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# Effect of oral contraceptives on energy balance in women: A review of current knowledge and potential cellular mechanisms

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- 13 **No conflict of interest to declare**
- 14 **Abbreviations:**
- 15 EB: Energy Balance
- 16 OC: Oral Contraceptive
- 17 EI: Energy Intake
- 18 EE: Energy Expenditure
- 19 BMR: Basal Metabolic Rate
- 20 REE: Resting Energy Expenditure
- 21 TEF: Thermic Effect of Food
- 22 ER $\alpha$ : Estrogen Receptor alpha
- 23 E2: 17 $\beta$ -estradiol
- 24 ARC: ARCuate nucleus of hypothalamus
- 25 POMC: ProOpioMelanoCortin
- 26 NPY: neuropeptide Y
- 27 AMPK: AMP-activated protein kinase
- 28 mTOR: mammalian Target Of Rapamycin
- 29 P4: Progesterone
- 30 CCK: Cholecystokinin
- 31 UCP1: Uncoupling protein 1

- 32 VMH: Ventro Medial Hypothalamus
- 33 FSH: Follicle Stimulating Hormone
- 34 LH: Luteinizing Hormone
- 35 FSHR: Follicle Stimulating Hormone Receptor
- 36 GnRH: Gonadotropin-Releasing Hormone
- 37 TEE: Total Energy Expenditure

38 **Abstract**

39 Body weight management is currently of major concern as the obesity epidemic is still a  
40 worldwide challenge. As women face more difficulties to lose weight than men, there is an  
41 urgent need to better understand the underlying reasons and mechanisms. Recent data have  
42 suggested that the use of oral contraceptive (OC) could be involved. The necessity of utilization  
43 and development of contraceptive strategies for birth regulation is undeniable and contraceptive  
44 pills appear as a quite easy approach. Moreover, OC also represent a strategy for the  
45 management of premenstrual symptoms, acne or bulimia nervosa. The exact impact of OC on  
46 body weight remains not clearly established. Thus, after exploring the potential underlying  
47 mechanisms by which OC could influence the two side of energy balance, we then provide an  
48 overview of the available evidence regarding the effects of OC on energy balance (i.e. energy  
49 expenditure and energy intake). Finally, we highlight the necessity for future research to clarify  
50 the cellular effects of OC and how the individualization of OC prescriptions can improve long-  
51 term weight loss management.

52

## 53 **Introduction**

54           Obesity is a global epidemic and there is an alarming progression of the prevalence of  
55 obesity and obesity-related comorbidities in women <sup>1,2</sup>. Despite more women trying to lose  
56 weight compared to men, weight management programs are less effective in women <sup>3</sup>. Thus  
57 there is an urgent need to understand the factors influencing weight management and hence  
58 energy balance (EB) in women across the lifespan. Many adult women of childbearing age use  
59 hormonal agents to support menstrual regularity and provide birth control with oral  
60 contraceptives (OC) being the most popular form <sup>4,5</sup>. The influence of female reproductive  
61 hormones, and specifically OC use, has well-described effects on substrate utilization at rest  
62 and during exercise. Surprisingly, despite weight gain being one of the most common side  
63 effects of OC use reported by women <sup>6,7</sup>, the influence of OC use on energy balance and  
64 specifically energy intake (EI) and energy expenditure (EE) is not well-known. The aim of this  
65 narrative review is to propose potential mechanisms to explain the relationships between  
66 exogenous hormones contained in OC and EI and EE the two primary determinants of energy  
67 balance and to determine the influence of OC use on EI, EE and weight status.

## 68 **1-Energy Balance**

69 Weight regulation depends on subtle adaptations between EI and EE. Weight loss and weight  
70 gain involve a prolonged period of either negative or positive EB (i.e. energy imbalance),  
71 respectively, whereas weight maintenance is characterized by a period of achieving equilibrium  
72 between these two constructs <sup>8</sup>. Energy intake is defined as the dietary energy provided three  
73 macronutrients (i.e., carbohydrate, protein and lipids) and alcohol contained in foods and drinks  
74 <sup>9</sup>. Total daily EE is comprised of three compartments, namely basal metabolic rate (BMR; ~60-  
75 75% of daily EE), the thermic effect of food (TEF; ~10-15% of daily EE) and the energy  
76 expended in physical activity (~20-30% of daily EE) which can come from either structured  
77 physical activities or non-exercise activities <sup>8,10</sup>.

