2016 ESHRE 指南：女性过早卵巢功能不全的管理

POI 指南小组成员：L.Webber1,*, M. Davies1, R. Anderson2, J. Bartlett3, D. Braat4, B. Cartwright5, R. Cifkova6, S. de Muinck Keizer-Schrama7, E. Hogervorst8, F. Janse9, L. Liao1, V. Vlaisavljevic10, C. Zillikens11, and N. Vermeulen12
通讯电子邮箱：E-mail: lisa.webber@uclh.nhs.uk

2015 年 12 月 14 日提交；2015 年 12 月 14 日再次提交；2016 年 1 月 11 日被接受

2016 年 3 月，欧洲人类生殖及胚胎学会(ESHRE)发布了女性过早卵巢功能不全的管理指南，指南针对过早卵巢功能不全的诊断和管理共提出 31 个关键问题，其中关于过早卵巢功能不全的诊断和评估，指南提出了 17 条推荐意见；针对早卵巢功能不全的不同后遗症，监测结果和治疗共提出 46 条推荐意见；针对女性过早卵巢功能不全的激素替代疗法，指南提出了 24 条推荐意见。

研究的问题：基于目前现有的最佳证据，过早卵巢功能不全（POI）的女性的最理想的管理方案是什么？

总结：指南制定小组（GDG）针对妇女的 POI 的诊断和治疗，制定了 99 项建议，并以此回答了 31 个关键问题。

已知的情况：无。

研究设计、规模、持续时间：本指南是由该领域多学科的专家组，应用欧洲人类生殖及胚胎学会(ESHRE)指南发展手册中的方法共同讨论完成的。其方法包括对 2014 年 9 月之前的文献全面系统的检索、质量评估，并涵盖指南专家组的共识。为确保患有 POI 妇女的提供信息，GDG（指南制定小组）中有病人代表参加。该草案定稿后，将会被欧洲人类生殖与胚胎协会（ESHRE）成员和专业机构予以再次审查。

参与者/材料，设置，方法：无。

主要结果：在诊断与评价 POI 方面，指南提供了 17 条建议；在监测和治疗 POI 的转归及其不同的后果方面，提供了 46 条建议。此外，对 POI 患者激素替代治疗方面提出了 24 条建议，可选择与补充治疗方面提出 2 条。对诱发青春期提出了 5 条建议。

局限性与不足：该指南的主要局限性与不足，是由于缺乏数据，许多建议是基于专家意见，或对绝经后妇女以及患有特纳综合征妇女的研究的间接证据。

结果的深远影响：尽管有其局限性，指南制定团队相信该指南能够指导医护人员在现有的证据基础上对 POI 妇女提供最佳实践的管理。此外，考虑到在文献检索时知识点的差异，指南制定团队制定了研究建议，以期促进对 POI 的关键问题研究。

研究资金与利益冲突：该指南由 ERHRE 成立并发展，ESHRE 负责有关会议，文献检索与该指南的实施等费用。指南制定小组成员未收取任何费用。戴维斯博士声明，除提交作品之外，未从诺和诺德公司获得经济支持；其他作者也无任何信息。

试用注册号：无。

关键词：过早卵巢功能不全/ POI /欧洲人类生殖和胚胎协会/指南/循证

引言

欧洲人类生殖和胚胎协会（ESHRE）的这个指南，对卵巢功能不全（POI）的女性管理

提供了最佳实践建议，包括首次和后续的管理。患者人群包括 40 岁以下的女性（包括特纳氏综合征患者）和 40 岁以上但发病年龄小于 40 岁的女性。

此外，本临床指南对妇女的 POI 提供了初步评估和管理的建议。初步评估包括诊断、病因评估和基础评估。管理包括激素治疗。除妇科问题外，POI 对健康影响也被描述。POI 的预后治疗方案包括以下方面：生育和避孕、骨骼健康、心血管问题、精神性欲的功能、心理功能和神经功能。

此外也讨论了其他问题：青春期的诱导，妇女的预期寿命，和 POI 有关的影响。

本指南限用于 POI，不适用于卵巢储备功能低下的妇女。

材料与方法：该指南是根据全部的 ESHRE 指南，规范的、良好的方法总结、发展而来。(Vermeulen et al., 2014).

总之，31 个关键的问题是由指导小组制定，以 PICO（患者，干预，比较，结果）形式构成。对于每个问题，我们检索了 PubMed、Medline、Cochrane 图书馆、PsycInfo 等数据库，从初始到 2014 年 4 月 1 日所有文献。文献语言仅限于英语。根据证据，并在构建证据表和质量评估后，建议草案由指定的专家组成员撰写。另外还组织了两次会议，讨论有关的证据和建议，并就建议的最后制定达成共识。

每个推荐根据证据的强度，分为 A-D 四个等级（得分 1 ++ - 4）。在缺乏证据的情况下，指南制定小组（GDG）基于临床经验（见表一）予以判断合适的实践点（GPPs）。.

