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Võtan aktiivselt osa erialaseltsi tööst nii Eestis kui Euroopa organisatsioonis. Olen Eesti Naistearstide Seltsi juhatuse liige, olin Seltsi eelmine president

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Enneaegne ovariaalne puudulikkus (POI)

Helle Karro

PERH interdistsiplinaarne seminar „Munasari“

29.märtsil 2019

Käsitletavad teemad

- Enneaegne munasarja puudulikkus (POI) – mõiste ja kriteeriumid
- Levimus
- POI põhjused ja riskitegurid
- Diagnoos, uurimis- ja ravitaktika
- POI mõju viljakusele ja elukvaliteedile

Enneaegne ovariaalpuudulikkus

on kliiniline sündroom, mille korral aktiivne munasarja talitlus lakkab enne 40. eluaastat, esinevad menstruaaltsüklihäired (oligo- või amenorröa) ja kõrge gonadotropiinide (FSH >25IU/l) ning madal östradiooli tase

FSH – folliikuleid stimuleeriv hormoon

ESHRE guideline for managing premature ovarian insufficiency, 2016
ACOG guideline, 2017

Enneaegne munasarja puudulikkus

- Munasarja talitluse enneaegset lakkamist (*primary ovarian insufficiency*) kirjeldati esmakordselt 1942.a. Albreight et al, 1942
- Aegade jooksul erinevad nimed ja definitsioonid:
  - Enneaegne menopaus, *premature menopaus* (< 40 eluaastat)
  - *Enneaegne munasarja „võimetus“, premature ovarian failure (POF)*
  - *Enneaegne munasarja vananemine, premature ovarian aging*
  - *Premature ovarian senescence*

  - ***Premature ovarian insufficiency (POI) –***

    Enneaegne munasarja puudulikkus

Enneaegse munasarja puudulikkuse/varase menopausi levimus

- ~1% -l naistest vanuses < 40 eluaastat
- 0,1% naistest vanuses < 30 eluaastat
- 5% naistest menopaus < 45 eluaastat

Coulam et al, 1986; Sullivan et al, 2016

Lagergren *et al. BMC Women's Health* (2018) 18:175
https://doi.org/10.1186/s12905-018-0665-2

BMC Women's Health

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RESEARCH ARTICLE Open Access

The prevalence of primary ovarian insufficiency in Sweden; a national register study

Katarina Lagergren, Mats Hammar, Elizabeth Nedstrand, Marie Bladh and Gunilla Sydsjö*

Abstract

Background: The current estimates of the prevalence of primary ovarian insufficiency (POI) are very variable, but are in most studies believed to be around 1%. It is also very likely tat the prevalence of POI differs between countries and over time. We therefore aimed to assess the prevalence of primary ovarian insufficiency in Sweden.

Methods: All 1,036,918 women born between 1973 and 1993 in Sweden were included. The prevalence of POI was based on data from the Swedish Patient Register through the diagnosis code or through the Prescribed Drug Register. The number of women below 40 years of age diagnosed with the ICD-10 diagnoses E28.3 or E89.4, and women who had been dispensed drugs for treatment of climacteric symptoms were included.

Results: Out of the 1,036,918 women, 19,253 (1.9%) had POI. The prevalence of spontaneous POI was 1.7% and the prevalence of iatrogenic POI was 0.2%. Most women (98.8%) with POI were identified from the Prescribed Drug Register; only 4.1% were found in the Patient Register, whereas 2.9% were identified in both registers.

Conclusions: The total prevalence of POI was 1.9%, 95% CI: 1.7–2.1, indicating a higher prevalence than often previously reported.

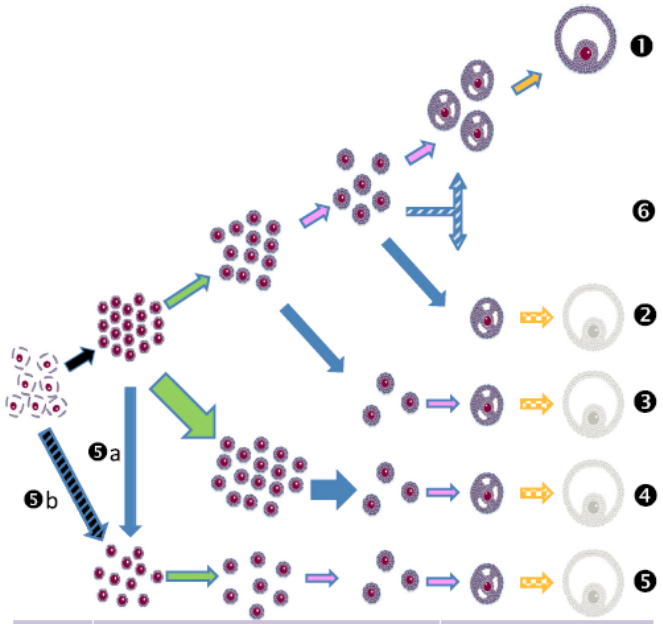
Keywords: Primary ovarian insufficiency, Register study, Prevalence

Table 1 Number (%) of patients diagnosed with primary ovarian insufficiency (POI) in Sweden during 1973–1993, out of the total 1,036,918 women included in the study

POI	Inpatient care n (%)	Outpatient care n (%)	Patient Register[c] n (%)	Prescribed Drug Register n (%)	Total n (%)
Total	120 (0.60)	783 (4.10)	794 (4.10)	18,883 (98.10)	19,253 (100.00)
Spontaneous	4 (0.02)	116 (0.68)	120 (0.70)	17,117[a] (99.60)	17,185 (100.00)
Iatrogenic	10 (0.50)	667 (32.20)	674 (32.60)	1,766[b] (85.40)	2068 (100.00)

[a]drug usage without a cancer diagnosis
[b]drug usage with a cancer diagnosis
[c]Either inpatient care or outpatient specialist care

- Registripõhine uuring
- Kaasati 1,036 918 naist (sünniaasta 1973-1993), RHK-10 E28.3 ja E89.4
- POI levimus oli 1,9% (19 253 naisel), neist : spontaanne 1,7% ja iatrogeenne 0,2%



	Fetal life	Fetal life to menopause			Puberty to menopause	
	Assembly	Activation	Basal follicular growth phase		Final growth phase	
	Primordial follicles		Primary follicles	Secondary follicles	Early antral follicles	Preovulatory follicles
❶	Normal	Normal	Normal	Normal	Normal	Normal
❷	Normal	Normal	Normal	↘ by atresia	↘	↘
❸	Normal	Normal	↘ by atresia	↘	↘	↘
❹	Normal	↘ by activation	↗ by activation	↘ by atresia	↘	↘
❺a	Normal	↘ by atresia	↘	↘	↘	↘
❺b	↘	↘	↘	↘	↘	↘