78 For several decades, the influences of EI and EE on body weight regulation have been  
79 considered independently. Evidence shows that important interactions exist between EI and EE  
80 to affect body weight. For example, energy consumed at rest by tissues and organs represents  
81 the major part of daily EE, and at the same time there is a functional association between body  
82 composition and EE<sup>9</sup>. Exercise impacts EI, appetite sensation and food reward<sup>11,12</sup>. Likewise,  
83 EI has been shown to be influenced by fat-free mass and resting metabolic rate (RMR)<sup>13</sup>. Thus,  
84 energy balance is a dynamic regulatory system with EE and EI influencing each other<sup>14</sup>.  
85 However, little is known regarding the potential mechanisms of the effect of synthetic hormones  
86 used in OC formulation on both components of energy balance.

## 87 **2 -Possible mechanisms of Oral Contraceptives on EE and EI**

88 Surprisingly, while many women of childbearing age use OC<sup>15,16</sup> there are few data  
89 investigating synthetic hormones effects on both component of energy balance. A large variety  
90 of combined OC are available which differ by their constituents; particularly the type of  
91 progestin (derivatives of testosterone with different degrees of androgenic and estrogenic  
92 properties), and the dose of synthetic estrogen (i.e.ethinylestradiol) which ranges from 10 to  
93 50µg. Progestin can be derivatives of testosterone with different degrees of androgenic and  
94 estrogenic properties. Hence, in the following section, we describe the cellular mechanisms that  
95 can link OC use with EI or EE. Specifically, we highlight the role of cerebral energy sensors  
96 but will not be discussed in the context of puberty onset, as it has been recently reviewed<sup>17</sup>.

### 97 *2.1- Sex steroids, OC and EI*

#### 98 *2.1.1- Cellular data*

99 Animal studies have provided a number of insights into the mechanisms that may be involved  
100 in the regulation of energy balance by sex steroids. The brain is characterized as the central  
101 command center for food regulation and brain networks communicate with peripheral organs  
102 to insure metabolic and energetic regulations<sup>18</sup>. In 2018, Xu and Lopez reviewed the

103 interactions between brain estrogen and hormonal/neuronal signals involved in the regulation  
104 of EI. Estrogen Receptor  $\alpha$  (ER $\alpha$ ) is expressed in brain areas that are implicated in EI (i.e.,  
105 arcuate nucleus of the hypothalamus, nucleus of the solitary tract, dorsal raphe) and may be up  
106 or downregulated by the potency of appetite-regulatory signals (e.g., leptin, cholecystokinin,  
107 ghrelin). Several groups have summarized compelling evidence to describe the effect of 17 $\beta$ -  
108 estradiol (E2) on overall energy homeostasis exerted at the central level (for review see <sup>19</sup>).  
109 It has been previously reviewed that estrogen have an effect on food intake, and overall energy  
110 balance and these actions may be mediated through interactions with orexigenic and  
111 anorexigenic hormones in the brain <sup>20-22</sup>. Leptin and insulin are two main actors driving  
112 information about energy status between periphery and brain. Both can modulate food intake  
113 <sup>23</sup>. Thus, high level of estrogen increase sensitivity to leptin's anorexigenic action and decrease  
114 insulin sensitivity in the brain <sup>23</sup>. Ghrelin is mainly produced by the stomach and acts on growth  
115 hormone secretagogue receptors (GHSRs) in the hypothalamus to increase food intake. There  
116 may be an interrelationship between estrogens and GHSRs. Indeed, while underlying  
117 mechanisms remain unclear, it seems that estrogen reduce the orexigenic action of ghrelin  
118 possibly via downregulation of ghrelin and its receptors' activity <sup>21,24</sup>. Finally, E2 has also been  
119 shown to modulate glucagon-like peptide-1 (GLP1) anorexigenic effects but cellular pathways  
120 driving this action remain to be elucidated <sup>25</sup>. Yet, the effects of synthetic hormones, such as  
121 those found in OC formulation, on the action of the previously mentioned hormones are still  
122 not known.

123 Anorectic effects of E2 occur in the arcuate nucleus of hypothalamus (ARC), particularly in  
124 proopiomelanocortin (POMC) neurons where ER $\alpha$  is highly expressed <sup>26</sup>. During the last  
125 decade two main energy sensors in brain have gained in interest for their potential implication  
126 in energy intake; the AMP-activated protein kinase (AMPK) and the mammalian target of  
127 rapamycin (mTOR). Suppression of estrogen production induced by ovariectomy in rats



128 increased food intake, body weight gain and was associated with increased phosphorylation of  
129 AMPK in the hypothalamus<sup>27</sup>. These effects were reversed after E2 replacement<sup>27</sup>. However,  
130 whether the decrease in AMPK activation drives the anorectic effect of E2 remains to be  
131 investigated. Only one study has shown that pharmacological activation of central AMPK could  
132 reverse the anorectic effects of E2 in rats<sup>28</sup>.

