

Significant fall in hormone replacement therapy prescription in general practice

ALM Lagro-Janssen*, MWA Knufing, L Schreurs and C van Weel

Department of Primary Care and Community Care, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands.

*Correspondence to A L M Lagro-Janssen, Department of Primary Care and Community Care, Women's Studies Medicine, Radboud University Nijmegen Medical Centre, 117 ELG, Postbus 9101, 6500 HB Nijmegen, The Netherlands; Email: a.lagro-janssen@elg.umcn.nl

Received 17 February 2009; Revised 16 February 2010; Accepted 15 March 2010.

Background. Hormone replacement therapy (HRT) in the past has been used in one of five women but not without significant short-term and long-term consequences.

Objective. The aim of the study is to assess the prescription of HRT in general practice to women consulting with menopausal symptoms, before and after publication of the Women's Health Initiative (WHI) study (2002), the Million Women Study and the Lancet Editorial (2003), and to correlate these with co-morbidity, co-medication and frequency of GP consultation.

Methods. The study was performed using data collected by a Dutch Continuous Morbidity Registration. We selected women who presented with menopausal symptoms for the first time during the period 1999–2007 ($n = 341$). Women who were prescribed HRT between 2002 and 2007 were compared with women presenting with menopausal symptoms without HRT prescription and women who did not consult for menopausal symptoms. Both control groups were matched for age, socio-economic status and general practice.

Results. HRT prescription decreased considerably: from 37% in all women who present with menopausal symptoms at the GP 2002 to 14% in 2003 and 4% in 2004. Women who consulted for menopausal symptoms, irrespective of HRT prescription, presented with nervous functional complaints more often, were prescribed more tranquillizers and visited the GP more frequently than women who did not consult for menopausal symptoms.

Conclusions. These GPs were very quick to implement new recommendations on HRT prescription. The decision to prescribe HRT was not correlated with specific emotional or psychiatric problems of the menopausal women.

Keywords. General practice, hormone replacement therapy, menopausal symptoms.

Introduction

Hormone replacement therapy (HRT) has been used in one of five women aged ≥ 50 years in the last decade of the 20th century.¹ The therapeutic goal of HRT was defined as decreasing vasomotor symptoms and preventing osteoporosis and cardiovascular diseases.² The Women's Health Initiative (WHI) study in 2002³ and the Million Women Study (MWS) in 2003,⁴ accompanied by an editorial in *The Lancet*,⁵ launched a new debate on the side effects of HRT.

Both studies concluded that the use of HRT increases the risk of breast cancer, cardiovascular diseases, cerebrovascular accidents, dementia and venous thromboembolic disorders. As a consequence, HRT prescription in the USA decreased by 34%.⁶ Apparently, many patients stopped using HRT or used HRT in lower doses. In The Netherlands too, a dramatic change took place in the

prescription of HRT. The Dutch Association of General Practitioners (Nederlands Huisarts Genootschap: NHG) developed a guideline Menopause in 2001, which was very reluctant in prescribing HRT. The editorial in *The Lancet*, mentioned above, was in the summer of 2003 accompanied by much general media publicity in The Netherlands. In 2006, the NHG College published a short 'Point of view' in addition to the existing guideline of 2001.

Menopausal symptoms may severely impede daily life.⁷ About 70% of women experience symptoms, but only a minority of these will visit their GP.⁸ In general, only 10% of episodes of experienced ill health are presented to the GP, which includes menopausal symptoms.⁹ As a consequence, the use of HRT has been associated by some GPs with inadequate coping strategies of menopausal women, who are not able to cope well with symptoms relating to a 'natural' phase of transition.¹⁰

It is important, therefore, to study the context of women who consult for menopausal symptoms. Improved understanding of co-morbidity can lead to a better understanding of the context in which women ask for help and why they were prescribed HRT. The WHI and MWS studies were performed in the general population and not in general practice among women who consulted the GP for menopausal symptoms. They also lack control groups. The Continuous Morbidity Registration (CMR) Project at Radboud University Nijmegen Medical Centre offers an ideal opportunity to investigate these questions. The CMR is a practice-based long-standing database, recording all health problems that patients present to their GPs.¹¹ The CMR, therefore, gives us the opportunity to follow a cohort through time and to study characteristics of menopausal women.