表格 1　对女性 POI 的初始评估和管理建议(Vermeulen et al., 2014)

推荐等级	支持的证据
A	Meta 分析，系统评价或多个 RCT（高质量）
B	Meta 分析，系统评价或多个 RCT（中等质量） 单独个 RCT，大的非随机临床试验，病例对照研究或队列研究（高质量）
C	单独的 RCT，大的非随机临床试验，病例对照研究或队列研究（中等质量）
D	非分析性研究，病例报告或病例系列（高或中等质量）
GPP	专家意见

建议的等级只是基于支持证据的强度。在制定强或弱的建议时，除了支持证据的强度之外，指导组还与医生患者的利弊和倾向进行了权衡。

该指南草案终结后，ESHRE 网站上发出了评论邀请。此外，ESHRE 人类生殖内分泌特殊兴趣小组的成员（N=6000）以及人类生殖、妇科、内分泌和更年期相关的专业机构（N=79）也纷纷受到了评论邀请。来自 34 位评审员的 398 条评论由方法学专家(N.V.)以及 GDG（指南制定小组）主席进行处理——将建议纳入指南或给评审员回复。评论处理过程总结在评论报告中并发表于 ESHRE 网站。

该指南出版 4 年后将更新，发表 2 年后予以中期评估是否需要更新。

主要问题和建议

本文件总结了临床实践中的关键问题和建议。详细的背景信息和每一项建议的支持证据，可以在该指南的完整版本中找到：http://www.eshre.eu/Guidelines-and-Legal/Guidelines.

如何命名？

原发性卵巢功能不全（Primary ovarian insufficiency）于 1942 年首次提出，此后出现了很多不同的名称和定义（Albright et al., 1942）。

GPP

在研究和临床实践中，应采用“过早卵巢功能不全（premature ovarian insufficiency）”

来描述这种情况。

POI 的定义？

POI 是一种 40 岁之前由卵巢功能缺失导致的临床综合症。POI 的特点是高促性腺激素和低雌激素引起的月经紊乱（闭经或月经稀发）。

普通人群中的患病率是什么？

POI 的患病率是 1%。不同种族可能有不同的患病率。

考虑到 POI 对健康的远期影响，应努力降低 POI 的发病率。

可调整的因素包括：（i）妇科手术，（ii）生活方式，如吸烟，（iii）恶性和慢性疾病的改良治疗方案。

POI 的诊断

表 II 诊断检查总结

检查项目	意义	
	阳性试验	阴性试验
基因/染色体的检查		
核型分析（诊断特纳综合症）	涉及内分泌疾病、心脏病及遗产疾病	复查上皮细胞的核型（临床高度怀疑患者）
Y 染色体检查	考虑行性腺切除术	
脆性 X 染色体	涉及遗传性疾病	
常染色体基因检测 [a]		
抗体 [b]		
肾上腺皮质抗体/21OH 抗体	涉及内分泌疾病	具有临床症状及体征者予以复查
甲状腺抗体	每年检查 TSH	

fra-x，脆性 X 染色体；TPO 抗体，甲状腺抗体；ACA，肾上腺皮质抗体。

[a] 目前 POI 的妇女并非是检查指征，除非有证据表明一个特定的基因突变（例如 BPES）。

[b] POI 的病因不明，可能与免疫性疾病有关。

POI 的临床症状有哪些？

GPP

对月经稀发或闭经妇女，临床医生应了解其有关雌激素过低的情况。

GPP

诊断 POI，需要排除年龄低于 40 岁的闭经、月经稀发或低雌激素的情况。

诊断 POI 应该进行什么检查？

POI 的诊断是基于月经紊乱及生化检查。

GPP

尽管缺乏准确 POI 的适当诊断方法，GDG 推荐诊断标准如下：（i）月经稀发/闭经至少 4 个月，和（ii）两次相隔 4 周 FSH 水平升高（＞25 IU/L）。

哪些是已知的 POI 病因，应如何检查？

C

非医源性 POI 妇女应该予以染色体分析(Bachelot et al., 2009; Rocha et al., 2011; Jiao et al., 2012; Kalantari et al., 2013)。

C

所有检测到 Y 染色体的妇女建议行性腺切除术(Rocha et al., 2011)

B

POI 女性应行脆性 X 前突变检测(Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada et al., 2008; Bachelot et al., 2009)

