Estriol review: Clinical applications and potential biomedical importance

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Abstract
The clinical relevance and biological significance of estriol (E3), one of the three major human estrogens, are presented in this review. While initially having limited therapeutic indications, research has demonstrated E3’s utility as a biomarker to screen for disease, to test for placental function, and as a novel drug for human use. Current research is further exploring E3’s potential as a diagnostic and therapeutic tool.

Introduction
Estrogens are natural endogenous hormones with various physiological actions. Estriol (E3) is a dominant estrogen during pregnancy, and is secreted mainly by the placenta [1]. E3 tests of placental or feto-placental function are widely used in high-risk pregnancies to predict adverse fetal outcome [2]. It is also used as a part of hormonal replacement therapy in the United Kingdom and European Union but is used less due to safety concerns in the US and Canada [3]. The objective of this review is to address the biological and pharmacological properties and the clinical utility of E3.

Formation and metabolism
Estriol (3,16,17 trihydroxy 1,3,5-oestriene, E3) was first isolated by Edward Adelbert Doisy in 1923 at St. Louis University. Termed theelin by Doisy, E3 was isolated along with two other estrogenic female sex hormones, now known as estrone and estradiol from urine obtained from pregnant women [4]. E3, like the other two estrogens is an 18 carbon steroid (C₁₈H₂₄O₃), but it is distinguished by being 16-hydroxylated [5] (Figure 1).

E3 is the weakest of the three major estrogens with regards to estrogen receptor binding. In non-pregnant premenopausal women, E3 arises mainly as a product of the metabolism of estradiol and estrone in the liver. In small quantities it is also synthesized in the ovary by the inner sheath and granular cells of ovarian follicles and the corpus luteum [6,7].

E3 of fetal origin originates exclusively from the 16-hydroxylation of either dehydroepiandrosterone (DHEA) or DHEA sulfate (DHEAS) in the fetal liver, and is metabolized by steroid sulfatase in the placenta. DHEA undergoes aromatization by the aromatase enzyme (CYP19) in the syncytiotrophoblasts of the placenta as blood flows from the conceptus to the mother (Figure 2). Due to the hemochorial nature of the placenta, more than 90% of estriol formed in the syncytiotrophoblast enters the maternal circulation [8].

Once in the maternal circulation, E3 is transported to the liver. The maternal liver rapidly conjugates E3 by glucurononyltransferase enzyme to make it more water soluble for urinary excretion. About 80-90 percent of E3 circulates as the glucuronide conjugate, and 10-15 percent as unconjugated E3 (uE3) [6,9]. The maternal half-life of uE3 is 20 to 30 minutes. In pregnancy, the average concentration of urinary E3 increases gradually until the 12th week of gestation, and then increases more rapidly until term, with characteristic surge preceding the onset of labor [10].

Estriol urinary excretion in non-pregnant women ranges between 0.02-0.1 mg/24 hrs, while in near-term pregnant women the range is between 50-150 mg/24 hrs [11]. The plasma concentrations of estriol and other estrogens increase as human pregnancy progresses [1] (Figure 3). While E3 is produced by conjugation of uE3 when in maternal circulation, uE3 is produced almost entirely by the fetoplacental unit, and therefore is a more sensitive indicator of fetal health [12].

Figure 1. The chemical structure of estriol: C₁₈H₂₄O₃.
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Functional significance and clinical applications

The functional and physiological roles of E3 are not fully understood [13-15]. E3 is a short-acting estrogen, which has a much lower affinity for the alpha and beta estrogen receptors than estrone and estradiol. It dissociates quickly from the activated estrogenic receptor [16]. Since induction of endometrial mitosis requires long-term interaction, estriol does not cause endometrial proliferation. However, its short-term interactions are capable of producing estrogenic effects in the vaginal epithelium including increase in intermediate and superficial vaginal cells [17].

During pregnancy, it is proposed that the hormone regulates uteroplacental blood flow and placental vascularization [18]. Moreover, E3 assays have been used to assess fetoplacental function since the early 1960's [19], and are a component of the current serum marker screens for fetal anomalies.

Estriol testing in pregnancy

E3 has been utilized in screening obstetric populations for adverse pregnancy outcomes since 1960 [20]. E3 can be measured in maternal blood or urine, and is used as a marker for prenatal biochemical screening for fetal health and well being (Table 1), and aids in the diagnosis of multiple congenital anomalies.