The aim of our study was to assess changes in HRT prescription by GPs in women with menopausal complaints before and after the publication of some leading articles about HRT and to investigate the differences in co-morbidity, co-medications and frequency of GP consultation between women presenting with menopausal symptoms who were prescribed HRT and those who were not and those who did not present with menopausal symptoms at all.

Methods

The morbidity and demographic data used in this historical cohort study were obtained from the Nijmegen Continuous Morbidity Registration Project. The methodology of the CMR has been described in detail elsewhere and can be summarized as follows. Since 1971, this registration project has been ongoing in four general practices (currently involving 10 GPs) in and around Nijmegen, The Netherlands, meticulously recording all morbidity and mortality data in the patient population of these practices.

The recording is anchored in the Dutch health care system, which is primary care based, with general practice being the main provider of health care and the gatekeeper of access to specialist medical care. Every citizen is listed with a personal GP, usually over a longer period of time. As a consequence, patients' general practice records are the focal point of all relevant medical information. The practice population comprises 12 000 patients, with 25–27% women in the age group 45–64 years old.¹²

The patient population is representative of the population of The Netherlands.¹¹ The available socio-demographic data for every patient include sex, age, socio-economic status (SES) and marital status (single, married/living together and widowed). SES is assigned in line with Centraal Bureau Statistiek Statistics Netherlands indicators, a composite scale of educational and occupational level, categorized into low, middle and high.¹³

Diagnostic coding in the CMR used to be based on the classification that was available in 1971 (the Dutch translation of the E-book), and, to ensure continuity, this classification has been maintained but made compatible with the International Classification of Primary Care (ICPC-2).¹⁴ The validity of the recorded diagnoses has been shown to be well above 80%, mainly due to the regular monthly meetings of the registering GPs to review and compare their classification.¹⁵

All newly diagnosed patients presenting with menopausal symptoms between 1999 and 2007 were identified. Coding of menopausal symptoms is done by the patient's own GP at the time of first presentation based on the diagnostic definition of menopausal symptoms. Two cohorts were formed. The first cohort, 1999–2002, related to the years preceding publication of the WHI study (2002), the MWS (2003) and The Lancet editorial (2003); the second cohort, 2003–07, related to the years after publication.

The following data were obtained from the computerized database:

- background characteristics: age, general practice, marital status and SES and
- co-morbidity at the time of presenting menopausal symptoms: nervous functional complaints, psychiatric disorders, chronic somatic diseases such as diabetes mellitus, overweight (body mass index > 25), thyroid disorders (hyper- and hypofunction), cardiovascular diseases and hypertension. Hysterectomy was also recorded.

In the CMR, nervous functional complaints are defined as a special and separate category of emotional disorders in general practice. Criteria for this diagnosis are: (i) absence of organic lesions that could explain complaints and (ii) positive findings of stress-related disorders that would explain complaints.

For psychiatric disorders, we focused on the most prevalent ones: depression and anxiety disorders. Cardiovascular diseases included myocardial infarction, angina pectoris, peripheral arterial disease, congestive heart failure, atrial fibrillation, transient ischaemic attack and cerebrovascular accident.

We derived the following data from patients' Electronic Medical Records (EMRs):

- information about first-choice treatment and, if not effective, treatment at the second consultation;
- prescription of analgesics, tranquillizers and antidepressants during the first year after diagnosis;
- frequency of GP consultation defined as number of face-to-face contacts between patient and GP other than for menopausal symptoms in the 2 years preceding the first presentation of menopausal symptoms. We divided the number of contacts into three categories: none, 1–8 and >8 contacts (frequent attenders).

