

临床医师深造双语读物

《影像学诊断问答》系列

绝经期和激素替代疗法

MENOPAUSE AND HORMONE REPLACEMENT THERAPY

SECOND EDITION

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INTRODUCTION

现代西方各国的女性都希望在绝经后再活 30 岁。这相当于她一生大约 1/3 的时间处于性激素缺乏的状态。每 6 个人中就有一名,甚至差不多每 5 个人中就有一名女性是绝经期年龄的妇女。这个数字相当于一个特定国家的退休群体的人数或所有在校学生人数(如果你把从小学到大学的所有学生都包括在内)。这么多数量的人群也是对日益减少的医疗资源的一种挑战。

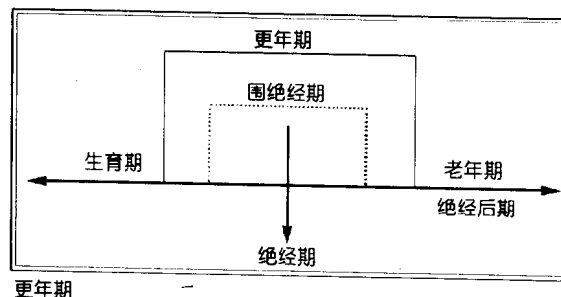
因为激素替代疗法对妇女们主诉的几种疾病都能产生正面的影响,所以传播现有的知识,特别是妇产科领域以外的知识,就显得尤为必要了。

在不久的将来,非专业人员就能护理大多数绝经后的妇女。虽然激素替代疗法(HRT)的一般原则正逐渐被大多数医生所熟知,但医生在为病人开出 HRT 处方时仍有许多需要慎重考虑的实际问题。原先所患疾病的影响和对健康状况的关注,这些都需要根据每个人的具体情况加以考虑。把最新的医学资料和各项病例病史结合起来就可以明确那些与激素缺乏有关的内科疾病的目前情况。

现代科学对我们深入了解与绝经期激素缺乏有关的问题做出了广泛的贡献。虽然诸如生物化学、内分泌学、内科学、妇科学、矫形外科学、精神病学和社会科学等各

导言

种学科已把更年期妇女的问题细分为几个部分,包括月经周期、骨骼、心血管系统、激素、潮红和正面益处。但完整的临床知识仍然很缺乏,而且病人之间主要的个体差异也常被忽视。



仅在最近才建立起一些绝经期专科诊所,而且也发挥了学科之间相互探讨的优势。绝经期专科诊所可提供各种信息交流,把多种来源的知识汇集到临床中心进而进入临床实践。

“绝经”定义为最后一次阴道自然出血。在确定为绝经时,妇女必须至少一年没有阴道出血;因此,绝经的时间只能回顾性地确定。“更年期”是指绝经前后的 5 ~ 10 年,在此期间可能出现一些绝经症状。更年期持续 10 ~

15 年以上的很少见。“围绝经期”是指绝经前后 2~3 年。这种术语常在讨论各种治疗方案中用到。

更年期的特征

在月经模式发生任何改变之前,促卵泡激素(FSH)的血清激素浓度大约从 45 岁开始升高。月经模式随着年龄的增长而变化。年轻女性月经周期平均为 28 天,行经期通常是 3~5 天。到 45 岁时,月经周期逐渐缩短到 24~25 天,行经天数也增加到 7 天左右。另外,出血量也经常偏多。

更年期的典型主诉	
出血量大	阴道灼热,干燥
乳房体积减少	失眠
不规则出血	尿失禁
面部毛发生长	神经紧张
热潮红	关节疼痛
阴毛减少	情绪波动
出汗/性欲减退	皮肤干燥,眼睛发干
心悸	触痛性阴道炎
	体重增加

