Management of women with premature ovarian insufficiency

SUMMARY

Guideline of the European Society of Human Reproduction and Embryology

POI Guideline Development Group

December 2015

Disclaimer

The European Society of Human Reproduction and Embryology (hereinafter referred to as 'ESHRE') developed the current clinical practice guideline, to provide clinical recommendations to improve the quality of healthcare delivery within the European field of human reproduction and embryology. This guideline represents the views of ESHRE, which were achieved after careful consideration of the scientific evidence available at the time of preparation. In the absence of scientific evidence on certain aspects, a consensus between the relevant ESHRE stakeholders has been obtained.

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However, adherence to these clinical practice guidelines does not guarantee a successful or specific outcome, nor does it establish a standard of care. Clinical practice guidelines do not override the healthcare professional's clinical judgment in diagnosis and treatment of particular patients. Ultimately, healthcare professionals must make their own clinical decisions on a case-by-case basis, using their clinical judgment, knowledge, and expertise, and taking into account the condition, circumstances, and wishes of the individual patient, in consultation with that patient and/or the guardian or carer.

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INTRODUCTION

This ESHRE guideline on the management of women with premature ovarian insufficiency offers best practice advice on the care of women with premature ovarian insufficiency, both primary and secondary. The patient population comprises women younger than 40 years (which includes Turner Syndrome patients) and women older than 40 years, but with disease onset before 40.

Furthermore, this clinical guideline provides recommendations on the initial assessment and management of women with premature ovarian insufficiency. The initial assessment includes diagnosis, assessment of causation, and basic assessment. The management includes hormonal treatment. Since POI has consequences for health apart from gynaecological issues, these are also described. Consequences of POI and treatment options are included in the following domains: fertility and contraception, bone health, cardiovascular issues, psychosexual function, psychological function, and neurological function.

Other topics discussed are puberty induction, life expectancy, and implications for relatives of women with POI.

This guideline is limited to POI and does not apply to women with low ovarian reserve.

Summary document

This summary document contains all recommendations, as formulated by the guideline development group based on clinical evidence, taking into consideration the preferences of patients and clinicians, and benefits and harms.

For background information, a summary of the clinical evidence and the methodology, the full version of the guideline can be consulted at the ESHRE website (www.eshre.eu/guidelines)

Interpretation on the grades of recommendations 1

Grades of recommendations	Supporting evidence
A	Meta-analysis, systematic review or multiple randomized controlled trials (RCTs) (high quality)
B	Meta-analysis, systematic review or multiple RCTs (moderate quality) Single RCT, large non-randomized trial, case-control or cohort studies (high quality)
C	Single RCT, large non-randomized trial, case-control or cohort studies (moderate quality)
D	Non-analytical studies, case reports or case series (high or moderate quality)
GPP	Expert opinion

The grades of the recommendations is only based on the strength of the supporting evidence. In formulating strong or weak recommendations, the guideline group took the strength of the supporting evidence into account, but weight it against the benefits and harms, and the preferences of clinicians and patients.

RECOMMENDATIONS

Premature Ovarian Insufficiency (POI)

What should this condition be called?

The term "premature ovarian insufficiency" should be used to describe this condition in research and clinical practice.	GPP

How should POI be defined?

Premature ovarian insufficiency is a clinical syndrome defined by loss of ovarian activity before the age of 40.
POI is characterised by menstrual disturbance (amenorrhea or oligomenorrhea) with raised gonadotropins and low estradiol.

What is the prevalence of POI in the general population?

The prevalence of POI is approximately 1%. Population characteristics such as ethnicity may affect the prevalence.
In view of the long-term health consequences of POI, efforts should be made to reduce the incidence of POI. Modifiable factors may include:

- gynaecological surgical practice
- lifestyle – smoking
- modified treatment regimens for malignant and chronic diseases.

Diagnosis of POI

What are the symptoms of Premature Ovarian Insufficiency?

Clinicians should enquire about symptoms of estrogen deficiency in women presenting with oligomenorrhea or amenorrhea.	GPP
POI needs to be excluded in women with amenorrhea/oligomenorrhea or estrogen-deficiency symptoms below the age of 40 years.	GPP

What investigations should be performed for diagnosis of premature ovarian insufficiency?

The diagnosis Premature Ovarian Insufficiency is based on the presence of menstrual disturbance and biochemical confirmation.	
Although proper diagnostic accuracy in POI is lacking, the GDG recommends the following diagnostic criteria: • oligo/amenorrhea for at least 4 months, and • an elevated FSH level > 25 IU/l on two occasions > 4 weeks apart.	GPP

What are the known causes of POI and how should they be investigated?

Chromosomal analysis should be performed in all women with non-iatrogenic Premature Ovarian Insufficiency. [2-5]	C
Gonadectomy should be recommended for all women with detectable Y chromosomal material.[3]	C
Fragile-X premutation testing is indicated in POI women. [6; 2]	B
The implications of the fragile-X premutation should be discussed before the test is performed.	GPP
Autosomal genetic testing is not at present indicated in women with POI, unless there is evidence suggesting a specific mutation (e.g. BPES).	GPP
Screening for 21OH-Ab (or alternatively adrenocortical antibodies (ACA)) should be considered in women with POI of unknown cause or if an immune disorder is suspected. Refer POI patients with a positive 21OH-Ab/ACA test to an endocrinologist for testing of adrenal function and to rule out Addison's disease.[7-10]	C
Screening for thyroid (TPO-Ab) antibodies should be performed in women with POI of unknown cause or if an immune disorder is suspected. In patients with a positive TPO-Ab test, thyroid stimulating hormone (TSH) should be measured every year. [11-13]	C

There is insufficient evidence to recommend routinely screening POI women for diabetes.[11]	D
There is no indication for infection screening in women with POI. [14]	D
The possibility of POI being a consequence of a medical or surgical intervention should be discussed with women as part of the consenting process for that treatment.	GPP
Although no causal relation has been proved for cigarette smoking and POI, there is a relation to early menopause. Therefore, women who are prone to POI should be advised to stop smoking.	GPP
In a significant number of women with POI, the cause is not identified and these women are described as having unexplained or idiopathic POI.	

How often should tests for autoantibodies be repeated?

If 21OH-Ab/ACA and TPO-Ab are negative in women with POI, there is no indication for re-testing later in life, unless signs or symptoms of these endocrine diseases develop.[15]	C

Test	Implications	
	Positive test	Negative test
Genetic/Chromosomal		
Karyotyping (for diagnosis of Turner syndrome)	Refer to endocrinologist, cardiologist and geneticist	a second analysis of the karyotype in epithelial cells (in case of high clinical suspicion)
Test for Y-chromosomal material	Discuss gonadectomy with the patient	
Fra-X	Refer to geneticist	
Autosomal genetic testing[a]		
Antibodies[b]		
ACA/21OH antibodies	Refer to endocrinologist	Re-test in case of clinical signs or symptoms
TPO-Ab	Test TSH every year	

[a] *not at present indicated in women with POI, unless there is evidence suggesting a specific mutation (e.g. BPES).*

[b.] *POI of unknown cause or if an immune disorder is suspected.*

What are the implications for relatives of women with POI?

