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Review

Exploratory study of the association of steroid profiles in stimulated ovarian follicular fluid with outcomes of IVF treatment

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ABSTRACT

Steroid concentrations in stimulated follicular fluid (sFF) samples have been linked to the quality of oocytes used in IVF treatments. Most of the published studies focused on evaluating the association of the IVF outcomes with only a few of the steroids, measured by immunoassays (IA). We performed a treatment outcome, prospective cohort study using stimulated FF sampled from 14 infertile women undergoing IVF treatment; single oocyte was used per IVF cycle. Fourteen endogenous steroids were analyzed in 22 ovarian follicle aspirations, which corresponded to the embryos used in the IVF. Ten oocytes were associated with live birth (LB) and 12 with no pregnancy (NP). Steroids were analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. Differences in distribution of concentrations in association with the pregnancy outcome (LB or NP), and receiver operating characteristic (ROC) curves analysis were performed for the entire cohort and for within-women data. The predominant androgen and estrogen in stimulated sFF were androstenedione (A4) and estradiol (E2), respectively. Lower concentrations of pregnenolone (Pr), lower ratios of A4/ dehydroepiandrosterone (DHEA), testosterone (Te)/DHEA, and greater ratios of E2/Te, and estrone/A4 were observed in sFF samples associated with LB. Among the oocytes associated with NP, in four out of 12 samples total concentration of androgens was above the distribution of the concentrations in the oocytes corresponding to the LB group. Observations of the study indicated increased consumption of precursors and increased biosynthesis of estrogens in the follicles associated with LB. Our data suggest that potentially steroid profiles in sFF obtained during oocyte retrieval may serve as biomarkers for selection of the best embryo to transfer after IVF.

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Abbreviations: IVF, in vitro fertilization; sFF, stimulated follicular fluid; IAs, immunoassays; Pr, pregnenolone; 17OHP, 17 hydroxy pregnenolone; A4, androstenedione; Te, testosterone; DHEA, dehydroepiandrosterone; E1, estrone; E2, estradiol; E3, estriol; P4, progesterone; 17OHP4, 17 hydroxy progesterone; 11DC, 11 deoxycortisol; Allopr, allopregnanolone; PROGEST, progestins; PREGN, pregnanes; GLUC, glucocorticoids; ESTR, estrogens; ANDR, androgens; LB, live birth; NP, no pregnancy; FDR, false discovery rate; ROC, receiver operating characteristic; AUC, area under curve.

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1. Introduction

In women of fertile age, ovarian follicles are the main source of biosynthesis of estrogens (ESTR) and progestins (PROGEST); ovarian follicles also contribute to circulating androgens with the adrenal cortex serving as another source of androgen biosynthesis [44,40]. In addition to bioactive hormones, ovarian follicular fluid (FF) also contains large number of intermediate steroids of the steroid biosynthesis pathway (Fig. 1) [22,34]. Follicular steroids are secreted by granulosa and theca cells under the control of gonadotropins; the hormonal microenvironment in the follicles affects the follicular development and the oocyte viability [40]. It is known that a higher concentration of estradiol (E2) in FF is associated with healthy mature follicles containing oocytes capable of meiosis, while a higher concentration of androgens is indicative of atretic changes in the follicles [12].

A number of studies have focused on analyzing steroids in FF samples of women undergoing ovarian stimulation for in vitro fertilization (IVF) treatment, and assessing the relationship between the concentrations and the follicular development [5,10,11,26,2,37,14]. Local steroid production in ovarian follicles is controlled by enzymes expressed in the ovaries, which regulate conversion between the steroids and availability of precursors [22,34] (Fig. 1). In a number of studies, associations between IVF outcomes and FF concentrations of progesterone (P4), E2, and testosterone (Te) were evaluated [45]. However, the published information on the association of FF steroid concentrations with IVF outcomes is conflicting. Lower concentrations of P4 [35], higher E2 [30], and higher androstenedione (A4) [15] in FF have been reported in association with pregnancy following IVF treatment, while other studies have demonstrated lower E2 [36], higher P4 [27] or no association [45]. Lewicka et al. [29] reported that lower concentrations of cortisol in FF and increased cortisol/cortisone ratio have been associated with pregnancy, while Michael et al. [33] observed association with lower concentrations of cortisol and cortisone. Due to the discrepancy

