Prescription of Combined HRT in Non-Hysterectomised Women in General Practice

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ABSTRACT
Objective: The prescribing practice of combined hormone replacement therapy (HRT) medication in non-hysterectomised women in one Dublin general practice (GP) surgery from 1996 to 2003 was investigated in this study. The aim of the study was to explore whether Irish GP prescribing practice reflected the Irish College of General Practitioners (ICGP) guidelines from the Saffron Initiative (referenced in the Monthly Index of Medical Specialties (MIMS)) which guide the timing of prescription of combined cyclical HRT (CYHRT) versus continuous combined HRT (CCHRT) according to age. **Methods:** Using the GP Clinical Computer program in the practice, the number of prescriptions of combined HRT, the age of women at the time of their first prescription, the average age of prescription of CYHRT versus CCHRT and the percentage of women older or younger than the recommended ages for each type of combined HRT were calculated. **Results:** A total of 90 prescriptions for CYHRT were identified during the time period 1996 to 2003. The age range of the women was 40 to 57 years with an average age of prescription of 49.73 years. It was found that 24% of the prescriptions made were to women above the recommended cut-off point of 51 years. A total of 60 prescriptions for CCHRT were found for the time period 1996 to 2003. The age range of these women was 44 to 61 years with the average age of prescription being 51.33 years, of whom 32% were below 51 years. **Conclusion:** The age cut-off point of 51 years applied to most patients in terms of prescribing CYHRT versus CCHRT. It did not apply to all patients though and this fact is in keeping with updated ICGP guidelines from the Saffron Initiative. This emphasises the importance of evaluating each patient on an individual basis.

INTRODUCTION

The menopause commonly occurs between the ages of 45 and 55 years with a mean age of 51 years. This onset has not changed for at least two centuries and appears to be unrelated to age at menarche, socioeconomic factors or body mass index.[1] Menopause means cessation of menstruation and is said to have commenced when a woman has been amenorrhoeic for 12 months. The menopause is caused by ovarian failure. Ovarian failure can produce a range of symptoms that affect both the quality of life and well-being of women of this age. Hormone replacement therapy (HRT) has long been used to address these symptoms.

HRT generally implies oestrogen-based therapy (with or without additional progestogen). In non-hysterectomised women, combined HRT preparations are preferred as the additional progestogen has a protective effect on the endometrium. These are divided into cyclical (CYHRT) and continuous combined HRT (CCHRT) preparations.

During the early stages of the perimenopausal period women commonly experience irregular and/or heavy vaginal bleeding. Vaginal bleeding has been cited as the most frequently reported reason for stopping HRT with approximately one-third of women stopping it for this reason.[2,3]

Cyclical HRT often helps combat the perimenopausal symptom of irregular bleeding.[4] Irregular bleeding has been shown to occur more frequently with CCHRT than with CYHRT during the first 6 months of follow-up. However, this risk diminishes over time and amenorrhoea is normally achieved within one year in those taking CCHRT. Overall, women have approximately a 1 in 3 chance of incurring irregular bleeding in the first few years of starting either CCHRT or CYHRT.[5]

The decision to commence HRT is becoming more and more complicated both for patients and medical practitioners alike. Long-term health safety concerns battle with quality of life issues in this risk-benefit analysis. The latest research in this area shows a significant increased risk of breast cancer with only 1-2 years use of combined HRT and a potential cardiovascular risk during the first year of use of HRT.[6]

The Chairman of the Committee for the Safety of Medicines (CSM) in the UK has been recently quoted as saying "the decision to start HRT is individual for each patient and should be re-assessed annually". The CSM itself reports that "for short-term use of HRT for the relief of menopausal symptoms, the benefits outweigh the risks for many women".[7]

GPs are the initiators of approximately 84% of all HRT prescriptions.[8] HRT is generally thought to be under-prescribed and even when issued, compliance with long-term therapy is

relatively poor. Less than 50% of women prescribed HRT are using it after nine months.[2]

In Ireland, the Saffron Initiative, which takes its name from the late flowering Saffron Crocus, was established in 1997 with a view to identifying opportunities for improving the health of women in the second half of their lives. The Saffron Initiative Steering Committee was comprised of a multidisciplinary highly experienced group of members in the field of women's health.[9]