Fig. 1 The different mechanisms inducing POI. Folliculogenesis (●) begins after assembly (*black arrows*) of primordial follicles during second trimester of pregnancy. Activation of primordial follicles (*green color*) to enter the growth phase of folliculogenesis is continuous from third trimester of fetal life to menopause. This activation is driven by local factors and is independent of gonadotropins. Basal follicular growth (*pink color*) is driven by paracrine factors. From the early antral follicle stage, their growth depends on gonadotrophins to enter the final phase (*orange color*) up to ovulation. From the beginning, follicles undergo physiological atresia (*blue lines around arrows*), that participate to the decrease of the pool with years. Mechanisms leading to POI (symbolized by a final pale preovulatory follicle,): • decrease of the pool of primordial follicles (●) either due to massive atresia (●a) or default in assembly (●b). • increase in follicular apoptosis concerning any other follicular stage (● and ●). • increase of the activation (*large green arrow*) of the resting pool of primordial follicles (●) resulting in its exhaustion. It is generally followed by increased atresia at following follicular stages (*large blue arrow*). • default in basal follicular growth leading to its arrest before the antral stages preventing ovulation while the pool of primordial follicles is normal (●)

Vabre *et al. Environmental Health* (2017) 16:37

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Miks tekib POI?

Primordiaalfolliikuleid on algselt vähem

Folliikulite atreesia on suurenenud

Primordiaalfollikulite küpsemine ja/või värbamine on häiritud

POI kliiniline väljendus

- Hiline puberteet ja primaarne amnorröa
- Sekundaarne amenorröa (SA) või oligomenorröa (OM) >= 4 kuud
- Menstruatsiooni taastumine ja spontaanseid rasestumisi võib esineda, kui SA on kestnud lühiaegselt
- Esinevad östrogeeni toime lakkamise ja östrogeenivaegusega seotud sümptomid
- Enamasti diagnoositakse liiga hilja, kui pöördumatu mõju on toimunud ja munasarja talitluse taastumine ei ole võimalik

POI – etioloogilised tegurid

- Geneetilised
- Autoimmuunsed
- Metaboolsed
- Toksilised
- Infektsioossed
- Iatrogeensed

90% primaarse ovariaalse puudulikkuse juhtudest on idiopaatilised, põhjus jääb teadmata

Nelson, 2009; Welt, 2008

Ülevaade geneetilistest põhjustest

Trends in Endocrinology & Metabolism

CellPress REVIEWS

Trends in Endocrinology & Metabolism, November 2018, Vol. 29, No. 11 https://doi.org/10.1016/j.tem.2018.07.002

Review

Molecular Genetics of Premature Ovarian Insufficiency

Xue Jiao,[1,2,3,4] Hanni Ke,[1,2,3] Yingying Qin,[1,2,3,*] and Zi-Jiang Chen[1,2,3,5,6,*]

Trends in Endocrinology & Metabolism

CellPress REVIEWS

Trends in Endocrinology & Metabolism, June 2018, Vol. 29, No. 6 https://doi.org/10.1016/j.tem.2018.03.010

Review

Advances in the Molecular Pathophysiology, Genetics, and Treatment of Primary Ovarian Insufficiency

Ilpo Huhtaniemi,[1] Outi Hovatta,[2] Antonio La Marca,[3] Gabriel Livera,[4] Danielle Monniaux,[5] Luca Persani,[6,*] Abdelkader Heddar,[7] Katarzyna Jarzabek,[8] Triin Laisk-Podar,[9,10] Andres Salumets,[9,10] Juha S. Tapanainen,[11,12] Reiner A. Veitia,[13] Jenny A. Visser,[14] Peter Wieacker,[15] Slawomir Wolczynski,[16] and Micheline Misrahi[7,*]

CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Clin Genet 2017: 91: 183–198
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CLINICAL GENETICS
doi: 10.1111/cge.12921

Invited Review

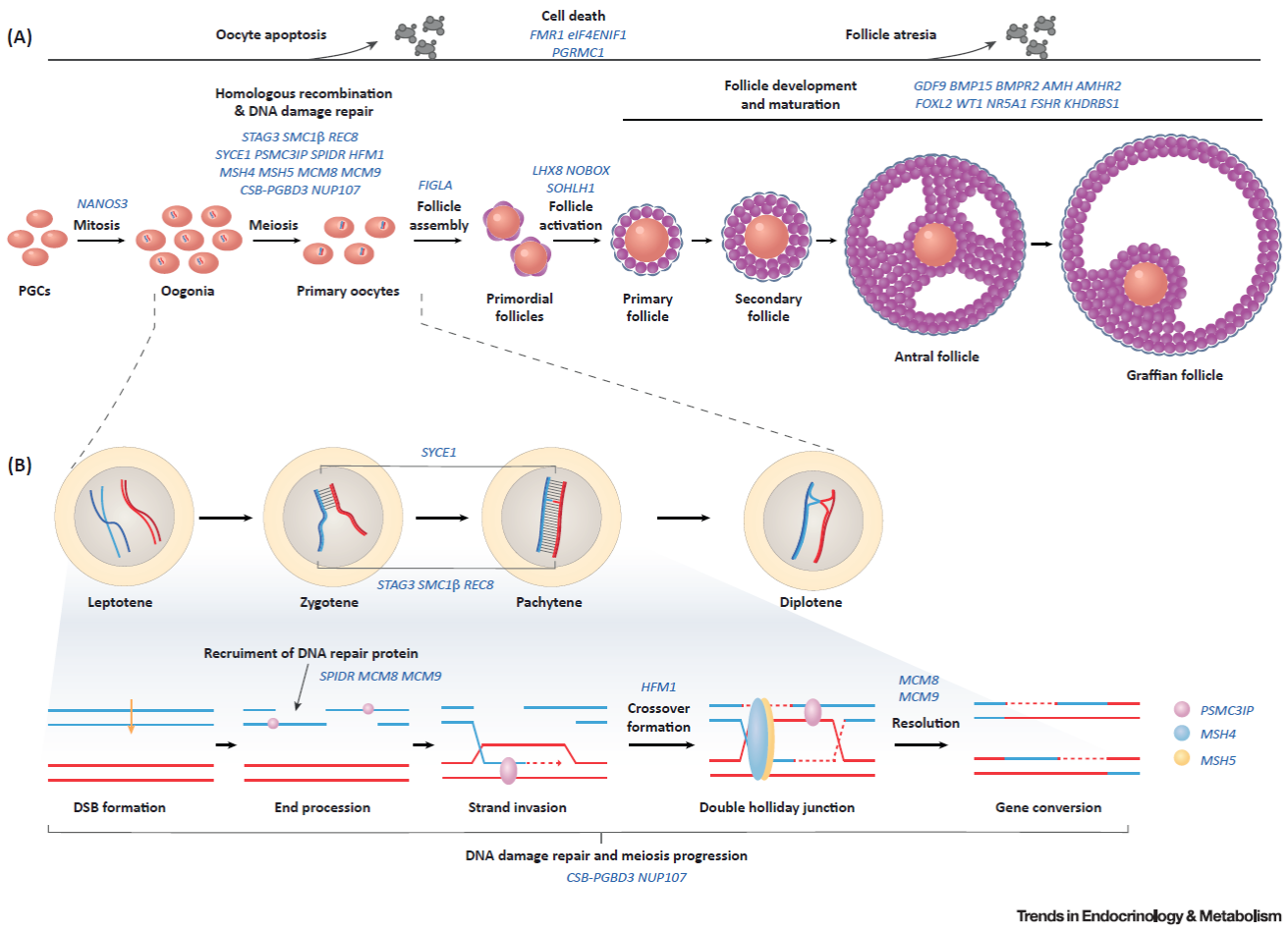
Genetics of primary ovarian insufficiency

Rossetti R., Ferrari I., Bonomi M., Persani L. Genetics of primary ovarian insufficiency.

