

Overweight and IVF – Strategies to reduce overweight before IVF

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Implications of overweight/ obese

- Alterations in hormones

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Adiposity and sex hormones across the menstrual cycle: the BioCycle Study

Edwina H. Yeung, PhD¹, Cullin Zhang, MD, PhD¹, Paul S. Albert, PhD¹, Sunni L. Mumford, PhD¹, Aijun Ye, PhD¹, Neil J. Perkins, PhD¹, Jean Wactawski-Wende, PhD^{2,3}, and Enrique F. Schisterman, PhD¹

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30 kg/m², n=25)
FSH (-23%,

P=0.001) and higher free E2 (+22%, p=0.001) across the cycle. To lesser magnitudes, overweight women (BMI: 25–30, n=60) also exhibited differences in the same directions for mean levels of free E2, FSH, and LH. Obese women experienced greater changes in amplitude of LH (9%, p=0.002), and FSH (8%, p=0.004), but no differences were observed among overweight women. Higher central adiposity by top compared to bottom tertile of trunk-to-leg fat ratio by DXA was

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

Supplementary information is available at International Journal of Obesity's website.

	Total E2	Free-E2	Progesterone	FSH	LH
A) Mean, %[‡]					
Overweight	5.30% (4.6)	15.17% (4.1)**	3.35% (3.7)	-15.60% (4.1)**	-10.12% (5.0)*
Obese	1.39% (6.4)	22.13% (5.6)**	-15.00% (5.1)**	-22.51% (5.7)**	-16.91% (6.9)*
<i>p-trend</i>	<i>P=0.51</i>	<i>P<0.0001</i>	<i>P=0.04</i>	<i>P<0.0001</i>	<i>P=0.004</i>

Implications of overweight/ obese

- Alterations in hormones
- Increased gonadotrophins required per IVF cycle

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RESEARCH ARTICLE

Open Access

Does obesity have detrimental effects on IVF treatment outcomes?

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Abstract

Background: The aim of this study was to investigate the influence of body mass index (BMI) on the in vitro fertilization (IVF) treatment outcomes in a cohort of women undergoing their first IVF, using an intracytoplasmic sperm injection (ICSI).

Methods: This retrospective cohort study included 298 cycles from women younger than 38 years old undergoing IVF-ICSI at a university infertility clinic. The treatment cycles were divided into three groups according to the BMI of the women involved: normal weight (18.5 ≤ BMI < 25 kg/m², 164 cycles), overweight (25 ≤ BMI < 30 kg/m², 70 cycles), and obese (BMI ≥ 30 kg/m², 64 cycles). The underweight women (BMI < 18.5 kg/m²) were not included in the analysis due to small sample size (n = 22). The patient characteristics and IVF-ICSI treatment outcomes were compared between the BMI groups.

Results: The total gonadotropin dose (p < 0.001) and duration of stimulation (p = 0.008) were significantly higher in the obese group when compared to the normal BMI group. There were no significant differences across the BMI categories for the other IVF-ICSI cycle outcomes measured, including the number of retrieved oocytes, mature oocytes, embryos suitable for transfer, proportion of oocytes fertilized, and cycle cancellation rates (p > 0.05 for each). Additionally, clinical pregnancy, spontaneous abortion, and the ongoing pregnancy rates per transfer were found to be comparable between the normal weight, overweight, and obese women (p > 0.05 for each).

Conclusion: Obese women might require a significantly higher dose of gonadotropins and longer stimulation durations, without greatly affecting the pregnancy outcomes.

Background

Obesity has become a worldwide epidemic, with approximately 1.6 billion adults being overweight and 400 million being obese [1]. Obesity has several serious consequences on health, including hypertension, diabetes mellitus, chronic heart disease, lipid disorders, uterine cancer, and breast cancer [2, 3]. Moreover, obesity has negative effects on reproductive health. It has been established that obesity is associated with decreased natural fecundity, a decreased ovulation rate, increased time until conception, and increased rates of miscarriage [4, 5]. Additionally, an increased rate of pregnancy complications, including gestational hypertension, preeclampsia, gestational

diabetes, postpartum hemorrhage, and fetal macrosomia, are all associated with obesity [6, 7]. Since the incidence of obesity is continually rising, an increasing number of overweight and obese women are seeking fertility treatments through assisted reproduction technology (ART) [8]. Consequently, there is a need to understand the full impact of obesity on in vitro fertilization (IVF) treatments.