GPP

在进行脆性 X 前突变检测前应充分与患者讨论其有关的影响。

GPP

目前无需对 POI 女性进行常染色体基因检测，除非有证据表明一个某个特定的基因突变（如：BPES：睑裂狭小内眦赘皮和上睑下垂综合征）(e.g. BPES:blepharophimosis–ptosis–epicanthus versus syndrome)

C

对于原因不明的 POI，或怀疑有免疫性疾病，应予以筛查 21OH-抗体（或者选择肾上腺皮质抗体（ACA））。

对于 21OH-抗体/ACA 阳性的 POI 患者，建议内分泌科就诊行肾上腺功能检测，除外阿迪生病（又名：艾迪生病，肾上腺皮质功能衰竭症，肾上腺皮质机能减退）(Chen et al., 1996; Bakalov et al., 2002; Dal Pra et al., 2003; Husebye and Lovas, 2009)。

C

对于原因不明的 POI，或怀疑有免疫性疾病，应予以筛查甲状腺抗体（TPO-Ab）。

TPO-抗体检测阳性的患者应每年检查促甲状腺激素（TSH）Kim et al., 1997; Hollowell et al., 2002; Goswami et al., 2006)

D

没有足够的证据推荐 POI 女性行常规糖尿病筛查 POI (Kim et al., 1997)

D

对于 POI 女性，没有必要进行感染筛查(Kokcu, 2010)

GPP

内科治疗或外科手术后可能导致 POI，治疗前应予以充分告知并取得患者同意。

GPP

尽管没有证明吸烟和 POI 的因果关系，但可以导致更年期提前。因此，易患 POI 的女性应该建议戒烟。

部分病因不能明确的 POI 妇女，可以被界定为原因不明的 POI，或特发性 POI。

多长时间应复查自身抗体试验？

GPP

21OH-AB / ACA 和 TPO-Ab 阴性的 POI 妇女，有关内分泌疾病的体征或症状如果没有进展，无需再次检测。(Betterle et al., 1997)

POI 女性的亲属有何影响？

B

患有脆性 X 前突变女性的亲属应予以遗传咨询和检测(Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada et al., 2008; Finucane et al., 2012)

GPP

非医源性 POI 患者的女性亲属，如果他们担心发展为 POI 的风险时，应告知：（i）目前没有适当的预测试验以明确患者将发展为 POI，除非已经检测到与 POI 有关的基因突变，（ii）没有有效的 POI 预防措施，（iii）生育保护似乎是一种很有前途的选择，尽管缺乏研究，以及（iv）在有生育计划的时候，应该考虑到早绝经的潜在风险。

POI 的后遗症

在预期寿命方面，POI 有何影响？

C

未治疗的 POI 与预期寿命的减少有关，很大程度上是由心血管疾病导致的。(Ossewaarde et al., 2005; Amagai et al., 2006; Rocca et al., 2006; Hong et al., 2007; Wu et al., 2014)

GPP

应该告知患有 POI 的妇女戒烟、规律锻炼和保持健康体重以减少心血管疾病的发生。

生育方面，POI 有何影响？

GPP

应告知 POI 患者，尽管机会很小，但仍有自然妊娠的可能。

GPP

无妊娠计划的 POI 患者应建议其避孕。

有效的生育干预措施是什么？

A

告知患有 POI 的妇女，目前没有增加卵巢活力和提高自然受孕率的可靠干预措施(van Kasteren and Schoemaker, 1999)。

C

选择卵子捐献，是患有 POI 妇女期望生育的一个选择。(Sauer et al., 1994; Templeton et al., 1996; Sung et al., 1997; Oyesanya et al., 2009)

C

告知 POI 女性，从姊妹中获得捐献卵子可能带来更高的停经风险。(Sung et al., 1997)

GPP

确诊为 POI 后，即不可能有保存生育力的机会了

与 POI 有关的产科风险是什么？

B

可以确信，原发性（特发性）或大多数化疗后 POI 妇女，与普通人群相比，自然妊娠后产科和新生儿风险没有升高。(Signorello et al., 2012; Scottish Intercollegiate Guidelines Network (SIGN), 2013)

C

卵母细胞移植妊娠具有更高的风险，应由适宜的产科团队管理。孕妇与其配偶应向产科医生告知其为卵母细胞移植妊娠。(Pados et al., 1994; Abdalla et al., 1998; Soderstrom-Anttila et al., 1998; Nelson and Lawlor, 2011; Stoop et al., 2012)

C

产前非整倍体筛选应基于卵子捐献者的年龄。(Bowman and Saunders, 1994; Donnenfeld et al., 2002)

