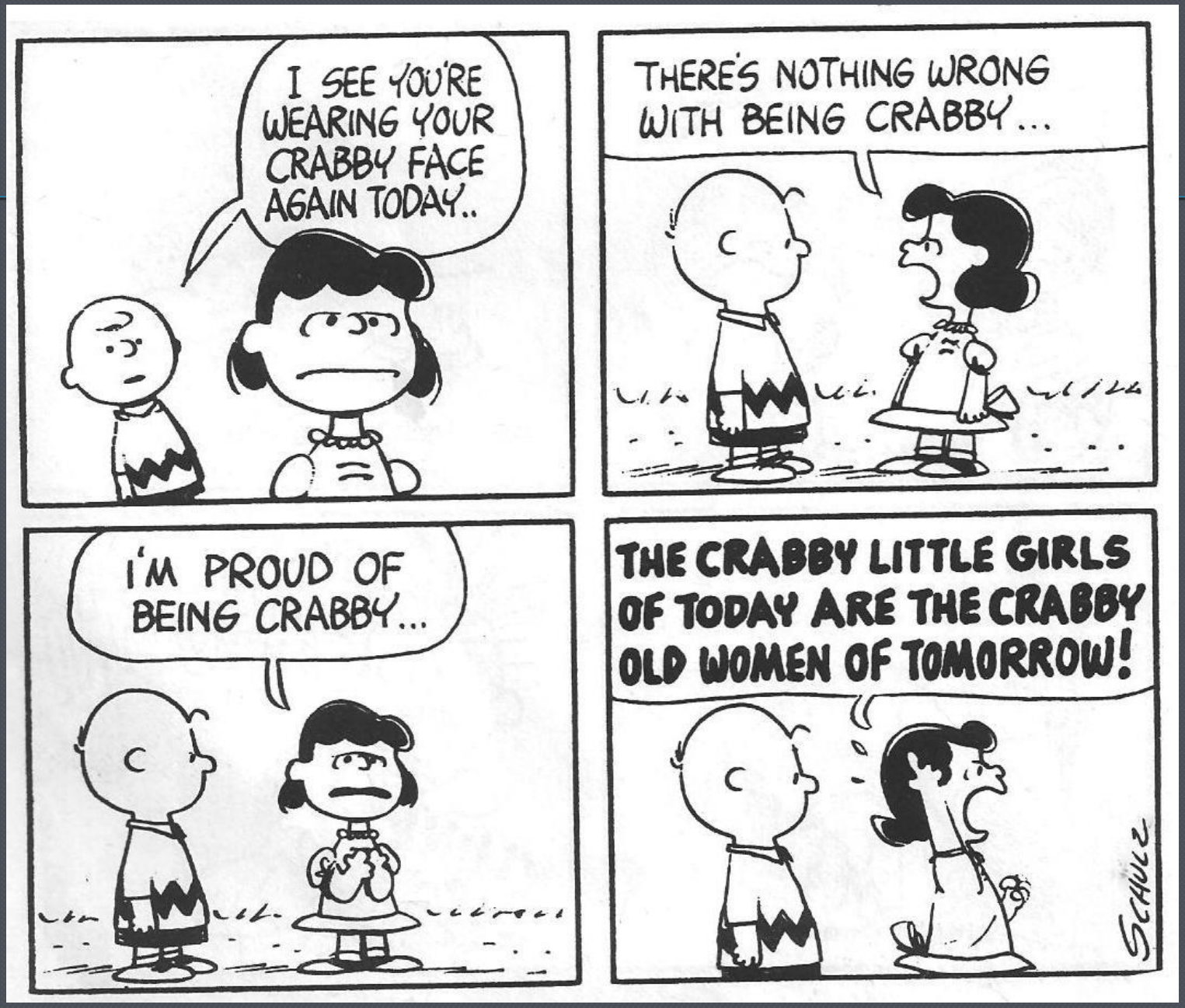
- Adolescents should have normal FSH and generally their FSH levels are WELL below 10.
- Elevated FSH levels without an E2 level cannot be interpreted.
  - Could be ovulatory
  - Could be falsely low due to downregulation

General Mechanisms

- Failure to form an adequate initial pool of primordial follicles
- An accelerated loss of follicles
- Autoimmune or toxic damage

Who warrants work up?