The Saffron Initiative published guidelines in 2000 for GPs which recommended that non-hysterectomised women below the age of 51 years or those who were less than one year postmenopausal should be prescribed CYHRT. It recommended that non-hysterectomised women over 51 years or those at least one year postmenopausal should be prescribed CCHRT.[10] The rationale behind this was to minimise the potential for irregular vaginal bleeding. This information is published along with an explanatory flow chart (figure 1) in current editions of the Monthly Index of Medical Specialties (Ireland) (MIMS).[11] The British National Formulary (BNF) gives similar advice without using an age cut-off point. It recommends that CCHRT preparations should not be used by women who are perimenopausal or those within 12 months of their last menstrual period.[12]

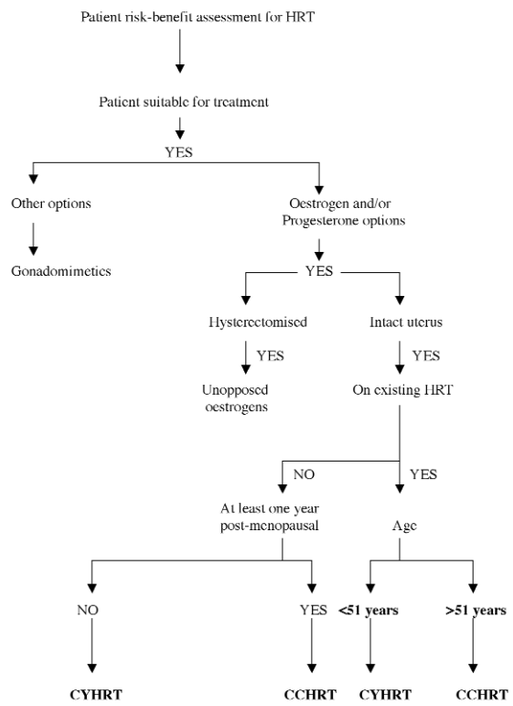

Figure 1 : HRT – Guide to Selection
Source : MIMS Ireland July 2003[11]

The aim of this study was to explore whether Irish GP prescribing reflected recommended Irish guidelines in relation to the timing of CYHRT and CCHRT prescriptions during the time period 1996-2003.

METHODS

The research was carried out as part of a two-week GP summer elective. Access to the GP Clinical Computer system of the busy three-doctor practice in Dublin was granted and a review of combined HRT prescriptions from 1996 (when the computer system was introduced in the practice) until July 2003 was performed.

The GP Clinical Computer system contained data on all patients (clinical records and medications prescribed) from 1996. The July 2003 edition of MIMS provided the list of CYHRT and CCHRT medications on the market for some or all of the study period (table 1 and table 2).[11]

Criteria for inclusion in the study were women with intact uteri who were prescribed the combined HRT medication whose starting date for the medication was clear from the records. Criteria for exclusion were hysterectomised women and women prescribed the medication with insufficient data (on the computer system or from written medical notes) as to their exact starting date on the medication.

For the purposes of this study, each medication listed in table 1 and table 2 was entered in turn into the GP Clinical Computer Programme. This provided a list of patients to whom the particular form of CYHRT or CCHRT had been prescribed since 1996. Each individual patient's computerised notes were subsequently investigated to find out the first date the HRT had been prescribed and the age of the woman at that date. Any alterations in HRT medication (and the age of the woman with each alteration) were also noted. If a woman was prescribed different forms of HRT, each prescription was counted as a separate entry in terms of data collection. In cases where there was a lack of clarity regarding the age of the woman at the start of her combined HRT or where she had already started HRT, old written medical case notes were accessed and checked for this information.

The recommendations used to assess the prescribing practice in this study were published for the attention of Irish GPs by the Saffron Initiative in March 2000 and this investigation examined records back as far as 1996. Subsequent to March 2000, monthly editions of MIMS produced a flow chart (figure 1) as well as written guidelines detailing the recommended prescription of combined HRT.[11] On close examination of the flow chart published monthly

Table 1. MIMS "July 2003" List of CYHRT.

Trade name	Oestrogen	Progesterone	Formulation
Estracombi	Oestradiol 50mcg/day	Norethisterone 250mcg/day	Transdermal patches
Estrapak	Oestradiol 50mcg/day	Norethisterone 1mg	Patch + oral tablet
Estalis Sequi	Estradiol 50mcg/day	Norethisterone 250mcg/day	Transdermal matrix patches
Femoston 2/10	Oestradiol 2mg	Dydrogesterone 10mg	Oral tablet
Femoston 2/20	Oestradiol 2mg	Dydrogesterone 20mg	Oral tablet
Nuvelle	Oestradiol 2mg	Levonorgestrel 75mcg	Oral tablet
Premique Cycle 10	Conjugated oestrogen 0.625mg	Medroxyprogesterone 10mg	Oral tablet
Prempak C	Conjugated oestrogens 0.625 or 1.25mgs	Norgestrel 0.15mg	Oral tablet
Trisequens	Oestradiol 2mg/1mg Oestradiol 4mg/1mg	Norethisterone 1mg Norethisterone 1mg	Oral tablet
Trisequens Forte			Oral tablet

