CASE REPORT

Spontaneous pregnancy in perimenopausal woman during Menopausal Hormone Therapy (MHT): a case study and clinical implications

Spontaniczna ciąża u kobiety w okresie okołomenopauzalnym, podczas menopauzalnej terapii hormonalnej (MHT): studium przypadku i implikacje kliniczne

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KEYWORDS:

- menopause
- spontaneous pregnancy
- contraception

ABSTRACT

Diagnosis of menopause in women is usually related to infertility. We reported the case of a 49-year-old woman treated with menopausal hormone therapy (MHT) who spontaneously conceived. The pregnancy terminated in an early miscarriage. Patients should be informed about the risk of a pregnancy during the first year of MHT, as also contraception should be considered, especially in perimenopausal women.

SŁOWA KLUCZOWE:

- menopauza
- spontaniczna ciąża
- antykoncepcja

STRESZCZENIE

Rozpoznanie menopauzy u kobiet jest zwykle związane z niepłodnością. W pracy przedstawiono przypadek 49-letniej kobiety leczonej hormonalną terapią menopauzalną (MHT), która zaszła w ciążę samoistnie. Ciąża zakończyła się wczesnym poronieniem. Pacjentki należy poinformować o ryzyku zajścia w ciążę w pierwszym roku stosowania MHT, należy także rozważyć antykoncepcję, zwłaszcza u kobiet w okresie okołomenopauzalnym.

Introduction

In recent years we observe trends to late motherhood. It is related to changes in lifestyles, due to professional career priorities, education, late and second marriages and available contraception. Delay of childbearing raises questions about women's fertility – its length, time of the end and treatment of pregnancy failures possibilities.

European data suggest that approximately 30% of women 45-49 years old are not using any contraception (5). It leads us to questions about fertility and unintended pregnancy risk among perimenopausal women. The potential risk to the mother is related to diseases that appear in old age: gestational diabetes mellitus, pre-eclampsia and with chromosomal abnormalities, congenital anomalies, spontaneous miscarriage, ectopic pregnancies and other complications such as preterm labour and caesarean delivery (6).

Natural physiology of fertility

In life of women, it's natural process which provide to gradual decrease of quantity and quality of the oocytes in ovaries. In the fourth month female foetus, the ovaries contain 6-7 million oocytes, surrounded by a layer of flat granulosa cells to form primordial follicles, at birth the ovaries contain only 1-2 million of primordial follicles because of apoptosis. The number of oocytes continues to decline, reaching in puberty 300 000-500 000 (7). During the reproductive period number of primordial follicles decreased an average of 1,000 per month. Only 400-500 follicles (less than 1%) ovulating, others are atresia and follicles loss accelerates after the age of 37 years. At the time of menopause, the number of remaining follicles has dropped clearly below 1000 (7, 8).

The reproductive consequences of human aging include a reduction in both the number and quality of ovarian

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follicles. The final oocytes ovulated prior to menopause but with a high rate of meiotic errors (meiotic nondisjunction, mtDNA mutations) (9). These errors cause unacceptably high rates of aneuploidy, genetic abnormalities and resulting in failed implantation, anomalous pregnancies, but on the other hand also increase the risk of congenital non-chromosomal anomalies (10).

The probability of pregnancy is only 15% per cycle at age 35-39 years and 0,8% per cycle at age above 42 (11). The risk of spontaneous abortion induced by chromosomal abnormalities is estimated to above 50% for mothers older than 45 years (1, 12).

Clinical manifestation, hormonal changes and diagnosis of menopause

Women over age 40 years often present irregular menstrual cycle with menopausal signs such as hot flashes, mood changes or sleep disturbances. The period between the onset of cycle irregularity and menopause is presumed 5 to 10 years (12, 13).