Relatives of women with the fragile-X premutation should be offered genetic counselling and testing.[6; 16]	B
Relatives of women with non-iatrogenic premature ovarian insufficiency who are concerned about their risk for developing POI should be informed that: • currently there is no proven predictive test to identify women that will develop POI, unless a mutation known to be related to POI was detected • there are no established POI preventing measures • fertility preservation appears as a promising option, although studies are lacking, and • their potential risk of earlier menopause should be taken into account when planning a family.	GPP

Sequelae of POI

LIFE EXPECTANCY

What are the consequences of POI for life expectancy?

Untreated POI is associated with reduced life expectancy, largely due to cardiovascular disease.[17-21]	C
Women with POI should be advised on how to reduce cardiovascular risk factors by not smoking, taking regular exercise, and maintaining a healthy weight.	GPP

FERTILITY AND PREGNANCY

What are the consequences of POI for fertility?

Women with POI should be informed that there is a small chance of spontaneous pregnancy.	GPP
Women with POI should be advised to use contraception if they wish to avoid pregnancy.	GPP

What fertility interventions are effective?

Inform women with POI that there are no interventions that have been reliably shown to increase ovarian activity and natural conception rates.[22]	A
Oocyte donation is an established option for fertility in women with POI.[23-26]	C
Inform women considering oocyte donation from sisters that this carries a higher risk of cycle cancellation.[25]	C
In women with established POI, the opportunity for fertility preservation is missed.	GPP

What are the obstetric risks associated with POI?

Women should be reassured that spontaneous pregnancies after idiopathic POI or most forms of chemotherapy do not show any higher obstetric or neonatal risk than in the general population.[27; 28]	B
Oocyte donation pregnancies are high risk and should be managed in an appropriate obstetric unit. Women and their partners should be encouraged to disclose the origin of their pregnancy with their obstetric team.[29-33]	C
Antenatal aneuploidy screening should be based on the age of the oocyte donor.[34; 35]	C

Pregnancies in women who have received radiation to the uterus are at high risk of obstetric complications and should be managed in an appropriate obstetric unit.[36-39; 28]	C
Pregnancies in women with Turner Syndrome are at very high risk of obstetric and non-obstetric complications and should be managed in an appropriate obstetric unit with cardiologist involvement.[40-43]	D
A cardiologist should be involved in care of pregnant women who have received anthracyclines and/or cardiac irradiation. [44; 28]	D

How should fitness for pregnancy be assessed in women with POI?

Women presenting for oocyte donation who are suspected of having POI should be fully investigated prior to oocyte donation, including thyroid and adrenal function as well as karyotype.[30]	C
Women previously exposed to anthracyclines, high dose cyclophosphamide or mediastinal irradiation should have an echocardiogram prior to pregnancy, and referral to a cardiologist if indicated.[45-49]	D
Women with Turner Syndrome should be assessed by a cardiologist with a specialist interest in adult congenital heart disease and should have a general medical and endocrine examination.	GPP
Women with POI should have their blood pressure, renal function, and thyroid function assessed prior to pregnancy. [50]	C
Pregnancy in some women can be of such high risk that clinicians may consider oocyte donation to be life threatening and therefore inappropriate.	GPP

BONE HEALTH

What are the consequences of POI for bone health?

POI is associated with reduced bone mineral density (BMD). [51-58; 2; 59; 60]	B
Reduced BMD is very likely to indicate that POI is associated with an increased risk of fracture later in life, although this has not been adequately demonstrated.	GPP

What are the treatment options for bone protection and improvement?

Women should maintain a healthy lifestyle, involving weight-bearing exercise, avoidance of smoking, and maintenance of normal body weight to optimize bone health.	GPP
A balanced diet will contain the recommended intake of calcium and vitamin D. Dietary supplementation may be required in women with inadequate vitamin D status and/or calcium intake, and may be of value in women with low BMD. [61; 62]	C
Estrogen replacement is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture. [63-65]	C
The combined oral contraceptive pill may be appropriate for some women but effects on BMD are less favourable.[66]	C
Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist. Particular caution applies to women desiring pregnancy.[67; 68]	C

How should bone health be monitored in women with POI?

It is important to consider bone health at diagnosis in POI, and during ongoing care.	GPP
Measurement of BMD at initial diagnosis of POI should be considered for all women, but especially when there are additional risk factors.[65]	C
If BMD is normal and adequate systemic estrogen replacement is commenced, the value of repeated DEXA scan is low.	GPP
If a diagnosis of osteoporosis is made and estrogen replacement or other therapy initiated, BMD measurement should be repeated within 5 years. A decrease in BMD should prompt review of estrogen replacement therapy and of other potential factors. Review by a specialist in osteoporosis may be appropriate.	GPP

CARDIOVASCULAR HEALTH

What are the consequences of POI for the cardiovascular system?

Women with POI are at increased risk of cardiovascular disease and should be advised of risk factors that they can modify through behavioural change (e.g. stopping smoking, taking regular weight-bearing exercise, healthy weight).[69-78; 20; 79-81]	B
All women diagnosed with Turner Syndrome should be evaluated by a cardiologist with expertise in congenital heart disease.[82-84]	C

Is estrogen replacement cardio-protective?

Despite lack of longitudinal outcome data, hormone replacement therapy with early initiation is strongly recommended in women with POI to control future risk of cardiovascular disease; it should be continued at least until the average age of natural menopause.[85; 78; 86; 87]	C

Should cardiovascular risk factors be monitored?

Cardiovascular risk should be assessed in women diagnosed with POI. At least blood pressure, weight and smoking status should be monitored annually with other risk factors being assessed if indicated.	GPP
In women with Turner Syndrome, cardiovascular risk factors should be assessed at diagnosis and annually monitored (at least blood pressure, smoking, weight, lipid profile, fasting plasma glucose, HbA1c) [60]	C

WELLBEING AND QUALITY OF LIFE

What are the consequences of POI on psychological wellbeing and quality of life?

A diagnosis of POI has a significant negative impact on psychological wellbeing and quality of life.[88-90]	D

What are the Management options for reduced quality of life associated with POI?

Psychological and lifestyle interventions should be accessible to women with POI.[91-93]	B

SEXUAL AND GENITO-URINARY FUNCTION

What are the consequences of POI for sexuality?

Routinely inquire about sexual wellbeing and sexual function in women with POI.	GPP

What are the management options for the effects of POI on sexuality?

Adequate estrogen replacement is regarded as a starting point for normalising sexual function. Local estrogen may be required to treat dyspareunia.[94-96]	C
Women with POI should receive adequate counselling about the possibility of using testosterone supplementation so that they can make an informed choice, in the knowledge that long-term efficacy and safety are unknown.[97; 98]	B

What treatments are available for genito-urinary symptoms in POI?

Local estrogens are effective in treatment of genito-urinary symptoms.[99]	A
Clinicians should be aware that despite seemingly adequate systemic hormone replacement therapy (HRT), women with POI may experience genito-urinary symptoms. Local estrogens may be given in addition to systemic HRT. [96]	D
Lubricants are useful for treatment of vaginal discomfort and dyspareunia for women not using HRT.[100; 101]	C

NEUROLOGICAL HEALTH

What are the consequences of POI on neurological function?