133 As an energy sensor mTOR seems to demonstrate opposite effects of AMPK on EI regulation  
134 in the brain. In hypothalamus, mTOR co-localize with NPY and POMC neurons and activation  
135 of mTOR signaling has been shown to reduce food intake<sup>29</sup>. Estrogen and leptin have both  
136 been shown to mediate their anorectic effects by activating mTOR pathway and inhibiting  
137 AMPK<sup>28-30</sup>. The interplay between E2 and leptin in this regulation is still unknown. Currently  
138 we do not know if a synthetic E2 such as ethinyl estradiol has the same central effect on AMPK  
139 and mTOR signaling.

140 Other brain regions are involved in potential action of E2 on EI. Thus, few studies have also  
141 evaluated the relationship between hindbrain activation of AMPK, E2 and food intake<sup>31,32</sup>.  
142 Results of these studies suggest that E2 could exert a permissive action toward AMPK  
143 activation in a fasted state whereas this effect is not found in a fed state<sup>31</sup>.

144 Progesterone (P4), in the presence of estrogen, favors EI. However, much remains unknown  
145 regarding the underlying mechanisms explaining such a relationship. P4 receptors are expressed  
146 in many regions of the central nervous system (i.e., hypothalamus, hippocampus, cerebellum  
147 and frontal cortex)<sup>33</sup>, which are related to food and appetite regulation, and thus P4 may act  
148 directly or indirectly on appetite-regulatory signals. Most of the information available concerns  
149 effects of P4 on hypothalamus. The transcriptional regulator Forkhead box protein O1, which  
150 is known to interact with both P4 receptor isoforms, increases EI in upregulating neuropeptide  
151 Y and agouti-related protein mRNA expression (i.e., orexigenic neuropeptides)<sup>34,35</sup> (Figure1).  
152 Interestingly, Stelmanska & Sucajty-Szulc<sup>36</sup> observed that increased EI in P4-treated female

153 rats was related to upregulated neuropeptide Y and downregulated cocaine- and amphetamine-  
154 regulated transcript (i.e. anorexigenic neuropeptides) gene expression in the hypothalamus  
155 (Figure 1). P4 receptor activation has been shown recently to interact with kinase as mTOR in  
156 brain <sup>34</sup> but whether it is related to EI regulation remains unknown. It may be questioned  
157 whether the synthetic hormones contained within OC (i.e., ethinyl estradiol and progestin) will  
158 have similar affinity with estrogen and P4 receptors within the brain and if synthetic hormones  
159 will mimic the effects of endogenous estrogen and P4 on EI. In ovariectomized rats treated with  
160 E2 benzoate, progestin (i.e. R 5020) was more potent than P4 on EI, body weight and adiposity  
161 <sup>37</sup>. No difference in EI, body weight and adiposity was observed for ovariectomized rats not  
162 treated with estradiol benzoate.

163 These results highlight the possible interaction between estrogen and progestin components on  
164 EI and metabolic regulations; yet, notably it does not represent what is commonly used in OC  
165 formulation for women today.

166

### 167 *2.1.2- Appetite related hormones*

168 Few clinical studies have investigated the effects of OC use on EI and appetite-related  
169 hormones. Interestingly, Caldwell and colleagues <sup>38</sup> observed that women with overweight or  
170 obesity using various forms of hormonal contraceptives tended to decrease their protein  
171 consumption during weight-loss maintenance. Considering the satiating effect of protein, the  
172 authors speculated that this could partly explain an increase in EI observed in these women in  
173 comparison to women not taking hormonal agents. The authors concluded that hormonal  
174 contraceptives may affect long term weight maintenance for women with overweight and  
175 obesity.

176 Interventional studies have suggested a potential effect of OC use on cholecystokinin (CCK)  
177 metabolism. In 1992, Karlsson et al. <sup>39</sup> showed in a longitudinal study that 2 to 3 months of

178 monophasic combined OC use decreased the 24-hour profile of cholecystokinin (CCK)  
179 concentrations. Knowing that CCK has a satiating effect, the lowered CCK concentrations  
180 observed with OC use may be associated with increased appetite and EI reported by women  
181 using OC <sup>39</sup>. Interestingly, Hirschberg et al. <sup>40</sup> also observed a decrease in CCK concentrations  
182 following 5 months of monophasic combined OC use although participants reported no change  
183 in satiety or hunger. These studies did not objectively measure changes of EI following OC use  
184 and the combined OC does not allow for the independent effects of ethinyl estradiol and  
185 progestins to be studied.