R. Rossetti[a], I. Ferrari[a], M. Bonomi[a,b] and L. Persani[a,b]

POI geneetilised põhjused

- Kromosomaalsed põhjused, 10-15% POI juhtudest Jiao,2017
  - X-kromosoomiga seotud hälbed (struktuuri ja arvu muutused)
    - X-monosoomia, X-trisoomia, X-kromosoomi mosaiiksus, deletsioonid, duplikatsioonid või tasakaalustatud X.autosoom translokatsioonid
- Geenimuutused, 20-25% POI juhtudest
  - Perekondlik esinemine, 12,7% van Kasteren, 1999
  - Geneetiline heterogeensus:
    - NGS (*next generation sequencing* ja WES (*whole exome sequencing*) abil selgitatud, et üle 60 kandidaatgeeni on seotud POIga
  - Sündroomina või sporaadiliselt



POlga seotud geenid, mis mõjutavad:

- primordiaalsete sugurakkude migratsioon ja proliferatsioon (*NANOS3*),
- rakusurm (*PGRMC1* ja ***FMR1***),
- ootsüütide spetsiifilised transkriptsiooni faktorid (*FIGLA*, ***NOBOX***),
- teised follikulogeneesiga seotud transkripts faktorid (*NR5A1, WT1, FOXL2*),
- transformeeruva kasvuvfaktor β superperekond (***BMP15*** ja *GDF9*)
- hormoonid ja retseptorid (*FSHR, AMH, AMHR2*)

Trends in Endocrinology & Metabolism, November 2018, Vol. 29, No. 11 https://doi.org/10.1016/j.tem.2018.07.002

Sündroomne POI, kliiniline väljendus

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BPES sündroom (FOXL-2) – blefarofimoos- *ptosis-epicantus inversus´e* sündroom

Autoimmuunne polüendokrinopaatia, APECED (AIRE)

Galaktoseemia, autosoomne retsessiivne haigus, (GALT)

Enneaegse vananemisega seotud sündroomid

Table 1. Clinical Presentations of Syndromic POI.[a]

Diagnosis	Menstrual history	Ovarian phenotype	Particular features	OMIM #	Gene(s) involved
WT1-related XX-DSD	PA or SA	Streak gonads, partial ovarian dysgenesis	Nephropathy, diaphragmatic hernia	194070	*WT1*
SF1-related XX-DSD	PA or SA	Streak gonads, partial ovarian dysgenesis	Adrenal insufficiency	612964	*NR5A1/SF1*
BPES	PA or SA	Rare or absent follicles	Blepharophimosis, ptosis, epicanthus inversus	110100	*FOXL2*
FMR1 premutation	SA	Follicle depletion	X-linked mental retardation in family. Fragile X tremor/ataxia syndrome	300624	*FMR1*
Autoimmune polyendocrinopathy syndrome. APS-PGA type 1	PA or SA	Autoimmune oophoritis	Addison disease, candidiasis, vitiligo, hypoparathyroidism, diabetes mellitus, hepatitis, malabsorption, keratopathy, alopecia	240300	*AIRE*
Autoimmune APS-PGA type 3		Autoimmune oophoritis	Autoimmune thyroid disease, atrophic gastritis, vitiligo		
Pseudohypopara thyroidism	SA	Follicular cysts but no corpora lutea in one case	Brachydactyly, short stature, hypocalcemia and hyperphosphatemia, hypothyroidism, obesity	#103580	*GNAS*
Galactosemia	PA	Streak ovaries or few nonmaturated follicles	Neonatal jaundice, failure to thrive, cirrhosis, cataract, intellectual disability, food intolerance, hypoglycemia, renal dysfunction.	230400	*GALT*
Disorders of glycosylation (CDG1A)	PA	Absent ovaries in some patients by US or laparoscopy	Growth retardation, microcephaly, encephalopathy, peripheral neuropathy, retinitis pigmentosa, cardiac myopathy, hepatomegaly, nephrotic syndrome, psychomotor retardation	212065	*PMM2*
Ataxia telangiectasia	PA		Cerebellar ataxia, telangiectasia, recurrent infections, malignancies, and increased levels of alpha fetoprotein	208900	*ATM*
Nijmegen breakage syndrome	PA or SA	Streak gonads, small ovaries	Prenatal growth retardation, progressive mental deterioration, microcephaly, recurrent infections, increased risk for neoplasias such as lymphoma	251260	*NBN*
Fanconi anemia	PA or SA	Decreased number of primordial follicles	Pancytopenia, small stature, microcephaly, ear anomalies, heart defects, kidney malformations, radial aplasia and thumb deformities, intellectual disability, café-au lait-spots	#227650 #227645 #614082	*FANCA* *FANCC* *FANCG*
XRCC4-related disorder	SA		Short stature, microcephaly, developmental delay, diabetes mellitus	#616541	*XRCC4*
Bloom syndrome	SA	Possibly accelerated follicular atresia	Premature aging with chromosomal instability, short stature, skin rashes and telangiectatic skin on sun-exposed areas, increased risk for neoplasias, immunodeficiency	#210900	*BLM*
Werner syndrome	SA	Possibly accelerated follicular atresia	Premature aging with chromosomal instability, pre- and postnatal growth deficiency, sclerodermic skin changes, cataract, arteriosclerosis, increased cancer risk, diabetes mellitus	#277700	*WRN*
Rothmund-Thomson syndrome	SA	Gonadotropin resistance	Short stature, cataract, saddle nose, teeth anomalies, premature graying of hair	#268400	*RECQL4*
GAPO	SA	Follicle depletion	Growth retardation, alopecia, pseudoanodontia, optic atrophy, high forehead, midface hypoplasia	#230740	*ANTXR1*
Perrault syndrome	PA, SA	Streak ovaries, lack of ovaries, small ovaries	Deafness Neurologic symptoms in PRLTS1, PRLTS3, and PRLTS5	#233400 #614926 #614129 #615300 #616138	*HSD17B4, HARS2, LARS2 CLPP C10orf2, CLDN14+ SGO2 KIAA0391 ERAL1*
Woodhouse-Sakati syndrome	PA	Streak ovaries	Alopecia, deafness, hypogonadism, diabetes, intellectual disability	#241080	*C2orf37*
Vanishing white matter disease Ovarioleukodystrophy	SA	Ovarioleukodystrophy streak ovaries	Progressive cerebellar ataxia, spasticity, cognitive impairment with white matter lesions on brain imaging. Onset from early infancy to adulthood	#603896 #615889	*EIF2B* *AARS2*
Retinal dystrophy with or without extraocular anomalies	SA		Retinal dystrophy, goiter, intellectual disability, hypogonadism	#617175	*RCBTB1*
Progressive external ophthalmoplegia	SA	Diminished follicle reserve	Ptosis, progressive external ophthalmoplegia, sensorineural hearing loss, axonal neuropathy, muscle weakness, ataxia, dysarthria, dysphagia and late onset Parkinsonism	#157640	*POLG*
Acromesomelic chondrodysplasia with genital anomalies	PA		Severe brachydactyly with radial deviation of the fingers, ulnar deviation of the hands, fusion of the carpal/tarsal bones, aplasia of the fibula, bilateral clubfeet with small broad feet and short toes	#609441	*BMPR1B*
Interphalangeal joint synostosis	SA		Symphalangism, hearing loss	#185800	*NOG*