The possible detrimental effect on cognition should be discussed when planning hysterectomy and/or oophorectomy under the age of 50 years, especially for prophylactic reasons.[102-106]	D

What are the management options for the effect of POI on 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.[107-112; 106]	C
Women with POI should be advised to take lifestyle measures (e.g. exercise, cessation of smoking, maintaining a healthy weight) to reduce possible risks for cognitive impairment.	GPP

HORMONE REPLACEMENT THERAPY (HRT)

Hormone replacement therapy is indicated for the treatment of symptoms of low estrogen in women with POI.[113-115]	C
Women should be advised that HRT may have a role in primary prevention of diseases of the cardiovascular system and for bone protection. [63; 64; 85; 78; 86; 87; 65]	C

What are the risks of hormone replacement therapy?

Women with POI should be informed that HRT has not been found to increase the risk of breast cancer before the age of natural menopause.[116; 117; 21]	D
Progestogen should be given in combination with estrogen therapy to protect the endometrium in women with an intact uterus.[118]	B

What are the options for hormone replacement therapy?

17β-estradiol is preferred to ethinylestradiol or conjugated equine estrogens for estrogen replacement.[87; 66]	C
Women should be informed that whilst there may be advantages to micronized natural progesterone, the strongest evidence of endometrial protection is for oral cyclical combined treatment.	GPP
Patient preference for route and method of administration of each component of HRT must be considered when prescribing, as should contraceptive needs.	GPP

Monitoring

Once established on therapy, women with POI using HRT should have a clinical review annually, paying particular attention to compliance.	GPP
No routine monitoring tests are required but may be prompted by specific symptoms or concerns.	GPP

HRT in women with POI and special issues

Turner Syndrome

Girls and women with POI due to Turner Syndrome should be offered HRT throughout the normal reproductive lifespan.[119; 120; 82; 121-125; 66; 126]	C

BRCA gene mutation or after breast cancer

HRT is generally contra-indicated in breast cancer survivors.[127]	B
HRT is a treatment option for women carrying BRCA1/2 mutations but without personal history of breast cancer after prophylactic bilateral salpingo-oophorectomy (BSO). [128; 129; 114]	C

Endometriosis

For women with endometriosis who required oophorectomy, combined estrogen/progestogen therapy can be effective for the treatment of vasomotor symptoms and may reduce the risk of disease reactivation.[130]	C

Migraine

Migraine should not be seen as a contraindication to HRT use by women with POI.	GPP
Consideration should be given to changing dose, route of administration or regimen if migraine worsens during HRT.	GPP
Transdermal delivery may be the lowest-risk route of administration of estrogen for migraine-sufferers with aura.[131]	D

Hypertension

Hypertension should not be considered a contraindication to HRT use by women with POI.	GPP
In hypertensive women with POI, transdermal estradiol is the preferred method of delivery.[132; 87]	C

History of prior VTE

Women with POI and a history of prior venous thromboembolism (VTE) or thrombophilic disorder should be referred to a haematologist prior to commencing HRT.	GPP
Transdermal estradiol is the preferred route of delivery for women with POI at increased risk of VTE.[133]	B

Obesity

Transdermal estradiol is the preferred method of delivery for women with POI requiring HRT who are obese or overweight.[134]	C

Fibroids

Fibroids are not a contraindication to HRT use by women with POI.[135; 136]	B

Androgens

Women should be informed that androgen treatment is only supported by limited data, and that long-term health effects are not clear yet.[137-144]	C
If androgen therapy is commenced, treatment effect should be evaluated after 3-6 months and should possibly be limited to 24 months.	GPP

COMPLEMENTARY TREATMENTS

What complementary treatments are available in POI?

Women with POI should be advised of risk factors that they can modify through behavioural change (e.g. stopping smoking, taking regular weight-bearing exercise, healthy weight).	GPP
Women should be informed that for most alternative and complementary treatments evidence on efficacy is limited and data on safety are lacking.[145]	B

PUBERTY INDUCTION

How should puberty be induced?

Puberty should be induced or progressed with 17β-estradiol, starting with low dose at the age of 12 with a gradual increase over 2 to 3 years.[146-148]	C
In cases of late diagnosis and for those girls in whom growth is not a concern, a modified regimen of estradiol can be considered.[149]	D
Evidence for the optimum mode of administration (oral or transdermal) is inconclusive. Transdermal estradiol results in more physiological estrogen levels and is therefore preferred.[150-156]	B
The oral contraceptive pill is contra-indicated for puberty induction.[157; 158]	D
Begin cyclical progestogens after at least 2 years of estrogen or when breakthrough bleeding occurs.[157; 118]	C

Table 13.1: Estrogen substitution therapy in adolescence (adapted from [157])

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[a] 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[b] 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[c]

[a] *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.*

[b] *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.*

[c] *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 [159].*

GUIDELINE GROUP

This guideline was developed by a guideline development group (GDG) set up by the ESHRE Special Interest Group reproductive endocrinology. The GDG constituted clinicians with special interest in women with premature Ovarian Insufficiency, including an expert in bone health, cardiology, psychology and neurology, a literature methodology expert and a patient representative.

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REFERENCES

1 Vermeulen N, D'Angelo A, de Sutter P, Nelen WLDM. Manual for ESHRE Guideline Development 2014; Version 2.0, Available from www.eshre.eu.

2 Bachelot A, Rouxel A, Massin N, Dulon J, Courtillot C, Matuchansky C, Badachi Y, Fortin A, Paniel B, Lecuru F, Lefrere-Belda MA, Constancis E, Thibault E, Meduri G, Guiochon-Mantel A, Misrahi M, Kuttenn F, Touraine P, Group P-GS. Phenotyping and genetic studies of 357 consecutive patients presenting with premature ovarian failure. *Eur J Endocrinol* 2009;**161**: 179-187.

3 Rocha VB, Guerra-Junior G, Marques-de-Faria AP, de Mello MP, Maciel-Guerra AT. Complete gonadal dysgenesis in clinical practice: the 46,XY karyotype accounts for more than one third of cases. *Fertil Steril* 2011;**96**: 1431-1434.

4 Jiao X, Qin C, Li J, Qin Y, Gao X, Zhang B, Zhen X, Feng Y, Simpson JL, Chen ZJ. Cytogenetic analysis of 531 Chinese women with premature ovarian failure. *Hum Reprod* 2012;**27**: 2201-2207.

5 Kalantari H, Madani T, Zari Moradi S, Mansouri Z, Almadani N, Gourabi H, Mohseni Meybodi A. Cytogenetic analysis of 179 Iranian women with premature ovarian failure. *Gynecol Endocrinol* 2013;**29**: 588-591.

6 Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada, Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists, Chitayat D, Wyatt PR, Wilson RD, Johnson JA, Audibert F, Allen V, Gagnon A, Langlois S, Blight C, Brock JA, Desilets V, Farell SA, Geraghty M, Nelson T, Nikkel SM, Skidmore D, Shugar A. Fragile X testing in obstetrics and gynaecology in Canada. *J Obstet Gynaecol Can* 2008;**30**: 837-846.

