Epidemiological and Clinical Aspects of Hormone Therapy

Background

Treatment with sex hormones is widely used in Sweden, and has been so for many years. Most women use some kind of sex hormones for various reasons during their lifetime, and most of them are healthy before, meantime and after the treatment. In the beginning of the 21st century approximately 1 million Swedish women used some kind of hormone treatment, i.e hormone replacement therapy (HRT) or contraceptives. (1)

Hormone therapy is used on different indications, following the lifecycle. The main indication among young women is contraception, but hormone treatment is also used for menstrual bleeding disturbances, dysmenorrhoea, endometriosis etcetera. Among older women the indication for hormone therapy is usually menopause-related symptoms such as vasomotor symptoms that affect the quality of life in a negative direction. As most women are on hormone therapy for benign reasons, and not because of any serious illness, the acceptance of side effects must be very low. Harmless side effects worse than the symptoms supposed to be treated cannot be tolerated. Moreover, serious side effects such as a high risk increase of cancer, thromboembolism or other severe disorders are unacceptable.

Hormonal contraceptives

Hormonal contraceptives can be combined or contain only progestogen. Combined hormonal contraceptives (CHC) have both a progestogen and an estrogen component. The progestogen is the main ovulation inhibiting substance, and the estrogen is added primarily to achieve better bleeding control. The combined hormonal contraceptive methods can be either oral, transdermal or vaginal. The pills taken orally can be either monophasic or multiphasic regarding the amount and proportion of hormones. The hormone doses vary depending of the type of pill. The transdermal patch is a monophasic regimen and the patch is replaced once a week, with a pause every 4th week. The vaginal ring, also monophasic, is used for 3 weeks and after one week of withdrawal a new ring is inserted.

Hormone releasing intrauterine devices (levonorgestrel intrauterine systems , LNG-IUS) are contraceptive methods being more and more popular. The devices release levonorgestrel,

which has an antiestrogen effect in the endometrium and thickens the cervical mucus. The LNG-IUS is replaced every 3rd or 5th year.
Implant contraception means that a "plastic" rod containing a progestogen is placed under the skin of the dorso-lateral side of the upper arm. The progestogen is released subcutaneously yielding stable serum concentrations over three years and then has to be replaced.
As the LNG-IUS and the subcutaneous implant are long acting contraceptive methods, there might be a methodology problem when designing trials studying the prevalent usage. There are prescription data, but there is no information in registers regarding insertion or withdrawal.

Data from the statistics database of National Board of Health and Welfare shows that 26% of all women in Sweden aged 20-44 had at least one dispensed prescription of oral contraceptives in 2014, including both combined oral contraceptives (COC) and progestogen only pills (POP)(1). COC are widely used to prevent unwanted pregnancies and to increase bleeding control. Approximately 80 percent of Swedish women are supposed to be ever-users of COC (2). 14% of the Swedish women are obese and consequently a substantial number of over-weight and obese women have used or are using hormonal contraceptives (3).
Overweight (BMI > 25) and obesity (BMI >30) are risk factors for several diseases including venous thromboembolism. According to the recommendations from the Swedish medical products agency (MPA), CHC should be prescribed with caution to obese women. Obesity may also have an impact on the effects of many pharmacological treatments. There are few smaller studies indicating a variation in pharmacokinetics of COC depending on BMI, but it is uncertain whether it is of clinical significance or not (4, 5). Westhoff and co-workers however, could not find that obese women on COC ovulated more often than normal weight women on the same treatment and consequently the contraceptive effect can be assumed to be the same in obese and lean women.

Data on the side effects of hormonal contraceptives in obese women are, however, sparse. As the prevalence of these conditions is increasing globally, it will be necessary to investigate whether it affect the effect and side effects of modern contraceptive methods.

Hormone Replacement Therapy during and after the menopausal transition

Local treatment

For local urogenital symptoms, such as itching and burning sensations, local low dose estrogen treatment is widely used in Sweden in order to strengthen the vaginal mucosa after menopause. Presently, there are no known serious side effects of local estrogen therapy.