典型的更年期主诉(之所以这样称呼是因为它们是由激素改变引起的)包括月经紊乱、热潮红、出汗和阴道干燥。这些症状和其他一些症状,如经血过多、严重血管

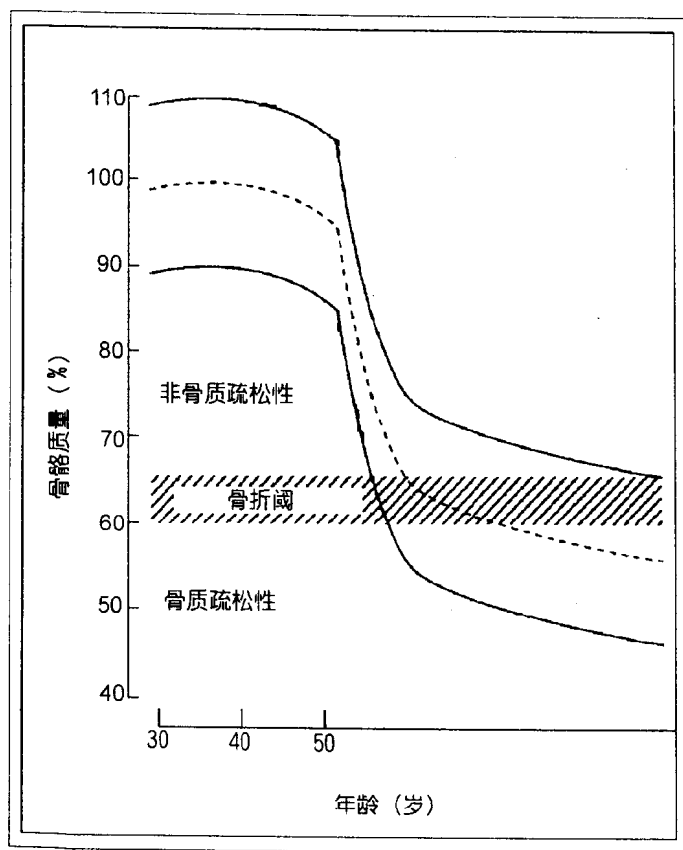
运动性病症、泌尿道感染和尿失禁,明显影响了日常生活。出血问题通常预示着更年期的到来,它是生命进程中绝经前期的开始。

有许多但不是所有的女性,在出现经血过多之后会出现血管运动性症状,如热潮红和出汗,特别是夜间。精神症状,如易怒、焦虑和抑郁心境,可能会因血管运动性症状的出现而加重,也可能是更年期综合征本身的一部分。不要忘记中年女性还会遇到若干重要的社会挑战,如:失业,当了婆婆,有了孙子孙女,以及不得不照顾年老的父母(他们经常有病或在其他方面受到社会不公平待遇),这些负担会加重所有这些症状。

性激素(特别是雌激素)的减少会引起泌尿生殖道内对雌激素敏感的组织萎缩,因而增加尿失禁、阴道干燥、性交疼痛和复发性泌尿生殖道感染的可能性。

雌激素缺乏的长期后果是骨质疏松性骨折和心血管疾病(特别是心肌梗死)的危险性增大。最新资料还表明雌激素缺乏会使患早老性痴呆的危险性增加。其他常与雌激素缺乏有关的症状是雄激素活性增加,以及皮肤结缔组织、腺体功能和关节的萎缩性病变。因而,绝经期妇女的皮肤又薄又苍白,而且阴道炎和无菌性炎性关节病(如网球肘)也较常见,同时出现阴道、眼和口的干燥。

看起来,性激素的减少对大多数器官或器官系统均产生了负面影响。此外,各种症状还存在有很大的个体内和个体间的变异,因此个体女性可能表现出完全不同的症状;但是,雌激素的缺乏仍然是其共同的特性。



骨密度图表示出第5、第50和第95百分位距和绝经期的影响。图中标出了假设的“骨折阈”。

《绝经期和激素替代疗法》的第二版分为若干章和若干小节,用以强调其某些共同的表现、临床程序、护理和绝经期病症的治疗。家庭医生对此都有一定的实践经验。显然,这些临床医生能有效地帮助有更年期病症的女性。治疗的有效性和病人的依从性在很大程度上取决于医生提供给病人的信息。

这本重要而独特的出版物,为了涵盖最新的医疗信息,已做过多次修订,它是按照公认的医疗信息、实际的临床病史和与更年期妇女常见疾病有关的例证编排的。在编著本书时,首先考虑了获取这些独立而可靠的资料来源的需求和权利。

要求读者在了解绝经期和激素替代疗法的学习过程中解释和诊断这些特征。我们相信本书将填补现有医学文献中关于这些课题的空白,而且它的教育价值是无法估计的。

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1: SKIN AND TISSUE SYMPTOMS

Androgen and estrogen receptors have been found to exist in the skin. With advancing age, the concentration of androgen receptors decreases. This results in a thinning of pubic hair, less secretion by the sebaceous glands and reduced collagen fiber synthesis. In addition, fibroblast proliferation is impeded. As a result of androgen activity on the skin, the size of the sebaceous glands increases and the amount they secrete also rises.