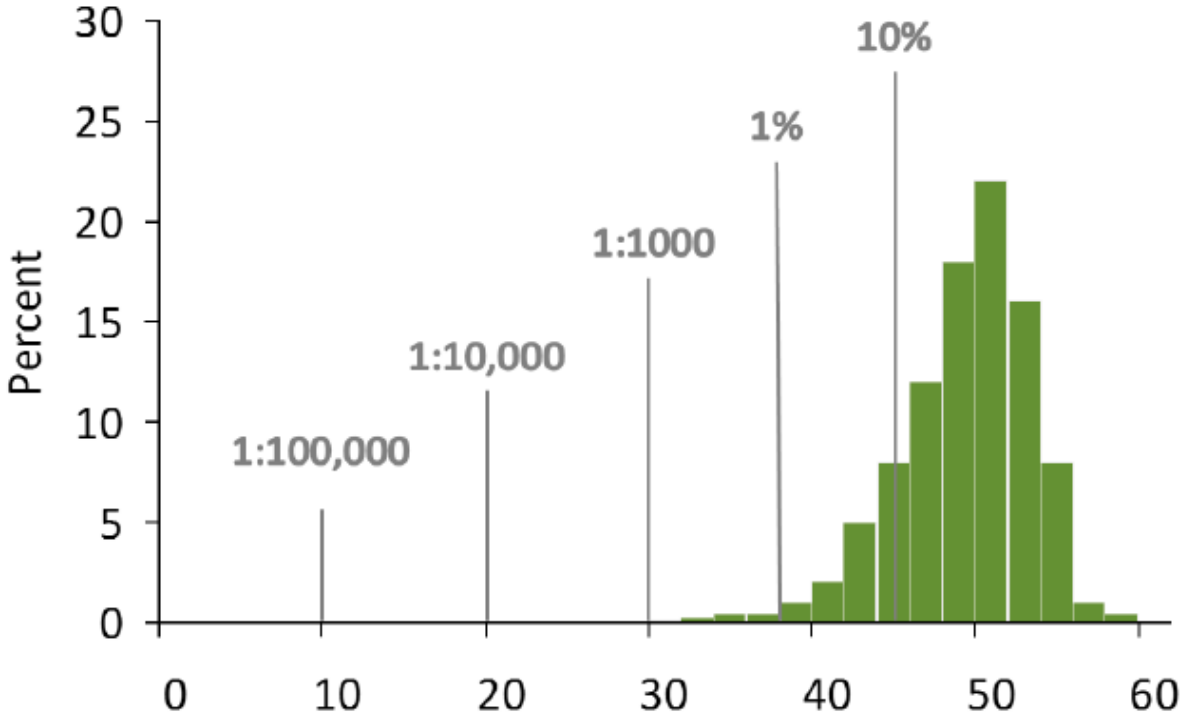
- Absence of menses by 15 years with secondary sexual characteristics
- Delayed Puberty
- Cessation of menses for >/=4 months
- Cycle interval of greater than 90 days
- Adolescents with AUB particularly those with previously normal cycles
- Patients that have symptoms of estrogen deficiency <40 years old


I SEE YOU'RE WEARING YOUR CRABBY FACE AGAIN TODAY..
THERE'S NOTHING WRONG WITH BEING CRABBY...
I'M PROUD OF BEING CRABBY...
THE CRABBY LITTLE GIRLS OF TODAY ARE THE CRABBY OLD WOMEN OF TOMORROW!
SCHULZ

Epidemiology

- 0.3-0.9% occurrence in general population
- 5-10% of women with amenorrhea
- 90% no underlying cause
- 5-10% have spontaneous resumption of ovarian function

Figure 1.2. Distribution of age at menopause.



ESHRE GUIDELINE

Causes

- Idiopathic
- Iatrogenic
- Genetic
- Autoimmune

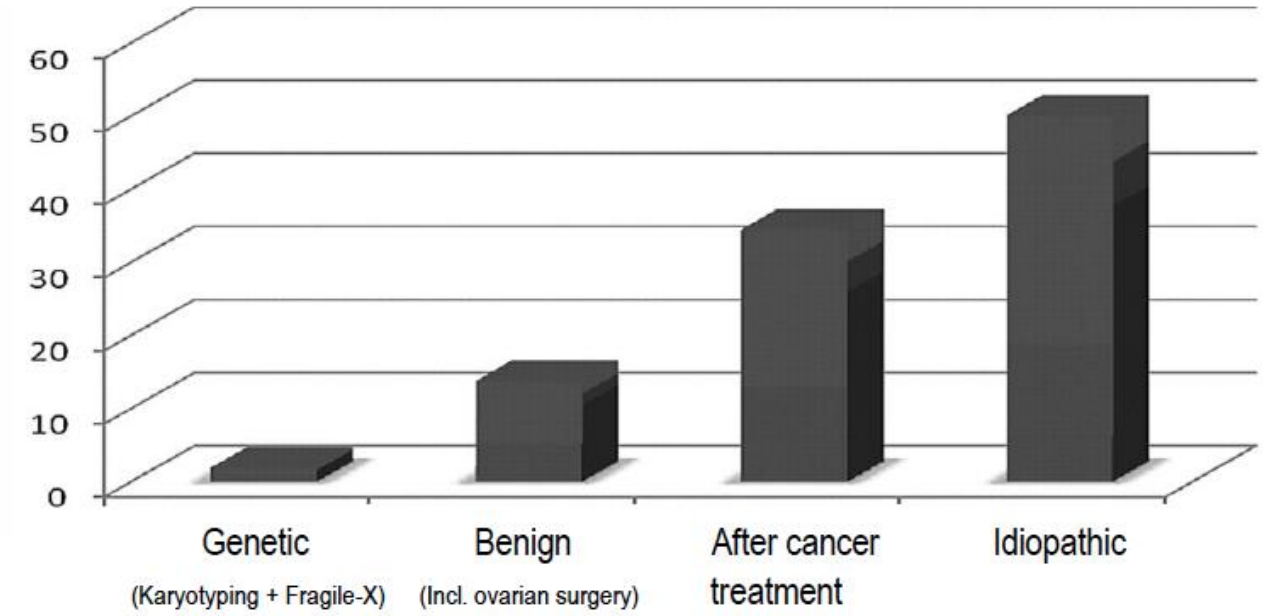
Table 1
Patients Diagnosed with Premature Ovarian Insufficiency