C

已接受子宫放射治疗的妇女妊娠，是产科并发症的高风险人群，应由适宜的产科团队管理。(Bath et al., 1999; Larsen et al., 2004;Wo and Viswanathan, 2009; Signorello et al., 2010; Scottish Intercollegiate Guidelines Network (SIGN), 2013)

D

特纳综合征孕妇发生产科和非产科并发症的风险非常高，应由适宜的产科团队以及心脏病专家共同管理(Bryman et al., 2011; Hadnott et al., 2011; Karnis, 2012; Hagman et al., 2013)

D

接受蒽环类药物和/或心脏放射后的孕妇，应与心脏病专家共同管理。(Mulrooney et al., 2009; Scottish Intercollegiate Guidelines Network (SIGN), 2013)

患有 POI 的妇女如何评估是否适孕？

C

怀疑 POI 的女性在接受捐赠卵子之前应予以全面检查，包括甲状腺、肾上腺以及染色体核型(Abdalla et al., 1998)

D

曾经暴露于蒽环类药物、高剂量环磷酰胺，或纵隔放射治疗的女性，妊娠前应予以超声心动图检查，必要时咨询心脏病专家(Felker et al., 2000; Gorton et al., 2000; Bar et al., 2003; van Dalen et al., 2006; Altena et al., 2012)

GPP

特纳综合征妇女应请成人先天性心脏病专家予以评估，应予以普通的内科和内分泌检查

C

患有 POI 的女性在怀孕前应予以评估血压、肾功能及甲状腺功能(Haddow et al., 1999)

GPP

某些高风险女性，临床医生可能认为卵母细胞移植是有致命性的危险，故不宜行卵母细胞移植

POI 对女性骨骼有何影响？

B

POI 与骨密度（BMD）减少有关(Ratcliffe et al., 1992; Hadjidakis et al., 1999; Park et al., 1999;Conway et al., 1996; Castaneda et al., 1997; Bakalov et al., 2003; Han et al., 2008; Michala et al., 2008; Bachelot et al., 2009; Popat et al., 2009; Freriks et al., 2011)

GPP

尽管没有充分证据，但骨密度降低提示在以后的生活中，POI 患者骨折风险很有可能增加

如何进行骨保护和改善骨健康？

GPP

女性应该保持健康的生活方式，包括负重运动，戒烟，维持正常体重以期获得良好的骨健康

C

均衡食谱是含有推荐剂量钙和维生素 D 的。维生素 D 摄入不足和/或钙摄入不足的低骨密度女性，可以给予膳食补充剂(Bours et al., 2011; Challoumas et al., 2013)

C

建议使用雌激素来保持骨骼健康和预防骨质疏松症，降低骨折风险(Prior et al., 1997; Lindsay et al., 1980; Kanis et al., 2013)

C

复方口服避孕药可能适合某些人，但对改善 BMD 并不是最好的（Crofton et al.，2010）

C

其他的药物治疗，包括双膦酸盐类药物，只在骨质疏松症专家建议后可以考虑使用。计划怀孕的女性应谨慎使用(Stevenson et al., 2005; Shapiro et al., 2011)

POI 女性如何监测骨骼健康？

GPP

诊断 POI 时应考虑到骨健康的重要性，并予以持续关注

C

所有首次诊断 POI 的女性都应测量骨密度（BMD），尤其是合并有其他危险因素时（Kan et al.，2013）

GPP

如果骨密度正常，并已经开始全身雌激素替代治疗，再次 DEXA 扫描意义不大

GPP

如果确诊骨质疏松并予以雌激素替代治疗或其他治疗，5 年内应予以监测骨密度（BMD）。骨密度下降提示应立即评估雌激素替代治疗及其他潜在的危险因素。最好由骨质疏松症专家予以评估。

POI 对心血管系统有何影响？

B

患有 POI 的妇女，应告知其心血管疾病的发病风险较高，可以通过改变行为的降低风险（如戒烟，规律的负重运动、保持健康的体重）(van der Schouw et al., 1996; Cooper and Sandler, 1998;Huet al., 1999; Jacobsen et al., 1999, 2003, 2004; de Kleijn et al., 2002; Mondul et al., 2005; Atsma et al., 2006; Lokkegaard et al., 2006; Hong et al., 2007; Baba et al., 2010; Gallagher et al., 2011; Perk et al., 2012).