186

## 187 *2.2- Sex steroids, OC and Energy Expenditure*

188 Similar to EI, studies investigating the effects of OC on EE are scarce and potential mechanisms  
189 should be considered based mostly on animal studies investigating the effects of E2 and P4 on  
190 different tissues. Skeletal muscle and adipose tissue represent the major component of body  
191 weight and both play a role in EE regulation.

### 192 *2.2.1- Effects on skeletal muscle*

193 Skeletal muscle is involved in EE mainly through mitochondrial respiration and futile cycling  
194 <sup>41</sup>. E2 improves mitochondrial functioning by increasing complex I and III and mitochondrial  
195 oxidative phosphorylation system responsiveness and decreasing H<sub>2</sub>O<sub>2</sub> production <sup>42</sup> (Figure  
196 2). Estrogen signaling disruption in skeletal muscle has been shown to be associated with H<sub>2</sub>O<sub>2</sub>  
197 production, ceramide accumulation and impaired oxidative capacity <sup>43</sup>. Increase in  
198 intramuscular oxidative stress has been associated with a decrease in EE during a high fat diet  
199 regimen in rodents. Moreover, mitochondrial uncoupling decreased oxidative stress and  
200 normalized EE in rodents <sup>44</sup>. These results suggest that a specific cellular context that increases  
201 oxidative stress can decrease mitochondrial ability to respond to metabolic demand.

202 Clinical studies have shown that conversely to E2, P4 could promote H<sub>2</sub>O<sub>2</sub> production by  
203 skeletal muscle mitochondria in women<sup>45</sup>. As there is no apparent oxidative stress in healthy  
204 women with normal menstrual cycles, perhaps the protective effect of E2 on H<sub>2</sub>O<sub>2</sub> production  
205 is the ability to overcome the effect of P4. However, with OC use oxidative stress could be  
206 increased depending on the nature of contraceptive used<sup>46,47</sup>. This cellular stress could affect  
207 the ability of the mitochondria to respond to cellular energy demand and thus influence EE.  
208 Endogenous levels of E2 are lower in OC users hence its protective effect on oxygen reactive  
209 species production could be partially or totally abolished.

210

### 211 *2.2.2- Effects on liver*

212 Estrogen can modulate specific metabolic pathways in the liver via ER $\alpha$ . Studies using  
213 ovariectomized liver knockout-ER $\alpha$  mice demonstrated that E2 in this tissue did not impact  
214 body weight or body fat mass but was essential for insulin sensitivity and protection against  
215 steatosis<sup>48,49</sup>. These protective effects seem to be mediated through ER $\alpha$  signaling in  
216 hepatocytes<sup>48</sup>. Thus, a recent work from Allard and colleagues<sup>50</sup> showed that E2 stimulates  
217 the production of fibroblast growth factor 21 by liver which contributed to increase in whole  
218 body oxygen consumption and EE in female mice (Figure 2). Few studies have suggested that  
219 OC use can have deleterious effects on liver metabolism induced by oxidative stress after  
220 metabolism of ethinyl estradiol in rats<sup>51,52</sup>. Oxidative damages with OC use may impact cellular  
221 metabolism via hepatokine production but this hypothesis needs to be further investigated.

222

### 223 *2.2.3 Effects on adipose tissue*

224 The main function of adipose tissue is to facilitate energy homeostasis through storing and  
225 releasing lipids. Adipocytes are also specific location where testosterone could be converted in

226 estrogens by aromatase. Estrogen can increase thermogenesis in adipose tissue through central  
227 and peripheral processes. In vitro and in vivo studies on rodents have suggested that activation  
228 of ER $\alpha$  in adipocytes can induce beiging of white adipose tissue<sup>53,54</sup> (Figure 2). This effect is  
229 mediated by rapid activation of AMPK, which promotes adipose triglycerides lipase-dependent  
230 lipolysis, followed by an increase in uncoupling protein 1 (UCP-1) expression<sup>55</sup>. Specific  
231 genetic manipulation of ER $\alpha$  has shown that brain, particularly ventro medial hypothalamus  
232 (VMH), is involved in estrogen mediated effects on EE in rodents<sup>56</sup>. Thermogenesis in brown  
233 adipose tissue (BAT) is mainly regulated by VMH and by expression level of  $\beta$ 3-Adreno  
234 receptors at brown adipocyte surface<sup>57</sup>. Indeed, administration of E2 can increase BAT  
235 thermogenesis by decreasing AMPK activation in the VMH<sup>28</sup>. Thus, estrogen in VMH  
236 stimulates EE by increasing firing rate of the sympathetic nerves connected to BAT which in  
237 turn increase UCP1 protein level (Figure 2). The same group also showed that a central injection  
238 of E2 to ovariectomized rats suppressed lipotoxicity induced by an increase level of ceramide  
239 in the VMH<sup>58</sup>. This improvement to lipid metabolism was associated with a decrease in  
240 endoplasmic reticulum stress and an increase whole body EE, lipid oxidation, and body  
241 temperature<sup>58</sup>.