Analysis of the EMR gave us the women with menopausal symptoms who were prescribed HRT in the 2003–06 period. These women, matched for age, SES and general practice, were compared with a group of women who visited their GP with menopausal symptoms in the same period (coded as such in the ICPC-2) but who did not receive HRT prescription. Then, we compared all women who presented with menopausal symptoms in the 2003–06 period (irrespective of HRT prescription) with a group of women who had never presented with menopausal symptoms. This group was also matched for age, SES and general practice.

Data were analysed using the Statistical Package for the Social Sciences (SPSS version 12.0.1). Statistical analysis was performed using the chi-square test and Fischer's exact test. In our study, we defined results with a P -value <0.05 as significant.

Results

A total of 341 patients visited their GP with menopausal symptoms (Table 1). Women who presented with symptoms had no children or one child significantly more often than the general Dutch population. There were no differences in terms of SES.

HRT prescription

Prescription of HRT as treatment of choice decreased significantly after 2003: from ~37% ($n = 16$) in 2002

to 4% ($n = 1$) in 2004, with a slight increase in 2006 ($n = 5$) ($P = 0.001$) (Fig. 1). None of those prescribed HRT were given it at follow-up consultations neither did they perceive depressants instead of HRT prescription. Prescription of oral contraceptives to treat menopausal symptoms also decreased ($P = 0.01$). Information and guidance clearly replaced hormone therapy as a first-choice approach: from 34% in 1999 to 60% in 2006 ($P = 0.05$). Information and guidance increased throughout the study period, peaking when HRT prescription is lowest in 2004. That year the number of patients presenting with menopausal symptoms is also the least.

Women presenting with menopausal symptoms: HRT users versus non-users

The HRT users ($n = 33$) did not differ from the non-users in chronic somatic and psychiatric diseases, nervous functional complaints, prescription of analgesics or frequency of GP consultation (Table 2).

Women presenting with menopausal symptoms versus women not presenting with menopausal symptoms

Women with menopausal symptoms presented more often with nervous functional complaints ($P = 0.03$) and received more tranquillizers than women who did not present with menopausal symptoms to their GP (Table 3) ($P = 0.001$). They also attended the GP more frequently than women without menopausal symptoms ($P = 0.03$).

The women who presented with menopausal symptoms did not receive significantly more antidepressants, but the P -value ($P = 0.05$) was close to significance (Table 3). No differences in chronic somatic or psychiatric diseases were found between the two groups.

TABLE 1 Characteristics of patients who present with menopausal symptoms between 1999 and 2006 ($n = 341$)

Characteristic	% (n)
Mean age at the moment of first presentation	49.4 years (SD 4.3)
Civil status	
Married/co-habiting	74.8 (255)
Single	11.4 (39)
Widow	3.8 (13)
Divorced	9.4 (32)
Unknown	0.6 (2)
SES	
High	17.0 (58)
Middle	35.8 (122)
Low	32.0 (109)
Unknown	15.2 (52)
Number of children	
0 (14% ^a)	19.1 (65)
1 (14% ^a)	20.2 (69)
2	61.7 (107)
Co-morbidity	
Overweight	15.8 (54)
Hypertension/CVD	11.4 (39)
Nervous functional complaints	29.6 (101)
Psychiatric problems	8.8 (30)
Hysterectomy	9.3 (32)