[a]DSD, Disorder of sexual differentiation; PA, primary amenorrhea; SA, secondary amenorrhea; US, ultrasound. See text for references and [13].

Trends in Endocrinology & Metabolism, June 2018, Vol. 29, No. 6 https://doi.org/10.1016/j.tem.2018.03.010

POI ja fragiilne X sündroom

- 2-6% sporaadilise POI juhtudest esineb FMR1 premutatsioon Man et al, 2017
- Fragiilne X sündroom on sagedasim päriliku vaimse arengu mahajäämuse põhjus
- Põhjuslik geen FMR1 asukohaga Xq27.3 kodeerib RNAga seonduvat valku FMRP; sündroomi põhjuseks on trinukleotiidsete korduste (CGG) suurenemine üle teatud kriitilise piiri
- Mutatsiooni kandjatel on keskm 5 aastat varasem menopaus ja neil on kõrge risk POI tekkeks
- Kõiki naisi, kel ebaselge põhjusega kõrge FSH enne 40. eluaastat, tuleks testida FraX kandluse suhtes

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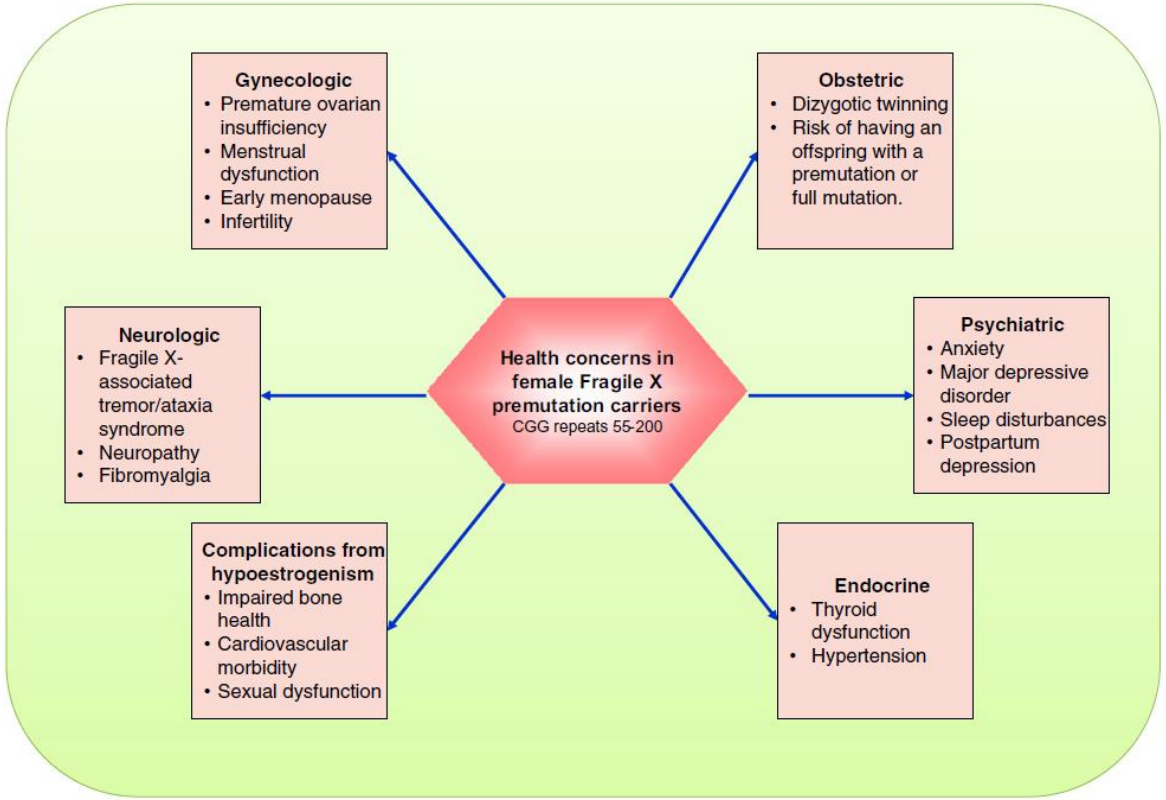

J Assist Reprod Genet (2017) 34:315–323
DOI 10.1007/s10815-016-0854-6

REVIEW

Fragile X premutation in women: recognizing the health challenges beyond primary ovarian insufficiency

Luis R. Hoyos[1] · Mili Thakur[2,3]

Fra X kandlus ja mõju tervisele

Võib esineda suurem risk:

- Menstruaaltsüklihäireteks, viljatuseks, varasemaks menopausiks või POI tekkeks
- Järglaste sünniks, kes premutatsiooni kandjad või kellel esineb mutatsioon
- Neuromuskulatoorseteks probleemideks (nt fibromüalgia, migreen jt)
- Meeleoluhäireteks (ärevus, depressioon jm)

POI autoimmuunsed põhjused

- 5-30% POI juhtudest on tingitud autoimmuunsetest põhjustest Silva, 2014
- Üksinda või komorbiidsus teiste autoimmuun- ja endokriinhaigustega
  - Neerupealise koore puudulikkus, Hashimoto türeoidiit, 1. tüüpi suhkrutõbi, Sjögreni sündroom, reumatoidartriit, SLE, põletikuline soolehaigus, SM, *myasthenia gravis*, alopeetsia
- Autoimmuunne polüglandulaarne sündroom
  - APS1: mukokutaanne kandidiaas ja ühe või mitme endokriinnäärme puudulikkus (hüpoparatüreoidism, neerupealise koore puudulikkus); POI esines 41% Reato et al,2011
  - APS2: autoimmuune adrenaliit, hüpotüreoos, 1.tüüpi suhkrutõbi; POI esines 16% Reato et al,2011
- POI tekib, kui esineb lümfotsüütne autoimmuunne ooforiit ja tsirkuleerivad adrenaalsed või ovariaalsed antikehad, mis mõjutavad steroidogeenseid ensüüme