242 Animal studies have recently shown that blocking follicle stimulating hormone (FSH) increases  
243 beiging of white adipose tissue with increased mitochondrial biogenesis and UCP1 expression  
244<sup>59</sup>. Based on these results it could be expected that women taking OC who have a decrease in  
245 FSH and luteinizing hormone (LH)<sup>60,61</sup>, would have an increase in BAT thermogenesis and  
246 thus an increase in EE. Furthermore, the decrease in endogenous estrogen with OC use, and  
247 subsequent activation of metabolic pathways mediated by ER $\alpha$ , could in turn blunt the increase  
248 of the FSH-Receptor (FSHR) mediated pathway. This raises several questions; what is the  
249 quantitative importance of those two pathways (ER $\alpha$  and FSHR) in EE in adipose tissue

250 being? How clinically meaningful could be the increase in EE induced by adipose tissue  
251 being?

252 Progesterone also seems to play a role in the modulation of uncoupling process in adipose tissue  
253 in cellular and rodent studies<sup>62-64</sup>. It have been suggested that P4 receptors are expressed on the  
254 adipose tissue mitochondrial membrane and could play a role in the regulation of energy  
255 demand<sup>64</sup>. P4 increases mitogenesis and UCP1mRNA expression in adipose tissue cell culture  
256 exposed to increased concentration of P4<sup>62,63</sup>.

257 Considering that OC use decreases gonadotrophin and E2 levels it could be assumed that all or  
258 some of the biological mechanisms presented above could be decreased or increased in women  
259 taking OC.

260 Altogether, these results indicate that besides the regulation of the reproductive function,  
261 endogenous ovarian hormones can impact energy homeostasis (i.e., EE and EI) and while  
262 underlying mechanisms have been explored in the brain and peripheral tissues, there are no  
263 straightforward conclusions.

264

### 265 **3-Effects of 17 $\beta$ -estradiol and progesterone on Energy Balance**

266 The clinical effects of E2 and P4 on EE and EI are better known than cellular mechanisms, and  
267 their potential involvement in weight gain and obesity have been recently reviewed<sup>65</sup>  
268 highlighting the need to explore cellular implication of ovarian hormones on energy balance.

#### 269 *3.1 Effects of 17 $\beta$ -estradiol and progesterone on Energy intake*

270 The decrease in E2 production after ovariectomy in rodents is most often followed by an  
271 increase in body fat and EI<sup>66</sup>. In premenopausal state, the effects of E2 and P4 on EI have been  
272 suggested by studies showing a decrease in EI during the follicular phase and an increase during

273 the luteal phase<sup>67,68</sup>. Due to the ovarian hormone fluctuations during the menstrual cycle (i.e.  
274 follicular phase: high level of E2; luteal phase: high levels of both E2 and P4); the assumptions  
275 raised following those studies would assume an anorexigenic effect of estrogen and an  
276 orexigenic effect of P4. The orexigenic effect of P4 has not been clearly demonstrated either in  
277 animal studies<sup>69</sup> or in women subjected to increasing doses of progestin<sup>70</sup>. The effects of E2  
278 and P4 on appetite sensations have also been questioned, but it seems that, as for EI, the  
279 orexigenic or anorexigenic context is associated with the level of E2 rather than P4 itself. Based  
280 on the current literature it seems difficult to state the isolated effect of E2 on EI. Indeed,  
281 although controversial, interactions with leptin, also involved in the central regulation of EI  
282 have been suggested<sup>71-73</sup>. This estrogen/leptin interaction in the regulation of EI was illustrated  
283 by Krishnan et al<sup>74</sup>. These authors showed that in young women with a regular menstrual cycle,  
284 the estrogen/leptin ratio during the luteal phase was positively associated with the consumption  
285 of sweet foods. Although estrogen can modulate EI and appetite sensations, it appears essential  
286 to consider its interaction with other hormones involved in appetite regulation, and its  
287 independent/isolated action still needs to be elucidated.