Systemic treatment

HRT is to date the most effective treatment to reduce menopause related symptoms such as hot flushes and nocturnal sweating. HRT is today recommended for more pronounced menopause-related symptoms, and has been used for this purpose for more than 50 years (6). There are different formulations and doses used. Women with an intact uterus are recommended a combination of estrogen and progestogen to prevent development of endometrial hyperplasia that may develop into endometrial cancer. Hysterectomized women, on the other hand, can advantageously be treated with only estrogen to reduce symptoms. The route of systemic administration can be oral or transdermal. Most studies investigating HRT have been done on oral HRT. Several studies have been undertaken also to investigate the effects and side effects of transdermal use but we still need more knowledge concerning certain issues.

In the past HRT was thought to reduce the risk for cardiovascular disease among postmenopausal women, but these results have been contradicted by more recent studies.(7) Although HRT has a good effect on symptoms associated with menopause, it has been observed to increase the risk of several serious diseases.

A Cochrane systematic review from 2012 investigated the effects and risks of HRT in postmenopausal women (7). The results were mainly based on the findings from the Women's Health Initiative trial (8) and the Heart and Estrogen/progestin Replacement Study (9), two large randomised controlled trials. The review concluded that combined HRT increased the risk of a coronary event and venous thromboembolism after one years' use. The risk of stroke was increased after three years of use and breast cancer incidence increased after 5.6 years of use.

The mean age among study subjects in this review was over 60 years (63 years in WHI and 67 in HERS) and no conclusions could really be drawn about the effects of HRT among premenopausal women, and women aged 40-60 years, which is the main age group for treatment in Sweden. Recent studies suggest that there might be a window of opportunity when HRT is initiated before 60 years of age or within 10 years of menopause. The hypothesis is that when HRT is used during this time period it might lower the risk of

cardiovascular diseases and increase quality of life by reducing menopausal symptoms. (10) Oral administration means a first passage metabolism in the liver, which might affect the hepatic synthesis of lipids and coagulation factors. As this is not the case with transdermal treatment, it has been suggested to be an option with lower risk for venous thromboembolism (VTE). However, this remains to be confirmed.

Current Swedish recommendations on HRT

The most recent published recommendations from the Swedish MPA was published in 2004, however, a more recent guideline was published by the Swedish Society of Obstetrics and Gynecology (SFOG) in 2010 (11). According to these recommendations women should be recommended the lowest effective dose of estrogen to reduce vasomotor symptoms and sleeping disorder combined with lowest possible dose of progestogen to protect the endometrium (if not hysterectomized). Treatment duration should, if possible, be limited to 5 years. Previously, HRT was used as prophylaxis for osteoporosis, but current guidelines recommend HRT only to women suffering from serious menopausal symptoms. Women without severe discomfort caused by changed hormone concentrations should not be recommended HRT.

On the other hand, women with premature menopause/premature ovarian insufficiency ***should*** be recommended HRT in order to prevent development of osteoporosis, cardiovascular disease and cognitive impairment. Treatment is recommended to continue at least until the normal age for menopause, thus around 50-52 years of age, and thereafter on the same indication as for other women. As mentioned above there are several different treatment regimens, but not enough studies have been undertaken in order to conclude what regimen to recommend in clinical use for this group of women (11, 12)

When the Swedish recommendations were formulated, the need for future studies was emphasized. The big WHI-study essentially included older women. There are not enough studies with large materials investigating the risks when using HRT at the time for menopause. There is an expressed requirement for studies focusing on different way of administration of HRT, and the risk for cancer and VTE varying with administration form.

Registers

The Personal identification number (PIN) was introduced in Sweden in 1947 and makes it possible to keep national registers of the entire Swedish population (13). In science it is widely used to link information on the same individuals in the different registers.

