While our Doubts are Answered, What Can We Do?

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A menopausal woman is a middle-aged woman

As a menopausal woman:

She is hypoestrogenic and will suffer, at various levels, from its consequences.

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As a middle-aged woman:

She will suffer from the process of natural ageing, both from a biological and a psychological perspective.

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1/3 of 35 years-old women have lesions of atherosclerosis !

A modern gynecologist must ...

know how to identify risk factors and to modify them in order to prevent diseases.

A tripod to support good health and longevity

- aerobic exercise
- rational nutrition
- pharmacological intervention

Pharmacologic interventions

- Symptomatic
- Preventive
  - Primary
  - Secondary

Pharmacologic interventions

- hormonal
- non hormonal

Nurses's Health Study (*NEJM, 2000*)

from 1980 to 1994 CHD ↓ 31%

↓ Smoking	↓ 13%
↑ Obesity	↑ 8%
↑ THS	↓ 9%
↑ Better nutrition	↓ 16%

Physical Exercise Activities and Risk of Breast Cancer

- 2 to 4 hours / week RR = 0.8
- > than 4 hours / week RR = 0.4

Relative Risk of Breast Cancer and Body Weight

- Weight (> 60 kg) and Age (>50 years)
- ***increase the RR between 1.2 and 1.8***

Epidemiological Studies

- How were they performed?

- What similarities do they have with our clinical practice?

- How to interpret them?

“Administration of raloxifene (and tamoxifen) to postmenopausal women reduces the number of breast cancers diagnosed by 50% to 80%. With the current methods of estimating risk, 25 to 100 women must take these medications to prevent “ 1” breast cancer” !

Santen RJ. NAMS Newsletter 2002

“The trial of pravastatin for primary prevention by WOSCOP (the west of Scotland coronary prevention study) would indicate that *of 10 000 patients with statin for five years, 9755 would receive no benefit*”

Freemand X et al.BMJ 1998;316:1241

Do not confuse…

Relative Risk

with

Absolute Risk!

Do not confuse…

Morbidity

with

Mortality!

Epidemiological Studies

PLEASE!

Do not read only the tittles

Do not read only the abstracts

Do read the full paper

Be critical!

Make up your own mind!

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“Clinicians must apply their expertise to assess the patients problem and must also incorporate the research evidence and the patient’s preferences or values before making a management recommendation”

Haynes RB et al.Evidence-Based Medicine.1996;1:196-8

"Subsequent versions of *evidence-based* decision making have emphasized that research evidence alone is not an adequate guide to action".

"Evidence alone does not make decisions".

Haynes RB et al.Evidence-Based Medicine.1996;1:196-8;BMJ 2002;321:1350

What is

a **woman /year** **?!**

100 woman/years = ***100 women treated during 12 months***

is it the same as

100 woman/years = 400 women treated ***during 3 months***

Epidemiological Studies

- Observational

- Clinical trials

Hormonal Therapies

- **Absolute risks**
- **Relative risks**
- **Odds ratios**

- Are very important indicators, but *devoid of clinical usefulness unless one knows how to extrapolate them* into practice (advise, counseling, information)

- ***RR*** or ***OR*** are fine for determining whether the link to harm was true, but don't tell us whether the link was clinically important.
- Similar ***RRs*** or ***ORs*** can lead to very different ***NNHs*** and you need the latter as well as the former to make your clinical decision about your patient.

Hormonal Therapies

It is urgent and essential to present the risk/benefit data in a more clinically meaningful and useful fashion.

- **PEER** = Patient's Expected Event Rate
- **RRR** = Relative Risk Reduction
- **ARR** = Absolute Risk Reduction = PEER x RRR
- **ARI** = Absolute Risk Increase

- ***NNT*** = Number Needed to Treat = 1/ARR
- ***NNH*** = Number Needed to Harm = 1/ARI

(with *Confidence Intervals*; better than ***p*** values)

Researchers from the University of California, at Davis, claim clinical trials are reported with misleading statistics

BMJ 2002;321:1353

"Most randomised trials of new treatments published in leading medical journals are reported in a potentially misleading way".

BMJ 2002;321:1353

359 randomised clinical trials of new treatments published between 1989 and 1998 in five major medical journals:

- **the Annals of Internal Medicine**
- **BMJ**
- **JAMA**
- **Lancet**
- **New England Journal of Medicine**

“Most of the trials report results based on relative risk reduction”!

“Only 18 of the papers reviewed considered absolute risk reduction”!