### 288 *3.2 Effects of 17 $\beta$ -estradiol and progesterone on Energy expenditure*

289 Researches on ovariectomized rodents show that E2 is involved in a decrease in EE<sup>75,76</sup> as well  
290 as in a decrease in spontaneous physical activity<sup>77</sup>. P4 seems to not play a major role in EE  
291 regulation as it has been shown that infusion of this hormone in ovariectomized rodents cannot  
292 prevent increase in body weight or fat mass<sup>78</sup>.

293 Concerning clinical data, similarly to EI, variations in EE have been identified according to the  
294 menstrual cycle phases. However, there appears to be considerable inter- and intra-variability  
295 in resting energy expenditure (REE) during the menstrual cycle<sup>79</sup>, making studies results  
296 inconsistent as to the magnitude and importance of this variation<sup>80,81</sup>. A recent meta-analysis  
297 including 26 studies suggests that the REE would be higher during the luteal phase<sup>82</sup>. The

298 authors highlighted significant risk bias for most of the studies included in the meta-analysis  
299 and therefore underscored that result from this work should be considered cautiously <sup>82</sup>. This  
300 increase in EE in the luteal phase would suggest an effect of P4 on EE, but there are currently  
301 no mechanistic studies to support this hypothesis. Furthermore, if one assumes that progestins  
302 have exactly the same cellular effect as endogenous progesterone, it has been shown that high-  
303 dose progestins did not result in a change in EE <sup>75</sup>. Genetic polymorphism for estrogen and P4  
304 receptors and their association with EE and EI will also need more investigation. Indeed, recent  
305 data shows that a specific genetic variant for *Esr1*, coding for ER $\alpha$ , was strongly associated  
306 with weight gain after progestin implants in healthy reproductive aged women <sup>83</sup>.

307 Several clinical studies have evaluated the effects of sex hormones and specifically E2 on EE  
308 in premenopausal women. The use of a gonadotropin-releasing hormone (GnRH) antagonist<sup>84</sup>  
309 or agonist<sup>85</sup> to abolish sex hormone production induces acute<sup>84</sup> and chronic <sup>85</sup> decrease in REE  
310 and exercise-related EE. When E2 is infused in parallel of the GnRH agonist, levels of EE are  
311 restored <sup>85</sup>. In this last study, TEE as well as sleep EE were decreased after GnRH agonist  
312 treatment without a corrective effect of E2 suggesting that E2 is not the only sex hormone  
313 involved in EE adaptation. More recent work by the same research team showed in women  
314 close to menopause that the suppression of female sex hormones tends to induce a decrease in  
315 TEE and resting REE and leads to fat mass gain <sup>86</sup>. All of these clinical results suggest an  
316 involvement of sex hormones and in particular estrogen in the regulation of EE. Taken together,  
317 the animal studies and clinical results show that the effects of E2 on EI or EE have been much  
318 more studied than those of P4. The involvement of E2 in EI but also in EE has been well  
319 demonstrated in animals with similar results but less marked on the clinical side.

320 The main limitation regarding the animal approach is the transferability of the results to  
321 humans. It is obvious that animal model can provide specific and important data on the cellular  
322 adaptations, tissue function and underlying mechanisms, that are easier to obtain than in



323 humans. Specifically, the exploration of brain adaptation to various levels of steroids is also  
324 easier in animals, allowing in vivo and in vitro data to be obtained. Yet, it is worth noting that  
325 rodents may not be the best model to study energy homeostasis given differences in metabolic  
326 regulations, structure and function of tissues (e.g. brain) between rodents and humans. In  
327 addition, energy expenditure and energy intake depend on intrinsic factors (genetics) and  
328 numerous extrinsic factors (i.e. culture, religion, lifestyle) which do not exist in rodents. The  
329 human physiology presents greater metabolic variability than the one of rodents which are  
330 raised and studied under very controlled conditions. This underscores the importance of clinical  
331 studies to validate the results obtained in animal studies.

332 The body of information concerning E2 clearly shows that this hormone acts in premenopausal  
333 women to increase EE and decrease EI through both central and multiple peripheral tissues and  
334 organ actions. Beside potential effects of E2 and P4 concerning EI and EE some clinical  
335 investigations have tried to highlight effects of OC on EI, EE and body weight status.