in MIMS (figure 1) it is seen that the age recommendation using 51 years as the cut off applied to women on existing HRT treatment. For those women starting treatment for the first time it was recommended to start CYHRT only if they were less than one year postmenopausal. For the purposes of this study this was taken also to mean that they were 51 years or younger as the mean age for the menopause is 51 years. Thus all women whether newly prescribed HRT or those with prior experience of HRT medication had 51 years of age as their cut-off point between CYHRT and CCHRT.

The number of prescriptions of combined HRT, the age of women at the time of their first prescription, the average age of prescription of CYHRT versus CCHRT and the percentage of women older or younger than the cut-off age of 51 years were analysed in this study.

RESULTS

There were 9112 patients registered on the computer in this general practice. This figure was estimated to account for over 95% of the practice population. Of the 9112 patients, 5057 were female and 4055 were male. Of the females, 2327 were over 40 years of age.

From the records, 90 prescriptions for CYHRT were identified during the time period from 1996 to 2003. The age range of these women

Table 2. Taken from MIMS "July 2003" list of CCHRT

Trade name	Oestrogen	Progesterone	Formulation
Activelle	Estradiol 1mg	Norethisterone 0.5mg	Oral tablet
Estalis	Estradiol 50mcg	Norethisterone 250mcg/day	Transdermal matrix patch
Evorel Conti	Oestradiol 50mcg/day	Norethisterone 170mcg/day Dydrogesterone 5mg	Transdermal patch
Femoston-Conti 1/5	Oestradiol 1mg	Medroxyprogesterone 2.5mg/5mg	Oral tablet
Indivina	Oestradiol 1mg/2mg	Norethisterone 1mg	Oral tablet
Kliogest	Oestradiol 2mg	Norethisterone 1mg	Oral tablet
Novofem	Estradiol 1mg Conjugated oestrogens	Medroxyprogesterone 5mg	Oral tablet
Premique 5	0.625mg		Oral tablet

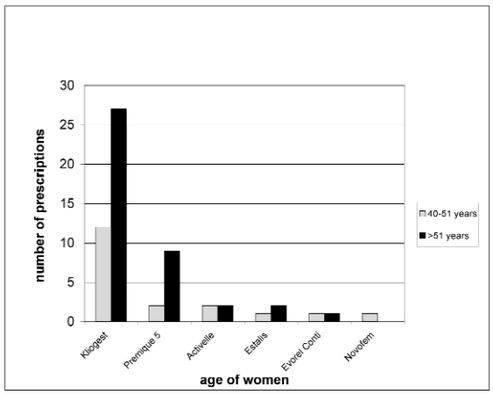

Figure 2: Number of prescriptions of CYHRT related to age at first prescription

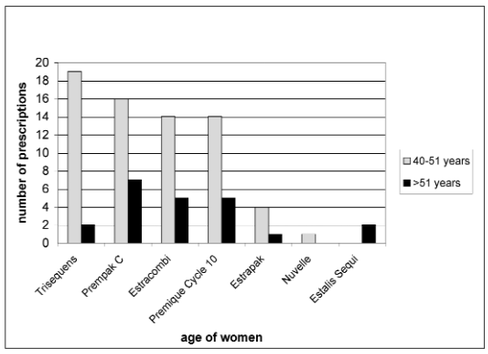

Figure 3: Number of prescriptions of CCHRT related to age at first prescription

was from 40 to 57 years. Despite the average age of prescription of this medication being 49.73 years, it was found that 24% of the prescriptions made were to women above the age of 51 years (figure 2).

Only 60 prescriptions for CCHRT were identified during the time period from 1996 to 2003. The age range of these women was from 44 to 61 years with the average age of prescription being 51.33 years. Of these, 32% of these women were below the age of 51 years on starting this medication (figure 3).

DISCUSSION

This study investigated the age-appropriateness of HRT prescription in non-hysterectomised women in one Dublin GP surgery. It found that the majority of prescriptions were appropriate and in keeping with the recommended guidelines. Approximately one in four women who were receiving CYHRT were being prescribed it above the age of 51 years, which may not be as effective as CCHRT prescription above this age. Of the women receiving CCHRT, approximately one in three were being prescribed it below the age of 51 years and as a result were possibly at an increased risk of unwelcome side effects such as breakthrough bleeding. Of course, not all women reach the menopause at the age specified in the guidelines. Some of the women in these groups may have had premature or late menopausal symptoms and thus the prescriptions used may have been clinically accurate. Thus the findings from this study suggest that GPs are assessing their patients on an individual basis and are not basing their prescribing decisions on a flow chart which may not adequately demonstrate the age diversity of menopausal onset.