Rosetti et al,2017; Rudnicka, 2018

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Infektsioonid POI põhjusena

- Epideemiline parotiidiviirus – mumpsiga seotud ooforiit
- HIV, antiretroviirus ravi
- Harvem, seos ei ole kindel: tbc, tuulerõuged, tsütomegaloviirus, malaaria

POI ja keskkonna mõju

Keskkonda saastavad tegurid

- Bisphenol A (plastikpakendid)
- Polüaromaatsed süsivesinikud
- Polüklooritud bifenüülid
- Pestitsiidid
- Dioksiin

Kemikaalid seonduvad östrogeeni või retseptoritega, mõjutavad folliikuli arengut;

Epigeneetiline mõju

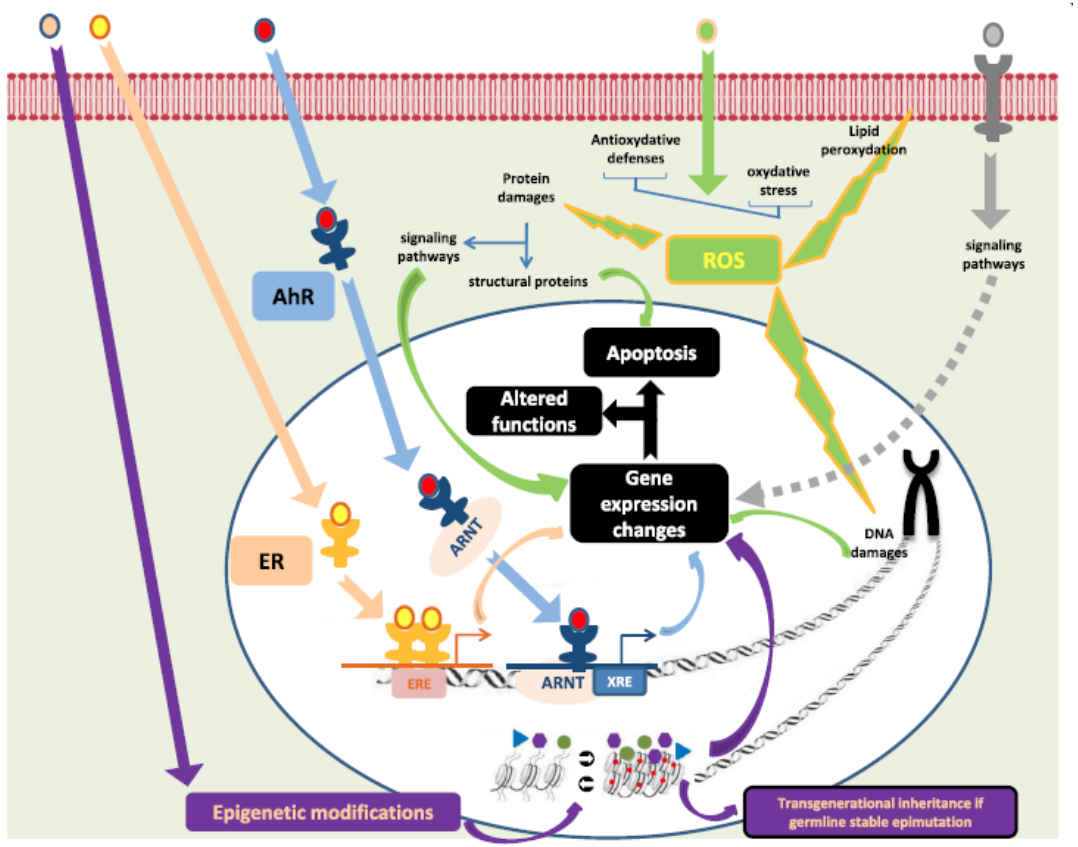

Fig. 3 The major ways used by environmental pollutants to induce defaults in folliculogenesis leading to POI. Environmental pollutants can act through several mechanisms. • actions as endocrine disruptors as ligands to nuclear estrogen receptors (ER, *salmon arrows*) and aryl hydrocarbon receptors (AhR, *blue arrows*). Once linked to AhR, they can bind to AhR nuclear translocator (ARNT) to interfere with xenobiotoc responsive elements (XRE) from promotors and affect gene expression, notably promoting pro-apoptotic genes and inhibiting anti-apopototic genes. • creation of an imbalance between oxydative defenses and oxydative stress favoring apoptosis at different follicular stages (*green arrows*). • Modification of epigenetic marks such as DNA methylation (●) or histones post-traductional modifications (▸, ⬢, ●) affecting the transcriptional state of chromatin and therefore gene expression. • binding to several membrane receptors suchs as membrane bound ER (mER) or receptor protein tyrosine kinases (RPTK) activating the PI3 Kinase pathway are suspected (*grey dotted arrows*)

Vabre *et al. Environmental Health* (2017) 16:37

Põletik, vananemine ja POI

Review Article

Inflamm-Aging: A New Mechanism Affecting Premature Ovarian Insufficiency

Yaoqi Huang,[1,2] Chuan Hu,[1,2] Haifeng Ye,[1,2] Ruichen Luo,[1,2] Xinxin Fu,[1,2] Xiaoyan Li,[3] Jian Huang,[1,2] Weiyun Chen,[1,2] and Yuehui Zheng[1,2]

Hindawi
Journal of Immunology Research
Volume 2019, Article ID 8069898, 7 pages
https://doi.org/10.1155/2019/8069898