#### 336 **4-Oral contraceptive use in women and energy intake**

337 To date, only five studies have been conducted to understand the effect of OC use on EI in  
338 women<sup>70,87-90</sup>. Food consumption was measured either by dietary recall<sup>87</sup>, daily food records  
339<sup>70,90</sup>, food frequency questionnaires<sup>88</sup> or in controlled laboratory conditions (weighed food)<sup>89</sup>.  
340 Four of the studies investigated the total EI and diet composition<sup>70,87,88,90</sup> and one study reported  
341 total EI and intake of sweet and savory snack items and hedonic food ratings<sup>89</sup>. Taken together,  
342 the findings of these few studies suggest that OC use does not affect total EI<sup>70,87-90</sup>. It is worth  
343 noting that Wallace and colleagues<sup>87</sup> observed significantly higher total EI when expressed  
344 relative to body weight (from dietary recall) in OC users compared to non-users. Results are  
345 less obvious regarding macronutrient intake. While some authors did not report any difference  
346 in diet composition<sup>87-90</sup>, Eck and colleagues<sup>70</sup> observed an increased fat and decreased

347 carbohydrate consumption in OC users compared to non-users using 5-day food records. The  
348 authors noted that it may predispose women using OC to fat mass gain.

349

350 It is relevant to highlight some shortcomings of the prior research that can limit the  
351 interpretation. Across these five studies, there are methodological discrepancies in terms of the  
352 population characteristics, OC formulation and EI measurement that are likely to partly explain  
353 the discrepancies observed. Most of the prior studies have involved young women of  
354 reproductive age (i.e., from 18 to 40 years) whereas Wallace et al.<sup>87</sup> included a large sample of  
355 women over 40 years. Procter-Gray et al.<sup>88</sup> focused on female runners and Ihalainen et al. on  
356 recreational athletes which represent a specific population<sup>90</sup>. Furthermore, some of the studies  
357 were performed prior to the year 2000<sup>70,87</sup> and with the continued reformulation to OC agents  
358 since then, a simple extrapolation of the findings to the OC commonly used today is  
359 problematic.

360

361 To better understand the relationship between female reproductive hormone status and EI,  
362 Arnoni-Bauer and colleagues<sup>91</sup> investigated the response of brain regions (i.e. homeostatic,  
363 emotional and attentional) to food cues. They observed that, in women using monophasic OC,  
364 brain activation patterns in response to food cues were similar to those of the women in the  
365 luteal phase but different from women in the follicular phase. Using functional magnetic  
366 resonance imaging this study suggests that a hedonic regulation is impacted by hormonal status.

367

368 Hormonal contraceptive use in women with overweight or obesity may affect EI during weight  
369 loss<sup>38</sup>. Using a self-reported assessment of EI, the change in total EI and macronutrient intake  
370 were similar in hormonal contraceptive users and non-users between 0 and 6 months (i.e.,  
371 weight loss phase). However, between 6 and 18 months (i.e., weight loss maintenance phase),

372 hormonal contraceptive users displayed an increase in EI which was characterized by a decrease  
373 in protein intake compared to non-users. Changes to fat and carbohydrate intake were similar  
374 between groups. These EI patterns from 6 to 18 months were consistent with the time course of  
375 weight regain in hormonal contraceptive users. It is worth noting that moderate to vigorous  
376 physical activity level was not different between hormonal contraceptive users and non-users  
377 and that weight changes were likely associated with changes in EI. Thus, hormonal  
378 contraceptive use may have a meaningful effect on weight-loss maintenance *via* EI. While  
379 further studies are needed, it may be questioned whether the effect of OC on EI is energy  
380 balance dependent supporting the need to promote individualized approach in contraception  
381 counselling in regard to weight management goals.

## 382 **5-Oral contraceptive use in women and energy expenditure**

### 383 *5.1 Resting state*

384 To our knowledge, only seven studies (Table 1) have investigated the effect of OC on EE at  
385 rest including BMR or REE. Of note, except the study of McNeil and colleagues <sup>92</sup>, all were  
386 cross-sectional or observational study designs and to our knowledge to date, there are no  
387 randomized controlled trials. Taken together the effect of OC use on BMR/REE is inconsistent.  
388 Compared with naturally menstruating women not using OC, five studies (71%) showed no  
389 difference in BMR/REE in women taking OC <sup>70,93-96</sup>, one study showed an increase <sup>97</sup> another  
390 a decrease <sup>92</sup>.

391 Since OC use may have an effect on body composition, and body composition is the primary  
392 determinant of BMR/REE, it is important to examine the effect of OC use independently of  
393 body composition. This is elegantly demonstrated by Kimm and colleagues <sup>97</sup>. REE was not  
394 different between OC users and women with normal menstrual cycles when expressed in  
395 absolute terms yet, after REE was adjusted for race, fat mass and fat-free mass, it was slightly  
396 higher in women using OC. McNeil and colleagues <sup>92</sup> conducted the only study that measured

397 EE in a cohort of women before and after OC use. While they observed a decrease in BMR,  
398 only five women were included in their study and the OC used is unfortunately not  
399 representative of the lower-dose prescriptions commonly used today. In a 12-month study of  
400 OC treatment for perimenopausal women, Napolitano and colleagues<sup>94</sup> found that desogestrel,  
401 a synthetic progestin, had a non-significant increase on REE. It is also important to note all of  
402 the prior studies with the exception of one (McNeill and colleagues), were observational studies  
403 which included women taking various OC prescriptions<sup>94 70,93,96</sup>. Due to the heterogeneity of  
404 the few available studies (i.e., study population, study design, OC formulation and dose) and  
405 the lack of randomized controlled trials current research does not provide conclusive evidence  
406 for an effect of OC use on resting energy expenditure.