There is conflicting evidence with regard to the effects of a raised body mass index (BMI) on the outcome of ART. Although some studies have reported no adverse effects of a raised BMI on IVF outcomes [9, 10], others have linked various negative impacts, including a higher dose of gonadotropin stimulation, longer stimulation duration, lower number of retrieved and mature oocytes, and decreased embryo quality [4, 11]. The aim of this study was to investigate the influence of BMI on the

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Implications of overweight/ obese

- Alterations in hormones
- Increased gonadotrophins required per IVF cycle
- Decreased numbers of good quality (MII) oocytes, embryos transferred
- Decreased live birth rate
- Increased rates of miscarriage

Extremities of body mass index and their association with pregnancy outcomes in women undergoing in vitro fertilization in the United States

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Objective: To investigate the associations among underweight body mass index (BMI), pregnancy, and obstetric outcomes among women using assisted reproductive technology (ART).

Design: Retrospective cohort study using national data and log binomial regression.

Setting: Not applicable.

Patients(s): Women undergoing IVF in the United States from 2008 to 2013.

Intervention(s): None.

Main Outcome Measure(s): Pregnancy outcomes: Intrauterine pregnancy, live birth rate per transfer, miscarriage rate per pregnancy, and low birth weight and preterm delivery rates among singleton and twin pregnancies.

Results: For all fresh autologous in vitro fertilization (IVF) cycles in the United States from 2008 to 2013 (n = 494,092 cycles, n = 482,742 transfers, n = 188,854 pregnancies) reported to the national ART Surveillance System, compared with normal weight women, underweight women had a statistically significant decreased chance of intrauterine pregnancy [adjusted risk ratio (aRR) 0.97; 95% confidence interval (CI), 0.96–0.99] and live birth [aRR 0.93; 95% CI, 0.93–0.98] per transfer. These women also had a statistically decreased likelihood of both [aRR 0.94; 95% CI, 0.94–0.96; aRR 0.82; 95% CI, 0.86–0.88, respectively]. Among cycles resulting in singleton pregnancy, both underweight and obese statuses were associated with increased risk of low birth weight [aRR 1.35; 95% CI, 1.25–1.54, aRR 1.28; 95% CI, 1.20–1.33, respectively] and preterm delivery [aRR 1.12; 95% CI, 1.01–1.23, aRR 1.42; 95% CI, 1.38–1.48, respectively]. The association between underweight status and miscarriage was not statistically significant [aRR 1.04; 95% CI, 0.98–1.11]. In contrast, obesity was associated with a statistically significantly increased miscarriage risk [aRR 1.23; 95% CI, 1.20–1.26].

Conclusions: Among women undergoing IVF, prepregnancy BMI affects pregnancy and obstetric outcomes. Underweight status may have a limited impact on pregnancy and live birth rates, but it is associated with increased preterm and low birth weight delivery risk. Obesity negatively impacts all ART and obstetric outcomes investigated. *Dev Biol Stand* 2016;106:1742–50. ©2016 by American Society for Reproductive Medicine.

Key Words: IVF, miscarriage, outcomes, preterm, underweight

Discussion: You can discuss this article with its authors and with other ASRM members at <https://www.fertstert.org/content/31/11/1742-1750>

16110-fertility-and-sterility/abstract/2452-22522

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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1742 |

As the obesity epidemic continues to plague the United States, numerous reports have been published and recommendations made regarding the negative impact of obesity on fertility (1), assisted reproductive technology (ART) effectiveness (2–5), and pregnancy and obstetric outcomes (5, 6). By contrast, limited and conflicting data exist on the impact of being underweight (body

Implications of overweight/ obese



Article
A Comprehensive Analysis of Body Mass Index Effect on *in Vitro* Fertilization Outcomes

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Variable	>18.50	18.50–24.99	25.0–29.99	≥30
Ongoing pregnancy	1.15 (0.67–1.96)	1.00	1.06 (0.68–1.66)	1.01 (0.49–2.06)
Miscarriage rate	1.37 (0.42–4.47)	1.00	2.24 (0.86–5.84)	4.75 (0.70–32.37)
Live birth	0.54 (0.17–1.79)	1.00	0.51 (0.18–1.41)	0.17 (0.02–1.31)
Gestational age (weeks)	37.89 ± 1.87	37.74 ± 3.03	37.59 ± 2.80	37.03 ± 4.41
Birth weight (g)	2887 ± 586	3053 ± 613	2932 ± 756	3131 ± 1186

age of infants [7,8]. Moreover, there is an increased prevalence of infertility among overweight and obese women [9,10]. Infertility affects one in seven couples and a significant proportion of these cases are thought to be either directly or indirectly related to obesity. Obese women in the general population have a lower chance of conception within one year of stopping contraception compared with normal-weight women. The combination of infertility and obesity confers some real challenges about the short and long term management of these women [11].

