Associations of different hormonal contraceptive methods with hair concentrations of cortisol, cortisone, and testosterone in young women
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1. Introduction

Steroid hormones are commonly used to index the physiological stress response (e.g., cortisol and cortisone) and to investigate behavioral differences (e.g., testosterone). The main physiological stress hormone is cortisol, a glucocorticoid released by the adrenal glands during the hypothalamic-pituitary-adrenal (HPA) in response to physical and psychological stress; its metabolite cortisone can be measured in parallel to provide a cumulative account of the body’s exposure to cortisol [1]. In contrast, testosterone is commonly used to investigate sex differences in behavior [2] or to assess male and female metabolic health [3].

Hair analysis enables precise, non-invasive, and stable measurement...
of the body’s cumulative exposure to a given hormone. Each centimeter of hair taken from the scalp indicates exposure over a period of approximately one month [4]. Accordingly, measurements of hormones in hair are less subject to circadian fluctuations that affect blood or urine samples. For that reason, hair cortisol concentration has been proposed as a stable marker of chronic stress [5].

In the largest meta-analysis of correlates of hair cortisol concentration to date, Stalder and colleagues (2017) examined 14 studies and identified a trend-level negative correlation between hair cortisol concentration and oral contraceptive use (r = −0.041, p = .071). However, that meta-analysis was confined to oral contraceptives, and subsequent studies reported higher levels of hair cortisol concentration among women who used hormonal contraceptives [6] or no association at all [7]. Thus, the current evidence is mixed, and previous studies also had some significant limitations, including small sample sizes and relatively few female participants using contraception.

A further limitation of the existing literature is the missed opportunity to examine the differing effects of contraceptive methods on levels of hair cortisol, cortisone, and testosterone. The steroid hormone composition and estrogen content of different contraceptives are known to influence cortisol levels. For example, Burke (1969) reported that contraceptive pills containing estrogen were associated with lower levels of non-protein-bound cortisol in plasma and urine, and Qureshi et al. (2007) found that estrogen preparations may raise total cortisol concentration by increasing circulating cortisol-binding globulin (CBG). In one randomized-controlled trial, estrogen-only and combined estrogen and progestrone treatments were found to differ in their effects on blood cortisol levels in post-menopausal women [8]. However, the effects of different hormonal contraceptive agents on hair cortisol are not yet understood. These effects may be different from those found in serum because hair cortisol is a marker of free cortisol and therefore less affected by protein binding [9]. A further source of variation is that contraceptive methods differ in form and frequency of administration. For example, daily oral pills and intrauterine implants that remain effective for several years are characterized by different patterns of hormone release. This variability has been neglected in previous studies involving hair steroid hormones.

The above limitations also apply to research involving testosterone; in fact, fewer studies have investigated associations of contraceptive use with testosterone levels, likely because this hormone is less often studied in females. There are reports of decreased salivary and serum testosterone concentrations in women using oral contraceptives [10]; and one meta-analysis found reduced levels of serum testosterone in women taking the combined oral contraceptive pill [11]. However, information about other contraceptive agents in this context remains limited, and no study has directly investigated whether contraceptive use is associated with testosterone levels in hair.

The present study thus analyzed associations of contraceptive method with levels of hair steroid hormones in a large community sample of twenty-year-old women. Based on detailed information about participants’ use of contraceptives, we hypothesized that observed levels of hair cortisol, cortisone, and testosterone would differ by method of contraception.

2. Method

2.1. Participants

Data came from a longitudinal community study: the Zurich Project on the Social Development from Childhood to Adulthood (e-proso) [12]. In 2004, cluster-stratified randomized sampling was used to recruit a target sample of children from 56 primary schools in the Swiss canton of Zurich. The present study was based on data from the Wave 8 of this study, which assessed participants when they were 20 years old. The data was collected between April 10 and September 22, 2018. Of 1180 participants at Wave 8, 1002 (503 female) provided hair samples of sufficient quality for analysis. The sample varied widely in ethnicity: while around 90% participants were born in Switzerland, 48% of participants had parents who were both born abroad. The mean household International Socioeconomic Index of Occupational Status was M = 47.1 (SEM = 0.9). The International Socioeconomic Index of Occupational Status is an internationally comparable index of socioeconomic status based on occupation-specific income and the required educational level, with scores ranging from 16 (e.g., unskilled worker) to 90 (e.g., judge) [13]. The study was approved by the Cantonal Ethics Committee of Zurich; all participants provided written informed consent. Only female’s data was used in the current study.

