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Safety of Hormone Replacement Therapy

A Review

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The recent publication of a number of large observational and experimental studies that assessed the safety of hormone replacement therapy (HRT) raised a generalised debate. These studies were conducted during a period of clear and rapid expansion of HRT in almost every country, and provided alarming associations between this therapy and several frequent chronic diseases. Subsequently to these findings, a substantial drop in the volume of prescriptions was observed internationally. However, many of the findings of these studies had already been suggested previously. Moreover, a number of methodological issues concerning the recent studies was raised and the validity of their associations questioned. The current absence of clear-cut guidelines on the use of HRT is probably a consequence of the conflicting evidence. In the Portuguese population this may partially account for the notorious lack of association between this therapy and hysterectomy or oophorectomy. Additionally, although sales data seemed to indicate an increasing trend in the prevalence of HRT up to 2002, the uptake of HRT was then a privilege of women in higher socioeconomic strata. Presently, the contribution of long-term hormone replacement therapy to women's health remains unclear and this subject increasingly demands a multidisciplinary approach.
Key-words: hormone replacement therapy; medicine safety; research design; review.

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Hormone replacement therapy (HRT) has recently been the subject of a deep and worldwide debate. In the last decade, the safety profile of unopposed or combined estrogens has been thoroughly studied as observational studies, randomised controlled trials, and reviews and meta-analyses of the original research proliferated.

HISTORICAL BACKGROUND

Questions about the adverse events related to hormone replacement therapies had been firstly addressed in the 1930s, when research on the potential danger of induction of malignancies by estrogen compounds, namely breast cancer, shortly followed the market release of these drugs (1). Nevertheless, the proportion of women undergoing menopause modulation with exogenous hormones increased during the following decades and, in 1966, the publication of 'Feminine forever', a best-seller book on the benefits of hormone replacement therapy, encouraged women to avoid aging and to preserve femininity by using HRT (2).

The popularity of HRT was rising, with the regulatory agencies considering that estrogen could be marketed as protective against heart diseases. However, during the 1970s, climacteric complaints were still the major therapeutic indication for hormone replacement therapy in peri and postmenopausal women. Scientific publications were scarce, and the self-called 'small but highly vocal group of doctors concerned with hormone replacement therapy in the climacteric' (3) debated indications and regimens in an informal fashion, strongly empirical, since they were based on physicians' experience in relatively small samples of women (4, 5). The popularity of HRT was growing and, beyond the relief of menopausal complaints, long-term therapeutic indications had already been suggested at that time (6). The description of an increased incidence of endometrial cancer among estrogen users caused the number of prescriptions to decrease between 1975 and 1980 but this was not an obstacle to the future wider use of HRT (7), as this risk could be diminished with the addition of progestogens.

During the 1980s and the 1990s, progestin-estrogen treatment for women with an intact uterus became widespread (8), mainly because HRT started to be widely regarded as a preventive strategy for chronic diseases, far besides resolving the menopausal syndrome. This idea grew popular, as studies devoted to long-term be-

nefits of estrogen favoured a protective effect of the drug on a number of frequent diseases, such as coronary heart disease (9), stroke (10) or osteoporosis (11). Much research work conducted then would be later criticised due to the use of surrogate endpoints, such as lipid profile (12) and vascular reactivity (13), inadequate definition of exposure (generic HRT instead of individualised drugs), and mostly lack of control for confounding variables. In fact, up to then generally more health-aware women were the obvious main target for this health technology.

RECENT EVIDENCE ON THE SAFETY OF HORMONE REPLACEMENT THERAPY

The uptake of HRT continued to rise through the 1990s, along with safety concerns. In order to clarify the accumulating contradictory evidence, large randomised controlled trials were conducted, such as the Heart and Estrogen/progestin Replacement Study (HERS) and the Women's Health Initiative (WHI). The results of both studies regarding combined therapy were alarming and, when a pooled analysis of large trials was carried out, higher risk estimates for breast cancer, coronary heart disease, stroke and pulmonary embolus were found for women undergoing HRT (14, 15). Although the incidence of endometrial cancer, colorectal cancer and hip fractures was lower among women receiving the active treatment, the risk profile of HRT was considered overall unfavourable for long-term prophylaxis. Additionally, a large observational study published later, the Million Women Study (MWS), was consistent with the previous trial results, namely regarding endometrial and breast cancers (16, 17). Sceptical opinions on HRT have grown and menopause has been currently considered 'medicalised' through the use of HRT, with a shift from a "curative" to a "risk management" perspective (18).

In response to the strong evidence produced, a number of methodological problems concerning the above-mentioned studies were raised. These were related to alleged limitations in the extrapolation of findings regarding individual drugs tried, dosages, compliance, and age ranges tested (19). Additionally, the absolute incidence of adverse outcomes in women undergoing HRT was thought to be low (20), as was, on the other hand, the incidence of beneficial effects.

The trial results urged for guidelines, and regulatory agencies and menopause societies rapidly produced public statements on the safety of hormone replacement therapy. The European Agency for the Evaluation of Medicinal Products (EMEA) recognised the benefit of HRT in the relief of climacteric symptoms and in the prevention of osteoporotic fractures but the same statement emphasized the increased risks of cardiovascular disease and cancer, especially in long-term therapy (21). Nevertheless, the European Menopause and Andropause Society (EMAS) produced a position statement in which, though the 'few absolute indications and contra-indications for HRT' were recognised, the conclusion was that after adequate individual clinical evaluation, for a group of women, 'the benefits will far outweigh any potential risks' (22).