Number	Age, Years	Height, cm	Presenting Complaint	Age at Menarche, Years	Age at Pubarche, Years	FSH, IU/L	Diagnosis	Additional Information
1	15.8	171	Oligomenorrhea	11.8	10	73.8	Unknown	
2	14.4	168	Primary amenorrhea	N/A	9		Unknown	Cisterna Magna Giant, Tanner stage B4
3	13.9	170	AUB	13.6		35	Unknown	Gradual recovery of FSH levels (FSH 14 IU/L 2 years after initial presentation)
4	16.7	171	Primary amenorrhea	N/A	11	105	Unknown	Tanner stage B3
5	14.5	155	AUB	12.7		12.2	Unknown	AMH 0.46 ng/mL
6	17	179	Delayed puberty	N/A	N/A	148	Unknown	Right oophorectomy in newborn period
7	15.5	165	Secondary amenorrhea	12.6		70.2	Unknown	
8	14.5	171	Delayed puberty	N/A	N/A	104	Unknown	Elevated anti-TPO Ag (1573.5 IU/mL); vesicoureteral reflux, laparotomy age 2
9	16.5	154	Delayed puberty	N/A	N/A	70.8	Unknown	
10	13.9	168	Secondary amenorrhea after AUB of 1 year	12		107	Unknown	
11	17	168	Delayed puberty	N/A	N/A	42.5	Unknown	
12	14	170	AUB from onset of menses	13	10	38	Unknown	Dextrocardia, interrupted inferior vena cava, common atrioventricular valve orifice with a large atrial septal defect, pulmonary valve stenosis, gastroesophageal regurgitation
13	16	151	Delayed puberty	N/A	N/A	102.1	45,X (30%)/46,XY (70%)	Gonadoblastoma in situ at gonadectomy
14	16	162	Oligomenorrhea	13.2		76.4	Unknown	
15	17	179	Delayed puberty	N/A	N/A	77	Swyer syndrome (46,XY)	Streak gonads at gonadectomy
16	16.9	166	Delayed puberty	N/A	N/A	56.9	Unknown	
17	16	167	Oligomenorrhea	14	12		46,X, add(X) (q22-> q?)	
18	16	165	AUB	12	9	163	Unknown	
19	14	152	AUB	13	11	104	Turner mosaic- 45,X (8%)/46,X,i(X) (52%)/46,X,psuidic(X) (30%)/47,X,i(X)x2 (10%)	
20	16.5	162	Oligomenorrhea	10.5		42	Unknown	Regular cycles for 3 years before oligomenorrhea
21	16	170	Delayed Puberty	N/A	N/A	76	Swyer syndrome (46,XY)	Dysgerminoma diagnosed at prophylactic gonadectomy (stage Ia; no further treatment required)
22	15.5	168	Primary amenorrhea	N/A	11	70.7	47,XXX	Tanner stage B3

AMH, anti-Müllerian hormone; AUB, abnormal uterine bleeding; FSH, follicle-stimulating hormone; N/A, not applicable; TPO Ag, thyroid peroxidase antigen
FSH levels are the initial levels at presentation.

Chaloutsou et al, 2017

Figure 3.1: Aetiology of premature ovarian failure cases managed at the West London Menopause and PMS Centre, London, UK (Maclaran and Panay, 2011).



ESHRE GUIDELINE

Physical Exam

- Tanner Stages
- Asses for a goiter
- Increased skin pigmentation or vitiligo
- Orthostatic hypotension if adernal insuffiency suspected
- Signs of atrophic vaginitis may be seen but not always
- Ptosis
- Features of Turner syndrome

Additional Work Up

- Complete Karyotype
- Fragile X testing
  - Important for counseling patient and family members re: risk of POI and to offspring
- Additional Genetic testing as warranted

Additional Work Up

- Autoimmune screen
  - Thyroid Disease
    - Commonly Hashimoto's thyroiditis
      - 14 to 27% at initial diagnosis
    - TSH
    - Thyroid peroxidase antibodies
  - Adrenal antibodies
    - Suggest adrenal antibodies as has major clinical consequences
    - ~4% will have positive adrenal antibodies
      - ½ of these will develop adrenal insufficiency
  - Full autoimmune screen not necessary unless symptomatic

Karyotype XX
Fragile X pre-mutation positive
Negative antibodies for Thyroid and Adrenal

What does this mean?

Fragile X Syndrome

- 2nd most common known congenital cause of primary ovarian insufficiency
  - 0.8–7.5% of idiopathic POI have the pre-mutation and upwards of 13% of those with FH of POI
  - >200 repeats of a CGG trinucleotide leads to fragile X syndrome.
  - 55 and 199 repeats is a unstable pre-mutation state

Fragile X Syndrome

- All males with the full mutation have manifestations of FXS
- Physical Features can be subtle
- Developmental Delay
  - ADHD
  - Autism
- Girls with full mutation presentation is variable
  - Depends on the amount of X inactivation
  - 50% have normal intellect
  - Generally milder cognitive delay
  - 20% autism spectrum disorder
  - ADHD, Anxiety and other psychiatric disorders

Pre-mutation

- Females who carry the pre-mutation
  - May expand to full mutation within one generation
    - Has implications for other female relatives in reproductive age group
  - 13– 15% with pre-mutation present with POI
  - The higher the number of repeats the greater the risk of POI
  - Fragile-X-associated tremor/ataxia syndrome

Vasomotor Symptoms

RX……

Management

- No RCTs
- Reasonable regimen
  - 100 µg of transdermal/transvaginal estradiol
    - Lowers risk of VTE
    - Minimal effect on hemostatic factors
    - Alternative if oral preferred
      - Conjugated estrogens 0.625 to 1.25 mg
      - Estradiol-17β 1 to 2 mg

Management

- 10 mg of cyclic oral medroxyprogesterone acetate has best evidence for endometrial protection
- 200mg micronized if patient doesn't tolerate medroxyprogesterone can be used but monitor closely to ensure appropriate conversion given higher dose of E2
- Levonorgesterel IUS has not been studied in this population but does offer reliable contraception for patients
- Patients should track menstrual cycles and do pregnancy test if missed cycle occurs

Management

- HRT
  - No increased risk of breast cancer in POI patients
  - HRT not CI'ed in patients with migraine with aura, hypertension or obesity but transdermal is best choice
  - Patients with a history of DVT should be consulted to a hematologist