While maternal serum uE3 as a single marker has poor predictive power, its inclusion improves the predictive value of maternal age and AFP in screening for Down syndrome [21]. uE3 is therefore a component of both the triple and quadruple serum marker antenatal screening tests for chromosomal and congenital anomalies [22]. The triple screen measures serum concentrations of alpha fetoprotein (AFP), human chorionic gonadotropin (hCG) and unconjugated E3, while the quad screen also includes pregnancy-associated plasma protein A (PAP-A). These tests may be performed in the early 2nd trimester to detect aneuploidy and other fetal anomalies, such as neural tube defects [23]. The levels of uE3 are abnormally low in trisomy 21 (Down syndrome) [22,24] and trisomy 18 (Edward’s syndrome) [25].

Maternal serum uE3 decreases during the second trimester of pregnancy in cases of fetal growth restriction [26]. Serial urine and serum uE3 measurements less than 0.75 multiples of the median between 30 and 42 weeks of gestation are associated with significant fetal growth restriction [27]. Mothers who carry growth-restricted fetuses have serum E3 levels that are about half the normal level [28-30]. In addition, association studies have correlated low early 2nd trimester E3 levels with fetal demise [31], and low 1st trimester levels of uE3 are associated with pregnancy loss [32,33].

E3 has also been studied in association with other perinatal clinical applications. E3 rises approximately 4 weeks before the onset of labor. A high level of uE3 or a sudden increase in maternal uE3 levels are potential markers of impending labor [34], and multiple studies have examined the potential use of uE3 as a biomarker for predicting the onset of labor [35-37]. However, it has not been found to be a reliable marker for either prediction of the onset of labor or when to induce labor. A recent resurgence of interest has occurred in looking at E3 as a marker for preterm birth [38]. Research continues regarding the...
role of E3 as a biomarker for the fetal response to various pregnancy conditions [39-41].

Therapeutic uses

In a randomized, placebo-controlled trial, treatment of postmenopausal women with daily E3 (2-4 mg) demonstrated a significant ability to treat hot flashes [42,43]. Also, E3 reduced urinary urgency and leakage [44], and the frequency of urinary tract infections [45-47]. In addition, E3 promotes restoration of normal vaginal flora, and improves vaginal atrophy in menopausal women without associated endometrial side effects [48,49]. In addition, E3 used in hormone replacement therapy regimens has been noted to improve bone density [50,51] without negatively impacting lipids [52-54], liver function [55,56], breast tissue [57,58], or blood pressure [42].

Interestingly, E3 treatment has been found to improve clinical symptoms of multiple sclerosis and to reduce cerebral lesions. These same cerebral lesions increased in size when treatment was stopped and decreased when treatment was restarted [59]. Another clinical trial in males found that, compared to placebo, E3 ameliorated symptoms of encephalomyelitis, a disease that shares a lot of characteristics with multiple sclerosis [60]. The proposed mechanism is that pro-inflammatory cytokine production is decreased by E3 treatment, while antibodies to the autoantigen responsible for the demyelination or destruction of the nerves are increased [60,61]. Another suggested mechanism is that at a concentration consistent with late pregnancy, E3 inhibits nitric oxide production by microglial cells activated in response to inflammatory cytokines [62]. Research findings have also suggested that E3 decreases T cell expression of matrix metalloproteinase-9, which is responsible for the demyelination process [63]. Thus, E3 may contribute to treatment of some inflammatory or neurological conditions.

Estriol measurements

Because of fluctuating and pulsatile E3 secretion, diurnal variation, and its short half-life, testing for E3 at a single time point by serum or saliva is imprecise. The most accurate way to assess estriol is by 24-hour urine collection [64]. However urine collections for this purpose are inconvenient. Although serum and plasma E3 have been widely used to test for E3, a venipuncture for blood assays requires clinic visits, and can be painful and stressful. Salivary E3 has also been an enticing target for biomarker research in pregnancy. Dullien et al. emphasized the biological utility of measuring salivary E3 concentrations in pregnant women. Plasma E3 circulates in a protein-bound state [65], whereas salivary E3 is a measure of uE3, which is the biologically active fraction of the circulating hormone. The overall advantages of using salivary versus serum E3 are numerous: saliva can be obtained noninvasively, is stable during transport, and E3 measurements in saliva are highly reproducible [66,67].

Summary

Estriol is a mainstay of current strategies in determining fetal anomalies through maternal serum screening. It is being used as an off-label component of therapies to treat menopausal symptoms as well. Although estriol is a component of several bio-identical hormone replacement therapy formulations, neither the FDA nor Health Canada approves or regulates these therapies. There are also studies currently underway to test for the efficacy of this molecule as a marker for various fetal responses to pregnancy conditions. Estriol may be important for a myriad of diagnostic, screening, and therapeutic uses.

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