FOLIA POMERANAE UNIVERSITATIS TECHNOLOGIAE STETINENSIS
Folia Pomer. Univ. Technol. Stetin. 2013, Agric., Aliment., Pisc., Zootech. 307 (28), 91–98

REVIEW ARTICLE

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ESTRIOL – ALTERNATIVE PREGNANCY DIAGNOSIS MARKER IN THE MINK?

ESTRIOL – ALTERNATYWNY MARKER DO DIAGNOZY CIĄŻY U NOREK?

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Streszczenie. Endogenne estrogeny, do których zalicza się estradiol, estron i estriol, to niejednorodna grupa żeńskich hormonów płciowych. Estriol jest hormonem steroidowym występującym w organizmie kobiety w małych ilościach. Rola estriolu w czasie ciąży jest bardzo ważna, ponieważ jego synteza zwiększa się w tym okresie i stanowi 90% wszystkich estrogenów. W warunkach prawidłowych produkcja estriolu wzrasta wraz z rozwojem płodu, a stężenie hormonu w trzecim trymestrze ciąży wzrasta trzykrotnie. Utrzymujące się niskie lub gwałtownie zmniejszające się stężenie estriolu sugeruje stan zagrożenia płodu. Użycie testu do pomiarów tego estrogenu w ślinie może pomóc we wczesnym wykryciu ryzyka porodu przedwczesnego. Ze względu na odmienny typ łożyska charakter ludzkiego metabolizmu estriolu może znacznie różnić się od metabolizmu samic norki. Ze względu na wyraźny wzrost stężenia estriolu dopiero w 2. połowie ciąży oraz ze względu na występowanie diapauzy jego atrakcyjność jako markera wczesnej ciąży dla hodowcy norek się zmniejsza. Jednakże warte rozważenia jest jego zastosowanie do monitorowania przebiegu ciąży, szczególnie w przypadku możliwości oznaczenia koncentracji w ślinie.

Key words: estriol, mink, pregnancy.
Słowa kluczowe: estriol, ciąża, norka.

INTRODUCTION

Estrogens – which include estriol, estrone and estradiol – are the most important female sex hormones. In addition to the commonly known effects that they have on the female body, the hormones also have a wide range of activity on the male organism. The ovaries are the primary organs of their synthesis, but their pleiotropic effect spans over the variety of other cells and tissues. Estriol is the weakest estrogen; in pregnancy, however, estriol becomes one of the most important biochemical markers in diagnosis of fetal well-being, allowing exclusion or confirmation of fetal chromosomal abnormalities. Serum levels of estriol have been superseded by other, more accurate diagnostic techniques (ultrasound), but in the light of current research, the saliva of pregnant women may be a promising material for analysis of free estriol.

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CHEMICAL STRUCTURE AND FORMATION OF ESTRIOL

Cholesterol is the precursor of five major classes of steroid hormones. Among these are progestogens, estrogens, androgens, glucocorticoids and mineralocorticoids. The main sites of their formation are: the corpus luteum and – during pregnancy – placenta for progestogens, ovaries for estrogens, testes for androgens, and adrenal cortex for gluco- and mineralocorticoids (Żak 2011).

Endogenous estrogens, which include estradiol, estrone and estriol, are a heterogeneous group of female sex hormones. They are derivatives of estrane, an 18-carbon compound having a set of four rings, of which three are six- member rings and one is a five-member ring. Different structures determine their spatial arrangement. Trans-fused rings and a hydrogen located at the fifth carbon below the plane characterize α-estrane. On the other hand, the rings in β-estrane have cis configuration and the hydrogen projects above the plane. Different settings of hydroxyl groups allow identification of individual estrogens (Malinowska-Kołodziej et al. 2006, Pobiega 2011).