The number of estrogen receptors does not seem to change with age. An estrogen receptor related protein has actually been found as a marker of estrogen activity in the epidermal exocrine sweat glands, sebaceous glands and hair follicles (Figures 1 and 2).

After the menopause, some of the most noticeable changes on examination are a decrease in blood flow through the dermis as well as the epidermis, which results in whitening of the skin, a change in vessel diameter and rarefaction of vessels.

The thickness of the epidermis is dependent upon estrogens, as the hormones stimulate the epidermal mitotic rate. Estrogens al-

1: 皮肤和组织的症状

现已发现,雄激素和雌激素受体存在于皮肤中。随着年龄的增长,雄激素受体的浓度在下降。这就导致阴毛变稀少、皮脂腺分泌减少及胶原纤维合成减少。此外,成纤维细胞增生也受到抑制。雄激素活性对皮肤的作用导致皮脂腺体积增大,因而它们分泌的数量也增多。

雌激素受体的数量似乎不随年龄的增长而改变。现在已发现了一种与雌激素受体相关的蛋白,它是雌激素在表皮外分泌汗腺、皮脂腺和毛囊中活性的标志(图 1 和 2)。

绝经后,体检时的一些最值得注意的改变是通过真皮及表皮的血流减少;这将导致皮肤变白、血管直径的改变和血管的稀少。

表皮的厚度取决于雌激素,因为激素会刺激表皮有丝分裂的速率。雌激素还影响着皮脂腺,减少它们皮脂

so affect the sebaceous glands, reduce their production of sebum (Figure 3), and induce an increase in vascularization. Fibroblasts are stimulated so that the production of elastic fibers increases. Also, the synthesis rate of collagen fibers is positively affected and their fragmentation reduced. As part of the manifestations, common skin complaints occur including, itching, dryness, thinning and occasionally a feeling of bruising.

It has been estimated that collagen content of skin, falls by 2% annually in the postmenopausal period, irrespective of chronological age. During the first few years after the menopause this process is quickest, and around 30% of collagen is lost during the first five years after the menopause. Fewer than two years of hormone replacement therapy can counteract or cure this condition. Estrogens also stimulate the synthesis of a ground substance rich in hyaluronic acid, which, through its hygroscopic effect, improves skin tone (Figure 4).

Changes within the skin depend both on chronological and menopausal age. It must be remembered that environmental factors such as smoking, exposure to the sun and heat radiation may well affect the appearance and physical properties of the skin. Symptoms like flushing, thinning and dryness appear to occur more readily when exposed to sun, than protected skin. Wrinkling of skin can be directly attributed to the aging effects of unprotected skin by exposure to the sun and environmental elements.

的生成(图3),并引起血管形成的增加。成纤维细胞受到刺激,致使弹性纤维生成增加。此外,胶原纤维的合成速率也会受到正面影响,并且它们的分裂在减少。作为临床表现的一部分,常见的皮肤主诉病症包括瘙痒、干燥、变薄及偶尔出现青肿感。

据估计,在绝经后期,不考虑计时年龄,皮肤中胶原的含量将以每年2%的速度下降。在绝经后的头几年内,这一过程进展最快,而且在绝经后的第一个5年内,大约有30%的胶原丧失了。不到2年的激素替代疗法便可消除或治愈这种病症。雌激素还会刺激一种富含透明质酸的基质的合成,通过这种基质的吸湿作用,可以改善皮肤的紧张度(图4)。

皮肤内的改变取决于计时年龄和绝经年龄。必须记住,环境因素(如吸烟,暴露于阳光和热辐射下)在很大程度上会影响皮肤的外观和物理性质。皮肤暴露于阳光下要比受保护的皮肤更容易出现如像潮红、变薄和干燥等症状。皮肤起皱纹可直接归因于未受保护皮肤暴露于阳光和各种环境成分下所引起的衰老作用。

Following estrogen deficiency, epidermal atrophy, together with a reduction effect of the lubricating effect of sebum and a loss of its moisture-retaining action, results in a thin, white and dry epidermis which becomes irritated more easily. Higher androgen activity also affects hair coverage and estrogen replacement therapy may affect these changes. The estrogenic effect is more rapid and pronounced in younger women. Therefore, better epidermal and dermal response to estrogen are encountered in young oophorectomized women than in their older, naturally postmenopausal counterparts. After only 4 – 6 weeks of estrogen therapy, skin restoration in young women may improve, but in postmenopausal women the full effect may take up to six months.

