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Salivary cortisol and cortisone responses to short-term psychological stress challenge in late adolescent and young women with different hyperandrogenic states

Marco Mezzullo[a], Flaminia Fanelli[a], Guido Di Dalmazi[a], Alessia Fazzini[a], Daniela Ibarra-Gasparini[a], Marianna Mastroroberto[b], Jenny Guidi[c], Antonio Maria Morselli-Labate[b], Renato Pasquali[a], Uberto Pagotto[a], Alessandra Gambineri[a,*]

[a] Endocrinology Unit, Department of Medical and Surgical Sciences, Centre for Applied Biomedical Research (C.R.B.A.), S. Orsola-Malpighi Hospital, Alma Mater University of Bologna, Bologna, Italy
[b] Department of Medical and Surgical Sciences, Alma Mater University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy
[c] Department of Psychology, Alma Mater University of Bologna, Bologna, Italy

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ABSTRACT

Hyperandrogenic disorders have been associated with psychological distress, reduced quality of life, anxiety and depression. The hypothalamic–pituitary–adrenal (HPA) axis plays a pivotal role in the adaptive response to stressor events. Salivary cortisol (SalF) and cortisone (SalE) testing have been proven to be useful in the evaluation of HPA-axis activity. This study investigated whether SalF and SalE responses to two putative stressor levels differed between the hyperandrogenic states in late adolescent and young women, thus measuring the HPA-axis adaptive response to acute stress events. We selected 161 drug-free females aged 16–19 years from a large population previously enrolled in a cross-sectional epidemiological study. Saliva was collected in the morning before and after two putative stressor events consisting in a self-filled questionnaire (weaker stressor) and in a structured interview plus physical examination by an endocrinologist (stronger stressor). SalF and SalE, as well as blood steroids, were assessed by liquid chromatography–tandem mass spectrometry. Subjects were subdivided into different groups according to the presence of: isolated menstrual irregularities (MI, oligo-amenorrhea; n = 22), isolated hirsutism (HIR, modified Ferriman–Gallwey score ≥ 8; n = 26), isolated hyperandrogenaemia (HT, testosterone > 0.438 ng/mL; n = 14), and polycystic ovary syndrome (PCOS, MI with HIR and/or HT, n = 16). The remaining 83 apparently healthy subjects were used as controls. SalF and SalE significantly decreased after the weaker stressor, following the physiologic diurnal loss, in all the groups except for isolated HIR, where they remained unchanged (P = 0.091 and P = 0.118, respectively). In contrast, SalF and SalE remained unchanged after the stronger stressor in isolated MI, isolated HT and controls, whereas SalF increased significantly in isolated HIR (P = 0.011), and SalE increased significantly both in isolated HIR (P = 0.005) and in PCOS (P = 0.011) groups. SalF percentage variation in response to the stronger stressor was positively associated with systolic blood pressure in PCOS (P = 0.018), and both SalF and SalE percentage variations were positively associated with diastolic blood pressure in the isolated HIR group (P = 0.010 and P = 0.006, respectively). In addition, in the isolated HIR group, the SalF percentage variation was negatively associated with HDL cholesterol levels (P = 0.005). Finally, SalF and SalE percentage variations were positively associated with circulating androstenedione (P = 0.031 and P = 0.011, respectively) and DHEA (P = 0.020 and P = 0.003, respectively) in the isolated HIR group. In conclusion, this study demonstrates that hirsute and PCOS adolescent and young women are characterized by HPA-axis overactivity in response to stressful stimuli, as detectable by salivary glucocorticoid measurements. These data also indicate that the higher the HPA-axis activity, the higher the adrenal androgen output and the worse the metabolic profile.

* Corresponding author at: Division of Endocrinology, Department of Medical and Surgical Science, St Orsola-Malpighi Hospital, Via Massarenti 9, 40138, Bologna, Italy.
E-mail address: alessandra.gambiner3@unibo.it (A. Gambineri).

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1. Introduction

Polycystic ovary syndrome (PCOS) and other hyperandrogenic states are chronic endocrine conditions usually arising during adolescence and young age. In a recent population-based study we found that PCOS as well as other hyperandrogenic states (i.e. isolated menstrual irregularity, isolated biochemical or clinical hyperandrogenism) are frequent and are associated with metabolic abnormalities in young age (Gambineri et al., 2013). A psychological characterization of these hyperandrogenic phenotypes was also performed, showing that isolated clinical hyperandrogenism, which identified subjects with isolated hirsutism, is the worse phenotype in terms of psychological distress and quality of life (Guidi et al., 2015), thus confirming the results of previous studies (Drosdzol et al., 2010; Laggari et al., 2010; Trent et al., 2010, 2005, 2003). In the multifaceted and variable frame of the PCOS phenotype, uncontrolled weight gain and hirsutism are the most common clinical manifestations associated with increased anxiety and depressive symptoms, probably because of their impact on women identity and body image (Moran et al., 2012). The "externally-visible" nature of these alterations can in fact interfere with the psychological state of these girls, particularly during adolescence when socio-sexual interactions usually start.

The hypothalamic–pituitary–adrenal axis (HPA-axis), together with the sympathetic nervous system, plays a pivotal role in the adaptive response to environmental, physiologic or psychological stressors, through the synthesis and secretion of adrenal glucocorticoids, in particular cortisol (Oster et al., 2017; Hucklebridge et al., 1999). By allowing multiple, pain-free self-collection, salivary cortisol (SalF) represents an established tool for evaluating acute stress responses (Hellhammer et al., 2009) as it reflected free circulating cortisol levels (Mezzullo et al., 2016; Perogamvros et al., 2009; Vining et al., 1983).