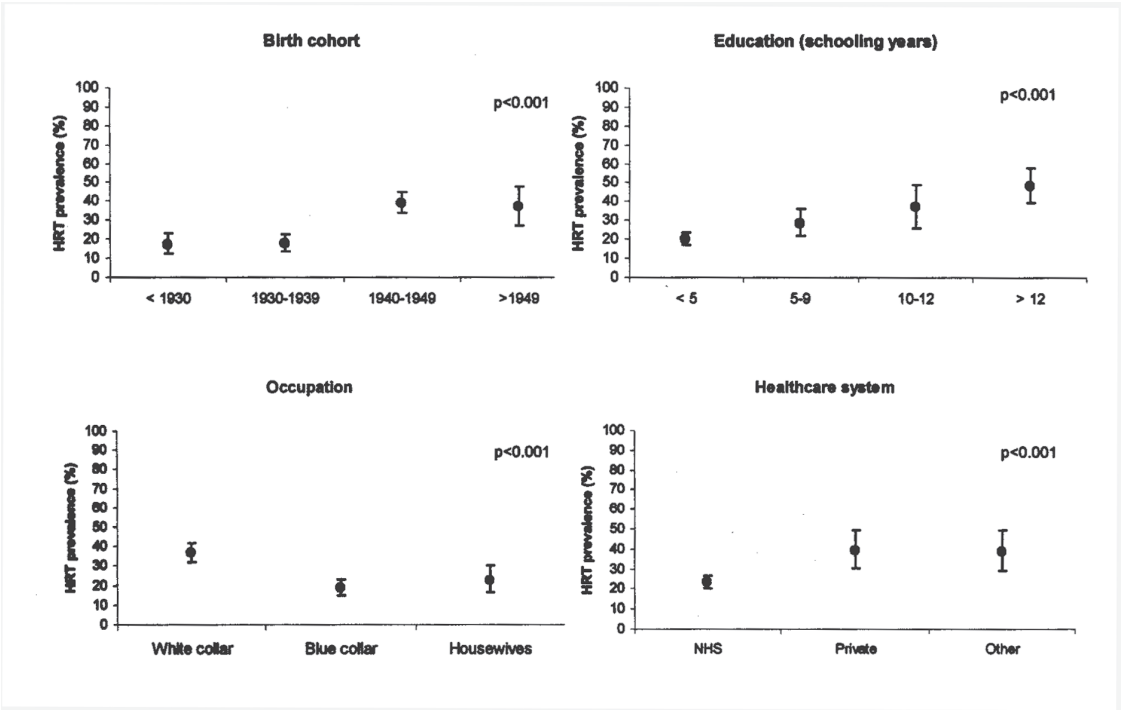

Fig. 1 - Life prevalence of hormone replacement therapy according to selected socio-demographic characteristics.

HORMONE REPLACEMENT THERAPY IN PORTUGUESE WOMEN

The Portuguese regulatory agency (Instituto Nacional da Farmácia e do Medicamento, INFARMED), in accordance with EMEA, has generated six national official statements regarding the safety of hormone replacement therapy from 2002 to 2005 (23-28).

In our country, a recent study on the national sales of drugs used in the treatment of osteoporosis showed that the number of HRT packages per 1000 women increased 30 to 40% from 1998 to 2001/2002, which further dropped in similar magnitude up to 2004 (29).

In addition to national sales figures, HRT uptake profiles in Portugal were studied, using the recruitment data of a cohort of Portuguese adults, the EPIPorto study (30). In this sample of 908 women, representative of the post-menopausal women living in Porto, about one quarter had ever used some kind of hormone replacement therapy. Users were younger, had had menopause more recently and had generally higher socioeconomic status than nonusers, as measured by formal education, occupation, and healthcare system (Figure 1). Probably also reflecting the well known 'healthy user profile' described in other countries, ever smokers, ever users of oral contraceptives and women reporting regular physical activity used HRT more frequently. Although the findings for our country regarding overall life prevalence and socioeconomic determinants of HRT use were similar to those found in other settings (31-33), in Portuguese women neither hysterectomy nor oophorectomy determined the use of hormone replacement therapy. In view of the increasing concern on the safety of HRT and the consequent narrowing of its therapeutic indications, this represents a particularly important finding, with potential impact on healthcare evaluation.

Over the last seven decades, the subjects of efficacy and safety of hormone replacement therapy have been far from consensual. Indeed, a theory on the stages of medical innovation has been applied to this therapy, which was initially regarded as a promising report and then developed into a standard procedure through a final stage of erosion and discreditation (34). Indeed, however arguable the results of experimental studies may be, it is evident that the perspective over HRT has changed substantially, particularly in the last few years.

Nevertheless, the few therapeutic indications for hormone replacement therapy probably account for the current absence of widely accepted guidelines or risk management programmes. Even though the contribution of long-term hormone replacement therapy to women's health is still unclear, this subject increasingly demands a multidisciplinary approach.

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