C

所有被诊断患有特纳综合征的妇女应由先天性心脏病专家予以评估(Gravholt et al., 1998; Bondy, 2008; Sharma et al., 2009)

雌激素替代有保护心脏作用吗？

C

尽管缺乏纵向数据结果，强烈建议患有 POI 的女性予以早期激素替代治疗（HRT）以控制未来心血管疾病的风险；它至少应该维持到自然绝经的平均年龄(Kalantaridou et al., 2004; Lokkegaard et al., 2006; Ostberg et al., 2007; Langrish et al., 2009)

心血管疾病风险因素是否应被监测？

GPP

诊断为 POI 的女性应予以评估心血管风险。至少每年应监测血压、体重、吸烟状况，以及评估其他危险因素

C

特纳综合征的妇女，得出诊断时就应评估心血管风险并每年监测（至少包括血压、吸烟、体重、血脂、空腹血糖、糖化血红蛋白）(Freriks et al., 2011)

POI 对心理健康和生活质量有哪些影响？

D

确诊 POI，对患者的心理健康和生活质量有明显的负面影响(Liao et al., 2000; Schmidt et al., 2011; Mann et al., 2012a,b)

如何管理与 POI 相关的生活质量下降？

B

心理和生活方式的干预是 POI 女性的最佳选择(Boivin, 2003; Duijts et al., 2012; Mann et al., 2012a,b)

POI 影响性欲吗？

GPP

对 POI 患者，应常规询问性生活情况、性功能等。

如何管理 POI 对性欲的影响？

C

适当的雌激素替代是保障正常性功能的基础。性交困难时可以局部使用雌激素。(Sarrel, 1987; Rubinow et al., 1998; Pacello et al., 2013)

B

患有 POI 的女性应予以充分告知补充睾酮的可能性，以及利与弊，以助患者做出合适的选择。目前，长期使用睾酮制剂的功效及安全性是未知的。(Alexander et al., 2004; Kingsberg et al., 2008)

如何治疗 POI 患者的泌尿生殖系统症状？

A

局部雌激素治疗泌尿生殖症状有效(Suckling et al., 2006)

D

临床医生应该意识到：看似已经使用足量的全身 HRT，患有 POI 的女性仍然可能出现泌尿生殖系统症状。局部雌激素治疗可以补充全身 HRT 的不足。(Pacello et al., 2014)

C

不使用 HRT 的女性，可用润滑剂缓解阴道不适和性交疼痛(Le Donne et al., 2011; Grimaldi et al., 2012)

POI 对神经系统的功能有何影响？

D

50 岁以下患者，计划行子宫切除术和/或卵巢切除术时，尤其是预防性手术切除时，对患者认知功能可能造成的不利影响应予以分析评估。(Rocca et al., 2007; Rocca et al., 2008; Vearncombe and Pachana, 2009; Phung et al., 2010; Bove et al., 2014)

如何管理 POI 对神经功能影响？

C

为降低对认知障碍可能的风险，POI 患者的雌激素替代治疗，至少要持续到自然绝经的平均年龄(Sherwin, 1988; Phillips and Sherwin, 1992; Sherwin, 1994; File et al., 2002; Kritz-Silverstein and Barrett-Connor, 2002; Hogervorst and Bandelow, 2010; Bove et al., 2014)

GPP

应建议患有 POI 的妇女采用健康的生活方式（如运动、戒烟、保持健康体重），以减少发生认知功能障碍的可能风险

治疗

HRT 的指征

C

HRT 是指对患有 POI 的女性出现低雌激素症状时采取的治疗手段(Piccioni et al., 2004; Madalinska et al., 2006; Absolom et al., 2008)

C

应告知女性患者，HRT 可能对心血管系统疾病有初级预防和骨保护作用(Lindsay et al., 1980; Prior et al., 1997; Kalantaridou et al., 2004; Lokkegaard et al., 2006; Ostberg et al., 2007; Langrish et al., 2009; Kanis et al., 2013)

HRT 的风险是什么？

D

应告知患有 POI 的女性，尚未发现应用 HRT 后，在自然绝经前发生乳腺癌的风险升高(Benetti-Pinto et al., 2008; Soares et al., 2010; Wu et al., 2014)

B

具有正常子宫的女性，应予以孕激素与雌激素联合治疗，以保护子宫内膜(Furness et al., 2012)

HRT 的药物选择

C

雌激素替代治疗，E2 优于炔雌醇或共轭雌激素(Langrish et al., 2009; Crofton et al., 2010)

GPP

女性应该了解，虽然微粉化孕酮可能对子宫内膜的保护具有自然优势，有证据显示口服、周期、联合用药治疗是最好的选择

GPP

应用 HRT 时应考虑到患者对用药的途径、方法的偏好，同时应考虑到避孕的需求。

HRT 的监测

GPP

一旦开始治疗，使用 HRT 的 POI 女性每年应予以临床回顾总结，尤其要注意到患者的依从性

GPP

没有必须的、常规的监测手段与方法，但特定的症状或关注点应予以关注

雄性激素的应用

C

应告知患者，仅有有限的数据支持予以雄激素治疗，且对健康的长期影响尚不清楚(Shifren et al., 2000; Braunstein et al., 2005; Buster et al., 2005; Simon et al., 2005; Davis et al., 2006, 2008; Tamimi et al., 2006; Panay et al., 2010)

