更年期賀爾蒙治療指引

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2002年7月WHI荷爾蒙治療臨床研究報告，發表於JAMA雜誌後，立即引起醫界及民眾廣泛的關注及討論。

Hormone Therapy Guidelines: 2007 Taiwanese Menopause Society Position Statement

(荷爾蒙治療包括雌激素、黃體素（Progestogens）、雌激素合併黃體素所有製劑及Tibolone)

1、 使用荷爾蒙治療前，所有婦女都應接受完整的評估及檢查，持續使用荷爾蒙治療的婦女，每年至少應接受定期檢查一次。

2、 醫師應提供專業諮詢，告知婦女荷爾蒙療法的效益與可能發生的風險，以決定是否需要使用。

3、 荷爾蒙治療仍爲緩解婦女更年期症狀（如熱潮紅、盜汗、心悸、失眠、陰道萎縮乾澀、泌尿道萎縮症狀等）最有效的方法。如僅爲治療局部症狀(如陰道萎縮、性交困難、萎縮性尿道炎等)建議使用局部性雌激素療法。低劑量陰道雌激素治療不需合併使用黃體素。

4、 荷爾蒙治療已證明可降低停經後骨質疏鬆症骨折及大腸癌的危險。停經婦女應做一次DXA（Spine AP View）之骨密度測定，若確定爲骨質疏鬆症，且無特殊禁忌，則建議使用荷爾蒙治療五年以上。早期卵巢衰竭及年齡小於60歲的停經婦女，若經評估有骨質疏鬆症危險因子者，應得以荷爾蒙療法爲首選治療藥物。

5、 目前證據充分顯示，60歲以前使用荷爾蒙治療，具有保護心臟血管的作用；長期持續使用超過60歲則建議須評估風險。但建議不要只爲了預防心血管疾病而使用荷爾蒙治療，對停經並保有子宮的婦女，可使用其他藥物或方法來降低心血管疾病。

6、 停經初期婦女（Early Post Menopause）如使用賀爾蒙治療，引起乳癌增加的機率極低。雌激素合併黃體素治療超過五年，發生乳癌危險性會少許升高，但乳癌風險升高的程度，並不具統計學的意義。

7、 根據2004年WHI研究報告顯示，子宮切除之停經婦女單獨使用雌激素，會增加中風之危險，但顯著減少股骨頸骨折之危險。平均使用雌激素6.8年，乳癌的發生率稍減，同時不會影響冠心病發生率。

8、 子宮完整的婦女使用雌激素治療時，應同時處方適當的黃體素，以預防子宮內膜增生；對無子宮的婦女則無需處方黃體素。合成黃體素（Progestins）似乎會有促進乳癌及冠心病之不良作用。

9、 針劑荷爾蒙療法，因其長期使用之療效及危險性仍未確定，不建議使用。

10、 荷爾蒙治療在停經10年以內就開始使用，則其效益高且風險低，使用時應優先考慮低劑量療法。

11、 停經婦女不需常規補充男性荷爾蒙，但對男性荷爾蒙缺乏之停經婦女（如曾接受雙側卵巢切除或腎上腺功能失調婦女），則有顯著療效（如提昇生活品質及改善性功能）。

12、 雖然有些報告認爲植物性雌激素對更年期症狀之改善有所幫助，但其療效有限，與安慰劑相比較，無顯著差異。因臨床研究證據不足，在選擇此類產品時，須謹記「並非所有植物性雌激素皆安全有效，臨床驗證與否是唯一的保障」。

更年期荷爾蒙治療(HT)的演進

(A) 連續性 : continuous combined HRT

(I) Combined →E + P

(II) 子宮切除: →E

更年期荷爾蒙治療(HT)的演進

(B) 週期性 : cyclic HRT (E + P)

(I)

P 至少要吃 12-14 天以上

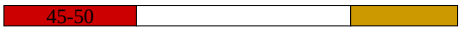
(II)

更年期荷爾蒙治療(HT)的演進

依照年齡區分 (Age)

1)停經前;亂經期 (peri-menopause)

around 45-50 y/o



*使用藥物: 低劑量調經藥

Low-dose OCP

更年期荷爾蒙治療(HT)的演進

依照年齡區分 (Age)

2)停經期 (早期, 中期), around 50-60 y/o

(Early – Mid, post-menopause)

*使用藥物: 標準 HRT

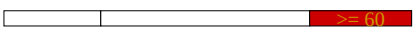
1) 0.625 mg E + 2.5-5 mg P
2) Oestrogel + P
3) Livial
4) Raloxifen

更年期荷爾蒙治療(HT)的演進

依照年齡區分 (Age)

3)停經期 (後期), >= 60 y/o

(Late, post-menopause)