Estrogens are synthetized by aromatization of androgens. Estriol, a natural hormone showing weak estrogenic effect, originates from the peripheral metabolism of estrogens, chiefly estrone. Compared with estradiol, estriol works shortly by stopping the estriol-receptor complex in the cell nucleus and through rapid metabolism, and hence it has a weak central activity (Yaron et al. 1999). Another series of changes of the remaining hormones comprises converting of androstenedione, from which estrone is formed, whereas aromatization of ring A in the cyclo-pentane perhydro-phenanthrene system of testosterone leads to the formation of 17-β-estradiol (Pobiega 2011). Its hydroxyl group at position 17 is readily oxidized to a keto group under the influence of 17β-dehydrogenase. The resultant estrone is 10–12 times more active than estradiol. Transformation of estradiol into estrone is a reversible process regulating the amount 17β-estradiol circulating in the body (Dąbrowska and Szukalski 1966). Multistage transformation of cholesterol to estrogens results in reduction in the number of carbon atoms in the molecule (from 27 to 18), through the action of cytochrome P450-group oxidative enzymes. Estrogens molecules are strongly hydrophobic and lipophilic. Thanks to these properties, they can naturally penetrate the blood–brain barrier (Malinowska-Kołodziej et al. 2006). Estrogens demonstrate their biological activity being released in an unbound state from the site of synthesis, while in the blood they remain associated with serum proteins. Estrone in 90% binds to albumins, whereas estradiol binds to globulins, which in turn bind steroid hormones (Świtalska and Strządała 2007).

17β-estradiol (E2), a derivative of testosterone, is an estrogen of the highest biological activity (Świtalska and Strządała 2007). In a healthy adult woman at childbearing age greatest amounts of this estrogen are secreted by the ovaries, exactly by the granulosa cells and thecal cells of the follicle, maturing just prior to ovulation and in the mid-luteal phase of the cycle (Enmark and Gustafsson 1999, Gustafsson 1999). Small amounts of estradiol are also formed in target tissue by conversion from estrone or aromatization of dehydroandrosterone and testosterone. estrone (E1) shows about 5 to 10 times weaker biological activity in relation to 17β-estradiol (Pobiega 2011). During pregnancy, feto-placental unit produces many times more estrogen than the ovaries during the peak period of

the menstrual cycle. It is predominantly estriol (E3), which at this time represents 90% of total estrogens (Yaron et al. 1999, Zang et al. 2002, Malinowska-Kołodziej et al. 2006). Estriol is the weakest of estrogens being primarily a product of metabolized estradiol and estrone (Kalita, et al. 2004). In view of the varying potency of estrogens, E3 and E1 were includes in the group of so-called weak estrogens, and the potency ratio of E2 : E1 : E3 is like 10 : 5 : 1, or even – depending on the stimulated receptor – like 12 : 1 : 0.1 (Enmark and Gustafsson 1999, Gustafsson 1999).

SIGNIFICANCE OF ESTRIOL IN PREGNANCY

The role of estriol during pregnancy is very important, because it becomes a good marker of pregnancy and fetal development, which is the reason for a detailed discussion of this hormone (Suri et al. 2008). Of the three main placental estrogens – estradiol, estrone, and estriol – estriol is the primary estrogen in term pregnancies (Semczuk and Krzyżanowski 2011). Estriol is produced in fetal metabolic processes in the liver, adrenal glands, and placenta (McGregor et al. 1999, Stembalska et al 2011). This hormone is produced in the placenta from 16-alpha-hydroxy-DHEA, whose synthesis occurs only in fetal tissues in the absence of 16-alpha-hydroxylase in the placenta (Egerman et al. 1998, Yaron et al. 1999). Dehydroepiandrosterone sulfate (DHEA-S) produced in fetal adrenal glands is a precursor of estriol, the production of which during the final period of pregnancy is about 75 mg per day (Sieroszewski et al. 2010). The level of this estrogen increases gradually during the first and second trimester of pregnancy, whereas in the third trimester a particularly rapid growth is observed. The peak in the secretion of this hormone is seen 3–4 weeks before term-, pre-term-, or post-term birth (Heine et al. 1999, Semczuk and Krzyżanowski 2011).

It is also produced by the adrenal glands of the mother, but in much smaller quantities. As the pregnancy proceeds, at the end of the third trimester, the proportion of maternal DHEA-S in estriol production decreases to only 10% (Słomko et al. 2005). Hydroxylation of DHEA-S is the next step in the synthesis of estriol, which occurs almost entirely in the fetal liver; it results in the formation of 16-alpha-hydroxy-dehydroepiandrosterone, which passes to the placenta. In the placenta, under the influence of placental sulfatase, it is hydrolyzed to free alpha-hydroxy-dehydroepiandrosterone, which – still in the placenta – undergoes final aromatization to estriol, E3 (Egerman et al. 1998, Goodwin 1999, Yaron et al. 1999, Sieroszewski et al. 2010).