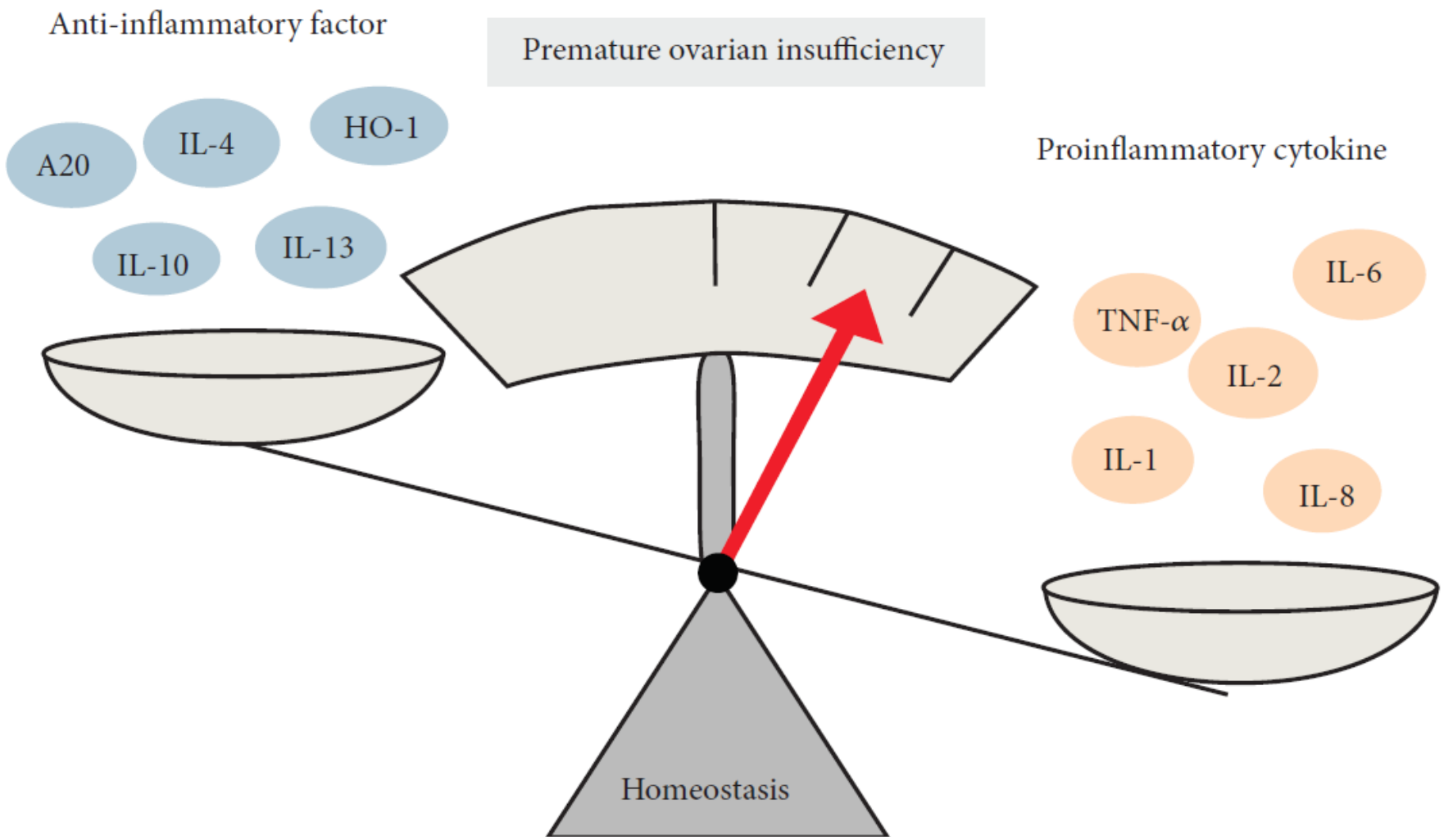

Figure 2: Regulation of proinflammatory cytokines and anti-inflammatory cytokines on premature ovarian insufficiency. Proinflammatory cytokines and anti-inflammatory cytokines maintain a dynamic balance in the normal body. Pathological inflammation in premature ovarian insufficiency is caused by an imbalance of the inflammatory cytokine network.

Iatrogeenne POI

- Kirurgiline ravi munasarjadel
- Kiiritus- või keemiaravi
  - Olulised tegurid on vanus ravi ajal, ravim ja raviannus
  - Kõige sagedasem on POI alküleerivate ainete e. prokarbasiinide kasutamisel
  - Ravi nooremas eas – suurem tõenäosus, et mõned folliikulid säiluvad
  - Risk POI tekkeks on suurem, kui kogu keha, aju, vaagna või lülisamba piirkonna kiiritus
  - Vaagna piirkonna kiiritus ja doos > 10Gy – suur risk ägeda POI tekkeks
  - Kemo- ja radioteraapia kombineerimine suurendab riski
  - Isegi, kui ravi järgselt menstruatsioonid, on elu jooksul risk POI tekkeks suurem

ACOG, 2016

POI diagnoos

Diagnoosi kriteeriumid:

- Vanus alla 40 eluaasta
- Oligo/amenorröa vähemalt 4 kuud
- Hüpergonadotroopne hüpogonadism:
  - FSH >25IU/l , mõõdetuna kahel korral >4 nädalase vahega
  - Madal östradiooli tase

Ovariaalse reservi hindamine:

- Sonograafial antraalsete folliikulite arvu hindamine
- Anti-Mülleri hormooni tase vereseerumis

POI dgn korral uurimistaktika

Human Reproduction, Vol.31, No.5 pp. 926–937, 2016
Advanced Access publication on March 22, 2016 doi:10.1093/humrep/dew027
human reproduction ESHRE PAGES

ESHRE Guideline: management of women with premature ovarian insufficiency†

The ESHRE Guideline Group on POI, L. Webber[1,*], M. Davies[1], R. Anderson[2], J. Bartlett[3], D. Braat[4], B. Cartwright[5], R. Cifkova[6], S. de Muinck Keizer-Schrama[7], E. Hogervorst[8], F. Janse[9], L. Liao[1], V. Vlaisavljevic[10], C. Zillikens[11], and N. Vermeulen[12]

- Kromosoomi analüüs kõigil, kel mitte-iatrogeenne POI
- Fragiilse X sündroomi premutatsiooni testimine (Fra-X)
- Ebaselge põhjuse või autoimmunnhaiguse kahtlusel
  - TPO-Ab
  - 21-OH-Ab või ACA test
- Vajadusel geneetiku, endokrinoloogi konsultatsioon

POI ja hormoonravi

Human Reproduction, Vol.31, No.5 pp. 926–937, 2016
Advanced Access publication on March 22, 2016 doi:10.1093/humrep/dew027

human reproduction ESHRE PAGES

ESHRE Guideline: management of women with premature ovarian insufficiency†

The ESHRE Guideline Group on POI, L. Webber[1,*], M. Davies[1], R. Anderson[2], J. Bartlett[3], D. Braat[4], B. Cartwright[5], R. Cifkova[6], S. de Muinck Keizer-Schrama[7], E. Hogervorst[8], F. Janse[9], L. Liao[1], V. Vlaisavljevic[10], C. Zillikens[11], and N. Vermeulen[12]

- POI korral on hormoonasendusravi (HAR) näidustatud ja omab rolli kardiovaskulaarsete haiguste primaarses preventsioonis ning luude tervise toetamisel
- Adekvaatne HAR on oluline elukvaliteedi parandamisel ja terviseriskide vähendamisel
- Endomeetriumi kaitseks on vajalik östrogeenravi kombineerida progestageeniga
- Enne loomuliku menopausi vanust alustatud HAR ei ole seotud suurenenud riskiga rinnavähiks
- Genitourinaarse sündroomi korral on vajalik täiendavalt paikne östrogeenravi