*使用藥物: 低劑量 HRT

1) 0.3 mg E + 2.5 mg P
2) Livial
3) Raloxifen

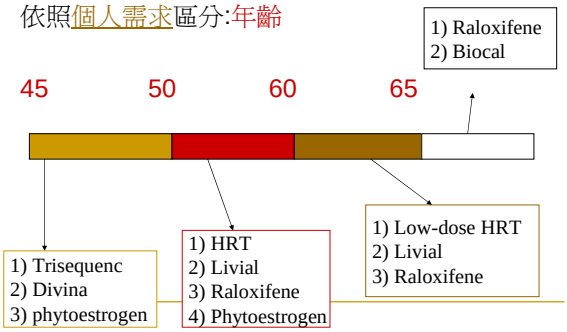
更年期荷爾蒙治療(HT)的演進

依照個人需求區分

1) 年齡
2) 症狀
3) 需求
    1) 害怕乳癌
    2) 害怕不規則陰道出血
    3) 欲規則月經否?
    4) 其他藥物或健康食品的配合

更年期荷爾蒙治療(HT)的演進

依照個人需求區分:年齡



更年期荷爾蒙治療(HT)的演進

依照個人需求區分:症狀

1) 更年期症狀: 是否影響日常生活
    1) 早期
    2) 中期
    3) 晚期

更年期荷爾蒙治療(HT)的演進

依照個人需求區分: 需求

1) 各期症狀的解除
    1) Vasomotor syndrome
    2) Osteopenia, Osteoporosis
2) 癌症恐慌; 家族史
3) 特殊內科疾病史 (Contraindications)
4) 特殊婦產科開刀史

更年期荷爾蒙治療(HT)的因應

1) HRT 使用以 5 年爲一階段
    1) 超過5 年, 先改爲半劑量
    2) 配合替代療法
2) 每年固定健檢
3) 不要自行停藥或改變吃法
4) 注意醫學新知; 切勿道聽途說
5) 規則運動, 飲食改善

更年期荷爾蒙治療(HT)的因應

- 荷爾蒙替代療法
- 1) 類荷爾蒙製劑
    - SERM: Raloxifene
    - Livial
- 2) 骨質補充
    - 雙磷酸鹽酸: Forsamax, Alendronate
    - 活性鈣: Biocal, Cal-citrate, E-cal, 挺立
- 3) 植物性類荷爾蒙: 異黃酮類
    - Phytoestrogen: Soygerm, Phytosoya

那些人不適合接受荷爾蒙治療

有幾類情況之下，不宜給予女性荷爾蒙治療

(1)不明原因的陰道出血

(2)急性肝病

(3)急性血栓靜脈炎

(4)不易控制的高血壓

(5)曾有乳癌或子宮內膜癌

大豆吃太多 女性恐致肝癌

自由時報 2009/3/11

- 大豆製品所含的大豆異黃酮（Isoflavone）因具有降低乳癌發病機率的功效，相關營養產品也受到廣大女性歡迎。
- 但是日本，官方的大規模研究指出，大量食用大豆製品的女性，罹患肝癌的風險比不太食用大豆製品的女性高二到將近三倍。
  - 日本厚生勞動省的研究班自一九九三至二〇〇五年爲止，針對全國約兩萬名男女進行長期健康追蹤調查
  - 食用量最多（一天豆腐八十公克以上、納豆三分之二包以上）女性，罹患肝癌風險約爲食用量最少（一天豆腐不到四十公克、納豆不到三分之一包）女性的三・二至三・九倍。男性的大豆食用量與肝癌發病機率之間，則未發現明確關聯性。

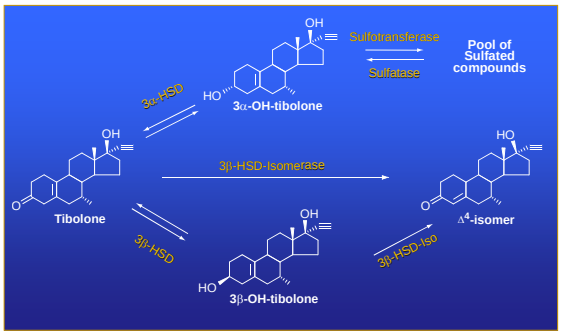
STEAR

(Selective, Tissue Estrogenic Activity Regulator)

Mode of action:
- Parent compound and/or metabolite
  - act as a complete E_2 receptor agonist (ERα)
- Pre-receptor regulation of estrogenic action by
  - enzyme regulation (inhibition and/or induction)
  - tissue selective metabolism

Clinical effects of a STEAR:
- Prevents
  - climacteric symptoms
  - bone loss
- Does not stimulate
  - breast
  - endometrium

Metabolism of tibolone



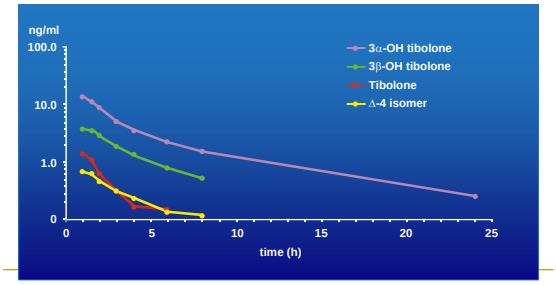
Receptor profile of tibolone and its metabolites

	ER	PR	AR	* enzyme inhibition
Tibolone	+	+/-	+/-	+
3α-OH-tibolone	+	-	-	+
3β-OH-tibolone	+	-	-	+
Δ^4 -isomer	-	+	+	-