Repeated or chronic environmental challenges impacting the HPA-axis are known to result in a flattened diurnal cortisol curve (Chrousos and Gold, 1992; Dallman, 1993; Hellhammer et al., 2009) and to cause metabolic impairment (Oster et al., 2017). Although the psychological correlates of hyperandrogenic states have been characterized through questionnaires and interviews (Cooney et al., 2017; Moran et al., 2012; Veltman-Verhulst et al., 2012; Dokras et al., 2011, 2012; Barry et al., 2011), only a few authors have attempted to evaluate biochemical tools for detecting HPA-axis perturbation in hyperandrogenic women (Milutinović et al., 2011; Benson et al., 2009; Gallinelli et al., 2000). On the other hand, it has been demonstrated that obesity are associated with a subtle dysregulation in the HPA-axis, resulting in slightly but inappropriately elevated net glucocorticoid production, either continuous or episodic, which can be the cause of dysmetabolic conditions (Pasquali et al., 2008). However, little is known about the metabolic consequences of HPA imbalance driven by hyperandorgenic states in a critical phase of life such as adolescence.

We hypothesized that the questionnaire completion and physical examination, used in our epidemiological study, could represent different types of stressors, thus suitable for investigating the different degrees of adaptation to environmental stress exposure. We also hypothesized that HPA-axis responsiveness to such stressors, as measured by salivary cortisol and cortisone, could differ between hyperandrogenic states.

The first aim of the present study was therefore to assess the HPA-axis responsiveness to a two stage short-term environmental stress challenge, consisting in a weaker followed by a stronger stressor, in different hyperandrogenic states in adolescent and young females. The second aim was to investigate whether a perturbed HPA-axis responsiveness to stressful events is accompanied by an unfavorable metabolic profile as assessed by anthropometric, metabolic and hormonal parameters.

2. Materials and methods

2.1. Study design

The study population consisted of 161 girls participating in a cross-sectional population-based study focusing on the prevalence of hyperandrogenic states among adolescents and young adults, as detailed elsewhere (Gambineri et al., 2013) (Fig. 1). The study was approved by the Ethic Committee of the S. Orsola-Malpighi Hospital, Bologna (protocol 49/2007/U/Tess). All participants, as well as the parents of

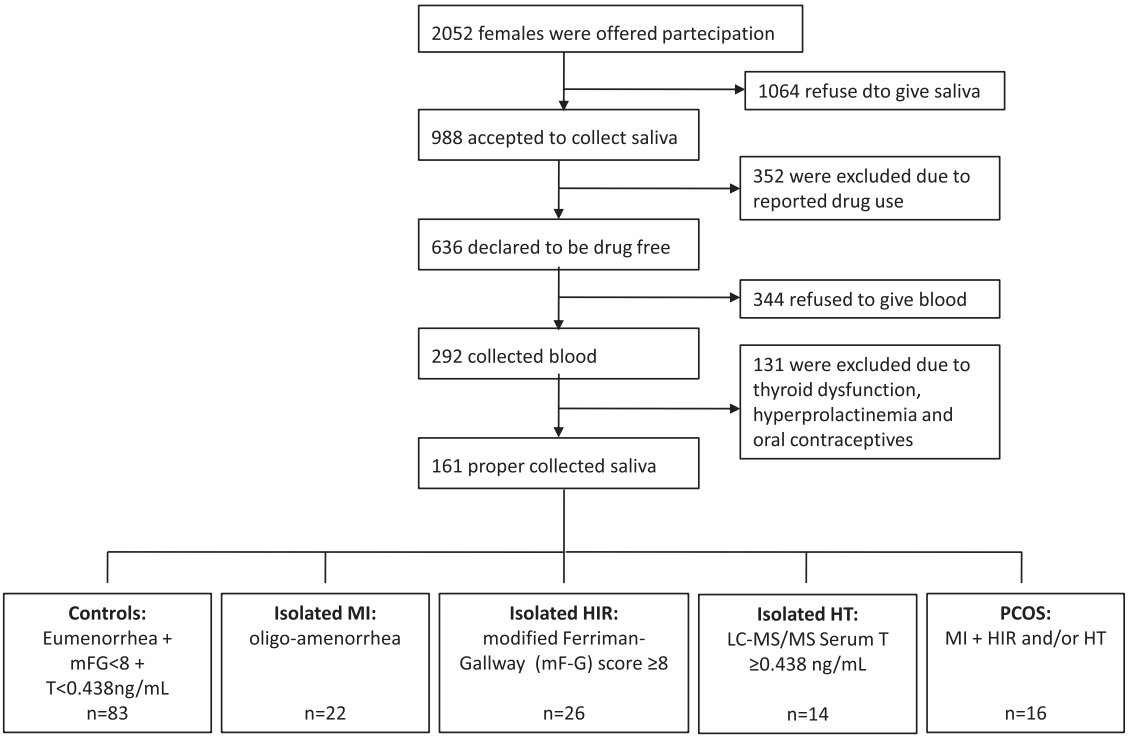

Fig. 1. Flowchart of participation in the study and stratification of subjects.