7 Chen S, Sawicka J, Betterle C, Powell M, Prentice L, Volpato M, Rees Smith B, Furmaniak J. Autoantibodies to steroidogenic enzymes in autoimmune polyglandular syndrome, Addison's disease, and premature ovarian failure. *J Clin Endocrinol Metab* 1996;**81**: 1871-1876.

8 Bakalov VK, Vanderhoof VH, Bondy CA, Nelson LM. Adrenal antibodies detect asymptomatic auto-immune adrenal insufficiency in young women with spontaneous premature ovarian failure. *Hum Reprod* 2002;**17**: 2096-2100.

9 Dal Pra C, Chen S, Furmaniak J, Smith BR, Pedini B, Moscon A, Zanchetta R, Betterle C. Autoantibodies to steroidogenic enzymes in patients with premature ovarian failure with and without Addison's disease. *Eur J Endocrinol* 2003;**148**: 565-570.

10 Husebye ES, Lovas K. Immunology of Addison's disease and premature ovarian failure. *Endocrinol Metab Clin North Am* 2009;**38**: 389-405, ix.

11 Kim TJ, Anasti JN, Flack MR, Kimzey LM, Defensor RA, Nelson LM. Routine endocrine screening for patients with karyotypically normal spontaneous premature ovarian failure. *Obstet Gynecol* 1997;**89**: 777-779.

12 Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 2002;**87**: 489-499.

13 Goswami R, Marwaha RK, Goswami D, Gupta N, Ray D, Tomar N, Singh S. Prevalence of thyroid autoimmunity in sporadic idiopathic hypoparathyroidism in comparison to type 1 diabetes and premature ovarian failure. *J Clin Endocrinol Metab* 2006;**91**: 4256-4259.

14 Kokcu A. Premature ovarian failure from current perspective. *Gynecol Endocrinol* 2010;**26**: 555-562.

15 Betterle C, Volpato M, Rees Smith B, Furmaniak J, Chen S, Greggio NA, Sanzari M, Tedesco F, Pedini B, Boscaro M, Presotto F. I. Adrenal cortex and steroid 21-hydroxylase autoantibodies in adult patients with organ-specific autoimmune diseases: markers of low progression to clinical Addison's disease. *J Clin Endocrinol Metab* 1997;**82**: 932-938.

16 Finucane B, Abrams L, Cronister A, Archibald AD, Bennett RL, McConkie-Rosell A. Genetic counseling and testing for FMR1 gene mutations: practice guidelines of the national society of genetic counselors. *J Genet Couns* 2012;**21**: 752-760.

17 Ossewaarde ME, Bots ML, Verbeek AL, Peeters PH, van der Graaf Y, Grobbee DE, van der Schouw YT. Age at menopause, cause-specific mortality and total life expectancy. *Epidemiology* 2005;**16**: 556-562.

18 Amagai Y, Ishikawa S, Gotoh T, Kayaba K, Nakamura Y, Kajii E. Age at menopause and mortality in Japan: the Jichi Medical School Cohort Study. *J Epidemiol* 2006;**16**: 161-166.

19 Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ, 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. *Lancet Oncol* 2006;**7**: 821-828.

20 Hong JS, Yi SW, Kang HC, Jee SH, Kang HG, Bayasgalan G, Ohrr H. Age at menopause and cause-specific mortality in South Korean women: Kangwha Cohort Study. *Maturitas* 2007;**56**: 411-419.

21 Wu X, Cai H, Kallianpur A, Li H, Yang G, Gao J, Xiang YB, Ji BT, Yu T, Zheng W, Shu XO. Impact of Premature Ovarian Failure on Mortality and Morbidity among Chinese Women. *PLoS One* 2014;**9**: e89597.

22 van Kasteren YM, Schoemaker J. Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. *Hum Reprod Update* 1999;**5**: 483-492.

23 Sauer MV, Paulson RJ, Ary BA, Lobo RA. Three hundred cycles of oocyte donation at the University of Southern California: assessing the effect of age and infertility diagnosis on pregnancy and implantation rates. *J Assist Reprod Genet* 1994;**11**: 92-96.

24 Templeton A, Morris JK, Parslow W. Factors that affect outcome of in-vitro fertilisation treatment. *Lancet* 1996;**348**: 1402-1406.

25 Sung L, Bustillo M, Mukherjee T, Booth G, Karstaedt A, Copperman AB. Sisters of women with premature ovarian failure may not be ideal ovum donors. *Fertil Steril* 1997;**67**: 912-916.

26 Oyesanya OA, Olufowobi O, Ross W, Sharif K, Afnan M. Prognosis of oocyte donation cycles: a prospective comparison of the in vitro fertilization-embryo transfer cycles of recipients who used shared oocytes versus those who used altruistic donors. *Fertil Steril* 2009;**92**: 930-936.

27 Signorello LB, Mulvihill JJ, Green DM, Munro HM, Stovall M, Weathers RE, Mertens AC, Whitton JA, Robison LL, Boice JD, Jr. Congenital anomalies in the children of cancer survivors: a report from the childhood cancer survivor study. *J Clin Oncol* 2012;**30**: 239-245.

28 Scottish Intercollegiate Guidelines Network (SIGN). Long term follow up of survivors of childhood cancer. Edinburgh: SIGN; 2013 *(SIGN publication no 132)* 2013;Available from URL: http://www.sign.ac.uk.

29 Pados G, Camus M, Van Steirteghem A, Bonduelle M, Devroey P. The evolution and outcome of pregnancies from oocyte donation. *Hum Reprod* 1994;**9**: 538-542.

30 Abdalla HI, Billett A, Kan AK, Baig S, Wren M, Korea L, Studd JW. Obstetric outcome in 232 ovum donation pregnancies. *Br J Obstet Gynaecol* 1998;**105**: 332-337.

31 Soderstrom-Anttila V, Tiitinen A, Foudila T, Hovatta O. Obstetric and perinatal outcome after oocyte donation: comparison with in-vitro fertilization pregnancies. *Hum Reprod* 1998;**13**: 483-490.

32 Nelson SM, Lawlor DA. Predicting live birth, preterm delivery, and low birth weight in infants born from in vitro fertilisation: a prospective study of 144,018 treatment cycles. *PLoS Med* 2011;**8**: e1000386.

33 Stoop D, Baumgarten M, Haentjens P, Polyzos NP, De Vos M, Verheyen G, Camus M, Devroey P. Obstetric outcome in donor oocyte pregnancies: a matched-pair analysis. *Reprod Biol Endocrinol* 2012;**10**: 42.

34 Bowman MC, Saunders DM. Rates of aneuploidy in oocytes of older women: are equivocal findings of concern for postmenopausal embryo recipients? *Hum Reprod* 1994;**9**: 1200-1201.

35 Donnenfeld AE, Icke KV, Pargas C, Dowman C. Biochemical screening for aneuploidy in ovum donor pregnancies. *Am J Obstet Gynecol* 2002;**187**: 1222-1225.