GPP

如果予以雄激素治疗，在 3-6 个月后应予以评估治疗效果，应限于 24 个月内

POI 女性应用 HRT 的其他注意事项

特纳综合征女性

C

因特纳综合征导致的POI女性，整个生殖期应予以HRT治疗(Downey et al., 1991; Swillen et al., 1993; Gravholt et al., 1998; Romans et al., 1998; Ross et al., 1998; Elsheikh et al., 2000; Khastgir et al., 2003; Mortensen et al., 2009; Crofton et al., 2010; Kodama et al., 2012)

患有 POI 并携带 BRCA 突变基因或确诊乳腺癌的女性

B

乳腺癌生存者通常禁用 HRT (Antoine et al., 2007)

C

对携带 1 / 2BRCA 基因突变且没有乳腺癌病史的女性，预防性切除双侧输卵管卵巢术后可以选择 HRT 治疗(Armstrong et al., 2004; Rebbeck et al., 2005; Madalinska et al., 2006)

POI 与子宫内膜异位症

C

患有子宫内膜异位症需行卵巢切除术的患者，雌激素/孕激素联合疗法是针对血管舒缩症状的有效治疗，并可以降低疾病复发的风险(Dunselman et al., 2014)

POI 与偏头痛

GPP

偏头痛不是使用 HRT 治疗 POI 女性的禁忌症

GPP

HRT 治疗过程中偏头痛加重，可以考虑改变剂量、用药途径

D

先兆偏头痛患者，雌激素经皮给药可能是风险最低的途径(Nappi et al., 2001)

POI 与高血压

GPP

高血压不是 POI 患者使用 HRT 治疗的禁忌症

C

POI 合并高血压的妇女，首选雌二醇经皮给药(White, 2007; Langrish et al., 2009)

POI 和静脉血栓栓塞病史（VTE）

GPP

POI 患者，如果有静脉血栓栓塞病史或血栓形成倾向者在开始 HRT 前应咨询血液病医生

B

POI 患者，在 VTE 高风险时应用雌激素首选经皮给药(Canonico et al., 2008)

POI 与肥胖

C

POI 患者需要 HRT 时，肥胖或超重女性首选经皮途径应用雌二醇(Canonico et al., 2006)

POI 与子宫肌瘤

B

子宫肌瘤不是 POI 患者使用 HRT 的禁忌症(Ang et al., 2001; Ciarmela et al., 2014)

POI 可用什么补充治疗？

GPP

POI 患者可以调整生活行为（如戒烟、规律的负重运动、保持健康的体重）以降低风险

B

应告知患者，目前大多数替代性和互补性的治疗方案，疗效是有限的，缺乏安全性方面的数据(Rada et al., 2010)

诱发青春期 (见表 III)

表 III 青春期雌激素替代疗法（2007 年邦迪与特纳综合征研究（修订版））

年龄	建议	剂型、剂量与说明
12-13 岁	病情若无进展且 FSH 升高，予以低剂量雌激素治疗	雌二醇（E2） 经皮给药：通过皮肤贴片每天 6.25μg[a] 口服微粒化雌二醇：5μg/kg/天或 0.25mg/天
12.5-15 岁	逐渐增加 E2 剂量，间隔 6-12 个月，用 2-3 年 [b] 以上的时间逐渐提升至成人剂量	经皮 E2：12.5，25，37.5，50，75，100μg/天(成人剂量：100–200μg/day) 口服 E2：5，7.5，10，15，μg/kg/天(成人剂量：2–4μg/天)
14-16 岁	雌激素应用 2 年后，或发生突破性出血时，开始周期性使用孕激素	周期第 12-14 天，口服微粒化黄体酮 100-200mg/天，或地屈孕酮 5-10mg/天 [c]

a.市售最低剂量的 E2 贴剂，每天提供 25 或 50 μ g；切分使用不能确定其剂量是同样等价分离的（如使用 1 / 8，1 / 6，1 / 4 的夜间贴，或日贴，或每月使用 7-10 天的整贴）。

b 应用 GH 治疗特纳综合征，为达到最佳的成人身高 E2 剂量的增加可能相对较慢；而晚期诊断和不考虑生长的患者，E2 可以以稍高剂量开始，且提升用药剂量相对较快。

c 长期使用孕酮患者，地屈孕酮和醋酸甲羟孕酮优于其他孕激素，因二者类脂物代谢的副作用和雄激素作用影响较小（LOBO，1987）。

如何诱发青春期？

C

在 12 岁时用 E2 以低剂量开始启动青春期，并促进其进展，用至少 2-3 年时间逐渐加量。(Reiter et al., 2001; van Pareren et al., 2003; Stephure and Canadian Growth Hormone Advisory Committee, 2005)