Management

- Oral contraceptive vs 12 months of transdermal physiologic HRT
  - Evidence supports significantly lower blood pressure, better renal function, and reduced activation of the renin-angiotensin-aldosterone system
- There is also evidence that HRT is more preferable for Bone Health as well

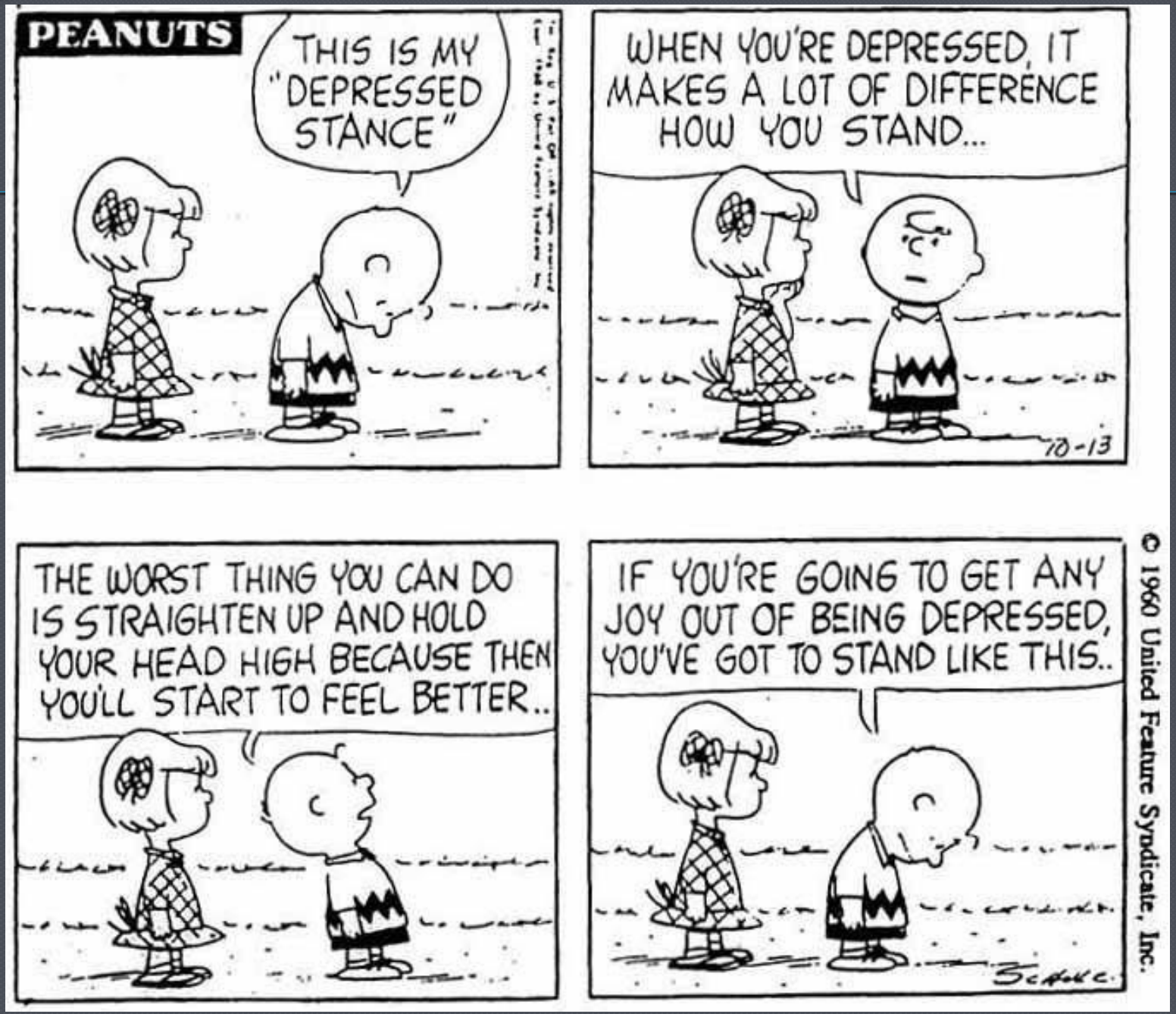
Sullivan et al, 2016

Testosterone and Androgens

- Testosterone evidence not clear in this population if its helpful (Sullivan et al, 2016).
- DHEA may have some benefit from reproductive point of view

Reality…..Despite morbidity

- A recent study found 52% of patients with POI don't start or continue HRT! (Sullivan et al, FS, 2016)


PEANUTS
THIS IS MY "DEPRESSED STANCE"
WHEN YOU'RE DEPRESSED, IT MAKES A LOT OF DIFFERENCE HOW YOU STAND...
10-13
THE WORST THING YOU CAN DO IS STRAIGHTEN UP AND HOLD YOUR HEAD HIGH BECAUSE THEN YOU'LL START TO FEEL BETTER..
IF YOU'RE GOING TO GET ANY JOY OUT OF BEING DEPRESSED, YOU'VE GOT TO STAND LIKE THIS..
© 1960 United Feature Syndicate, Inc.