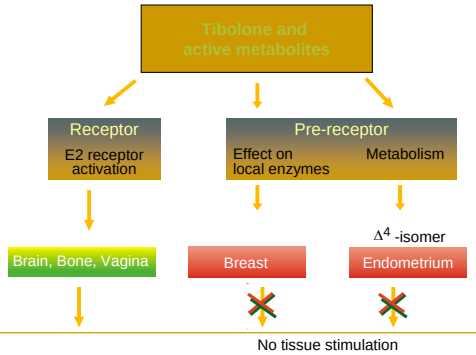
*** enzymes regulate estrogen**

de Gooyer et al., Steroids 2003

Plasma concentration of tibolone and its metabolites postmenopausal women after 2,5 mg of tibolone



Tissue selective effects of tibolone



Tibolone: clinical recommendations and practical guidelines

International Tibolone Consensus Group

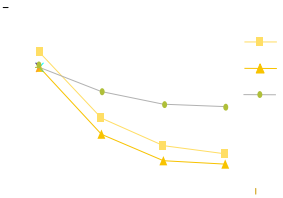
P. Kenemans , L. Speroff

Climacteric symptoms

- Tibolone is as effective as currently used EPT/ET regimens in the management of climacteric symptoms.

Control of vasomotor symptoms

Effect on relief of hot flushes



Urogenital symptoms

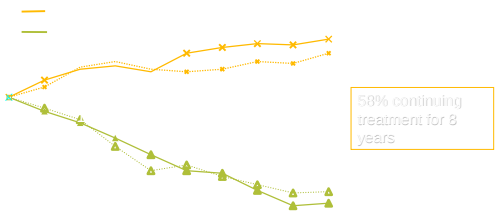
- Tibolone treats vaginal atrophy and relieves urogenital symptoms

Prevention of bone loss

- Tibolone is as effective as EPT/ET in preventing bone loss.

LIFT

Bone effects after 8 Years Tx with Livial 2.5 mg Daily



p < 0.001

Safety and tolerability

- Tibolone causes less breast tenderness and mastalgia than EPT.

Breast density

- Tibolone dose not increase mammographic density .

Factors associated with an increased risk for breast cancer in women

Relative Risk	Factor
1.1-2.0	Menarche before age 12 years
	Recent and long-term use of postmenopausal HT
	High socioeconomic status
	Nulliparity
	Never having nursed an infant
	First full-term pregnancy after age 30 years
	Alcohol consumption
2.1-4.0	One first-degree relative with breast cancer
	Biopsy-confirmed atypical hyperplasia
	High bone density (postmenopausal)
> 4.0	*BRCA1* and/or *BRCA2* mutations
	Increase mammographic breast density

Breast safety

- Randomised controlled trial investigating breast cancer incidence and tibolone are awaited before any firm conclusion can be drawn regarding tibolone and breast cancer.

LIBERATE

Tibolone increases the risk of recurrence in breast cancer patients, while relieving vasomotor symptoms and preventing bone loss

IMS: Date of release: 09 March, 2009

Hormone therapy after breast cancer is controversial

- mean age was 52.7 ± 7.3 years
- either tibolone 2.5 mg daily or placebo
- After a median follow-up of 3.1 years (range 0.01–4.99 years)
  - 237 of 1556 (15.2%) women on tibolone had a recurrence
  - 165 of 1542 (10.7%) on placebo
  - hazard ratio (HR) 1.40; (95% confidence interval (CI) 1.14–1.70; *p* = 0.001).

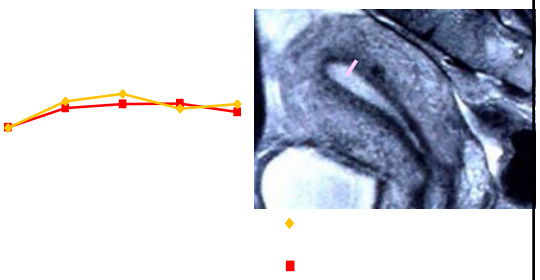
- Data from the LIBERATE study show that tibolone should remain contraindicated for women with a history of breast cancer.
- However, in healthy postmenopausal women, the breast safety profile of this compound seems reassuring.
  - In the recent LIFT trial , there was a decrease in risk of invasive breast cancer (HR 0.32; 95% CI 0.13–0.80). Also, in the large GPRD database, there was no increase in risk of breast cancer from tibolone .

Endometrium

- Tibolone dose not stimulate the endometrium and the addition of a progestogen is not required. It is associated with a high amenorrhoea rate and a lower incidence of irregular vaginal bleeding than continuous EPT. Standard endometrial surveillance is not required.

THEBES

Endometrial thickness



Cardiovascular

- Cardiovascular clinical outcomes from randomised controlled trial are not available yet. Surrogate endpoint studies for arterial disease and venous thromboembolic disease are inconclusive with regard to benefit or risk.

OPAL

Overall tolerability

- Tibolone is well tolerated. It has no major clinical impact on body weight.

Thanks for your attention

Thanks for your attention