POI ja luude tervis

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- POI diagnoosimisel tuleb tähelepanu pöörata luutihedust mõjutavatele teguritele, vajalik on DEXA (eriti täiendavate riskitegurite esinemisel)
- Kui BMD on normaalne ja jätkub adekvaatne HAR, pole DEXA kordamine vajalik
- Kui algne luutihedus on vähenenud ja HAR alustatud, on vajalik kordusuuring 5 aasta möödudes
- Hormoonasendusravi on sobivaim meetod osteopeenia/osteoporoosi ravis ja vähendab luumurru riski
- Kombineeritud hormonaalse kontratseptsiooni mõju luutihedusele on vähem tõhus

POI - viljakus ja viljatus

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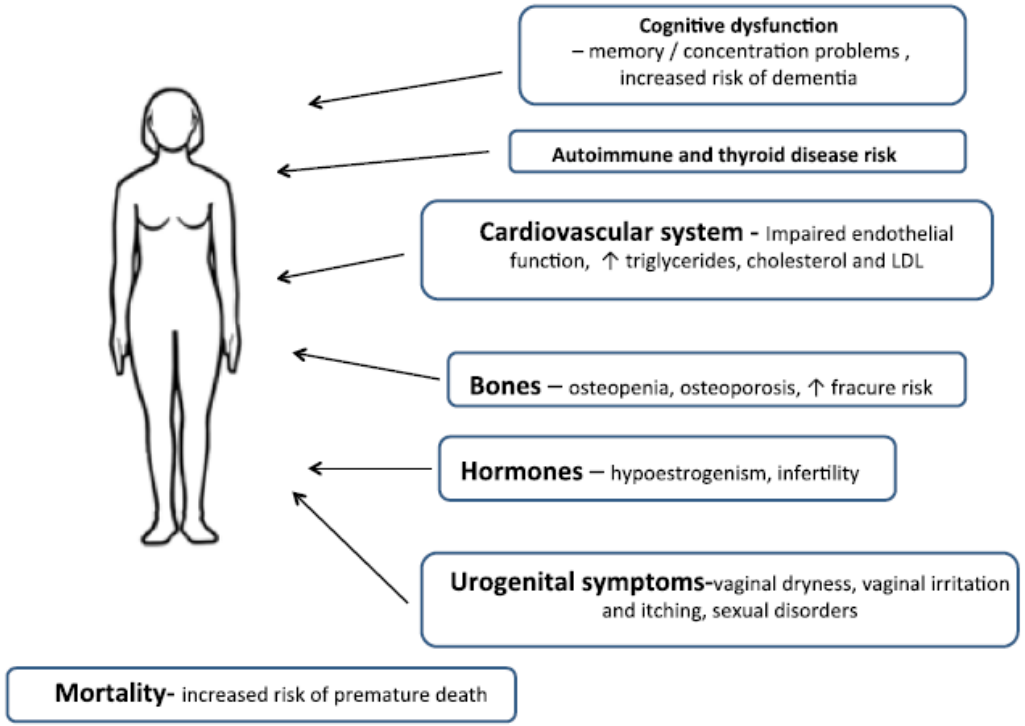
- On olemas väga väike tõenäosus spontaanseks raseduseks, vajadusel soovitada kontratseptsiooni meetodit
- Hetkel ei ole ühtegi ravimeetodit, mis aitaks taastada munasarja reservi ja suurendada loomuliku rasestumise tõenäosust
- Ootsüütide doonorlus on sobiv ja aktsepteeritud meetod viljatusravis
- Õe munaraku kasutamisega on suurem risk viljatusravi tsüklite katkestamiseks
- Kui POI on väljakujunenud, puuduvad võimalused viljakuse säilitamiseks

POI ja elukvaliteet

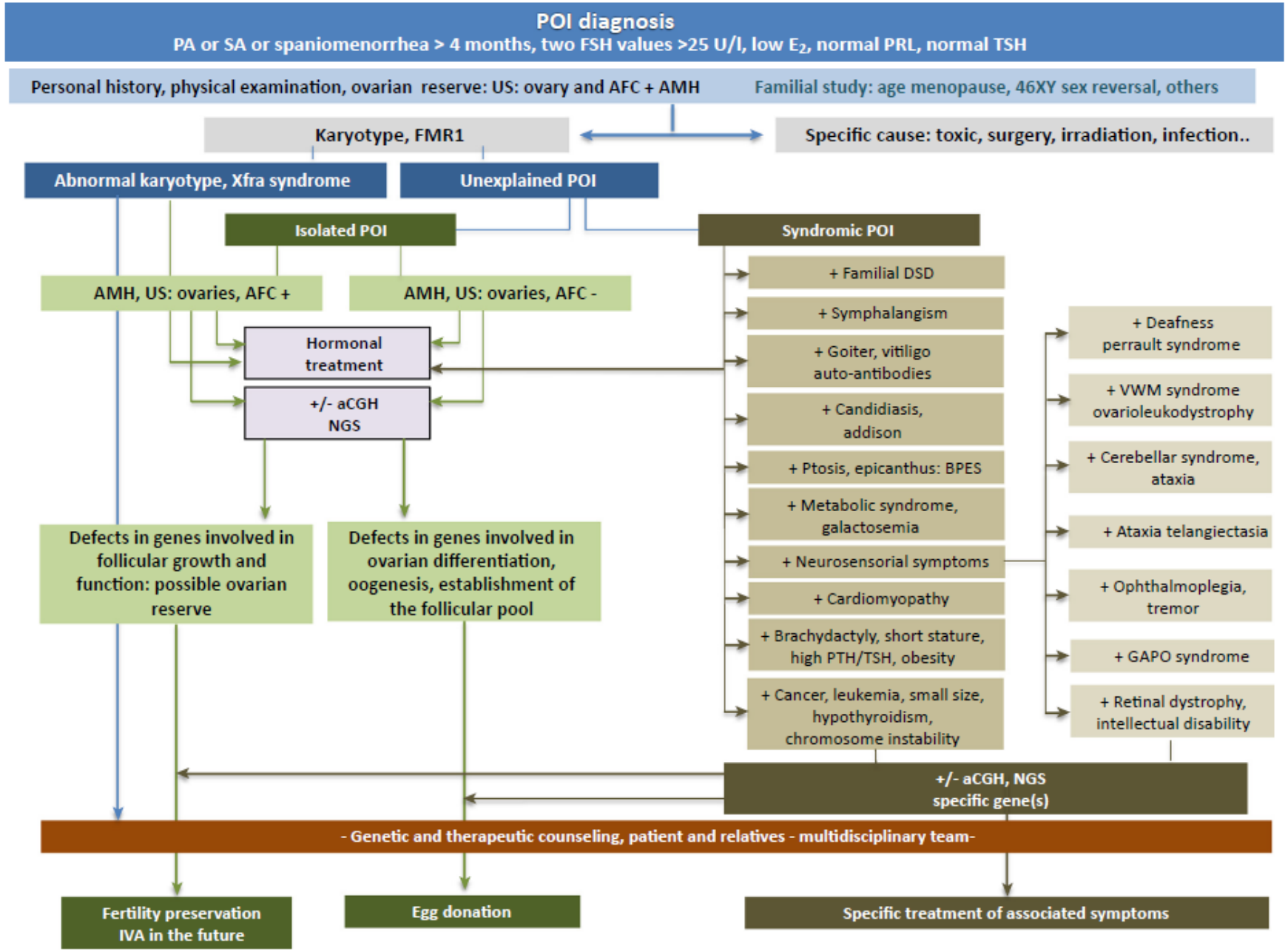
- Lisaks ravile oluline preventsioon
  - Suitsetamise lõpetamine
  - Liikumine
  - Normaalne kehakaal
  - Vererõhu mõõtmine