Patti

13 year old with no secondary sexual characteristics

Patti
N Development
Healthy
N Pregnancy SVD
Surgeries Nil
Family History
15 year old sister normal
puberty
No meds

Patti

Tanner Stage Ix2
Slight web neck
Low Set Hairline
Wide Carrying Angle

FSH 67
LH 52
E2 <37

TSH normal
Prolactin Normal

Karyotype
45X0/46XX

X Chromosome

- Structural
- Numerical
  - Turners
  - Mosaic Turners
  - Trisomy X
- Largest subgroup with POI
  - Up to 10-12% of patients with POI have a genetic reason. Upwards of 20% in primary amenorrhea
    - 94% are X related

Turner's Syndrome

- Commonly Primary Amenorrhea or Delayed Puberty
  - One X chromosome allows ovarian differentiation,
  - BUT two active X chromosomes are needed for oocyte development
  - Results in oocyte apoptosis after 12 weeks
  - Oocyte depletion in first 10 years of life

Mosaic Turner

- 45,X/46,XX
  - 45X/46XY and other possibilities
  - Patients found to have portion of Y chromosome require gonadectomy
- May have a normal menarche and puberty
- Secondary Amenorrhea
- Variable Phenotype
  - Imprinting
  - Karyotype
  - Degree of mosaicism

Gonadal Dysgenesis

- Primary Amenorrhea
  - Swyer Syndrome
    - Uterus and gonads present
    - Gonads are dysgenetic
      - Risk of malignancy
  - Other 46XY female conditions with gonadal dysgenesis

Autosomal Causes

- Autosomal genes mutations
  - FOXL and BPES
- Mutations of gonadotropin genes and receptors
  - Sufficient ovarian follicles

Management

- Pre pubertal POI
  - Mimic normal puberty
  - Promotion of Breast Development
    - Avoid progestin till breast mound and areola develop
  - Start with 25 µg of transdermal estradiol
    - Alternative 0.3 mg of conjugated estrogens orally
    - Continue alone for up to six months or until break through bleeding
  - Add 2.5-5mg of medroxyprogesterone acetate cylic every 30-60 days at six months
    - Final dose will require at least 10mg of medroxyprogesterone acetate
  - Gradually increase estrogen to 100µg increasing in increments every 6 months

Table 13.1: Estrogen substitution therapy in adolescence (adapted from (Bondy and Turner Syndrome Study Group, 2007))

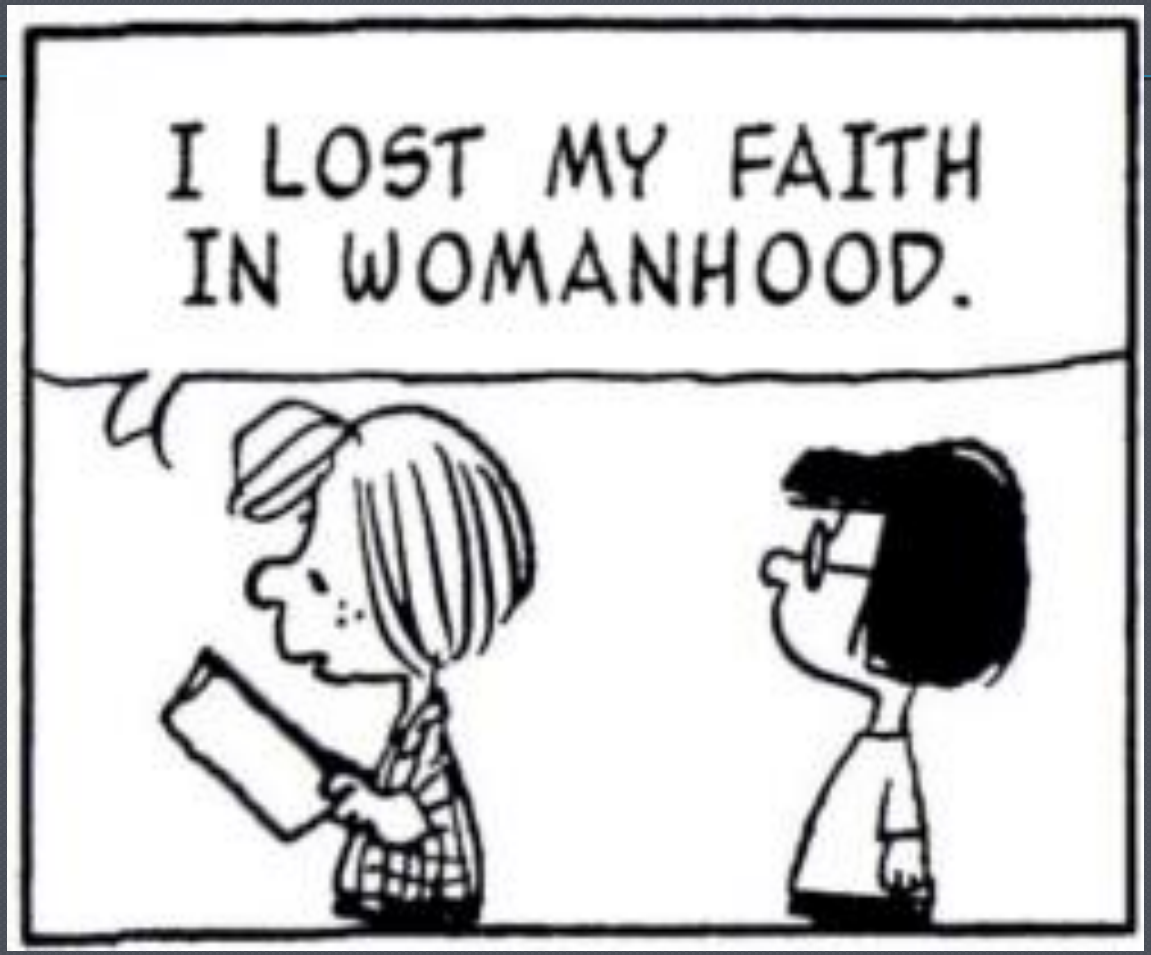
Age	Age-specific suggestions	Preparation/dose/comments
12 -13 years	If no spontaneous development and FSH elevated, start low dose estrogens	17β-estradiol (E2) Transdermal: 6.25 µg/day[1] E2 via patch Oral micronized E2: 5 µg/kg/day or 0.25 mg/day
12.5 - 15 years	Gradually increase E2 dose at 6-12 months interval over 2 - 3 years[2] to adult dose	Transdermal E2: 12.5, 25, 37.5, 50, 75, 100µg/day. (*Adult dose: 100-200 µg/day*) Oral E2: 5, 7.5, 10, 15 µg/kg/day. *(Adult dose: 2-4 mg/day)*
14 – 16 years	Begin cyclic progestogen after 2 years of estrogen or when breakthrough bleeding occurs	Oral micronized progesterone 100-200 mg/day or dydrogesterone 5-10 mg/day during 12 – 14 days of the month[3]