D

对于诊断较晚以及不考虑生长发育的女性可以考虑予以改良的 E2 方案。(Davenport, 2008)

B

目前尚不能确定口服或经皮哪个是最佳的用药途径。经皮应用可以保证雌二醇的维持在生理雌激素水平，因此首选经皮给药。(Illig et al., 1990; Cisternino et al., 1991; Ankarberg-Lindgren et al., 2001; Piippo et al., 2004; Mauras et al., 2007; Nabhan et al., 2009; Torres-Santiago et al., 2013)

D

诱发青春期禁用口服避孕药(Bondy and Turner Syndrome Study Group, 2007; Davenport, 2010)

C

雌激素应用 2 年后，或发生突破性出血时，开始周期性使用孕激素(Bondy and Turner Syndrome Study Group, 2007; Furness et al., 2012)

讨论

ESHRE 对妇女的 POI 管理指南，包括了 95 建议，4 条 POI 的诊断、转归及治疗说明。这些建议是根据现有的最佳证据，有关的专家进行审查后，由多学科专家小组共同制定完成的。本指南是根据目前有关 POI 的文献制定的，其依据是有一定局限性的。这 95 条建议，33 条（34.7%）是根据专家的意见提出的，标记为 GPP。31 个关键问题中仅仅有 15 个是关于治疗和管理的观点，其余是关于诊断、监测和转归方面的。干预方面的 61 项建议（不包括监测），12 项（19.7%）可能是基于高质量的证据（A 级或 B），35 项（57.4%）是基于中等质量的证据（C 或 D），和 14 项（22.9%）是根据专家的意见制定的。

目前缺乏对患者干预治疗的高质量的证据，是导致目前本指南局限性的主要原因，由此引发了未来研究的一些课题：（i）在 POI 的诊断过程中生化标记的准确性（如 FSH、抗苗勒氏管激素），（ii）POI 患者的长期预后，吸烟、长期使用 HRT 的影响等有关因素的随访（iii）POI 患者的生育治疗，以及相关的产科风险，（iv）POI 患者的终生骨折风险、以及干预措施的效果，（v）POI 患者的心血管危险因素，（vi）POI 及其干预措施对健康，以及生活质量的影响，（vii）HRT 的疗效比较，患者的满意度、不同方案的副作用，及（viii）对肿瘤性 POI 患者的最佳方案。

Panay 和 Fenton2012 年曾经建议，对 POI 患者进行注册并进行长期的数据搜集。

尽管本指南具有一定的局限性，以及支持本指南的证据同样存在一定的局限性，GDG 确信本指南将使得患有 POI 的女性得到最佳的管理。并且在指南的传播和实施方面继续努力。

致谢

感谢受邀专家 Frank Broekmans, Gerard Conway, Alberto Falorni, Angela Maas 以及 Anette Tonnes Pedersen，作为特定领域的专家，他们为本多学科指南提供了建设性的意见。同时对许多临床医生和患者组织为本指南提供的帮助一并致谢。

作者分工

L.w.：负责 GDG，为收集证据，撰写的稿件和处理审稿人意见的主要负责人。

N.V.：为方法学专家，进行了所有的文献指南检索，提供方法学支持，是总协调员。

M.D.：到 2014 年 12 月，任 GDG 联席主席。

J.B.：指南小组的患者代表。

所有其他作者，按字母顺序排列。作为 GDG 成员，通过起草关键问题，合成证据，撰写的指南，讨论不同意见直到小组内达成共识，贡献相同。

资金

该研究没有外部资金；所有费用由 ESHRE 负担。

利益

声明：除提交工作之外，戴维斯博士声明未从诺和诺德公司获得财务支持；其他作者没有说明。

参考文献：

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.

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

Albright F, Smith P, Fraser R. A syndrome characterized by primary ovarian insufficiency and decreased stature. Am J Med Sci 1942;204:625 – 648.

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.

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

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.

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. 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.

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.

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.

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.

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.

Bachelot A, Rouxel A, Massin N, Dulon J, Courtillot C, Matuchansky C, Badachi Y, Fortin A, Paniel B, Lecuru F et al. Phenotyping and genetic studies of 357 consecutive patients presenting with premature ovarian failure. Eur J Endocrinol 2009;161:179 – 187.

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.

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.

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.