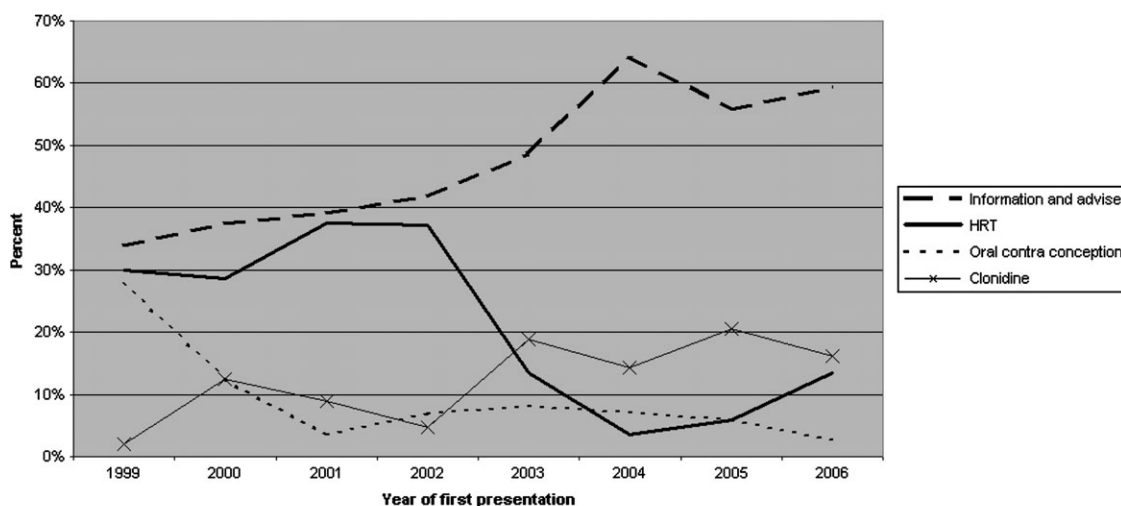
CVD, cardiovascular diseases.

^aPercentage women in The Netherlands with none/one child.¹⁴

Discussion

The publication of the studies about the side effects of HRT had a tremendous impact on prescription behaviour in general practice, showing a significant policy change from GPs prescribing HRT to their giving information and guidance. This is in accordance with the recommendations we made in the editorial of *The Lancet*.⁵ Not prescribing HRT is not followed by an increase in HRT prescriptions at follow-up consultations.

Remarkably, women presenting with menopausal symptoms also had more nervous functional complaints, had higher consultation rates and used more tranquillizers, irrespective of HRT use. This may be to control anxiety or insomnia due to night flushed or is related to the functional nervous complaints. We conclude that the most important difference in co-morbidity and frequency of GP consultation between menopausal women is not whether they received a prescription of HRT or not, but rather whether they seek



Numbers belonging to figure 1
Year of diagnosis and treatment at first presentation of menopausal symptoms (n=341)

	1999	2000	2001	2002**	2003**	2004	2005	2006		P-value
Number of patients	50	56	56	43	37	28	34	37	341	
Information and advise	17 34,0%	21 37,5%	22 39,3%	18 41,9%	18 48,6%	18 64,3%	19 55,9%	22 59,5%	155	0,05*
HRT	15 30,0%	16 28,6%	21 37,5%	16 37,2%	5 13,5%	1 3,6%	2 5,9%	5 13,5%	81	0,00*
Oral contraception	14 28,0%	7 12,5%	2 3,6%	3 7,0%	3 8,1%	2 7,1%	2 5,9%	1 2,7%	34	0,01*
Clonidine	1 2,0%	7 12,5%	5 8,9%	2 4,7%	7 18,9%	4 14,3%	7 20,6%	6 16,2%	39	0,08

*) P < 0,05
**) year of publications

FIGURE 1 First-choice treatment of the GP in women with menopausal symptoms (n = 341)

TABLE 2 Co-morbidity, co-medication and number of consultation in women with HRT prescription versus group with menopausal symptoms without HRT

	HRT users (n = 33), n (%)	Control group without HRT use (n = 33), n (%)	P-value Fischer's exact test
Chronic somatic diseases	11 (33.3%)	7 (21.2%)	0.408
Nervous functional complaints	15 (45.5%)	9 (27.3%)	0.200
Psychiatric diseases	4 (12.1%)	1 (3.0%)	0.355
Hysterectomy	1 (3.0%)	4 (12.1%)	0.355
Analgesics	8 (24.2%)	9 (27.3%)	1.000
Antidepressants	7 (21.2%)	1 (3.0%)	0.054
Tranquillizers	10 (30.3%)	8 (24.2%)	0.783
Number of consultations			
0	1 (3.0%)	2 (6.06%)	0.251
1-8	18 (54.5%)	21 (63.6%)	
>8	14 (42.4%)	10 (30.3%)	

help or not. Women not presenting with menopausal symptoms to their GP either do not suffer from any symptom or do not present to the health care system.

