Recent advances in the management of premature ovarian failure

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Welsh O&G Society
Swansea 2017

Recent advances in the management of premature ovarian failure insufficiency (POI)

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nomenclature

- Menopause before 40
 - "Premature Ovarian Insufficiency"
 - "Premature Menopause"

A spectrum: Overt, Biochemical, Occult (diminished ov reserve)

- Menopause between 40 to 45
 - "Early menopause"

Presentation

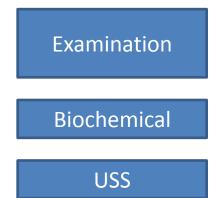
(Change in Menses pattern, Fertility)

menarche, puberty, COC, Pregnancy

(Estrogen deficiency symptoms)

Flushes, atrophic vaginitis

(low QoL score)



In contrast to chromosomal, autoimmune or coexisting

disorders Chemo/radio, Turners, Adrenal insufficiency (wt loss, abd pain, weakness, fatigue, anorexia), Hypothyroidism, vitiligo, myasthenia gravis, hypoparathyroidism, type 1 diabetes, fragile x (FMR1), developmental delay, deafness.

Diagnosis

- Amenorrhea not required, olio or irregular >3/12
- FSH level can be misleading, two occasions 6wks apart
- Estrogen
- Symptoms flushes, vag dryness, can be intermittent (25% of POI no symptoms)
- P4 Test for the spectrum
- USS endo thickness & AFC (75% may appear N)
- AMH
- Karyotype , FMR1, basic evaluation, particularly if <30/FH
- Adrenal autoantibodies, Thyroid &TSH antibodies
- Other: DEXA, BhCG, Prolactin
- Early Diagnosis Menstrual, bone health, Fertility, Emotional health, Coexisting disorders. The lack of proper diagnostic criteria for early stage POI, remains as a main problem.

Genetic Testing

Gene	Location	function
FMR1	Xq	Oocyte development & Number
SF1	11q	Maturation & Ov steroidogenesis
INHA (inhibin α) #	2q	Folliculogenesis
LHR	2р	Foll growth & maturation
FHSR #	2р	Foll development
FOXL2	3q	Ovarian dev (undif granulose)
FOXO3a	6q	Foll activation
ER1 #	6q	Folliculogenesis
CYP19A1	15q	Ov differentiation
CXCL12	10q	GC migration
FMR2	Xq	Unknown
NOBOX	7q	Early folliculogenesis
DIAPH2	Xq	Foll development
MTHFR	1p	Folliculogenesis
LAMC1	1q	High expression during ovulation

Microdeletion in X

Gene Polymorphism

Depletion vs Dysfunction

https://ukgtn.nhs.uk

www.orpha.net

Menstrual
HT
Fertility
Bone health
Emotional health

COC currently

- limited data to support particular regimens, simple, socially acceptable
- o symptoms pill-free wk
- supra-physiological doses

Estrogen currently

- transdermal preferred option adv: byP-hepatic metabolism & subsequent decrisk of ThFm
- E preparations

+ Progesterone

MPA 10 for 12, Mirena (ongoing RCT)

Cont comb/sequential

- o no data
- complicated by unscenduled breakthrough bleeding

Continuation with HT

- 7% stop within 5years;
- reassurance against the misperception surrounding HT in POI (No evidence of increased risk of breastCa)

Non-homronal

- vasomotor serotoninreuptake inhibitors
- o no bisphosphonates if wish conception
- no data supporting herbal/alternative therapy

General lifestyle

supplement Ca & VitD, smoking, exercise

Sexual well-being

- Low sexual satisfaction
- o complex, T no sig diff in QoL, counselling

Psychological

- Psychological distress high (regardless of HT) "traumatic"
- Depression, anxiety, reduced self-esteem, Neg self-image, overall life satisfaction.
- Counselling, support groups (<u>daisynetwork.org.uk</u>), psychologist.

Fertility

- 50% intermittent (FSH up-regulated, dec LH: dec inappr luteinisation).
- 5-10% conceive spontaneously
- COC intermittent, Inconclusive : DHEA, GnRHa, CC
- Oocyte donation highest chance of conception (40-50%/cycle)
- Embryo donation, Surrogacy, Adoption
- Fertility preservation prior to Chemo/Radio (<u>NICE</u>); Oo / embryo / Ov tissue
- Inconclusive: Ovarian suppression prior to chemo
- O Transposition & Shielding Ovarian tissue extremely sensitive, scattered radiation

Long-term

- Life expectancy 2 years less (Menop over 55)
- CVD, osteoporosis, neurocognitive decline (verbalfluncy & visual memory)

Future direction

- Much remains unknown
- Need for long-term studies (<u>www.poiregistry.org</u>)
- Standardisation of guidelines
- Interesting areas of research
 - 1. Identification of Oogonial stem cells (OSCs)
 - 2. Connected without nursing
 - 3. Cortical Ov tissue transplantation

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Thank You