In the late reproductive years before the onset of the menopausal transition, serum inhibin B begins to decrease, serum follicle-stimulating hormone (FSH) increases slightly, estradiol levels are preserved but luteal phase progesterone levels decrease as fertility potential begins to decline. Menstrual cycles are ovulatory, but the follicular phase (the first half of the menstrual cycle before ovulation occurs) begins to shorten. As the process of ovarian follicular depletion continues in midlife, women experience a change in intermenstrual interval. Women typically first notice an irregular cycles which are accompanied by more dramatic fluctuations in serum FSH and oestradiol concentrations (14). A random serum sample may demonstrate high FSH and low oestradiol concentrations consistent with menopause. One study reported that a random serum FSH >25 IU/L is characteristic of the late menopausal transition. Other endocrine changes include a progressive decrease in products of the granulosa cell: serum inhibin B and anti-müllerian hormone (AMH). In addition, ovarian antral follicle count (AFC), defined as follicles measuring 2 to 10 mm in diameter on transvaginal ultrasound, declines steadily from the reproductive years though postmenopause (11). Inhibin B, AMH, and AFC have all been used to assess ovarian reserve in the setting of assisted reproductive techniques (ART) but none are validated for the evaluation of menopausal status. A study has suggested AMH to be an even more accurate predictor of individual time to menopause than mother's age at menopause (15).

Twelve months of amenorrhea is considered to represent clinical menopause and is termed "postmenopause". The final menstrual period (FMP) is determined retrospectively. Although the median age at natural menopause is 51.4 years, the timing of menopause is affected by several factors, including genetics and smoking, which are reviewed separately. For a postmenopausal woman, FSH would be considerably higher in the 70 to 100 IU/L range (15, 16).

Case study

The history of 49 nulliparous woman revealed the final menstrual period in one year before the pregnancy. Her menarche had been at age 14 and though her teens and adults she had had regular menstrual cycles. The patient underwent clipping of the central cerebral artery at age 32 and was treated for hypertension. It was noted early pregnancy miscarriage at age 37 years.

She was diagnosed menopause at age 48 years. The hormonal tests showed high FSH (52,9 mIU/ml) and luteinizing hormone LH (30,8 mIU/ml) levels and low oestradiol (<5 pg/ml) level. Testosterone (42,1 ng/dl), prolactin (278,3 mIU/l) and thyroid-stimulating hormone (TSH 2,5 uIU/ml) were in the normal ranges. The patient started on the sequential hormone menopausal therapy with oestradiol valerate in a dose of 2 mg and medroxyprogesterone acetate in a dose of 10 mg because of menopausal syndromes, including hot flushes, sleep disturbances and as a prevention of osteoporosis.

A 49 year old nulliparous woman was referred by her general practitioner with amenorrhea during the sequential menopausal hormone therapy. The urinary pregnancy test was positive

She spontaneous conceived during the first year of the therapy. Hormonal analysis confirmed the pregnancy (human chorionic gonadotropin hCG level was 97 014 mIU/ml). FSH and LH levels were less 0,1 mIU/ml; oestradiol was 1142 pg/ml. Ultrasound pelvic examination revealed gestational sack with single embryo, crown rump length CRL was 12 mm – it responds gestational age 7 weeks and 3 days, but fetal heart rate wasn't revealed. Ovaries were normal. The diagnosis of spontaneous abortion was confirmed, and the patient underwent a procedure in hospital for the evacuation of retained products from the endometrial cavity. The diagnosis of natural miscarriage was made, and the patient was taken to hospital to remove the products of the endometrial cavity. Suction curettage was performed. Histopathology examination revealed chorionic villi and focal hyperplasia of trophoblast.

One month after the pregnancy, when patient do not use any hormonal treatment FSH level was 14,9 mIU/ml and LH level was 6,7 mIU/ml; oestradiol was 34,3 pg/ml and progesterone was 0,7 ng/ml; hCG level was less than 2,00 ng/ml. Ultrasound scan and pelvic examination were unremarkable.

Discussion

Although the presence of hot flashes with irregular menses at age 47-48 years strongly suggests the menopausal transition, the age at onset of the menopause is variable (16). The possibility of pregnancy must always be considered and serum hCG should be drawn in sexually active women who are not using reliable contraception.

Currently, births for women aged over 45 years make up approximately 0,05-0,2% of all births (1). In Poland, according to data from demographic yearbook of Poland, percentage of women who have given birth after 45 years increased about 56% (from 324 women in 2002 to 572 – in 2022) (2). Recent developments in assisted reproductive technologies (ART) offer pregnancy for peri- and postmenopausal women.