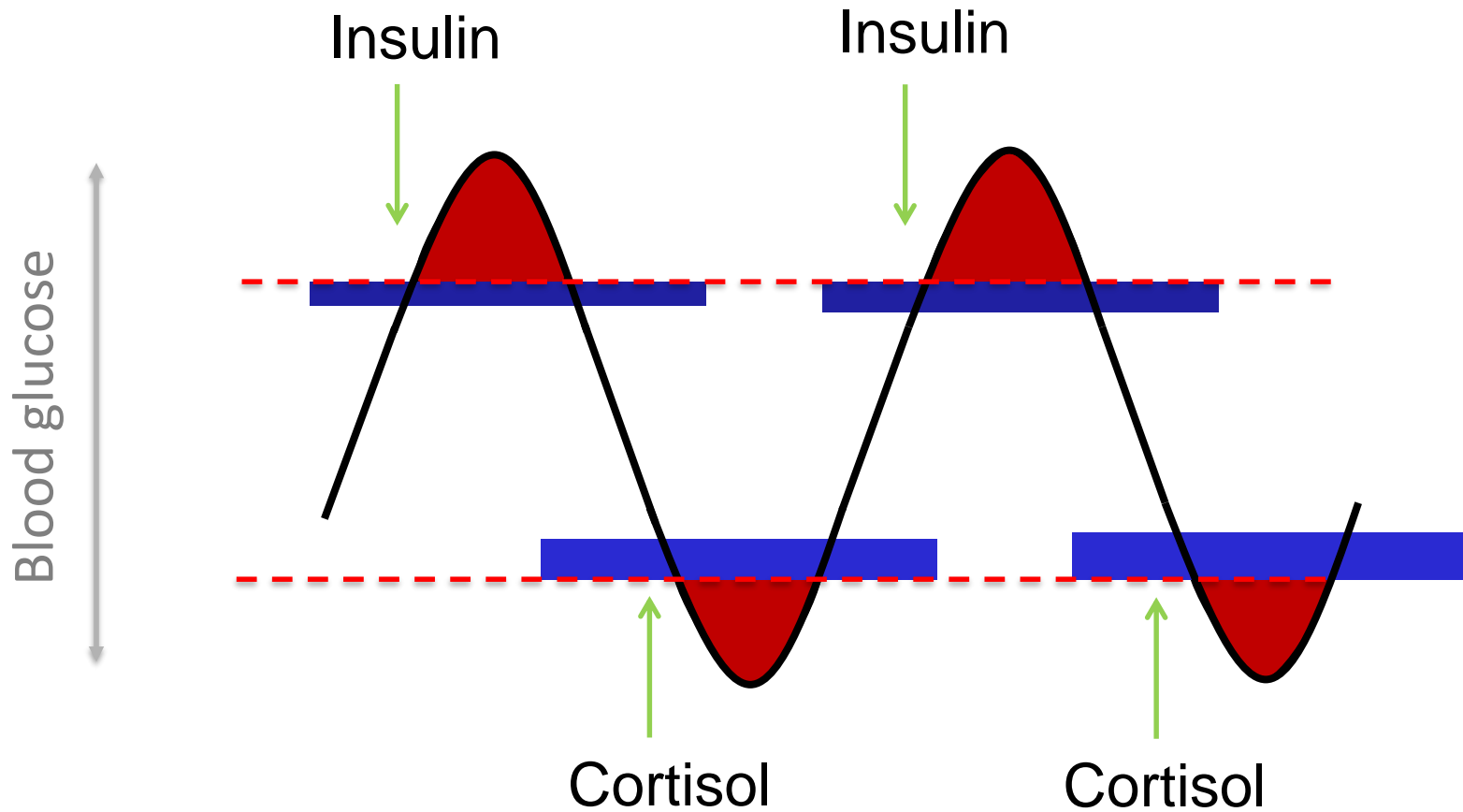
The mechanism through which obesity is thought to affect female reproductive function is complex. Adiposity increases peripheral aromatization of androgens to estrogens with a concurrent