36 Bath LE, Critchley HO, Chambers SE, Anderson RA, Kelnar CJ, Wallace WH. Ovarian and uterine characteristics after total body irradiation in childhood and adolescence: response to sex steroid replacement. *Br J Obstet Gynaecol* 1999;**106**: 1265-1272.

37 Larsen EC, Schmiegelow K, Rechnitzer C, Loft A, Muller J, Andersen AN. Radiotherapy at a young age reduces uterine volume of childhood cancer survivors. *Acta Obstet Gynecol Scand* 2004;**83**: 96-102.

38 Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. *Int J Radiat Oncol Biol Phys* 2009;**73**: 1304-1312.

39 Signorello LB, Mulvihill JJ, Green DM, Munro HM, Stovall M, Weathers RE, Mertens AC, Whitton JA, Robison LL, Boice JD, Jr. Stillbirth and neonatal death in relation to radiation exposure before conception: a retrospective cohort study. *Lancet* 2010;**376**: 624-630.

40 Bryman I, Sylven L, Berntorp K, Innala E, Bergstrom I, Hanson C, Oxholm M, Landin-Wilhelmsen K. Pregnancy rate and outcome in Swedish women with Turner syndrome. *Fertil Steril* 2011;**95**: 2507-2510.

41 Hadnott TN, Gould HN, Gharib AM, Bondy CA. Outcomes of spontaneous and assisted pregnancies in Turner syndrome: the U.S. National Institutes of Health experience. *Fertil Steril* 2011;**95**: 2251-2256.

42 Karnis MF. Catastrophic consequences of assisted reproduction: the case of Turner syndrome. *Semin Reprod Med* 2012;**30**: 116-122.

43 Hagman A, Loft A, Wennerholm UB, Pinborg A, Bergh C, Aittomaki K, Nygren KG, Bente Romundstad L, Hazekamp J, Soderstrom-Anttila V. Obstetric and neonatal outcome after oocyte donation in 106 women with Turner syndrome: a Nordic cohort study. *Hum Reprod* 2013;**28**: 1598-1609.

44 Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, Donaldson SS, Green DM, Sklar CA, Robison LL, Leisenring WM. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ* 2009;**339**: b4606.

45 Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000;**342**: 1077-1084.

46 Gorton H, Wilson R, Robinson A, Lyons G. Survivors of childhood cancers: implications for obstetric anaesthesia. *Br J Anaesth* 2000;**85**: 911-913.

47 Bar J, Davidi O, Goshen Y, Hod M, Yaniv I, Hirsch R. Pregnancy outcome in women treated with doxorubicin for childhood cancer. *Am J Obstet Gynecol* 2003;**189**: 853-857.

48 van Dalen EC, van der Pal HJ, van den Bos C, Kok WE, Caron HN, Kremer LC. Clinical heart failure during pregnancy and delivery in a cohort of female childhood cancer survivors treated with anthracyclines. *Eur J Cancer* 2006;**42**: 2549-2553.

49 Altena R, Gietema JA, van Veldhuisen DJ, Reyners AK. Pregnancy unbosoms the heart of breast cancer survivors. *Ann Oncol* 2012;**23**: 2206-2208.

50 Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999;**341**: 549-555.

51 Ratcliffe MA, Lanham SA, Reid DM, Dawson AA. Bone mineral density (BMD) in patients with lymphoma: the effects of chemotherapy, intermittent corticosteroids and premature menopause. *Hematol Oncol* 1992;**10**: 181-187.

52 Conway GS, Kaltsas G, Patel A, Davies MC, Jacobs HS. Characterization of idiopathic premature ovarian failure. *Fertil Steril* 1996;**65**: 337-341.

53 Castaneda S, Carmona L, Carvajal I, Arranz R, Diaz A, Garcia-Vadillo A. Reduction of bone mass in women after bone marrow transplantation. *Calcif Tissue Int* 1997;**60**: 343-347.

54 Hadjidakis D, Kokkinakis E, Sfakianakis M, Raptis SA. The type and time of menopause as decisive factors for bone mass changes. *Eur J Clin Invest* 1999;**29**: 877-885.

55 Park KH, Lee SJ, Kim JY, Kim JY, Bai SW, Kim JW. A concomitant decrease in cortical and trabecular bone mass in isolated hypogonadotropic hypogonadism and gonadal dysgenesis. *Yonsei Med J* 1999;**40**: 444-449.

56 Bakalov VK, Axelrod L, Baron J, Hanton L, Nelson LM, Reynolds JC, Hill S, Troendle J, Bondy CA. Selective reduction in cortical bone mineral density in turner syndrome independent of ovarian hormone deficiency. *J Clin Endocrinol Metab* 2003;**88**: 5717-5722.

57 Han TS, Goswami D, Trikudanathan S, Creighton SM, Conway GS. Comparison of bone mineral density and body proportions between women with complete androgen insensitivity syndrome and women with gonadal dysgenesis. *Eur J Endocrinol* 2008;**159**: 179-185.

58 Michala L, Goswami D, Creighton SM, Conway GS. Swyer syndrome: presentation and outcomes. *BJOG* 2008;**115**: 737-741.

59 Popat VB, Calis KA, Vanderhoof VH, Cizza G, Reynolds JC, Sebring N, Troendle JF, Nelson LM. Bone mineral density in estrogen-deficient young women. *J Clin Endocrinol Metab* 2009;**94**: 2277-2283.

60 Freriks K, Timmermans J, Beerendonk CC, Verhaak CM, Netea-Maier RT, Otten BJ, Braat DD, Smeets DF, Kunst DH, Hermus AR, Timmers HJ. Standardized multidisciplinary evaluation yields significant previously undiagnosed morbidity in adult women with Turner syndrome. *J Clin Endocrinol Metab* 2011;**96**: E1517-1526.

61 Bours SP, van Geel TA, Geusens PP, Janssen MJ, Janzing HM, Hoffland GA, Willems PC, van den Bergh JP. Contributors to secondary osteoporosis and metabolic bone diseases in patients presenting with a clinical fracture. *J Clin Endocrinol Metab* 2011;**96**: 1360-1367.

62 Challoumas D, Cobbold C, Dimitrakakis G. Effects of calcium intake on the cardiovascular system in postmenopausal women. *Atherosclerosis* 2013;**231**: 1-7.

63 Lindsay R, Hart DM, Forrest C, Baird C. Prevention of spinal osteoporosis in oophorectomised women. *Lancet* 1980;**2**: 1151-1154.

64 Prior JC, Vigna YM, Wark JD, Eyre DR, Lentle BC, Li DK, Ebeling PR, Atley L. Premenopausal ovariectomy-related bone loss: a randomized, double-blind, one-year trial of conjugated estrogen or medroxyprogesterone acetate. *J Bone Miner Res* 1997;**12**: 1851-1863.

65 Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY, Scientific Advisory Board of the European Society for C, Economic Aspects of O, Osteoarthritis, the Committee of Scientific Advisors of the International Osteoporosis F. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2013;**24**: 23-57.