An interesting observation was noted in an American study that followed 3,875 postmenopausal women for more than 20 years. The study reported that estrogen users had a 53% lower risk of dry skin and 58% lower risk for wrinkles. When examined for potential detriments such as age, body weight and degree of sunburn, there was still a 29% lower risk for dry skin and 33% lower risk for wrinkles.

An Austrian study reported on 60 women, who were not previously treated with estrogens and were given estrogen creams containing either estradiol or estriol during a time period of six

随着雌激素的缺乏、表皮的萎缩,连同皮脂润滑作用的降低及其保湿作用的消失,将导致表皮变薄、变白和干燥,因而更容易受到刺激。较高的雄激素活性还会影响毛发的覆盖,因此雌激素替代疗法可以影响这些改变。对于比较年轻的妇女,雌激素的影响更快,更突出。因此,做过卵巢切除术的年轻女性比自然绝经后相应的年长女性,表皮和真皮对雌激素治疗的反应更好。在雌激素治疗仅4~6周后,年轻女性的皮肤恢复就可以得到改善,而绝经后的妇女,完全起作用可能要花6个月时间。

美国的一项研究随访了3875名妇女20多年,发现了一个有趣的现象。据这项研究报道,雌激素使用者皮肤干燥的危险性较低,为53%,起皱纹的危险性较低,为58%。当按照潜在的危害因素(如年龄、体重和晒伤程度)进行调查时,皮肤干燥的危险性仍较低,为29%,起皱纹的危险性也较低,为33%。

据奥地利的一项研究报道,60名以前没有用雌激素治疗过的妇女,现在给她们涂含有雌二醇或雌三醇的雌激素乳膏治疗6个月。雌激素乳膏在晚上涂于面部。经

months. The estrogen creams were applied to the face in the evening. Blood circulation was improved, the turgor of the skin was also improved and the skin was less dry.

Another interesting observation was made by Ashcroft et al, comparing postmenopausal women with and without estrogens in wound healing, on identical experimental surgical wounds. It was found that the healing of wounds was much approved in the estrogen group. This observation is of potential clinical significance as it may infer that wound healing, not only after surgical procedures could be improved, but also pressure wounds and wounds due to circulation insufficiency can be markedly changed for the better.

过治疗,血液循环改善了,皮肤的充盈度也改善了,而且皮肤也不太干燥了。

Ashcroft 等人做了另一项有趣的观察:在同等实验性手术伤口情况下,比较了绝经后妇女在使用雌激素和不使用雌激素时伤口的愈合情况。他们发现,应用雌激素组的伤口愈合要好得多。这项观察具有潜在临床意义,因为由此可以推断:不仅手术后的伤口愈合可以得到改善,而且压力伤口和循环功能不全所引起的伤口也能明显地变好。

DECREASE IN SKIN COLLAGEN CONTENT AFTER THE MENOPAUSE			
n	Time after menopause	Skin collagen content ($\mu\text{g}/\text{mm}^2$)	
19	0 - 3 months	189.6	± 55.2
14	6 - 7 months	193.4	± 55.6
19	1 year	161.1	± 44.8
16	1.5 - 2 years	191.7	± 73.5
14	3 years	192.4	± 66.9
15	4 - 5 years	146.6	± 54.0
13	6 - 7 years	147.1	± 57.7
15	8 - 9 years	154.5	± 81.3
12	10 - 15 years	130.6	± 30.6
11	≥ 16 years	108.6	± 23.3

绝经后皮肤胶原含量的下降情况			
n	绝经后的时间	皮肤的胶原含量 ($\mu\text{g}/\text{mm}^2$)	
19	0 ~ 3 个月	189.6	± 55.2
14	6 ~ 7 个月	193.4	± 55.6
19	1 年	161.1	± 44.8
16	1.5 ~ 2 年	191.7	± 73.5
14	3 年	192.4	± 66.9
15	4 ~ 5 年	146.6	± 54.0
13	6 ~ 7 年	147.1	± 57.7
15	8 ~ 9 年	154.5	± 81.3
12	10 ~ 15 年	130.6	± 30.6
11	≥ 16 年	108.6	± 23.3