Implications of overweight/ obese

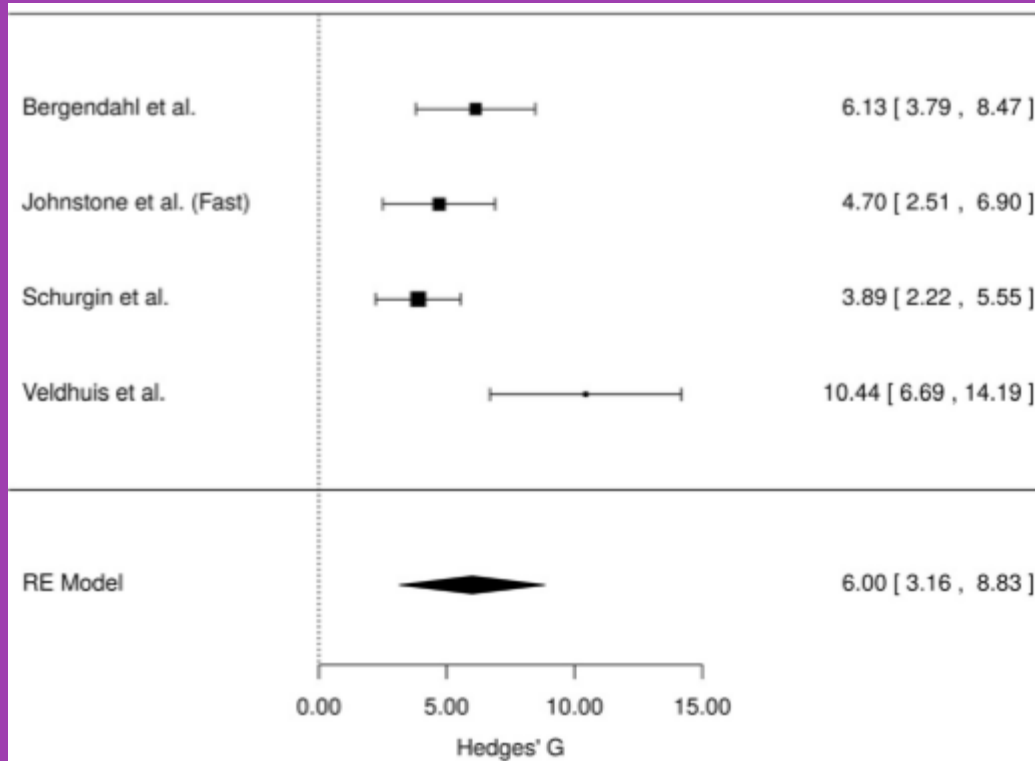
- Technical difficulties with egg retrieval
- Concerns for pregnancy
 - Gestational diabetes
 - Pre-eclampsia
 - Pre-term delivery
 - Macrosomia
 - Miscarriage/ still birth
 - Difficulties monitoring and delive



Blood Glucose/ Cortisol



Cortisol increases during fasting



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ORIGINAL RESEARCH REPORT

Systematic review and meta-analysis reveals acutely elevated plasma cortisol following fasting but not less severe calorie restriction

Yuko Nakamura¹, Brian R. Walker², and Toshikazu Itaka³

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Abstract

Elevated plasma cortisol has been reported following calorie restriction, and may contribute to adverse effects including stress-induced overeating, but results from published studies are inconsistent. To clarify the effects of calorie restriction on plasma cortisol, and to assess cortisol as an indicator of stress during calorie restriction, we conducted a systematic review and meta-analysis of published studies in which cortisol was measured following calorie restriction without other manipulations in humans. We further compared effects of fasting, very low calorie diet (VLCD), and other low calorie diet (LCD), as well as the duration of calorie restriction by meta-regression. Overall, calorie restriction significantly increased serum cortisol level in 12 studies (157 total participants). Fasting showed a very strong effect in increasing serum cortisol, while VLCD and LCD did not show significant increases. The meta-regression analysis showed a negative association between the serum cortisol level and the duration of calorie restriction, indicating serum cortisol is increased in the initial period of calorie restriction but decreased to the baseline level after several weeks. These results suggest that severe calorie restriction causes activation of the hypothalamic-pituitary-adrenal axis, which may be transient, but results in elevated cortisol which could mediate effects of starvation on brain and metabolic function as well as accelerate weight loss.

Keywords

Calorie restriction, cortisol, diet, endocrinology, hypothalamic-pituitary-adrenal axis, meta-analysis, stress, weight control

History

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Introduction

Adverse effects of dietary restrictions are a significant public health concern (Dicks & Leeseborough, 2006). While obesity itself is a health risk, attempts to reduce body weight can increase stress and result in adverse effects, including stress-induced overeating (Pudrovsch et al., 2010) and cognitive dysfunction (Hutchinson, 2011; Rolland Cachera et al., 2006; Vothara et al., 2006). Increased stress responses, both psychological and physiological, after dietary restrictions have been reported (Epid et al., 2001). There have been attempts to assess the increased stress after dietary restriction by measuring serum cortisol levels. In humans, cortisol can be reliably measured in saliva, blood and urine and is elevated by chronic stress (Nater et al., 2003; Staudenfeld et al., 2013). Elevated cortisol can stimulate appetite, alter mood and sensory and other peripheral metabolites in favor of weight gain, all of which might be disadvantageous during calorie restriction.

Previous studies suggest that calorie restriction increases cortisol levels (Dulac et al., 1988; Psaty et al., 2011; Treisman et al., 2010), but results are inconsistent.

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While fasting has been consistently shown to increase cortisol level, it is unclear whether lesser degrees of calorie restriction, such as those which are relevant during weight loss diets, cause elevated cortisol.