Literature reports from the 1960s and 1970s showed that the determination of maternal serum estriol between 30 and 40 weeks of gestation was used for fetal health assessment and detection of pregnancy pathology. However, in the early 1980s, the clinical test of maternal serum estriol has been superseded by other, less expensive and more effective methods, i.e. fetal heart rate monitoring and ultrasound (Goodwin 1999, Sieroszewski et al. 2010). In the 1990s, the determination of unbound estriol (uE3) was applied in non-invasive biochemical detection of defects in the second trimester of pregnancy (the triple test). Second trimester biochemical tests involve measurements of the concentration of the free beta subunit of human chorionic gonadotropin (β-hCG), α-fetoprotein (AFP) and free estriol (UE3) in the serum of pregnant woman, optimally in 15–17 weeks of gestation, using the effect of changes in concentrations of individual biochemical markers in pregnancies with fetal chromosomal aberrations in relation to normally developing pregnancy.

Based on these indicators, supplemented by the pregnant woman's age, weight, smoking, etc. one can calculate the risk of trisomy 18, 21, open fetal neural tube defects, monosomy X, triploidy, or abdominal wall defects of the fetus (Stembalska et al. 2007, Sieroszewski et al. 2010). One of the most common genetic diseases in the Polish population is Smith-Lemli--Opitz syndrome, which is diagnosed through lower uE3. This disease is characterized by a lack of the enzyme encoding 7-dehydrocholesterol reductase that causes blockage of the metabolic pathway and lowering cholesterol involved in embryogenesis. In the case of steroid sulfatase deficiency in the fetus, reduced free estriol in maternal serum causes ichthyosis symptoms in the child after birth (Bradley et al. 1997, Stembalska et al. 2011).

Prenatal screening (non-destructive testing – triple test) does not allow a 100% certainty to rule out fetal aneuploidy, but also does not fully confirm, since quite often there is a decrease in uE3 concentration in pregnancies free of genetic or structural defects of the fetus. This is mainly because of the possibility of false positives or false negatives, and a specific detection rate of chromosomal defects. The decrease of the hormone is associated with increased levels of AFP and β-hCG. A low concentration of free estriol less than 0.5 MoM (Multiples of the Median) with high levels of AFP and β-hCG is associated with preterm birth, increased risk of miscarriage, and fetal intrauterine growth restriction (IUGR). Also the work of many authors shows that an isolated decrease in the concentration of uE3, with a cut-off of less than 0.75 MoM, is associated with an increased risk of IUGR, low birth weight infants, and oligohydramnios. The mechanism of low concentrations of free estriol in the aforementioned pathologies of pregnancy is not completely understood; however, this estrogen remaining within the normal levels during pregnancy is a sign of good health of the fetus and the placenta functioning properly (Willows 1966, Jasińska and Wasiluk 2010). Low levels of estriol in pregnancies complicated by serological conflict implies a severe hemolytic disease of the fetus (Kempiak 2005).

ESTRIOL – A HORMONE FOR MONITORING PREGNANCY IN MINK?

In the available literature there are no reports on the use of estriol assay for the diagnosis of pregnancy in animals. Given the experience gained in the study on women, attempts have been made to determine the levels of estriol in female mink, since in the practice of mink breeding there is no reliable method for pregnancy detection. Attempts to the use progesterone for the purpose did not give fully satisfactory results (Felska-Błaszczyk et al. 2011). An alternative method would be the determination of estriol, the more that in animals it is the most active estrogen (Badowska-Kozakiewicz and Malicka 2009). Based on our research on female mink (unpublished), there is an increase in the concentration of this hormone during pregnancy, compared to non-pregnant females. Thus, determination of this estrogen could definitively determine whether the female is pregnant or not. It is also possible that the concentration of this hormone in the blood of pregnant females would allow estimation of the litter size.

This assumption is justified, since the production of estriol involves fetuses, so their number in the uterus may hypothetically affect the level of this hormone in the blood of the mother. On the other hand, missing labor in females diagnosed with a certain level of estriol would clearly identify females that have experienced the death of the fetus/fetuses. It should

be noted, however, that the model of estriol metabolism in women cannot by directly projected on animals. It is essential to take into account the differences in the structure of the placenta present between the two species, and that the specificity of human estriol metabolism may differ significantly from the metabolism of the hormone in female mink. American mink has a zonary placenta – which is characteristic of carnivores – with well--developed chorionic villi that branch out within the zone that encircles the center of the fetus (Przespolewska and Kobryń 2011).