It is important to mention that our study shows that women who were prescribed HRT should not be defined as a specific group of women with emotional or psychiatric problems. The HRT prescription is not correlated with emotional or psychiatric characteristics of menopausal women and has nothing to do with inadequate coping strategies. It is possible that severity of hot flashes played an important part in this decision and that therapy has been prescribed on a personal needs basis.

Women who were prescribed HRT do not suffer more frequently from chronic somatic and psychiatric diseases. Our results are largely consistent with an Australian study that revealed no differences between users and non-users of HRT in chronic diseases such as diabetes mellitus, asthma, arthritis, osteoporosis and

TABLE 3 Co-morbidity, co-medication and number of consultation: women with presented menopausal symptoms versus group without (presented) menopausal symptoms

	Presenters (n = 66), n (%)	Control group without (presented) symptoms (n = 33), n (%)	P-value Fischer's exact test
Chronic somatic diseases	18 (27.3%)	6 (18.2%)	0.260
Nervous functional complaints	24 (36.4%)	6 (18.2%)	0.033*
Psychiatric diseases	5 (7.6%)	1 (3.0%)	0.355
Hysterectomy	5 (7.6%)	4 (12.1%)	0.355
Analgesics	17 (25.8%)	8 (24.2%)	1.000
Antidepressants	8 (12.1%)	1 (3.0%)	0.054
Tranquillizers	18 (27.3%)	0 (0.0%)	0.001*
Number of consultations			
0	3 (4.5%)	6 (18.2%)	0.030*
1–8	39 (59.1%)	21 (63.3%)	
>8	24 (36.4%)	6 (18.2%)	

* $P < 0.05$.

obesity.¹⁶ Nor did hormone therapy users in the Australian study differ from non-users in quality of life.

A recent study re-emphasized the importance of increasing awareness of the negative side effects of HRT: 3 years after stopping HRT, there was still an increased risk of fatal and non-fatal malignancies.¹⁷ HRT is also associated with an increased risk of stroke and venous thromboembolism.^{18,19} The recent fall in use of HRT in Australia was followed by a reduction in breast cancer incidence, suggesting a causal relation.²⁰ This is consistent with the evidence that HRT-associated increased risk of breast cancer is reversible after ceasing HRT use.

Our study has some limitations. Firstly, it is a retrospective study based on data from medical records. GPs may have differed in when and how they classified complaints as menopausal symptoms and coded them as such, even if GPs are well trained in coding diseases and achieve high validity in their diagnoses.¹⁵ Secondly, the study is limited to four academic practices (with 10 GPs of the Department of General Practice), although the study population is representative of the general Dutch population. There is also a possibility that GP's practising in an academic practice and well schooled in providing the CMR data might be more compliant with prescribing change than other GP's. Thirdly, there were only a small number of women who were ultimately prescribed HRT.

A strength of our study is the long-term and precise morbidity registration in the CMR practices, which serves as a solid foundation for patient follow-up and to follow a cohort through time. The number of patients (341) and the absence of dropouts and selection bias also support the credibility of the findings. Lastly, the database allowed us to compose two appropriate control groups, within the cohort.

Conclusions

Following publication of leading articles about HRT at the beginning of the 21st century, GPs' HRT prescription in four Dutch practices changed. This implementation of evidence-based guidelines was rapid, showing significant reduction of HRT prescriptions to women with menopausal symptoms and significant increase in advice and guidance since. We think that the current prescription is more in line with an optimal treatment of menopausal symptoms than in the past.