DECREASE IN SKIN THICKNESS (X-RAY MEASUREMENTS) AFTER THE MENOPAUSE			
n	Time after menopause	Skin thickness (mm)	
12	0 - 3 months	0.88	± 0.14
10	6 - 9 months	0.77	± 0.15
20	1 year	0.75	± 0.16
17	1.5 - 2 years	0.81	± 0.13
9	3 years	0.80	± 0.14
15	4 - 5 years	0.77	± 0.14
14	6 years	0.73	± 0.12
12	7 - 10 years	0.81	± 0.12
12	11 - 19 years	0.69	± 0.14
12	≥ 20 years	0.64	± 0.12

绝经后皮肤厚度的减小(X线测量)			
n	绝经后的时间	皮肤厚度 (mm)	
12	0 ~ 3 个月	0.88	± 0.14
10	6 ~ 9 个月	0.77	± 0.15
20	1 年	0.75	± 0.16
17	1.5 ~ 2 年	0.81	± 0.13
9	3 年	0.80	± 0.14
15	4 ~ 5 年	0.77	± 0.14
14	6 年	0.73	± 0.12
12	7 ~ 10 年	0.81	± 0.12
12	11 ~ 19 年	0.69	± 0.14
12	≥ 20 年	0.64	± 0.12



Figure 1: Staining for the presence of a protein associated with estradiol receptors within the skin. The most intense staining is within the epidermis. The presence of this protein suggests that estrogen affects the skin. Dry, flaking, itching skin is commonly experienced postmenopausally when deprived of estrogen, and an improvement may often be seen with estrogen replacement therapy.

图 1: 染色检查皮肤内是否存有伴随雌二醇受体的某种蛋白。染色最强的是表皮内。这种蛋白的存在提示雌激素影响着皮肤。当雌激素丧失后, 绝经后期常会出现皮肤干燥、脱皮、瘙痒, 采用雌激素替代疗法常会使这种情况有所改善。

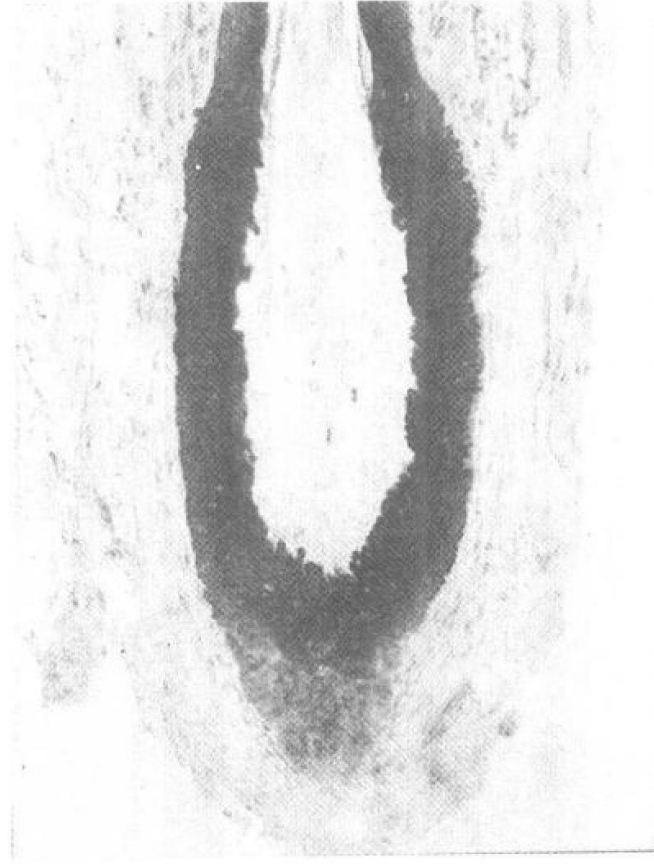


Figure 2: Traverse section through hair follicle stained with peroxide for the presence of a protein associated with estradiol receptors. This is indicated by the dense staining. Postmenopausal women often experience dry or thinning hair, which is improved with HRT. The presence of an estradiol receptor within the hair follicle would explain this response to lack of estrogen and replacement.

图 2: 对毛囊的横断面用过氧化物进行染色, 检查是否存在伴随雌二醇受体的某种蛋白。这可以通过浓厚染色来显示。绝经后期女性常会出现毛发干燥或变稀, 可用雌激素替代疗法加以改善。毛囊内存在雌二醇受体将能解释对雌激素缺乏和替代疗法的这种反应。



Figure 3: Staining for the presence of a protein associated with the estradiol receptor within a sebaceous gland. Staining was less dense than in the epidermis, but was present. This offers a further explanation for the dry texture of skin experienced by postmenopausal women.

