Psychoneuroendocrinology (2009) 34, 713—726

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

Putting a finger on potential predictors of oral contraceptive side effects: 2D:4D and middle-phalangeal hair

Kirsten A. Oinonen *

Department of Psychology, Lakehead University, 955 Oliver Rd., Thunder Bay, ON P7B 5E1, Canada

Received 20 June 2008; received in revised form 25 October 2008; accepted 27 November 2008

KEYWORDS
Oral contraceptives;
2D:4D;
Digit ratio;
Middle-phalangeal hair;
Testosterone;
Side effects;
Depression

Summary Many women experience emotional or physical side effects when taking oral contraceptives (OCs). Despite the potential impact on women's health and well-being, there are no valid methods to screen women for their risk of OC side effects. The present paper presents the results of two studies where anthropometric indicators of androgen exposure, 2D:4D and middle-phalangeal hair, were examined for their potential as predictors of OC side effects. In study 1, 2D:4D was associated with women's reports of a history of: (a) negative mood side effects; (b) discontinuation due to negative mood side effects; (c) specific mood side effects (i.e., crying, sadness, and altered trust in one's partners) and (d) specific physical side effects (i.e., headaches, fatigue, and decreased sex drive). In study 2, 2D:4D and/or middle-phalangeal hair was/were associated with a reported history of: (a) discontinuation due to negative mood side effects; (b) specific mood-related side effects (i.e., negative mood, disrupted sleep, increased aggression, and altered trust in one's partner) and (c) specific physical side effects (i.e., headaches, decreased menstrual cramps, and increased sex drive/arousal). The general pattern was that adverse OC side effects were experienced by women with lower 2D:4D and fewer middle-phalangeal hairs. Almost all relationships remained significant when response bias was controlled. These results suggest a possible role for prenatal testosterone exposure and both androgen action and sensitivity in women's experience of OC side effects. Furthermore, these two digit measures may be useful predictors of hormonal contraceptive side effects in women.

1. Introduction

Statistics indicate that 82—84% of women in North America have taken oral contraceptives (OCs) (Fisher et al., 1999; Mosher et al., 2004). Approximately 51% of women report experiencing at least one adverse side effect while taking OCs (Rosenberg et al., 1995), and 46% of new users discontinue use within 6 months due to side effects (Rosenberg and Waugh, 1998). These statistics suggest that approximately 43% of North American women will experience OC side effects in their lifetime. One prospective study found the following prevalence rates for adverse OC side effects: emotional side

* Tel.: +1 807 343 8096; fax: +1 807 346 7734.
E-mail address: koinonen@lakeheadu.ca.

0306-4530/$ — see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2008.11.009

effects (40%), physical side effects (27%), sexual side effects (19%), increased menstrual bleeding (16%), worsening of premenstrual syndrome symptoms (21%), and a decreased frequency of sexual thoughts (39%) (Sanders et al., 2001). In this same study, the most common reasons that women spontaneously reported for discontinuing OCs included physical (37%) and emotional (33%) side effects. In addition to the detrimental effect on women's well-being, experiencing side effects is associated with an increased likelihood of: missing pills, early discontinuation, and unintended pregnancy (Rosenberg et al., 1995). Thus, the ability to predict who will experience specific OC side effects could have beneficial effects on women's emotional and physical functioning, OC continuation rates, and unintended pregnancy rates. The main goal of the present project was to identify inexpensive measurable hormonally relevant predictors of OC side effects. A secondary goal was to examine the role of androgen exposure or sensitivity in OC side effects.

Very few studies have focused on identifying predictors of specific OC side effects (e.g., Graham et al., 2007). More studies have focused on predicting OC discontinuation (e.g., Rosenberg et al., 1995; Sanders et al., 2001). To date, there do not appear to be any objective predictors of hormonal contraceptive side effects. The identification of measurable predictors of OC side effects would help in understanding the etiology of OC side effects and may also have clinical utility in predicting and preventing their occurrence.

Pre-existing hormonal differences between women may account for individual differences in response to exogenous hormone exposure such as OCs. However, the few studies that have examined women's premorbid circulating hormone levels and/or changes in levels with OC use have not been very successful in predicting OC side effects (e.g., Alexander et al., 1990; Bancroft et al., 1991; Graham et al., 2007). This may be because serum or salivary hormone levels do not fully represent one's hormonal activity. In addition to circulating hormone levels (and the distinction between bound and free hormone), women also differ in terms of their prenatal hormone exposure (and the accompanying brain organizational effects), hormone receptor numbers, and hormone receptor sensitivity. These variables are difficult if not impossible to ethically quantify in humans. Thus, indicators of both prenatal hormone exposure and concurrent hormone *activity* (as opposed to blood levels) may be useful in determining how an individual's hormone activity and exposure are related to OC side effects.