Women who present with menopausal symptoms to their GP need special attention and care because of the presence of nervous functional complaints, the increased number of consultations and the use of tranquillizers. Hormone therapy is not recommended as treatment of choice; instead, information and guidance are prerequisites for therapy tailored to the individual. The decision to prescribe HRT, however, is not correlated with specific psychological or psychiatric characteristics of menopausal women.

Acknowledgement

We thank all the registering CMR GPs and Hans Bor for his advice on statistics.

Declaration

Funding: none.

Ethical approval: none.

Conflict of interest: none.

References

- 1 Faber A, Bouvy ML, Loskamp L *et al*. Dramatic change in prescribing of hormone replacement therapy in the Netherlands after publication of the Million Women Study: a follow-up study. *Br J Clin Pharmacol* 2005; **60**: 641–7.
- 2 Rymer J, Wilson R, Ballard K. Making decisions about hormone replacement therapy. *BMJ* 2003; **326**: 322–6.
- 3 Writing group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; **288**: 321–33.
- 4 Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; **362**: 419–27.
- 5 Lagro-Janssen T, Rosser WW, van Weel C. Breast cancer and hormone-replacement therapy: up to general practice to pick up the pieces. *Lancet* 2003; **362**: 414–5.
- 6 Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: Annual trends and response to recent evidence. *JAMA* 2004; **291**: 47–53.
- 7 Roberts H. Managing the menopause. *BMJ* 2007; **334**: 736–41.
- 8 Groeneveld FPMJ, Bijl D, Smulders M *et al*. Dutch Guideline Menopause. *Huisarts Wet* 2001; **44**: 436–45.
- 9 Woods NF, Mitchell ES. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. *Am J Med* 2005; **118**: 14–24.
- 10 van de Lisdonk EH. Perceived and presented morbidity in general practice. *Scand J Prim Health Care* 1989; **7**: 73–8.

- ¹¹ van Weel C. The Continuous Morbidity Registration Nijmegen: background and history of a Dutch general practice database. *Eur J Gen Pract* 2008; **14**: 5–12.
- ¹² Schers H, Bor H, van den Hoogen H, van Weel C. What went and what came? Morbidity trends in general practice from the Netherlands. *Eur J Gen Pract* 2008; **14**: 13–24.
- ¹³ CBS (Statistics Netherlands). *SBC (Standard Classification of Occupation 1992/2001)*. Dutch Standard Classification of Occupations (SBC) 1992, Den Haag [in Dutch].
- ¹⁴ ICPC WONCA International Classification Committee. *International Classification of Primary Care, ICPC-2*, 2nd edition. Oxford: Oxford Press, 1998.
- ¹⁵ van Weel C. Validating long term morbidity recording. *J Epidemiol Community Health* 1995; **49 (suppl 1)**: 29–32.
- ¹⁶ Taylor AW, MacLennan AH, Avery JC. Postmenopausal hormone therapy: who now takes it and do they differ from non-users? *Aust N Z J Obstet Gynaecol* 2006; **46**: 128–35.
- ¹⁷ Heiss G, Wallace R, Anderson G. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008; **299**: 1036–45.
- ¹⁸ Grodstein F, Manson JE, Stampfer MJ, Rexrode K. Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. *Arch Intern Med* 2008; **168**: 861–6.
- ¹⁹ Canonico M, Plu-Bureau G, Lowe GDO, Scarabin PY. Hormone replacement therapy and risk of venous thrombo-embolism in postmenopausal women: systematic review and meta-analysis. *BMJ* 2008; **336**: 1227–31.
- ²⁰ Canfell K, Banks E, Moa AM, Beral V. Decrease in breast cancer incidence following a rapid fall in use of hormone replacement therapy in Australia. *MJA* 2008; **188**: 641–4.