66 Crofton PM, Evans N, Bath LE, Warner P, Whitehead TJ, Critchley HO, Kelnar CJ, Wallace WH. Physiological versus standard sex steroid replacement in young women with premature ovarian failure: effects on bone mass acquisition and turnover. *Clin Endocrinol (Oxf)* 2010;**73**: 707-714.

67 Stevenson M, Jones ML, De Nigris E, Brewer N, Davis S, Oakley J. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. *Health Technol Assess* 2005;**9**: 1-160.

68 Shapiro CL, Halabi S, Hars V, Archer L, Weckstein D, Kirshner J, Sikov W, Winer E, Burstein HJ, Hudis C, Isaacs C, Schilsky R, Paskett E. Zoledronic acid preserves bone mineral density in premenopausal women who develop ovarian failure due to adjuvant chemotherapy: final results from CALGB trial 79809. *Eur J Cancer* 2011;**47**: 683-689.

69 van der Schouw YT, van der Graaf Y, Steyerberg EW, Eijkemans JC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. *Lancet* 1996;**347**: 714-718.

70 Cooper GS, Sandler DP. Age at natural menopause and mortality. *Ann Epidemiol* 1998;**8**: 229-235.

71 Hu FB, Grodstein F, Hennekens CH, Colditz GA, Johnson M, Manson JE, Rosner B, Stampfer MJ. Age at natural menopause and risk of cardiovascular disease. *Arch Intern Med* 1999;**159**: 1061-1066.

72 Jacobsen BK, Knutsen SF, Fraser GE. Age at natural menopause and total mortality and mortality from ischemic heart disease: the Adventist Health Study. *J Clin Epidemiol* 1999;**52**: 303-307.

73 de Kleijn MJ, van der Schouw YT, Verbeek AL, Peeters PH, Banga JD, van der Graaf Y. Endogenous estrogen exposure and cardiovascular mortality risk in postmenopausal women. *Am J Epidemiol* 2002;**155**: 339-345.

74 Jacobsen BK, Heuch I, Kvale G. Age at natural menopause and all-cause mortality: a 37-year follow-up of 19,731 Norwegian women. *Am J Epidemiol* 2003;**157**: 923-929.

75 Jacobsen BK, Heuch I, Kvale G. Age at natural menopause and stroke mortality: cohort study with 3561 stroke deaths during 37-year follow-up. *Stroke* 2004;**35**: 1548-1551.

76 Mondul AM, Rodriguez C, Jacobs EJ, Calle EE. Age at natural menopause and cause-specific mortality. *Am J Epidemiol* 2005;**162**: 1089-1097.

77 Atsma F, Bartelink ML, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause* 2006;**13**: 265-279.

78 Lokkegaard E, Jovanovic Z, Heitmann BL, Keiding N, Ottesen B, Pedersen AT. The association between early menopause and risk of ischaemic heart disease: influence of Hormone Therapy. *Maturitas* 2006;**53**: 226-233.

79 Baba Y, Ishikawa S, Amagi Y, Kayaba K, Gotoh T, Kajii E. Premature menopause is associated with increased risk of cerebral infarction in Japanese women. *Menopause* 2010;**17**: 506-510.

80 Gallagher LG, Davis LB, Ray RM, Psaty BM, Gao DL, Checkoway H, Thomas DB. Reproductive history and mortality from cardiovascular disease among women textile workers in Shanghai, China. *Int J Epidemiol* 2011;**40**: 1510-1518.

81 Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvanne M, Op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F, European Association for Cardiovascular P, Rehabilitation. European guidelines on cardiovascular disease prevention in clinical practice (version 2012) : the fifth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Int J Behav Med* 2012;**19**: 403-488.

82 Gravholt CH, Juul S, Naeraa RW, Hansen J. Morbidity in Turner syndrome. *J Clin Epidemiol* 1998;**51**: 147-158.

83 Bondy CA. Congenital cardiovascular disease in Turner syndrome. *Congenit Heart Dis* 2008;**3**: 2-15.

84 Sharma J, Friedman D, Dave-Sharma S, Harbison M. Aortic distensibility and dilation in Turner's syndrome. *Cardiol Young* 2009;**19**: 568-572.

85 Kalantaridou SN, Naka KK, Papanikolaou E, Kazakos N, Kravariti M, Calis KA, Paraskevaidis EA, Sideris DA, Tsatsoulis A, Chrousos GP, Michalis LK. Impaired endothelial function in young women with premature ovarian failure: normalization with hormone therapy. *J Clin Endocrinol Metab* 2004;**89**: 3907-3913.

86 Ostberg JE, Storry C, Donald AE, Attar MJ, Halcox JP, Conway GS. A dose-response study of hormone replacement in young hypogonadal women: effects on intima media thickness and metabolism. *Clin Endocrinol (Oxf)* 2007;**66**: 557-564.

87 Langrish JP, Mills NL, Bath LE, Warner P, Webb DJ, Kelnar CJ, Critchley HO, Newby DE, Wallace WH. Cardiovascular effects of physiological and standard sex steroid replacement regimens in premature ovarian failure. *Hypertension* 2009;**53**: 805-811.

88 Liao KL, Wood N, Conway GS. Premature menopause and psychological well-being. *J Psychosom Obstet Gynaecol* 2000;**21**: 167-174.

89 Schmidt PJ, Luff JA, Haq NA, Vanderhoof VH, Koziol DE, Calis KA, Rubinow DR, Nelson LM. Depression in women with spontaneous 46, XX primary ovarian insufficiency. *J Clin Endocrinol Metab* 2011;**96**: E278-287.

90 Mann E, Singer D, Pitkin J, Panay N, Hunter MS. Psychosocial adjustment in women with premature menopause: a cross-sectional survey. *Climacteric* 2012;**15**: 481-489.

91 Boivin J. A review of psychosocial interventions in infertility. *Soc Sci Med* 2003;**57**: 2325-2341.

92 Duijts SF, van Beurden M, Oldenburg HS, Hunter MS, Kieffer JM, Stuiver MM, Gerritsma MA, Menke-Pluymers MB, Plaisier PW, Rijna H, Lopes Cardozo AM, Timmers G, van der Meij S, van der Veen H, Bijker N, de Widt-Levert LM, Geenen MM, Heuff G, van Dulken EJ, Boven E, Aaronson NK. Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: results of a randomized, controlled, multicenter trial. *J Clin Oncol* 2012;**30**: 4124-4133.

93 Mann E, Smith MJ, Hellier J, Balabanovic JA, Hamed H, Grunfeld EA, Hunter MS. Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial. *Lancet Oncol* 2012;**13**: 309-318.

94 Sarrel PM. Sexuality in the middle years. *Obstet Gynecol Clin North Am* 1987;**14**: 49-62.

95 Rubinow DR, Schmidt PJ, Roca CA. Estrogen-serotonin interactions: implications for affective regulation. *Biol Psychiatry* 1998;**44**: 839-850.

96 Pacello PC, Yela DA, Rabelo S, Giraldo PC, Benetti-Pinto CL. Dyspareunia and lubrication in premature ovarian failure using hormonal therapy and vaginal health. *Climacteric* 2013.