图 3: 染色检查皮脂腺内是否存在有某种伴随雌二醇受体的蛋白。染色不及表皮内浓厚, 但却出现了。这为绝经后女性所出现的皮肤干燥肌理提供了进一步的说明。

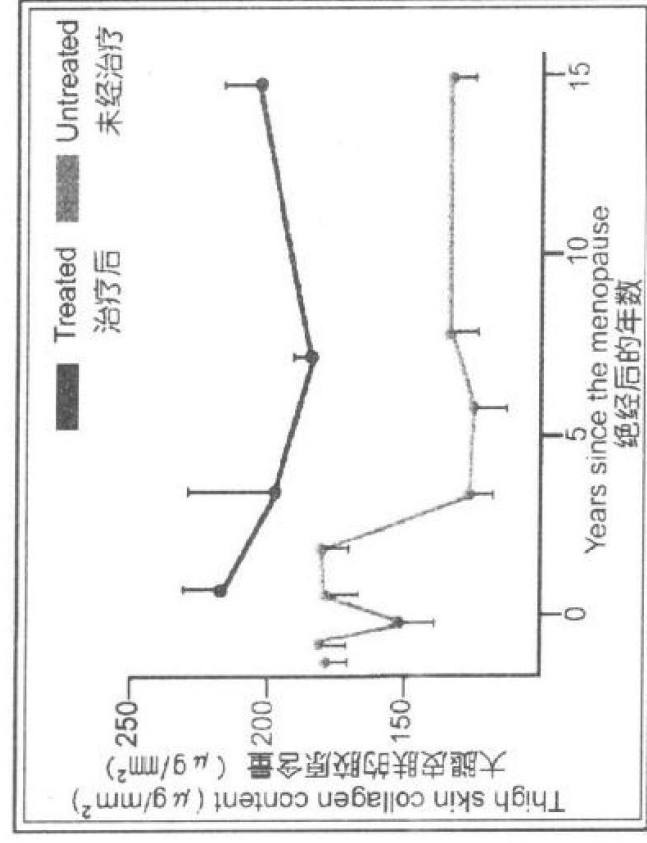


Figure 4: The effect of treatment with subcutaneous estradiol implants on thigh skin collagen in 59 postmenopausal women compared to 148 untreated women. Treatment was given between two and ten years. This figure indicates that with estrogen replacement, thigh skin collagen content is maintained.

图 4: 用雌二醇皮下埋入法对 59 名绝经后期女性的大腿皮肤胶原进行治疗, 将治疗效果同 148 名未经治疗的女性进行比较。这种治疗的疗程在 2 年至 10 年之间。本图示出, 经过雌激素替代治疗, 大腿皮肤的胶原含量保持不变。

CASE 1

Vaginal dryness, agonizing micturations and pain during intercourse are problems for a mid-sixties postmenopausal woman. For the past two years, she has not had any of the sweats or hot flushes she had experienced during the first two to three years after the menopause. The patient is embarrassed, however, because she can no longer control micturition. During a gynecological examination, it is seen that the woman's vaginal mucosa is thin and frail and there is clear-cut tenderness over the proximal part of the urethra. Abdominal examination is normal apart from a distended sigmoid, revealing constipation to which the patient admits.

Q1. What is the most likely diagnosis?

Q2. What other diagnostic procedures do you consider relevant?

Q3. What should be the first line of treatment?

Q4. What information should be given to the patient?

病例 1

一位 65 岁左右的绝经后的妇女, 出现阴道干燥、排尿困难以及性交时疼痛。最近两年, 她一点儿汗也不出, 也没有出现潮红, 而这些症状在绝经后的头两三年她都曾有。但是, 病人深感窘迫, 因为她再也不能控制排尿。在妇科检查中, 可见此妇女的阴道粘膜薄而脆弱, 尿道近端有明显的触痛。腹部检查结果除了乙状结肠膨胀, 发现病人有可忍受的便秘以外, 其他方面都正常。

问题 1. 最可能的诊断是什么?

问题 2. 你认为做哪些其他诊断程序比较适合?

问题 3. 一线治疗应是什么?

问题 4. 应向病人提供什么信息?