We therefore undertook a systematic review and meta-analysis of published studies to establish whether plasma cortisol is elevated during calorie restriction. We further studied the effects of graded calorie restriction (fasting, very low calorie diet (VLCD) and low calorie diet (LCD)). Finally, we used meta-regression to assess the influence of duration of calorie restriction on cortisol levels. In order to maximize the sample homogeneity (Andrew et al., 1998), only studies with serum cortisol, but not saliva or urine cortisol, were included in the meta-analysis.

Methods

In order to determine eligible studies for the meta-analysis, a MEDLINE search was performed for publications available on 7 November 2014. The following search terms was used [cortisol AND (calorie restriction) OR food restriction] OR dietary restriction OR diet restriction. Searches in Google scholar and Cochrane Library database were also conducted to supplement the MEDLINE search.

Nonhuman studies were first excluded and then human studies that did not include cortisol assessment or calorie

Cortisol increases during fasting

‘caloric restriction overall significantly increased serum cortisol, an effect which is attributable to fasting’



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ORIGINAL RESEARCH REPORT

Systematic review and meta-analysis reveals acutely elevated plasma cortisol following fasting but not less severe calorie restriction

Yuko Nakamura¹, Brian R. Walker², and Toshikazu Itaka³

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Previous studies suggest that calorie restriction increases cortisol levels (Dulac et al., 1998; Pothos et al., 2011; Treliyas et al., 2010), but results are inconsistent.

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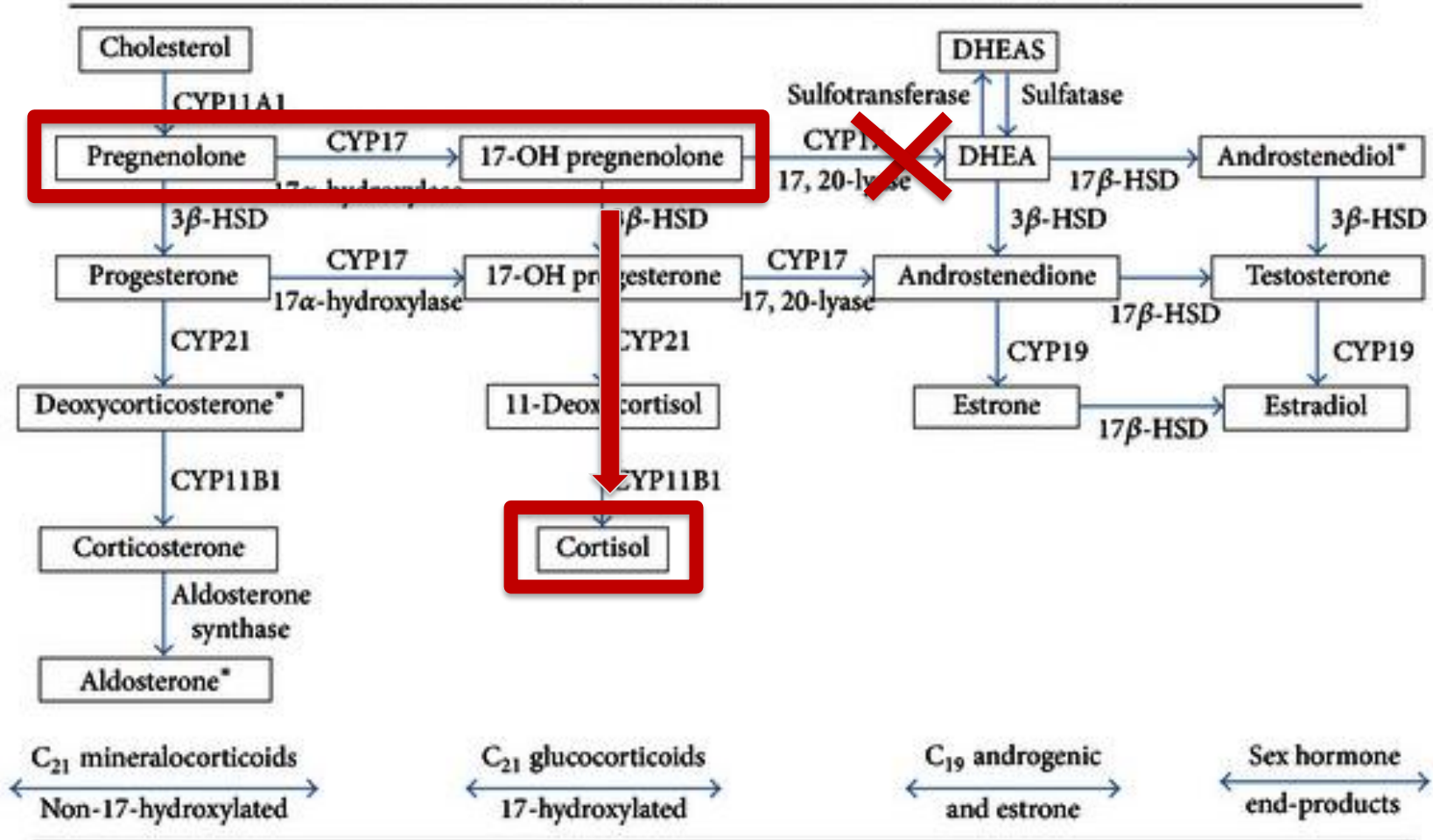
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Cortisol affects sex hormones