2.2. Measures and procedure

2.2.1. Hair analysis of steroid hormones

Trained research assistants collected a hair strand as close to the scalp as possible. The proximal 3 cm were analyzed for cortisol, cortisone, and testosterone, using liquid chromatography-tandem mass spectrometry, following established protocols at the Center for Forensic Hair Analytics of the University of Zurich described elsewhere [4,14].

2.2.2. Hair questionnaire, including contraceptive assessment

Participants completed a brief questionnaire, which asked about hair color, washing, and bleaching, as well as weight and height for calculating body mass index (BMI) and use of contraceptives. Those who used contraceptives were asked to indicate which of the following they used: etonogestrel implant, contraceptive patch, vaginal ring, progestin-only injectable contraceptive, hormonal intrauterine device (IUD), progestin-only oral “mini pill,” or combined estrogen + progestin “micro pill.”

We categorized contraceptives as either estrogen-progestin or progestin-only. The estrogen-progestin category included the contraceptive patch, the vaginal ring, and the combined oral pill; the progestin-only category included the etonogestrel implant, the hormonal intrauterine device (IUD), and the progestin-only pill.

2.2.3. Analysis

Of 503 females who provided a useable hair sample, 15 were excluded because they reported the use of emergency contraception in the previous three months, and a further 24 were excluded due to incomplete covariate data. The final sample comprised 464 women (M = 20.6 years; SEM = 0.02, range = 19–22), of whom about 40% reported using contraception during the previous three months. Of these, 147 reported the use of estrogen-progestin containing contraceptives, and 42 the use of progestin-only contraceptives (for complete information on frequency of use for each contraceptive, see Supplementary Fig. S1).

The hair hormone variables were log-transformed to address the positive skew of the raw data; in the testosterone data, one extreme outlier clearly reflected measurement error and was therefore excluded.

Multiple regression analyses tested the effects of these contraceptive groups on levels of hair testosterone, cortisol, and cortisone, and combined concentrations of cortisol and cortisone. Body mass index, hair washing frequency, hair color, and hair bleaching were included as covariates. Hair color was defined as blonde, brown, or black; dummy coding was used, with brown hair as the reference category.

In follow-up analyses, a multiple linear regression that included all methods of contraception used by ≥5 participants estimated the specific association of each contraceptive method with the steroid hormones. Each contraceptive method was dummy-coded, using “no contraceptive use” as the reference category. R (version 4.0.3) was used to analyze the data.

3. Results

Demographic and hair characteristics are shown in the supplementary material, Table S2. Mean concentrations for each hair hormone:
cortisol 5.51 pg/mg (SEM = 0.24); cortisone 23.61 pg/mg (SEM = 0.79); cortisol and cortisone 29.12 pg/mg (SEM = 0.96); and testosterone 0.45 pg/mg (SEM = 0.046).

In multiple linear regression models (Fig. 1; for complete regression results, see Supplementary Table S3), both contraceptive categories were associated with lower levels of hair cortisol (β_estrogen-progestin = -0.29, 95% CI = -0.49 to -0.09, p = 0.004; standardized mean difference (Cohen’s d) = 0.66; β_progestin = -0.49, 95% CI = -0.81 to -0.17, p = 0.003; d = 1.66). However, only contraceptives containing both estrogen and progestin were associated with lower levels of hair cortisone (β = -0.28, 95% CI = -0.49 to -0.08, p = 0.007; d = 0.71) and hair testosterone (β = -0.36, 95% CI = -0.56 to -0.17, p < 0.001; d = 0.81) compared to no use of contraception. Thus, contraceptive use was generally associated with reduced hair steroid hormones.