[1] *the lowest dose commercially available E2 transdermal patches deliver 25 or 50 µg/day; it is not established whether various means of dose fractionation (e.g., administering 1/8, 1/6, 1/4 patch overnight or daily or administering whole patches for 7-10 days per month) are equivalent.*

[2] *with concomitant GH therapy in Turner Syndrome, to achieve an optimal adult height the increase in E2 dose might be relatively slow; while in cases of late diagnosis and for those girls in whom growth is not a consideration, E2 may be started at somewhat higher doses and escalated more rapidly.*

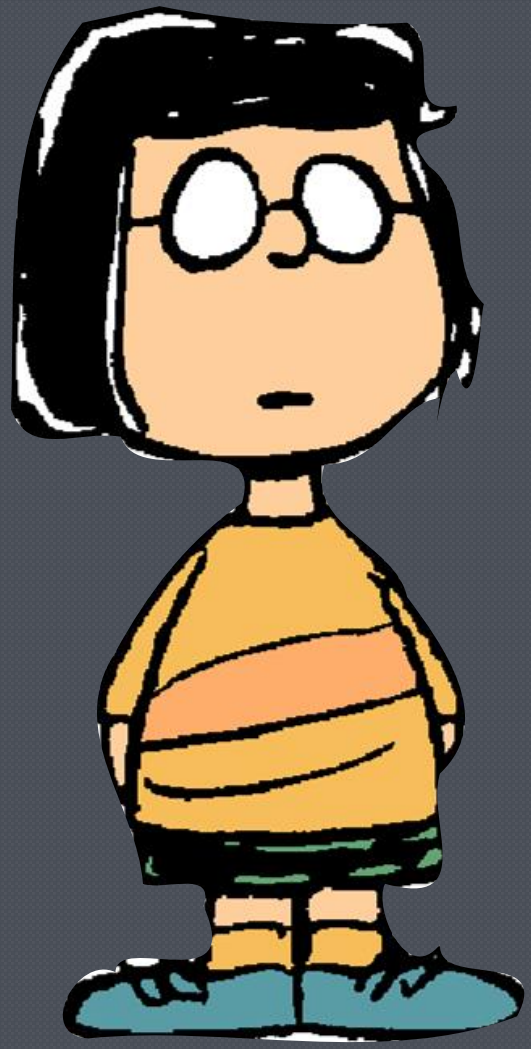
[3] *for prolonged treatment progesterone, dydrogesterone or medroxyprogesterone are preferred to other progestogens because of their less negative effect on lipid metabolism and less androgenic effects (Lobo, 1987).*

ESHRE Guideline


I LOST MY FAITH
IN WOMANHOOD.

Marcie

Known Early Menopause due to chemo
On HRT
Family has questions regarding long term consequences



Clinical Consequences

- Menopausal symptoms
- Decreased bone mineral density (BMD)
- Increased risk of fracture
- Infertility
- Increased risk of mood disorders
- Cognitive decline
- Sexual dysfunction
- Increased rates of autoimmune disease
- Increased risk of cardiovascular disease
- Increased risk of type 2 diabetes mellitus
- Dry eye syndrome

Sullivan et al, FS 2016

Bone Health

- Reduced bone mineral density in patients with POI
  - Increased risk
    - Delayed diagnosis of POI
    - Lack of Treatment
    - Lack of exercise
    - Low Vitamin D intake
- Preventative Measures
  - 1200mg of Elemental Calcium
    - Preferably from diet
    - Supplement if necessary
  - Vitamin D
    - 1000IU-2000IU
  - Weight bearing exercise

Bone Health

- 8-14% of patients with POI develop Osteoporosis
- Estrogen protects bones and should reduce fracture
- DEXA scans can have a role in screening
- If osteoporosis is diagnosed then repeat should be in 5 years (ESHRE Guideline) some say every 2 years
- If normal and on HRT then Dexa repeat may be limited (ESHRE Guideline 2016)

Bone Health

- Studies have also shown that bone decline can occur quickly with non compliance of HRT (Bachelot et al, 2016)

Long term Morbidity

- Patients with untreated POI are at risk for increased mortality
- Mayo Clinic cohort showed increased mortality was seen mainly in women who had not received estrogen up to the age of 45 years (Rivera, *et al.*, 2009)
- An article published in Climateric in 2015 by Faubion et al showed impact on bone, mood, sexual health, CVD and cognitive as well as early mortality.