in the results from these and other studies, association of concentrations of steroids in FF with IVF outcome remains unclear. Most of the published studies focused on evaluating the association of the IVF outcomes with a few of the steroids; no comprehensive studies have been aimed at the systematic examination of the association between concentrations of steroids of different classes with the IVF outcomes.

In earlier published studies [10,13,45,43,9,30] measurements of steroids in FF were performed using Immunoassays (IAs), which were shown to suffer from cross-reactivity with structurally-related compounds [41,42,19,22] or using gas chromatography mass spectrometry methods, which are more specific [3,8,6,38,7]. Advancements in biological mass spectrometry helped to overcome many of the pitfalls associated with IAs and enabled high specificity simultaneous accurate quantification of multiple steroids [17,23,24,18–22,25].

We hypothesized that steroid profiles in stimulated FF (sFF) could be associated with prognosis of IVF treatment and that analysis of such biomarkers could allow selecting oocytes more likely to result in a successful IVF outcome. Our study evaluated the associations between concentrations of steroids in sFF samples, corresponding to the oocytes used in IVF, and the IVF outcomes. Analyses of steroids were performed using validated LC-MS/MS methods.

2. Materials and methods

2.1. Participants

Stimulated FF was sampled from 14 women undergoing IVF treatment at Centre for Reproduction (Uppsala University hospital, Uppsala, Sweden). All participants except one were nulliparous and none were current smokers. Of the 22 oocytes from the studied sFF samples, 10 were associated with a live birth (LB), and 12 with no pregnancy (NP). Anthropometric and reproductive characteristics of the women, and information related to the treatment are

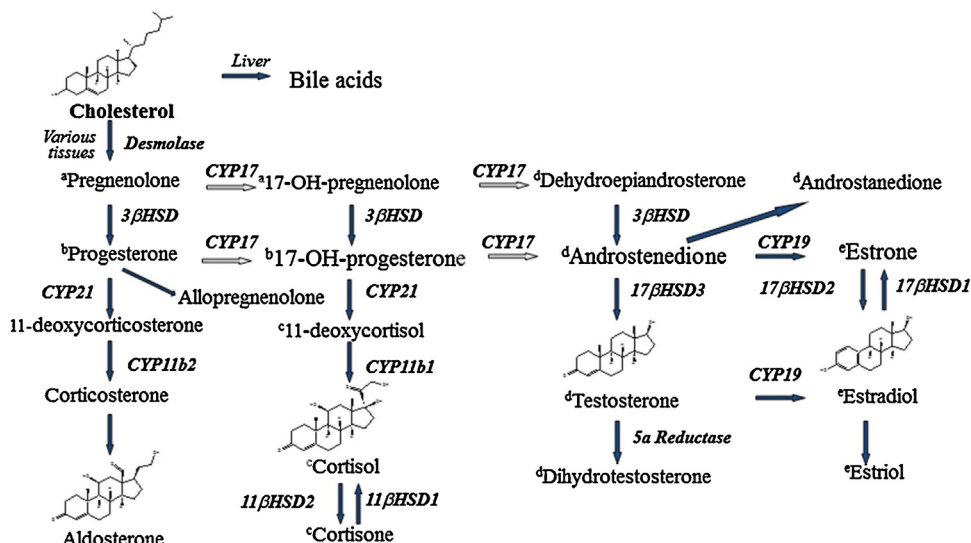


Fig. 1. Pathway of steroid biosynthesis (a-pregnenes, b-progestins, c-glucocorticoids, d-androgens and e-estrogens).

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