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Menopause and HRT – the state of the art in Europe

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Abstract

The HRT field has been dramatically affected by the publication on major randomised controlled trials of the long-term effects of HRT. The publicity surrounding the publication of these data has affected public and regulatory perceptions of HRT and its role in healthcare, including the relatively short-term use of HRT for the relief of menopausal symptoms.

An evidence-based appraisal of the role of HRT today is best achieved by considering the different components of the effects of HRT individually, based on the best trial evidence, and then considering these together in the context of the age of woman concerned and the specific components relevant to that woman's health profile. This paper summarises the effects of HRT using this approach in the context of European practice today and describes the events surrounding the regulatory and scientific society position statements.

Keywords: Menopause; Hormone therapy; Europe; State of the art; Osteoporosis

1. Introduction

The basics of the menopause and hormone replacement therapy (HRT) have been established over several decades yet we have seen the field appear to be turned upside down in the past half dozen years. This has occurred as a result of the impact of landmark trials carried out in the United States which have overturned some of the established ideas about the effects of HRT in postmenopausal women, have attracted considerable media attention and have affected the regulatory framework of HRT use in Europe as well as in the US [1–4].

This was able to happen with such an established therapy because what these recent trials were addressing were effects of HRT that were assumed from available data but had not been tested in randomised controlled trials (RCTs). Progressively over the past 15 years, the world of medical science has accepted the principle that the highest level of evidence for the effectiveness of a drug is provided by RCTs which report true disease event end-points and that other forms of evidence are less secure. Thus it has become established that RCTs with surrogate end-points, observational studies and mechanistic studies all provide evidence about the effects of drugs but represent a lower level of "proof". However, we would generally expect that all of these forms of evidence should point in the

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same direction. HRT has been in use for decades so how can it be, especially if you take your opinions from the media that recent RCTs can appear to have rewritten the story?

It is critical to an understanding of what has been happening to remember that postmenopausal estrogen is used to address several distinct clinical areas and the quality of the evidence on each of these differs. However in the public perception and in the media attention the information about HRT is compressed into relatively simple messages which collapse the different dimensions of HRT action into headline statements that summarise HRT as "good" or "bad". This kind of summary does no service to the place of HRT in medicine and, more importantly, does no service to the women who might benefit from the appropriate use of HRT.

Another level of complexity in the discussions and arguments that have come in the wake of the publication of these major US trials is around the potentially different outcomes that might have resulted if other estrogen and progestogen products common in European practice had been used or if different, possibly lower, doses had been employed in these mostly older postmenopausal women. Similarly there have been questions around the equivalence of the US population recruited and average European populations. These points have mostly not been addressed in the popular media attention to HRT since the publication of the trials. It is likely that we shall not see future major randomised trials address these important questions which will probably remain unresolved.

2. The different dimensions of HRT

What are the different dimensions of HRT that should be considered separately if there is to be a fair picture of the effects of using HRT and a comprehensible portrayal of the evidence? A summary list should include the following.

The treatment of menopausal vasomotor symptoms:

- Effectiveness proved by clinical end-point RCTs.
- Mainly relevant to women below 60 years of age.
- Risks relatively low below 60 years.
- Many placebo-controlled RCTs demonstrating effectiveness.
- Universally licensed indication.

The treatment of menopausal psychological dysfunction:

- Ill-defined clinical syndrome most common below 60 years of age.
- Some clinical end-point RCT evidence in favour of effectiveness.
- Risks relatively low at age at which this would be relevant.
- Generally not a licensed indication.

The treatment of symptoms of urogenital ageing:

- Multidimensional clinical syndrome which can be ongoing problem.
- Effectiveness proved in clinical end-point RCTs.
- Locally applied estrogen is effective and of low risk.
- Widely licensed indication.

The prevention of osteoporotic fracture:

- Clinical problem of postmenopausal women but the incidence is greatly increased in the elderly.
- Effectiveness had been dependent on observational studies and surrogate end-point trials but now proved by clinical end-point RCTs.
- At younger postmenopausal ages, risks are low but risks of HRT higher in the elderly age groups where fracture risk is highest.
- Has been licensed indication for many HRT preparations but regulatory revision has declared HRT not to be a first-line option.

The prevention of coronary heart disease:

- An important problem of postmenopausal women and a major killer.
- Effectiveness in women with established disease suggested by observational and mechanistic evidence but disproved by clinical end-point RCT.
- Effectiveness in women who have not experienced coronary disease events suggested by surrogate end-point trials, observational and mechanistic evidence but not confirmed by RCTs.
- Not a licensed indication for HRT.

  Ongoing discussion over whether HRT is effective if initiated when coronary arteries are healthy as suggested by surrogate end-point trials, observational