97 Alexander JL, Kotz K, Dennerstein L, Kutner SJ, Wallen K, Notelovitz M. The effects of postmenopausal hormone therapies on female sexual functioning: a review of double-blind, randomized controlled trials. *Menopause* 2004;**11**: 749-765.

98 Kingsberg SA, Simon JA, Goldstein I. The current outlook for testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. *J Sex Med* 2008;**5 Suppl 4**: 182-193; quiz 193.

99 Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev* 2006: CD001500.

100 Le Donne M, Caruso C, Mancuso A, Costa G, Iemmo R, Pizzimenti G, Cavallari V. The effect of vaginally administered genistein in comparison with hyaluronic acid on atrophic epithelium in postmenopause. *Arch Gynecol Obstet* 2011;**283**: 1319-1323.

101 Grimaldi EF, Restaino S, Inglese S, Foltran L, Sorz A, Di Lorenzo G, Guaschino S. Role of high molecular weight hyaluronic acid in postmenopausal vaginal discomfort. *Minerva Ginecol* 2012;**64**: 321-329.

102 Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, Melton LJ, 3rd. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. *Neurology* 2007;**69**: 1074-1083.

103 Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, Melton LJ, 3rd. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. *Neurology* 2008;**70**: 200-209.

104 Vearncombe KJ, Pachana NA. Is cognitive functioning detrimentally affected after early, induced menopause? *Menopause* 2009;**16**: 188-198.

105 Phung TK, Waltoft BL, Laursen TM, Settnes A, Kessing LV, Mortensen PB, Waldemar G. Hysterectomy, oophorectomy and risk of dementia: a nationwide historical cohort study. *Dement Geriatr Cogn Disord* 2010;**30**: 43-50.

106 Bove R, Secor E, Chibnik LB, Barnes LL, Schneider JA, Bennett DA, De Jager PL. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. *Neurology* 2014;**82**: 222-229.

107 Sherwin BB. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. *Psychoneuroendocrinology* 1988;**13**: 345-357.

108 Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. *Psychoneuroendocrinology* 1992;**17**: 485-495.

109 Sherwin BB. Estrogenic effects on memory in women. *Ann N Y Acad Sci* 1994;**743**: 213-230; discussion 230-211.

110 File SE, Heard JE, Rymer J. Trough oestradiol levels associated with cognitive impairment in post-menopausal women after 10 years of oestradiol implants. *Psychopharmacology* 2002;**161**: 107-112.

111 Kritz-Silverstein D, Barrett-Connor E. Hysterectomy, oophorectomy, and cognitive function in older women. *J Am Geriatr Soc* 2002;**50**: 55-61.

112 Hogervorst E, Bandelow S. Sex steroids to maintain cognitive function in women after the menopause: a meta-analyses of treatment trials. *Maturitas* 2010;**66**: 56-71.

113 Piccioni P, Scirpa P, D'Emilio I, Sora F, Scarciglia M, Laurenti L, De Matteis S, Sica S, Leone G, Chiusolo P. Hormonal replacement therapy after stem cell transplantation. *Maturitas* 2004;**49**: 327-333.

114 Madalinska JB, van Beurden M, Bleiker EM, Valdimarsdottir HB, Hollenstein J, Massuger LF, Gaarenstroom KN, Mourits MJ, Verheijen RH, van Dorst EB, van der Putten H, van der Velden K, Boonstra H, Aaronson NK. The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy. *J Clin Oncol* 2006;**24**: 3576-3582.

115 Absolom K, Eiser C, Turner L, Ledger W, Ross R, Davies H, Coleman R, Hancock B, Snowden J, Greenfield D, Late Effects Group S. Ovarian failure following cancer treatment: current management and quality of life. *Hum Reprod* 2008;**23**: 2506-2512.

116 Benetti-Pinto CL, Soares PM, Magna LA, Petta CA, Dos Santos CC. Breast density in women with premature ovarian failure using hormone therapy. *Gynecol Endocrinol* 2008;**24**: 40-43.

117 Soares PM, Cabello C, Magna LA, Tinois E, Benetti-Pinto CL. Breast density in women with premature ovarian failure or postmenopausal women using hormone therapy: analytical cross-sectional study. *Sao Paulo Med J* 2010;**128**: 211-214.

118 Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. *Cochrane Database Syst Rev* 2012;**8**: CD000402.

119 Downey J, Elkin EJ, Ehrhardt AA, Meyer-Bahlburg HF, Bell JJ, Morishima A. Cognitive ability and everyday functioning in women with Turner syndrome. *J Learn Disabil* 1991;**24**: 32-39.

120 Swillen A, Fryns JP, Kleczkowska A, Massa G, Vanderschueren-Lodeweyckx M, Van den Berghe H. Intelligence, behaviour and psychosocial development in Turner syndrome. A cross-sectional study of 50 pre-adolescent and adolescent girls (4-20 years). *Genet Couns* 1993;**4**: 7-18.

121 Romans SM, Stefanatos G, Roeltgen DP, Kushner H, Ross JL. Transition to young adulthood in Ullrich-Turner syndrome: neurodevelopmental changes. *Am J Med Genet* 1998;**79**: 140-147.

122 Ross JL, Roeltgen D, Feuillan P, Kushner H, Cutler GB, Jr. Effects of estrogen on nonverbal processing speed and motor function in girls with Turner's syndrome. *J Clin Endocrinol Metab* 1998;**83**: 3198-3204.

123 Elsheikh M, Bird R, Casadei B, Conway GS, Wass JA. The effect of hormone replacement therapy on cardiovascular hemodynamics in women with Turner's syndrome. *J Clin Endocrinol Metab* 2000;**85**: 614-618.

124 Khastgir G, Studd JW, Fox SW, Jones J, Alaghband-Zadeh J, Chow JW. A longitudinal study of the effect of subcutaneous estrogen replacement on bone in young women with Turner's syndrome. *J Bone Miner Res* 2003;**18**: 925-932.

125 Mortensen KH, Hansen KW, Erlandsen M, Christiansen JS, Gravholt CH. Ambulatory arterial stiffness index in Turner syndrome: the impact of sex hormone replacement therapy. *Horm Res* 2009;**72**: 184-189.

126 Kodama M, Komura H, Kodama T, Nishio Y, Kimura T. Estrogen therapy initiated at an early age increases bone mineral density in Turner syndrome patients. *Endocr J* 2012;**59**: 153-159.

127 Antoine C, Liebens F, Carly B, Pastijn A, Neusy S, Rozenberg S. Safety of hormone therapy after breast cancer: a qualitative systematic review. *Hum Reprod* 2007;**22**: 616-622.

128 Armstrong K, Schwartz JS, Randall T, Rubin SC, Weber B. Hormone replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision analysis. *J Clin Oncol* 2004;**22**: 1045-1054.

129 Rebbeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, Isaacs C, Olopade OI, Neuhausen SL, van 't Veer L, Eeles R, Evans DG, Tomlinson G, Matloff E, Narod SA, Eisen A, Domchek S, Armstrong K, Weber BL. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2005;**23**: 7804-7810.

130 Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A, Prentice A, Saridogan E, Soriano D, Nelen W, European Society of Human R, Embryology. ESHRE guideline: management of women with endometriosis. *Hum Reprod* 2014;**29**: 400-412.