ANSWER TO CASE 1

Diagnosis

This is also a characteristic case. Gynecological examination in the elderly may be painful and the use of lubricants is particularly prudent. Signs of atrophy include reddened and thin vaginal mucosa. Petechial bleeds may also be visible. Commonly, there is tenderness over the urethra and lower part of the bladder. Upon bimanual examination, the patient often has an urgent feeling to urinate.

The urethra and trigonal area of the bladder embryologically develop in close connection with the genital system. These tissues are also estrogen sensitive. When performing a urethroscopy, similar signs of atrophy in the mucosa of the trigonal area and the urethra may be seen. These changes resemble those of the vaginal mucosa.

The patient's history, plus clinical signs during examination, is sufficient for the diagnosis. No other laboratory tests are needed before estrogen is prescribed.

Treatment

Low dose estrogens could be administered without risking en-

病例 1 的答案

诊断

这也是一个典型的病例。老年人做妇科检查可能有疼痛而且使用润滑剂要特别慎重。萎缩的体征包括阴道粘膜变红和变薄。也可见到有出血瘀点。通常尿道和膀胱下部有触痛。双合诊时,病人常有急迫的排尿感。

尿道和膀胱三角区从胚胎学来讲是与生殖系统紧密相连发育的。这些组织也是雌激素敏感性的。当进行尿道膀胱镜检查时,在三角区和尿道的粘膜上可见相似的萎缩体征。这些改变类似于阴道粘膜的改变。

病人的病史,加上检查时的临床体征,足以做出诊断。在使用雌激素治疗之前,不需要做其他任何实验室检查。

治疗

给予低剂量雌激素治疗不会有子宫内膜增生的危

ometrial proliferation, rendering progestogen co-medication unnecessary. In some cases, preventive measures for osteoporosis and cardiovascular disease may be considered and hormone replacement therapy given systemically. The patient should be informed about the importance of estrogens. She should also be instructed to return to the clinic within three months if her condition does not substantially improve.

A urodynamic investigation may be needed to rule out other possible diagnoses such as kidney stones, tumors or neuromuscular disorders. Elderly women often become constipated. Estrogen treatment may also alleviate this problem but will not cure it.

险,因此孕激素联合治疗没有必要。在某些病例中,可以考虑对骨质疏松和心血管疾病采取预防措施,并全身性进行激素替代疗法。应告诉病人雌激素的重要作用。如果她的状况没有实质性改善,应指导她在3个月内复诊。

需要进行尿动力学检查,以排除其他可能的诊断,如肾结石、肿瘤或神经肌肉性疾病。老年妇女常会发生便秘。雌激素治疗也可减轻这一症状,但并不能治愈。

2:UROGENITAL AGING

The loss of gonadal functions in women results not only in the classic sweats and hot flushes, but also in a variety of symptoms and signs in the urogenital tract. These symptoms almost always occur as a result of atrophy and are sometimes accompanied by infections or additional inflammatory conditions. Urogenital symptoms do not usually become copious until a few years after the menopause, but may persist throughout life, suggesting estrogen dependency.

From the time of onset, it would seem that urogenital tissues do not atrophy until endogenously produced estrogens are well below the estrogen activity required to promote endometrial growth (Figure 5). With advancing age, severity of symptoms caused by urogenital aging and estrogen deficiency commonly increases along with the number of women afflicted by symptoms. It can be inferred from population based surveillance studies that about one-third of postmenopausal women complain of problems in controlling micturition. Vaginal problems such as dryness, dyspareunia and discharge are reported by two out of three women at the age of 75.

2:泌尿生殖器的衰老

妇女性腺功能的丧失不仅会引起典型的出汗和热潮红,而且会引起泌尿生殖道的各种症状和体征。这些症状几乎总是由于萎缩的结果而出现的,有时伴有感染或另外的炎症性疾病。泌尿生殖器的症状通常直到绝经几年后才变得很多,但可持续终生,提示有雌激素依赖性。

从症状出现时起,看来泌尿生殖器组织要在内源性生成的雌激素大大低于刺激子宫内膜生长所需的雌激素活性之后才开始萎缩(图5)。随着年龄的增长,泌尿生殖器老化和雌激素缺乏所导致的症状的严重程度通常会加重,同时,受症状折磨的妇女人数也会增多。根据按人口监督调查结果可以推测,大约 1/3 的绝经后妇女主诉有控制排尿障碍。阴道疾病,如干燥、性交疼痛和排出物,据报道占 75 岁妇女的 2/3。