It has been proposed that physical indicators of differential hormone sensitivity may be useful predictors of OC side effects (Oinonen and Mazmanian, 2002). Research in physical anthropology and evolutionary psychology suggests that it may be possible to estimate one's androgen exposure, activity, and sensitivity using anthropometric hand measures. Manning (2002) noted that most tissues of the fourth and third digits seem to be more sensitive to androgens than the other digits. Thus, two digit measures may be useful as indicators of individual differences in androgen sensitivity/exposure and as predictors of OC side effects: 2D:4D and middle-phalangeal hair. Each of these is discussed below.

Manning and others have contributed to a large literature suggesting that the ratio of the length of the second to the fourth digit (2D:4D) serves as an indicator of prenatal testosterone exposure (see reviews by Manning, 2002; Honekopp et al., 2007). 2D:4D is a sexually dimorphic measure that seems to be determined in utero by about the 13th week of gestation (Garn et al., 1975; Malas et al., 2006). Women tend to have higher 2D:4D (close to 1), indicating roughly equivalent second and fourth finger lengths, while men tend to have lower 2D:4D (usually less than 1), indicating a longer fourth than second digit (e.g., Manning et al., 2000). Lower 2D:4D is reflective of higher prenatal testosterone exposure and lower estrogen exposure, as the fourth digit is believed to be more sensitive to testosterone growth effects. The digit ratio also reflects variation in the androgen receptor gene (Manning et al., 2003) and may not be associated with circulating hormone levels in healthy adults (see meta-analytic review by Honekopp et al., 2007; but also see Mayhew et al., 2007). Associations between 2D:4D and sex-linked behavioural and medical variables seem to be more consistent in men (and more commonly studied). However, studies on women indicate that lower 2D:4D is associated with congenital adrenal hyperplasia (CAH; Brown et al., 2002), polycystic ovary syndrome (PCOS; Cattrall et al., 2005), later onset of breast cancer in individuals with the disease (Manning and Leinster, 2001), and lower risk of either cervical intraepithelial neoplasia or persistent infection with human papillomavirus (Brabin et al., 2008). Thus, if the organizational effects of prenatal testosterone exposure are relevant to a women's response to OCs, 2D:4D may serve as a predictor of OC side effects.

A second anthropometric hand measure that may be useful in predicting OC side effects is middle-phalangeal hair. Middle-phalangeal hair [also known as mid-digital hair, phalanx/phalange 2 hair (P2 hair)] refers to hair found on the middle segment of the finger. The term middle-phalangeal will be used here over mid-digital in order to avoid the incorrect assumption that one is referring to hair on the middle digit (as suggested by Garn, 1951). Also, given that I will be examining hair on the middle phalange of digits 2 and 4, the term P2 will be avoided in order to avoid the confusion of using numbers to refer to both digits and phalanges.

Danforth (1921) provided one of the first reports of individual and sex differences in middle-phalangeal hair. Interestingly, he also suggested that study of the middle-phalangeal region may be useful in understanding endocrinological conditions. In the early 1950s, Garn (1951) suggested that the occurrence of middle-phalangeal hair may be affected by circulating hormone levels, in addition to genetics. The impetus for his hypothesis came from accumulating evidence of sex differences in middle-phalangeal hair (i.e., males > females), age differences (i.e., adults > - children), gonadal differences (non-castrated > castrated men), and observational anecdotes of women with virilizing ovarian tumors having high mid-phalangeal hair counts (Garn, 1951). Subsequently, one study found that post-pubertal males are more likely to have middle-phalangeal hair and more fingers affected than pre-pubertal adolescents (Saldanha and Guinsburg, 1961). A similar trend was found for post-pubertal females to have more fingers with middle-phalangeal hair than pre-pubertal females. Subsequently, positive relationships have been found in healthy men between middle-phalangeal hair and serum concentrations of 5-alpha-dihyrotestosterone (DHT; Winkler and Christiansen, 1993) and with the ratio of serum DHT to total testosterone (DHT/T, Knussmann et al., 1992; Winkler and