On the other hand, we have older women conceived unplanned, due to the low awareness of necessity and several methods available contraception. Still rather little is known about unintended pregnancy risk and current contraceptive use among perimenopausal women (3).

In recent years, we have noticed the need to use contraception in perimenopausal age. There are more and more reports about what preparations are available and for which

women they are the best option. However, doctors still pay too little attention to these reports (4, 5).

Women in menopause have below 1% chance of pregnancy with the high > 50% risk of miscarriage. It is estimated that the prevalence of aneuploid oocytes approaches 99% after the age of 45 (16, 18).

There are many cases of pregnancy in perimenopausal women, but without hormone supplementation and many cases of pregnancy on hormonal replacement therapy but in younger woman (17, 18, 19).

In our study 49 years woman conceived spontaneously during the menopausal hormone therapy (MHT). The mechanism for the pregnancy is not clear, but it implies that Oestrogens might initiate the sequence of events leading to spontaneous conception (20). It was suggested that exogenous Oestrogens may suppress elevated gonadotropins' level and restore the ovarian FSH and LH receptors. After menopause a high level of FSH inhibits the proliferation of FSH receptors in granulosa cells in ovaries. Exogenous Oestrogens can promote FSH – receptor formation by decreasing the down – regulation effects of high FSH levels and it is itself a trigger for an increase in the development of FSH receptors. Additionally, oestradiol increases receptor sensitivity. Spontaneous ovulation during MHT might have happened (21, 22).

In the references few studies demonstrated biochemical and ultrasonographic evidence of ovulation in women with premature ovarian insufficiency during MHT (16). In women treated with subcutaneous oestradiol implants combined with cyclical oral norethisterone, significant follicular growth (measured by ultrasound) continued until the fourth treatment cycle (23, 24).

Nowadays, many women have prescribed MHT for menopausal symptoms and prophylaxis against osteoporosis before the menopause (16, 24).

Contraception should be continued in perimenopausal women because the natural Oestrogens – components of MHT preparations are of lower potency to inhibit spontaneous ovulation (24).

It becomes impossible to give accurate advice on when contraception can be safely discontinued as MHT will induce regular withdrawal bleeds and mask the fluctuation of serum FSH levels. It is necessary to question perimenopausal women about their sexual life and pregnancy planning. The American College of Obstetricians and Gynecologists (ACOG) specifies that women who want to avoid pregnancy should continue contraception until 50-55 years old (25).

Contraception in the Perimenopause

Many safe and effective contraception options are available to perimenopausal women. Methods of contraception available to women taking MHT who require additional contraception include barrier methods and the copper intrauterine device (Cu-IUD) (25).

In addition to preventing an unplanned pregnancy, contraception may improve abnormal uterine bleeding, menstrual disturbances. Long-acting reversible contraceptives, including the levonorgestrel intrauterine system (LNG-IUS) provide high efficacy without Oestrogen, markedly decreases menorrhagia commonly noted in perimenopause (25, 26).

For women in perimenopause without contraindications, combined hormonal contraceptives are also available. These methods are made with an Oestrogenic component, such as an ethinyl-estradiol (EE), a natural Oestrogen (E2) and more recently, an oestriol (E4) in combination with many progestins.

Oestrogen-progestin contraceptives with very low oestrogen doses are considered to be safe in healthy, nonsmokers up to the age of menopause (27). These preparations also improve vasomotor symptoms and irregular menstrual cycles.

We typically stop Oestrogen-progestin contraceptives by age 50 to 51 years, when the chance of conceiving is extremely low. The North American Menopause Society (NAMS) states that 90% of women will reach menopause by age 55 and recommends continuing contraception until mid-50s (4). Some clinicians measure serum FSH levels. If the level is more than 30 IU/l, the method can be continued for one more year and then stopped. However, contraceptives methods can also be stopped at the age of 55 years without FSH assessments (4).

Conclusion

Although fertility is declining and the probability of pregnancy may be very low in perimenopausal women, contraception should be considered, especially during the Menopausal Hormone Therapy. We need to be more aware of the risk of pregnancy when using Hormonal Replacement Therapy.

Disclosure

The authors report no conflict of interest. The case was described on the basis of medical records and the patient's consent to admission to hospital.

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