Although HRT is generally perceived to improve a menopausal woman's quality of life in the short term, recent evidence shows that this may not be the case. Not only are women at a possible increased risk of cardiovascular health problems and breast cancer when starting treatment but they may also be at risk of disruptive side effects such as irregular vaginal bleeding from HRT.[6,13]

A European study of 1871 women examined women's expectations of HRT. Cultural differences were apparent. Women in Germany and France were more unwilling to take HRT because of perceived contraindications compared to women in the UK (23% and 20% respectively versus 10%). Fear of side effects was highest in Germany (20%), followed by the UK (14%) and France (8%). The European study found that 72% of the women questioned were not taking HRT, mainly because it had not been suggested or recommended to them by their prescribing physician.[3] By comparison an Irish study found that 78% of Irish GPs would offer HRT to all eligible women.[14]

A survey of British women's views on the menopause and HRT found that 31% of women discontinued HRT within 6 months, 51% within 12 months and 74% within 3 years.[8] Withdrawal bleeding, lack of symptom control, oestrogenic and progestogenic side effects were the specific reasons for discontinuation in the majority of cases. Results from this British study suggest that women who were started on CYHRT in this study may have had side effects from this medication (possibly irregular bleeding) and thus were unwilling to continue with the medication. This may be relevant to the current study in light of the fact that 95 prescriptions were written for CYHRT and only 60 prescriptions for CCHRT. Irregular bleeding is a major cause for concern amongst postmenopausal women however it need only be investigated if it persists for longer than one year while on treatment.[13]

Less than 20% of peri- and post-menopausal women in the UK are currently taking HRT.[15]A survey of 600 Irish GPs published in 2000 found an average estimated prescribing rate

of HRT of 17.5% (interquartile range 10% to 30%).[14] The prescribing rate of HRT was not determined in the current study as it focused on combined HRT only. Any figure calculated would not be representative of total HRT prescriptions as oestrogen only preparations were not investigated.

The reason that figures from 1996 onwards were used in this study is that the research was limited to one general practice surgery with a patient population of approximately 9112 patients. Therefore, in order for this retrospective study to be meaningful in terms of patient numbers, it was deemed necessary to look at all cases from 1996 when the GP Clinical Computer Programme was introduced at the practice. This approach was felt to be both justifiable and appropriate as this study did not aim to conduct a strict statistical analysis. Rather this study looked at prescribing practice over a meaningful period of time and compared and contrasted this with guidelines which continue to be published in MIMS. It is pertinent to note that only 5 out of the 18 combined HRT drugs listed in MIMS 2003 were listed in MIMS 1996. There were also two other combined HRT medications listed in MIMS 1996 which are not in current use.[11,16] Thus, a retrospective study involving patients from more recent years could have yielded different results particularly as the Saffron Initiative guidelines were only published for the first time in the year 2000.[10]

It is interesting to note that the Saffron Initiative updated the GP guidelines in 2002 to reflect current knowledge about HRT in terms of benefit and risk. As part of that update, the recommendations regarding age cut-off were altered. The Saffron Initiative guidelines to GPs now recommend that only when a woman's periods become lighter on CYHRT or she is "approaching the ages of 53 or 54" should she change from CYHRT to CCHRT.[17] They thus have relaxed their guidelines and are no longer employing a strict age cut-off point to guide clinical decision making. This is more in keeping with what the BNF recommends and with current research findings.[12,13] Of note, these new Saffron guidelines have not yet been referenced in MIMS. It is still publishing the Saffron guidelines from the year 2000.[11]

Limitations of the study were lack of time to investigate reasons for combined HRT prescription, the length of time these women were compliant with these various forms of HRT, their incidence of side effects (including irregular bleeding) and their reasons for stopping the treatment. This information would have been particularly interesting in relation to those women whose prescription was not in keeping with the recommended age guidelines.

CONCLUSION

This study investigated the age-appropriateness of combined HRT prescriptions in non-hysterectomised women according to MIMS published guidelines. It showed that while the age cut-off point of 51 years applied to most patients, it may not suit all patients and this in fact, is in keeping with updated ICGP guidelines from the Saffron Initiative.[16] This finding emphasises the importance of evaluating each patient on an individual basis as has been recently recommended by the National Medical Informations Centre.[18]

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