There are no animal models which involve the role of estriol in the labor (Goodwin 1999). Noteworthy is also the specificity of the mink in terms of endocrine processes developing during pregnancy. Seasonal reproductive cycle of mink includes a short but inevitable period of embryonic diapause linked with delayed implantation. Within about eight days from mating the embryo reaches the uterus as a blastocyst. The cells in the blastocyst stop growing during this embryonic arrest, and their size increases only after implantation. It is estimated that the proper development of the fetus from the moment of implantation until birth lasts about 30 days. The length of diapause primarily depends on body's hormone levels, which in turn is strongly influenced by the photoperiod. Increasing the length of the light stimulates the secretion of prolactin, which is responsible for the moment of implantation.

Cyclic maturation of oocytes qualifies the female mink to repeatedly mate to the same or different males, since after the first fertilization the corpus luteum produces very small amounts of progesterone, allowing successive production of oocytes. Too high level of the hormone released by the corpus luteum could result in mortality of embryos, and therefore the corpus luteum is almost inactive during the diapause. In spring, extended day light initiates an increased prolactin secretion, which activates the corpus luteum to produce progesterone and embryo implantation becomes reality (Papke et al. 1980, Rose et al. 1986, Douglas et al. 1998, Desmarais et al. 2004, Felska-Błaszczyk et al. 2010). Current knowledge on the reproduction of the mink is insufficient, which is why scientists look to improve the fertility of the animals. Undoubtedly, if a method is developed for determination of estriol in samples collected in a non- or low-invasive way, it will facilitate its use in mink.

SALIVARY ESTRIOL CONCENTRATION

Increasing concentrations of estriol in pregnancy can be directly determined in blood serum or by increasing concentration in saliva, based on the estriol-to-progesterone ratio. Sampling saliva in pregnant females appears to be a better method, which offers many advantages. It is advocated by its non-invasive nature and simplicity in daily collection of the fluid, as pregnant women have an increased salivary secretion. Saliva is a readily available biological material and can be collected in a simple way by the patient. The collection procedure is not painful and samples do not require time consuming separation of serum. Saliva analysis has also proved to be a cheaper alternative to blood, sampling of which requires the help of a trained laboratory diagnostician and a visit of the patient in the clinic.

Saliva is a relatively stable solution that can be both transported and stored; it should be noted, however, that determination of estriol in the saliva should be done within the day, at 30 minutes after a meal. Namely, estriol passes to the saliva by passive diffusion to reflect the

intracellular concentration of unconjugated estriol, corresponding to the free biologically active hormone (UE3) in the serum of the pregnant. Estriol in saliva can be determined by EIA or RIA. Literature reports suggest that the hormone concentration in saliva is a valuable prognostic of parturition after 30th week of gestation if its salivary level in a pregnant woman is higher than 2.1 ng/ml. (Goodwin 1999, Voss 1999, Semczuk and Krzyżanowski 2011).

The above-described advantages of salivary estriol determination in women are much greater in the case of mink. Obtaining a saliva specimen does not undermine the integrity of the animal, as is the case with blood, and it would be less stressful. Possible use of estriol for the diagnosis of pregnancy in mink, however, has a practical drawback. Namely, a significant increase of this hormone occurs probably in the second half of pregnancy, which makes the method less attractive to farmers who would like to know the pregnancy status of animals as soon as possible after mating.

CONCLUSIONS

1. Estriol is a steroid hormone present in the female body in small amounts, and its synthesis increases during pregnancy, when it represents 90% of all estrogens.
2. In normal conditions estriol production increases with the growth of the fetus, and the serum concentration of the hormone triples in the third trimester of gestation.
3. Persistent low levels of estriol or its rapidly dropping levels suggest fetal distress.
4. Saliva is immediately available diagnostic material, collected in a non-invasive way, which allows precise determination of the concentration of unconjugated estriol. The test used for measurements of salivary estrogen may help in an early detection of preterm birth risk.
5. One must be very cautious with the direct transfer of research results on women to animals, since – due to the diversity of placenta types – the nature of human metabolism of estriol may differ significantly from its metabolism in the female mink.
6. Due to the significant increase in the estriol only in the second half of pregnancy and due to diapause, the attractiveness of estriol as a marker for early pregnancy is not very high for a mink breeder. However it is worth considering to use it to monitor the course of pregnancy, particularly if determination of its salivary concentration is possible.

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