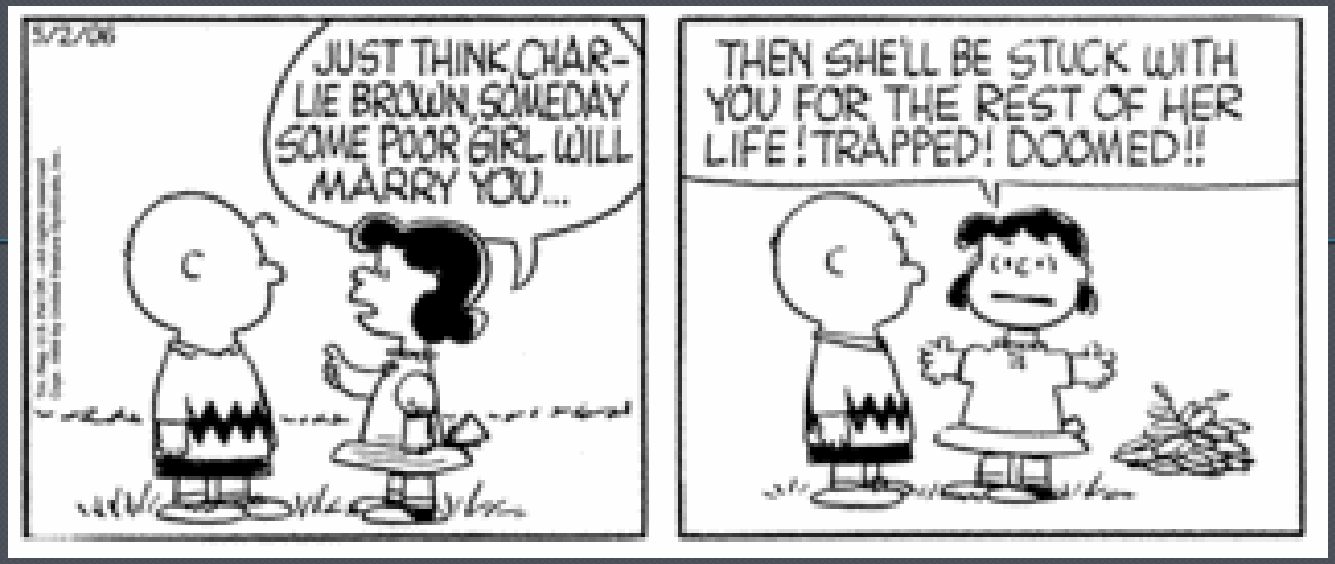
Long term Morbidity

- A Meta-analysis showed higher risk of death from all causes (pooled relative risk (RR) 1.39, 95% confidence interval (CI) 1.10-1.77) and ischemic heart disease (IHD) (pooled RR 1.48, 95% CI 1.02-2.16) when compared with women at normal age at natural menopause

Long Term Morbidity

Summary table of indication for the prescription of HRT in women with POI

Sequelae of POI	Indication for HRT	Supporting recommendation / conclusion
Vasomotor symptoms	YES	*Hormone replacement therapy is indicated for the treatment of vasomotor symptoms in women with POI.*
Genito-urinary symptoms	YES	*Both systemic & local estrogens are effective in treatment of genito-urinary symptoms.*
Life expectancy	?	*Life expectancy appears to be reduced due to cardiovascular mortality: HRT may be of indirect benefit.*
Bone health	YES	*Estrogen replacement is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture.*
Cardiovascular health	YES	*Despite lack of longitudinal outcome data, hormone replacement therapy with early initiation is strongly recommended in POI to control future risk of cardiovascular disease; it should be continued at least until* the average age of natural menopause.
Quality of life	?	*Quality of life appears to be reduced: HRT may be of indirect benefit.*
Sexual function	YES	*Adequate estrogen replacement is regarded as a starting point for normalising sexual function. Local estrogen may be required to treat dyspareunia.*
Neurological function	?	*Estrogen replacement to reduce the possible risk of cognitive impairment should be considered in women with POI at least until the average age of natural menopause.*


JUST THINK, CHARLIE BROWN, SOMEDAY SOME POOR GIRL WILL MARRY YOU...
THEN SHE'LL BE STUCK WITH YOU FOR THE REST OF HER LIFE! TRAPPED! DOOMED!!


OH, IF THERE WERE ONLY SOME WAY TO WARN HER...
BEWARE! BEWARE!

Autoimmune Follow up

- Individuals with Adrenal Antibodies
  - Annual corticotropin stimulation test
- Generally no need to repeat adrenal antibody screen if initial is negative
  - Consider if symptoms develop
- TSH annually may be considered
  - Particularly with positive antibodies

Pregnancy

- POI is not failure!
- 5 to 10% resumption of ovarian function
  - Generally brief
- No predictive markers of spontaneous resumption
- No therapies to improve function
- Family planning
  - Adoption
  - Egg Donation
    - Known
      - Sibling or friend
    - Anonymous
  - Embryo Donation

Pregnancy

- Patients with POI should be aware that using a sibling as an egg donor may result in poor response for IVF
- Patients that have a family history of POI could consider egg freezing especially if childbearing will be delayed

Pregnancy

- Patients with Turner's Syndrome who avail of donor egg should have full assessment prior to pregnancy
- Chemotherapy doesn't appear to impact pregnancy risk
- Radiation if uterus is exposed can increase obstetrics risk
- Anthracycline can cause cardiac issues

Turners Syndrome

- Fertility Preservation presents a challenge as follicle depletion starts pre-pubertal.
- Mosaic turners may have somewhat better ovarian reserve but should be assessed for aortic issues before pregnancy
- One article looked at the utility of using cryopreserved ovarian tissue for pubertal development. It was felt medical induced puberty was a better option.

Hum Reprod. 2017 Jan;32(1):2-6. Epub 2016 Nov 5.

A mother's gift of life: exploring the concerns and ethical aspects of fertility preservation for mother-to-daughter oocyte donation.

Balkenende EM[1], Dondorp W[2], Ploem MC[3], Lambalk CB[4], Goddijn M[5], Mol F[5].