Simplified schema of biosynthetic steps in adrenal and sex steroid pathways



Cortisol affects sex hormones

‘longer average menstrual cycle length’
‘affected luteinising hormone dynamics’



Review

Potential Benefits and Harms of Intermittent Energy Restriction and Intermittent Fasting Amongst Obese, Overweight and Normal Weight Subjects—A Narrative Review of Human and Animal Evidence

Michelle Harvie * and Anthony Howell

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Academic Editors: Amanda Sainsbury and Felipe Luz

Received: 28 September 2016; Accepted: 13 December 2016; Published: 19 January 2017

Abstract: Intermittent energy restriction (IER) has become popular as a means of weight control amongst people who are overweight and obese, and is also undertaken by normal weight people hoping spells of marked energy restriction will optimise their health. This review summarises randomised comparisons of intermittent and isoenergetic continuous energy restriction for weight loss to manage overweight and obesity. It also summarises the potential beneficial or adverse effects of IER on body composition, adipose stores and metabolic effects from human studies, including studies amongst normal weight subjects and relevant animal experimentation. Six small short term (<6 month) studies amongst overweight or obese individuals indicate that intermittent energy restriction is equal to continuous restriction for weight loss, with one study reporting greater reductions in body fat, and two studies reporting greater reductions in HOMA insulin resistance in response to IER, with no obvious evidence of harm. Studies amongst normal weight subjects and different animal models highlight the potential beneficial and adverse effects of intermittent compared to continuous energy restriction on ectopic and visceral fat stores, adipocyte size, insulin resistance, and metabolic flexibility. The longer term benefits or harms of IER amongst people who are overweight or obese, and particularly amongst normal weight subjects, is not known and is a priority for further investigation.

Keywords: intermittent energy restriction; fasting; weight loss; weight gain

Excess energy intake, weight gain and subsequent adiposity are consistently linked to illness, disability and mortality [1–3]. Randomised trials demonstrate that intentional weight loss reduces type 2 diabetes [4], all-cause mortality [5] and increases cognitive [6] and physical function [7]. The health benefits of weight loss and energy restriction in these human clinical trials are supported by a century of laboratory research in rodents, which has established that energy restriction (ER) prevents age-related disease including tumours, cardiovascular disease, diabetes and dementia; retards aging-related functional decline; and increases lifespan [8].

Most human and animal studies on weight loss have involved continuous energy restriction (CER) administered on a daily basis. More recently, interest has focussed on intermittent energy restriction (IER) defined as periods of energy restriction interspersed with normal energy intake.

IER is of potential interest to manage obesity and its metabolic sequelae and also for normal weight subjects hoping to optimise their health independent of weight loss for two main reasons: firstly, IER only requires the individual to focus on ER for defined days during the week which is potentially

Cortisol affects sex hormones

‘longer average menstrual cycle length’
‘affected luteinising hormone dynamics’
‘increased feelings of hunger, worse mood, heightened irritability, difficulties concentrating, increased fatigue, eating-related thoughts, fear of loss of control and over eating during non-restricted days’



Review

Potential Benefits and Harms of Intermittent Energy Restriction and Intermittent Fasting Amongst Obese, Overweight and Normal Weight Subjects—A Narrative Review of Human and Animal Evidence

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Abstract: Intermittent energy restriction (IER) has become popular as a means of weight control amongst people who are overweight and obese, and is also undertaken by normal weight people hoping spells of marked energy restriction will optimise their health. This review summarises randomised comparisons of intermittent and isoenergetic continuous energy restriction for weight loss to manage overweight and obesity. It also summarises the potential beneficial or adverse effects of IER on body composition, adipose stores and metabolic effects from human studies, including studies amongst normal weight subjects and relevant animal experimentation. Six small short term (<6 month) studies amongst overweight or obese individuals indicate that intermittent energy restriction is equal to continuous restriction for weight loss, with one study reporting greater reductions in body fat, and two studies reporting greater reductions in HOMA insulin resistance in response to IER, with no obvious evidence of harm. Studies amongst normal weight subjects and different animal models highlight the potential beneficial and adverse effects of intermittent compared to continuous energy restriction on ectopic and visceral fat stores, adipocyte size, insulin resistance, and metabolic flexibility. The longer term benefits or harms of IER amongst people who are overweight or obese, and particularly amongst normal weight subjects, is not known and is a priority for further investigation.