- Nõustamine!
  - Seksuaal- ja reproduktiivtervis, viljakus
  - Vaimne tervis

POI kaugmõjud



J Endocrinol Invest (2016) 39:983–990



Trends in Endocrinology & Metabolism, June 2018, Vol. 29, No. 6 https://doi.org/10.1016/j.tem.2018.03.010

POI- kas on lootust? Ravivõimalused tulevikus?

In vitro „uinuvate“ folliikulite aktiveerimine

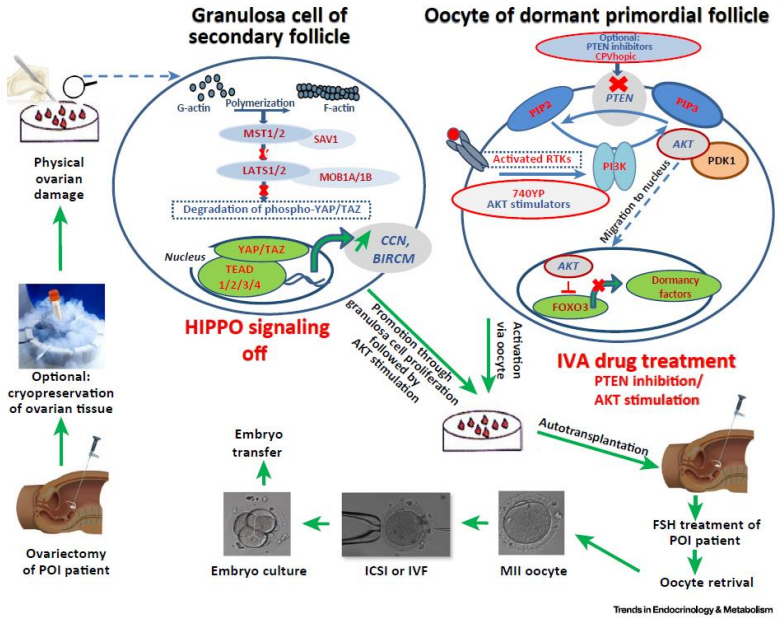


Figure 4. *In Vitro* Activation of Dormant Follicles. Ovarian cortical tissue is laparoscopically biopsied from the woman undergoing primary ovarian insufficiency (POI). The tissue is cut into slices for activation of Hippo signaling and initiation of follicular growth. Sliced tissue is then activated using a PTEN inhibitor or AKT stimulator *in vitro* for 24 hours. Thereafter, the tissue pieces can be transplanted back to the ovary of the donor woman. The activated follicles are stimulated using human recombinant follicle-stimulating hormone (FSH) for 6–10 days, until 15–17-mm sized antral follicles are seen by ultrasonography. The woman will be given human recombinant luteinizing hormone to induce the final maturation of the oocytes. The oocytes are collected 36 hours later using transvaginal ultrasound-guided needle aspiration. They are injected by intracytoplasmic sperm injection (ICSI) with sperm from the partner. The embryos are cultured for 3–5 days and the morphologically best embryo will be transferred to the intravaginal progesterone-treated female partner's womb. The rest of the embryos are cryo-stored for future transfers. IVA, *In vitro* activation; IVF, *in vitro* fertilization.

Tüvirakkude viimine munasarja

Herraiz et al, 2018; Fazeli et al, 2018;Sheikansari et al, 2018

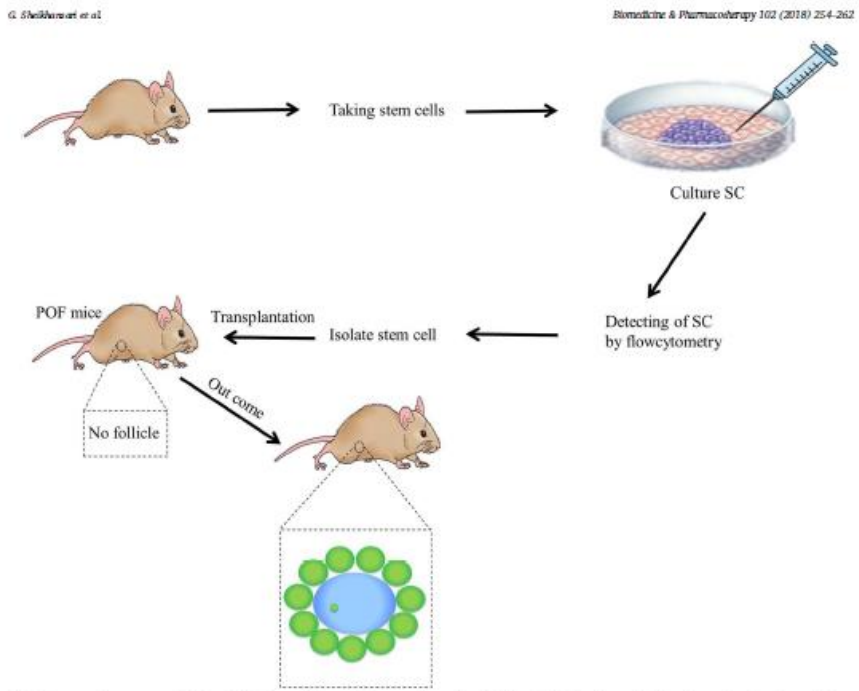


Fig. 3. Treatment of premature ovarian failure (POF) with stem cell therapy. Using stem cell to understand and treat POF mice and renewal follicle after transplantation of stem cell. Stem cell therapy leads to treatment of mice with POF.

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Kokkuvõttev sõnum

- POI on sündroom, mille korral munasarja aktiivne talitlus lakkab enne 40. eluaastat
- POI varane diagnoos on ülioluline!
  - Menstruaalfunktsiooni häire korral FSH määramine
- Õigeaegne diagnoos ja ravi alustamine võimaldab vähendada hilisemaid tüsistusi ja kaugmõjusid
- HAR võimaldab parandada elukvaliteeti
- Nõustamine: tervisemõjud, viljakus, seksuaaltervis

Tänan!

https://www.mimiwatercolorprints.com/products/ovary-watercolor-print-medical-art