Author information

Abstract

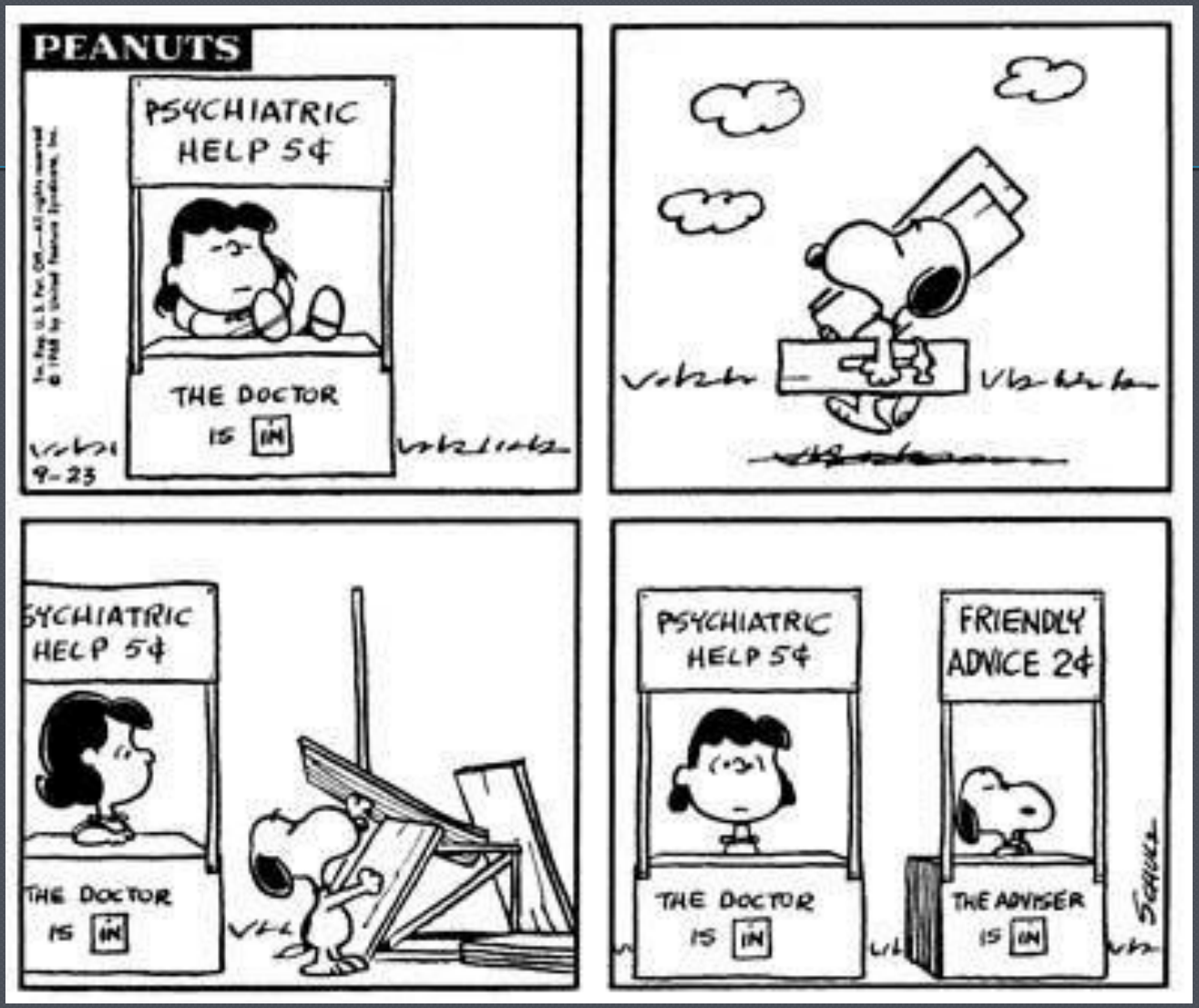
With the introduction of oocyte vitrification, a special form of intergenerational intrafamilial medically assisted reproduction (IMAR) has now become feasible: fertility preservation for mother-to-daughter oocyte donation (FPMDD). For girls diagnosed with premature ovarian insufficiency (POI), banking of their mothers' oocytes can preserve the option of having genetically related offspring. Since policy documents on IMAR do not discuss specific concerns raised by FPMDD, clinicians can feel at a loss for guidance with regard to handling these requests. Through a comparison of FPMDD with reproductive practices in which similar concerns were raised, proportionality of cryopreservation for self-use and pressure to use the oocytes in fertility preservation in minors, we argue that FPMDD can be acceptable under conditions. The paper ends with recommendations for handling FPMDD-requests, including different options for the legal construction of this form of oocyte donation.

Ovarian Reserve

- One study reported a significant effect of the age at maternal menopause on both the serum AMH levels and antral follicle count in daughters (Rosen, *et al.*, 2010; Bentzen, *et al.*, 2013).

Contraception

- Barrier method or possibly an intrauterine device.
- Patients with POI need to be aware of risk of pregnancy and the need for contraception


PEANUTS
PSYCHIATRIC HELP 5¢
THE DOCTOR IS IN
9-23
PSYCHIATRIC HELP 5¢
THE DOCTOR IS IN
PSYCHIATRIC HELP 5¢
THE DOCTOR IS IN
FRIENDLY ADVICE 2¢
THE ADVISER IS IN

References

- Management of women with premature ovarian insufficiency. ESHRE Guideline. 2016
- Poor Compliance to Hormone Therapy and Decreased Bone Mineral Density in Women with Premature Ovarian Insufficiency. Bachelot et al, 2016
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Questions???