Keywords: intermittent energy restriction; fasting; weight loss; weight gain

Excess energy intake, weight gain and subsequent adiposity are consistently linked to illness, disability and mortality [1–3]. Randomised trials demonstrate that intentional weight loss reduces type 2 diabetes [4], all-cause mortality [5] and increases cognitive [6] and physical function [7]. The health benefits of weight loss and energy restriction in these human clinical trials are supported by a century of laboratory research in rodents, which has established that energy restriction (ER) prevents age-related disease including tumours, cardiovascular disease, diabetes and dementia; retards aging-related functional decline; and increases lifespan [8].

Most human and animal studies on weight loss have involved continuous energy restriction (CER) administered on a daily basis. More recently, interest has focussed on intermittent energy restriction (IER) defined as periods of energy restriction interspersed with normal energy intake.

IER is of potential interest to manage obesity and its metabolic sequelae and also for normal weight subjects hoping to optimise their health independent of weight loss for two main reasons: firstly, IER only requires the individual to focus on ER for defined days during the week which is potentially

Cortisol Measurement via Saliva

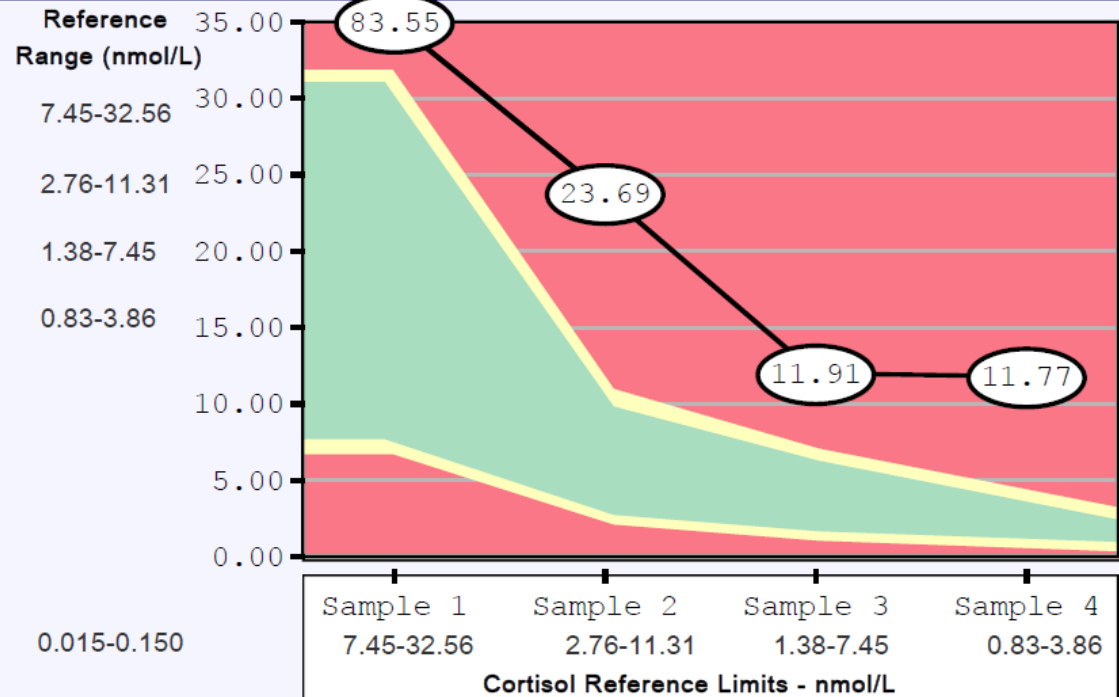
Salivary Cortisol and DHEA

Cortisol Levels

Sample	Value	Status	Reference Range (nmol/L)
Sample 1 Post Awakening	83.55	H	7.45-32.56
Sample 2 (+ 4 - 5 Hours)	23.69	H	2.76-11.31
Sample 3 (+ 4 - 5 Hours)	11.91	H	1.38-7.45
Sample 4 (Prior to Sleep)	11.77	H	0.83-3.86
Sum of Cortisol	130.9		