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.

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.

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

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

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

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.

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.

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.

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.

Braunstein GD, Sundwall DA, Katz M, Shifren JL, Buster JE, Simon JA, Bachman G, Aguirre OA, Lucas JD, Rodenberg C et al. 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.

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.

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.

Canonico M, Oger E, Conard J, Meyer G, Levesque H, Trillot N, Barrellier MT, Wahl D, Emmerich J, Scarabin PY et al. 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.

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. Br Med J 2008;336:1227 – 1231.

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.

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

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.

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.

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

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

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 2010;73:707 – 714.

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.

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.

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

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.

Davis SR, Moreau M, Kroll R, Bouchard C, Panay N, Gass M, Braunstein GD, Hirschberg AL, Rodenberg C, Pack S et al. Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med 2008; 359:2005 – 2017.

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.

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

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.

Duijts SF, van Beurden M, Oldenburg HS, Hunter MS, Kieffer JM, Stuiver MM, Gerritsma MA, Menke-Pluymers MB, Plaisier PW, Rijna H et al. Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatmentinduced menopausal symptoms in patients with breast cancer: results of a randomized, controlled,

multicenter trial. J Clin Oncol 2012;30: 4124 – 4133.

Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A et al. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014; 29:400 – 412.

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.

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.

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

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.

Freriks K, Timmermans J, Beerendonk CC, Verhaak CM, Netea-Maier RT, Otten BJ, Braat DD, Smeets DF, Kunst DH, Hermus AR et al. Standardized multidisciplinary evaluation yields significant previously undiagnosed morbidity in adult women with Turner syndrome. J Clin Endocrinol Metab 2011;96:E1517 – E1526.

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.

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.

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 et al. Fragile X testing in obstetrics and gynaecology in Canada. J Obstet Gynaecol Can 2008; 30:837 – 846.

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

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.

Gravholt CH, Juul S, Naeraa RW, Hansen J. Morbidity in Turner syndrome.

J Clin Epidemiol 1998;51:147 – 158.

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.

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

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.

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.

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.

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.

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.

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.

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.

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.

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

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.

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.

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.

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.

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.

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.

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

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.

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

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.

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.

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.

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.

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

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

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.

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.

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.

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

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

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

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.

Madalinska JB, van Beurden M, Bleiker EM, Valdimarsdottir HB, Hollenstein J, Massuger LF, Gaarenstroom KN, Mourits MJ, Verheijen RH, van Dorst EB et al. 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.

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

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 2012b;13:309 – 318.

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.

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

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

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.

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

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.

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.

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.

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 (Cambridge, Mass) 2005; 16:556 – 562.

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 2007; 66:557 – 564.

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.

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 2014;17:342 – 347.

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.

Panay N, Fenton A. Premature ovarian insufficiency: working towards an international database. Climacteric 2012;15:295 – 296.

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

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.

Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, Albus C, Benlian P, Boysen G, Cifkova R et al. 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.

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

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.

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.

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.

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.

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.

Rada G, Capurro D, Pantoja T, Corbala ń J, Moreno G, Letelier Luz M, Vera C. Non-hormonal interventions for

hot flushes in women with a history of breast cancer. Cochrane Database Syst Rev 2010:CD004923.

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.

Rebbeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, Isaacs C, Olopade OI, Neuhausen SL, van't Veer L et al. 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.

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

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.

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.

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.

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.

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.

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.

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

Sarrel PM. Sexuality in the middle years. Obstet Gynecol Clin North Am 1987;

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.

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 – E287.

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.

Shapiro CL, Halabi S, Hars V, Archer L, Weckstein D, Kirshner J, Sikov W, Winer E, Burstein HJ, Hudis C et al. 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.

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

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

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

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

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.

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.

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

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.

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.

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.

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.

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.

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

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.

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.

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

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.

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.

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.

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.

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 et al. 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.

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

Vermeulen N, D'Angelo A, de Sutter P, Nelen WLDM. Manual for ESHRE Guideline Development 2014, www.eshre.eu.

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

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.

Wu X, Cai H, Kallianpur A, Li H, Yang G, Gao J, Xiang YB, Ji BT, Yu T, Zheng W et al. Impact of Premature Ovarian Failure on Mortality and Morbidity among Chinese Women. PloS one 2014;9:e89597.

本文由山西医学科学院，山西大医院田青翻译，上海交通大学徐秋栋编辑排版，医脉通于梦佳审核

医脉通指南翻译组出品

“医脉通指南翻译组”是由医脉通组织的，

平等协作的国际指南翻译组织。

如果您想了解我们正在做的事情，

或者加入我们，欢迎点击以下链接：

http://group.medlive.cn/topic/92419