“Only 8 of the 359 trials reported the number needed to treat (N.N.T)”!

BMJ 2002;321:1353

"In the majority of cases, only the most favourable statistic- the *relative risk reduction*- was used when reporting the results of these studies".

BMJ 2002;321:1353

"Medical journals should require all authors to follow the recommendations of the CONSORT statement, which include use of absolute risk reduction and number needed to treat".

BMJ 2002;321:1353

“It is not unusual to see new drugs presented in terms of relative risk reduction rather than absolute risk reduction. Relative risk reduction is often much more impressive and seems more tangible”.

BMJ 2002;321:1353

“Relative risk reduction can appear quite large when the absolute risk reduction is actually very small”.

BMJ 2002;321:1353

Women are not statistics!

They must be treated individually.

Menopausal hormonal treatments are very good.

but

Treatments without hormones may also be very good for a woman’s health

***Look* for risk factors**

Cardiovascular

Cancer

Bone

CNS

The analysis

Benefit/risk

Benefit/cost

“IHD deaths are much more frequent in the USA than in Italy, whereas CeVD deaths are more common in Italy”

Ricci S et al.J Clin Basic Cardiol 2002;5:105-108

"In the light of these differences, long-term HRT should yield larger benefits in North American women – with higher IHD mortality and lower incidence of fatal CeVD – and probably less beneficial effects in Italian women, who exhibit a lower IHD mortality and a higher CeVD mortality".

Ricci S et al.J Clin Basic Cardiol 2002;5:105-108

“Our analysis of age group mortality indicates that in the 40-49 age group for each woman dying of IHD, 5 will die of BC in Italy but only 2 in the USA”

Ricci S et al.J Clin Basic Cardiol 2002;5:105-108

“Women who are to receive long-term HRT, should be selected much more carefully than in countries where IHD mortality is altogether higher and more frequent in younger women”

Ricci S et al.J Clin Basic Cardiol 2002;5:105-108

Monitor

The efficacy of your interventions in regard to the predetermined objectives/targets

For how long?

“Recently revised NCEP guidelines indicate that for women aged 45 to 75, the favorable effects of therapy with “statins” in clinical trials make <u>a cholesterol-lowering drug preferable to HRT for CAD risk reduction”</u>

Cleeman J. JAMA 2001;285(19):2486-97

- **The important issue, after all, is not HRT**

- **What is important is the *best possible approach* to preventive medicine in a middle-aged woman**

“Pharmaceutical companies are actively involved in *sponsoring the definition of diseases* and promoting them to both prescribers and consumers”

Moynihan R et al.BMJ 2002;324:886-90

Some

concepts

to remember ...

HRT

Hormone replacement therapy?

or

MHT

Menopusal hormonal therapy?

Never forget your advise about:

- Aerobic exercise
- Rational nutrition
- Reduced smoking
- Reduced Alchool consumption
- Develop Mental ocupations
- Pharmacologic interventions

An attending gynecologist must never overlook that his/her primary role is to promote health and to prevent diseases, other than being able only to diagnose and treat the illnesses of mature women.

The message is:

. To prescribe postmenopausal hormonal treatments <u>when clinically indicated</u>

. <u>No answers from ongoing clinical trials are indispensable</u> to practice today a good Medicine

- ***“If you are a clinician,***you must believe that you know what will help your patient; otherwise, you cannot counsel, you cannot prescribe”.
- ***“If you are a scientist,*** however, you must be uncertain – A scientist who no longer asks questions is a bad scientist…”

George Pickering “Physician and scientist”,Br Med J 1964;2:1615-9*(quoted by E Barrett-Connor.Keynote address.Menopause 2002;9(1):23-31)*

“The Menopause: an opportunity”

Leon Speroff

“The Menopause:

an alarm clock!”

M Neves-e-Castro

Science ...

is an art of probability

Medicine...

is an art of uncertainty

Sir William Osler

The take home message

The prescription of long-term hormonal treatments must depend always on a benefit/risk analysis ***in comparison with other non-hormonal medications and strategies*****.**

Preventing a woman from the benefits of **a sound postmenopausal hormone therapy** because of the fear of rare side effects ***does not seem to be satisfactory Medicine...***

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“Since *life itself is a universally fatal sexually transmitted disease*, living it to the full demands a balance between reasonable and unreasonable risk”

Skrabank P,McCormick J-*Follies and fallacies in Medicine*.Chippenham.Tarragon Press,1992