131 Nappi RE, Cagnacci A, Granella F, Piccinini F, Polatti F, Facchinetti F. Course of primary headaches during hormone replacement therapy. *Maturitas* 2001;**38**: 157-163.

132 White WB. Drospirenone with 17beta-estradiol in the postmenopausal woman with hypertension. *Climacteric* 2007;**10 Suppl 1**: 25-31.

133 Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ* 2008;**336**: 1227-1231.

134 Canonico M, Oger E, Conard J, Meyer G, Levesque H, Trillot N, Barrellier MT, Wahl D, Emmerich J, Scarabin PY, Estrogen, Group THRS. Obesity and risk of venous thromboembolism among postmenopausal women: differential impact of hormone therapy by route of estrogen administration. The ESTHER Study. *J Thromb Haemost* 2006;**4**: 1259-1265.

135 Ang WC, Farrell E, Vollenhoven B. Effect of hormone replacement therapies and selective estrogen receptor modulators in postmenopausal women with uterine leiomyomas: a literature review. *Climacteric* 2001;**4**: 284-292.

136 Ciarmela P, Ciavattini A, Giannubilo SR, Lamanna P, Fiorini R, Tranquilli AL, Christman GM, Castellucci M. Management of leiomyomas in perimenopausal women. *Maturitas* 2014;**78**: 168-173.

137 Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, Burki RE, Ginsburg ES, Rosen RC, Leiblum SR, Caramelli KE, Mazer NA. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000;**343**: 682-688.

138 Braunstein GD, Sundwall DA, Katz M, Shifren JL, Buster JE, Simon JA, Bachman G, Aguirre OA, Lucas JD, Rodenberg C, Buch A, Watts NB. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Arch Intern Med* 2005;**165**: 1582-1589.

139 Buster JE, Kingsberg SA, Aguirre O, Brown C, Breaux JG, Buch A, Rodenberg CA, Wekselman K, Casson P. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol* 2005;**105**: 944-952.

140 Simon J, Braunstein G, Nachtigall L, Utian W, Katz M, Miller S, Waldbaum A, Bouchard C, Derzko C, Buch A, Rodenberg C, Lucas J, Davis S. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab* 2005;**90**: 5226-5233.

141 Davis SR, van der Mooren MJ, van Lunsen RH, Lopes P, Ribot C, Rees M, Moufarege A, Rodenberg C, Buch A, Purdie DW. Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Menopause* 2006;**13**: 387-396.

142 Tamimi RM, Hankinson SE, Chen WY, Rosner B, Colditz GA. Combined estrogen and testosterone use and risk of breast cancer in postmenopausal women. *Arch Intern Med* 2006;**166**: 1483-1489.

143 Davis SR, Moreau M, Kroll R, Bouchard C, Panay N, Gass M, Braunstein GD, Hirschberg AL, Rodenberg C, Pack S, Koch H, Moufarege A, Studd J, Team AS. Testosterone for low libido in postmenopausal women not taking estrogen. *N Engl J Med* 2008;**359**: 2005-2017.

144 Panay N, Al-Azzawi F, Bouchard C, Davis SR, Eden J, Lodhi I, Rees M, Rodenberg CA, Rymer J, Schwenkhagen A, Sturdee DW. Testosterone treatment of HSDD in naturally menopausal women: the ADORE study. *Climacteric* 2010;**13**: 121-131.

145 Rada G, Capurro D, Pantoja T, Corbalán J, Moreno G, Letelier Luz M, Vera C. Non-hormonal interventions for hot flushes in women with a history of breast cancer. *Cochrane Database of Systematic Reviews* 2010from

146 Reiter EO, Blethen SL, Baptista J, Price L. Early initiation of growth hormone treatment allows age-appropriate estrogen use in Turner's syndrome. *J Clin Endocrinol Metab* 2001;**86**: 1936-1941.

147 van Pareren YK, de Muinck Keizer-Schrama SM, Stijnen T, Sas TC, Jansen M, Otten BJ, Hoorweg-Nijman JJ, Vulsma T, Stokvis-Brantsma WH, Rouwe CW, Reeser HM, Gerver WJ, Gosen JJ, Rongen-Westerlaken C, Drop SL. Final height in girls with turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. *J Clin Endocrinol Metab* 2003;**88**: 1119-1125.

148 Stephure DK, Canadian Growth Hormone Advisory Committee. Impact of growth hormone supplementation on adult height in turner syndrome: results of the Canadian randomized controlled trial. *J Clin Endocrinol Metab* 2005;**90**: 3360-3366.

149 Davenport ML. Moving toward an understanding of hormone replacement therapy in adolescent girls: looking through the lens of Turner syndrome. *Ann N Y Acad Sci* 2008;**1135**: 126-137.

150 Illig R, DeCampo C, Lang-Muritano MR, Prader A, Torresani T, Werder EA, Willi U, Schenkel L. A physiological mode of puberty induction in hypogonadal girls by low dose transdermal 17 beta-oestradiol. *Eur J Pediatr* 1990;**150**: 86-91.

151 Cisternino M, Nahoul K, Bozzola M, Grignani G, Perani G, Sampaolo P, Roger M, Severi F. Transdermal estradiol substitution therapy for the induction of puberty in female hypogonadism. *J Endocrinol Invest* 1991;**14**: 481-488.

152 Ankarberg-Lindgren C, Elfving M, Wikland KA, Norjavaara E. Nocturnal application of transdermal estradiol patches produces levels of estradiol that mimic those seen at the onset of spontaneous puberty in girls. *J Clin Endocrinol Metab* 2001;**86**: 3039-3044.

153 Piippo S, Lenko H, Kainulainen P, Sipila I. Use of percutaneous estrogen gel for induction of puberty in girls with Turner syndrome. *J Clin Endocrinol Metab* 2004;**89**: 3241-3247.

154 Mauras N, Shulman D, Hsiang HY, Balagopal P, Welch S. Metabolic effects of oral versus transdermal estrogen in growth hormone-treated girls with turner syndrome. *J Clin Endocrinol Metab* 2007;**92**: 4154-4160.

155 Nabhan ZM, Dimeglio LA, Qi R, Perkins SM, Eugster EA. Conjugated oral versus transdermal estrogen replacement in girls with Turner syndrome: a pilot comparative study. *J Clin Endocrinol Metab* 2009;**94**: 2009-2014.

156 Torres-Santiago L, Mericq V, Taboada M, Unanue N, Klein KO, Singh R, Hossain J, Santen RJ, Ross JL, Mauras N. Metabolic effects of oral versus transdermal 17beta-estradiol (E(2)): a randomized clinical trial in girls with Turner syndrome. *J Clin Endocrinol Metab* 2013;**98**: 2716-2724.

157 Bondy CA, Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab* 2007;**92**: 10-25.

158 Davenport ML. Approach to the patient with Turner syndrome. *J Clin Endocrinol Metab* 2010;**95**: 1487-1495.

159 Lobo RA. Absorption and metabolic effects of different types of estrogens and progestogens. *Obstet Gynecol Clin North Am* 1987;**14**: 143-167.