DHEA Levels

DHEA Mean	0.34		
DHEA : Cortisol Ratio	0.007	L	0.015-0.150

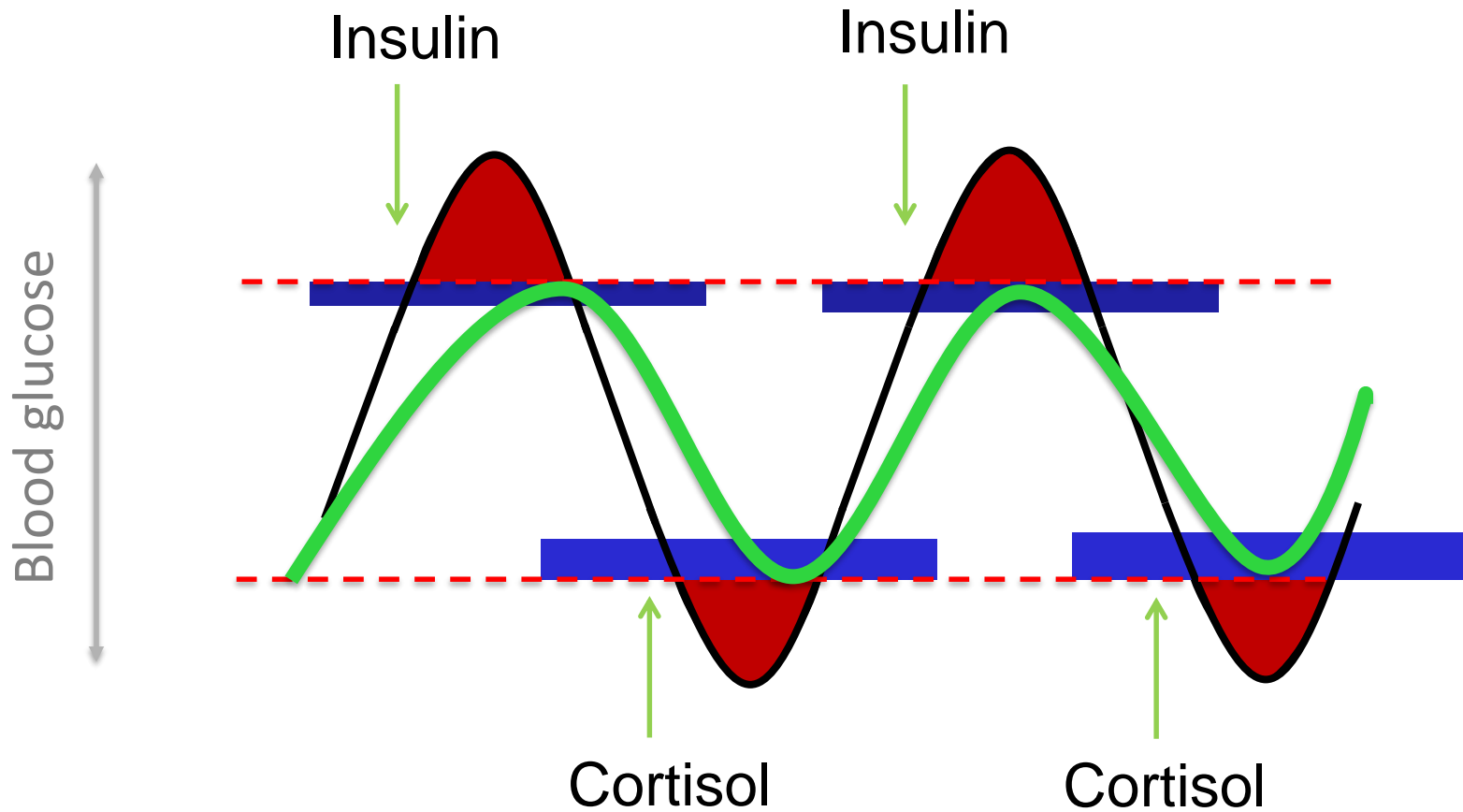


Hormones

Reference Range (nmol/L)

DHEA Sample 1 (am)	0.55	0.25-2.22
DHEA Sample 3 (pm)	0.12	0.25-2.22

Blood Glucose/ Cortisol



Blood Glucose/ Cortisol

- Eating little and often
- Slow- release wholegrain carbohydrates
- Paired with protein and/or healthy fat
- Including healthy snacks
- Restricting carbohydrates in the evening



Mediterranean Diet

- Wholegrains
- Plenty of fresh fruit and vegetables
- Nuts and seeds
- Pulses
- Reduced red meat
- Increased intake of fish

Support

- Focus on what you can have instead of what you can't
- Practical support
- Ongoing support and feedback
- Encouragement, positive re-enforcement

Recommendations

- Avoid extreme caloric restriction and fasting
- Slow steady weight loss
- Incorporate exercise
- Slow release energy, small meals throughout the day
- Nutrient dense meals to support fertility
 - High in antioxidants, minerals, omega-3
- Support your patients through weight loss

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