To assess whether the contraceptive categories differed in terms of their associations with steroid hormones, the same models were computed with the estrogen-progestin group as a reference category (For complete regression results, see Supplementary Table S4). We did not find a significant difference in steroid hormone levels between the two contraceptive categories estrogen-progestin and estrogen-only.

In follow-up analyses, multiple regression analyses tested the effects of specific contraceptive methods on hair hormone levels (Fig. 2). Use of the combined oral contraceptive pill was significantly negatively correlated with levels of hair cortisol (β = -0.28, 95% CI = -0.49 to -0.07, p = 0.010; d = 0.63), cortisone (β = -0.26, 95% CI = -0.48 to -0.04, p = 0.019, d = 0.58), and hair testosterone (β = -0.41, 95% CI = -0.62 to -0.20, p < 0.001; d = 0.97). Hormonal intrauterine devices (β = -0.53, 95% CI = -0.97 to -0.09, p = 0.017, d = -2.44) and etonogestrel implants (β = -0.85, 95% CI = -1.65 to -0.05, p = 0.038, d = 11.2) were significantly associated with reduced levels of hair cortisol only. Note that the effect sizes for the follow-up analyses should be interpreted with caution due to some small group sizes. For complete regression results, see Supplementary Table S5.

4. Discussion

Previous studies reported an association of contraceptive use with hair steroid hormones but failed to specify the individual effects of different contraceptive methods. In line with previous research [15], we found lower levels of hair cortisol in users of contraceptives. We also demonstrated that the use of progestin-only and estrogen-progestin contraceptives is associated with lower levels of hair cortisol and that the use of estrogen-progestin contraceptives is associated with lower levels of hair cortisone, with moderate to strong effect sizes.

We included cortisone as an additional marker because combined cortisol and cortisone may be a more stable marker of HPA axis functioning than cortisol alone [1]. While participants who used the combined oral contraceptive pill, IUD, or etonogestrel implant exhibited reduced levels of cortisol, only those using the combined oral contraceptive pill exhibited reduced levels of cortisone.

In contrast, one previous study reported changes in concentrations of hair cortisol but not in cortisone levels among those using oral contraceptives [1].

The effects of contraceptive use on hair testosterone have not previously been tested. Our findings show that estrogen-progestin contraceptives exhibit a strong significant negative association with testosterone, whereas progestin-only contraceptives do not. Specifically, the combined estrogen-progestin micro-pill seemed to drive this group effect, consolidating previous evidence of reduced levels of blood testosterone in users of the combined pill [11]. This may have significant
implications, as reduced testosterone levels can be harmful to metabolic health [3].

Our study has a number of limitations. First, statistical power was limited for detecting the effects of less common contraceptive methods (e.g., etonogestrel implant, vaginal ring). Second, we were unable to take into account the administration and hormone release profile of the different contraceptives, which may also influence hair hormone levels. Our findings show reduced levels of hair cortisol among women taking the oral contraceptive pill. We also identified a negative association between hair cortisol concentration and non-oral contraceptives like the IUD and etonogestrel implant. This is perhaps surprising, as non-oral contraceptives like patches, rings, and intrauterine devices might be expected to have less systemic effects on corticosteroids and testosterone; the specific underlying mechanisms remain unclear.

Finally, we did not ask about individual motives for contraceptive use (e.g., sexual activity, hormone intervention for acne), and it is possible that altered steroid hormone levels are associated with sexual activity or other behavioral and health factors rather than contraceptive use. Interestingly, one earlier study reported elevated saliva testosterone levels in naturally cycling women with higher levels of sexual desire but not in women using hormonal contraception [16]. Future studies should seek to clarify associations between sexual desire/activity, different types of contraception, and hair steroid hormones.

5. Conclusion

The results indicate a robust association between contraceptive use and levels of hair cortisol, cortisone, and testosterone. More specifically, contraceptives containing both progestin and estrogen were strongly associated with reduced levels of these hair hormones. Based on these findings, future studies of hair steroid hormones should take into account the specific type of contraceptive used, as this may affect study results.

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Declarations of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpnec.2022.100161.

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