The Swedish Prescribed Drug Registry was founded in 2005 and contains information on all prescribed drugs dispensed at pharmacies in Sweden. It is possible to analyse the content and use it for comparisons with other information, for instance from the National Inpatient Register (IPR) or the gynaecological surgery register (14). Epidemiological studies based on different registers can demonstrate temporal association, but not causality, between time of exposure and a studied outcome.

Hypotheses

- The prevalence and incidence of HRT-use will vary depending on the definitions used over time in Swedish registers
- The increased risk of pulmonary embolism when using HRT at the age 35-60 is not as high as previously found in elderly women.
- The risk of pulmonary embolism is lower when using transdermal HRT compared to oral.
- HRT is not prescribed in a sufficient extent to women with premature menopause/premature ovarian insufficiency caused by bilateral oophorectomy.
- Obese women using oral desogestrel-containing POP suffer from more bleeding disturbance compared to normal weight women.

Study I:

The use of HRT and hormonal contraceptives over time – methodological issues

Objectives

- Describe the use of HRT in different age groups over time from 1970 until today

- Describe the available datasets over time including methodological issues relating to classification of drugs and doses, different usage over time in different age-groups, life-time prevalence etc.
- Validate methods of defining incidence ratio, run-in period for incidence rates and duration of treatment

Material and Method

Historical data for dispensed HRT from 1970 onwards on aggregated level from the Swedish Prescribed Drug Register. Data on dispensed drugs on the individual level from the Swedish Prescribed Drug Register from July 2005 for all women. Sensitivity analysis on the effect of different run-in time on incident-rates for HRT and Oral Contraceptives respectively.

Study II: Use of HRT in women with premature surgical menopause

Objective

- To study the prescription and dispension of HRT in premenopausal women with bilateral oophorectomy on benign indication

Material and Method

Data on women who have undergone bilateral oophorectomy will be collected from the national gynaecological surgery register (gynop). PIN will be used to match data on the patients with dispensed drugs from the Swedish Prescribed Drug Register. The estimated number of persons included in gynop on benign indication since 2006 is approximately 2000 women. Patients operated because of malignancy will be excluded because of contraindication for HRT.

Study III: The risk of pulmonary embolism in women aged 35-60 years in relation to use of Hormone Replacement Therapy

Objectives

- To investigate the risk of pulmonary embolism (PE) among women aged 35-60 treated with HRT compared to non-users
- To compare the risk estimates for PE between oral and transdermal use, and to determine whether transdermal administration are associated with a lower risk for PE compared to oral administration

Material and Method

In this population-based register study, every woman in Sweden aged 35-60 years are included, resulting in a study group of more than two million women. Data on dispensed drugs are extracted from the Swedish Prescribed Drug Registry including data from year 2005. IPR covers 99% of all somatic hospital discharges from 1987 and onward. The diagnoses in the register are coded using International Classification of Diseases (ICD). By using the PIN, data from the two registers will be linked and analysed to investigate the risk for PE depending of the exposure for HRT at the time for menopause. Confounding by indication is a methodology problem to be observed. Women with relative contraindications to HRT might be prescribed transdermal preparations in bigger extent then the normal population, which would result in an accumulation of high-risk women in this group.

Study IV: Does obesity increase the risk of poor bleeding control and low adherence in women using hormonal contraceptives?

Objectives

- To study if the users´ BMI affect the bleeding control and compliance in women using oral desogestrel for contraception
- To study if obese women suffer from more side effects and poor bleeding control compared with normal weight women, and whether it results in more frequent contact with the healthcare

Material and Method

Case control study. Medical records will be scrutinized to identify women with BMI > 30 in order to map which contraceptive methods are used. Women with BMI> 30 using oral contraceptives containing only desogestrel will be compared to normal weight women using the same pill. Statistical analyses will be done to answer in what extent they seek

medical care and advices because of bleeding disturbances or other factors that can result in low compliance.

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