#### 407 *5.2 Thermic effect of food (or diet induced thermogenesis)*

408 To our knowledge, only two studies have investigated the effects of OC use on EE in response  
409 to a meal or the TEF<sup>95,98</sup> (Table 2). These cross-sectional studies from the same group of  
410 researchers compared the changes in EE following a high protein meal between women taking  
411 OC and women with normal menstrual cycles during both the follicular and luteal phases<sup>95</sup> or  
412 during the follicular phase only<sup>98</sup>. These studies reported that compared to women with normal  
413 menstrual cycles in the follicular and luteal phases, postprandial EE was decreased in women  
414 taking OC<sup>98</sup>. This observation should be interpreted with caution as these studies were limited  
415 to a small sample size (i.e., n=7 or 8 in each group). Cross-sectional studies provide preliminary  
416 evidence that OC use may effect diet-induced thermogenesis and future studies utilizing a  
417 randomized, controlled study design are needed to address this question.

#### 418 *5.3 Activity energy expenditure*

419 Volitional physical activity or exercise is one of the most effective ways to increase EE. Most  
420 of the studies of OC use and exercise have focused on exercise performance or substrate  
421 metabolism. Surprisingly, less is known regarding OC use and exercise EE. A recent systematic

422 and meta-analysis <sup>99</sup> reported a slightly decreased ‘exercise performance’ in women using OC  
423 compared to women not using OC, suggesting a potential lower aerobic capacity in women  
424 using OC. Some studies have reported lower maximal oxygen consumption and/or oxygen  
425 consumption at the anaerobic threshold in women using OC compared with women with normal  
426 menstrual cycles tested in the follicular and/or luteal phase <sup>100,101</sup>. While these studies imply  
427 potential effects of OC on aerobic fitness and energetic efficiency, other studies did not observe  
428 an effect of OC use on similar outcomes of aerobic fitness <sup>102-106</sup>. Methodological differences  
429 between studies (e.g., protocol design, OC formulation) can explain these discrepancies. Also,  
430 these studies have only included women who are young, healthy and with normal weight body  
431 mass index. Whether these findings are extrapolated to women with obesity and metabolic  
432 disruptions is not known.

433

434 As summarized in Table 3, there are four studies which reported the effect of OC use on EE  
435 during exercise <sup>101,103,107,108</sup>. In all published studies, exercise EE was not significantly different  
436 between women using OC and women with normal menstrual cycles tested in the follicular  
437 and/or luteal phases. It is relevant to note that in all the presented studies, EE was not the  
438 primary outcome and protocol designs were thus not conducted to specifically answer this  
439 question.

440 Overall, it may be hypothesized that while some differences in REE or postprandial EE may  
441 exist between women taking or not OC, the greater stimulus generated by exercise might  
442 override the modest effect of OC on EE. There is a lack of data and evidence regarding the  
443 effect of OC use on EE at rest and during metabolic challenge that need to be addressed to better  
444 understand the weight regulation of women.

445

446 **6-Oral contraceptive use in women and weight regulation**

447 Weight gain is one of the most reported and the most frequently cited reasons for OC  
448 discontinuation <sup>4,109</sup> yet there is no clear evidence of such a relationship. Indeed, in a  
449 comprehensive review, Gallo et al. <sup>6</sup> did not find evidence to support a significant effect of OC  
450 use (combined type) on weight change. Moreover, both observational studies <sup>4,110-116</sup> and  
451 rigorously conducted placebo-controlled trials <sup>117,118</sup> do not observe a significant change in  
452 weight with combined OC use. One exception is the study of Berenson and colleagues <sup>119</sup> which  
453 observed that 36 months of depot medroxyprogesterone acetate use significantly increased  
454 weight compared to women using a combined OC (20 µg ethinyl estradiol and 0.15 mg  
455 desogestrel) or non-hormonal forms of contraception (+5.12 vs +1.47 vs +2.05 kg).  
456 Contraceptive pills with only progestin are proposed to women that cannot or should not take  
457 estrogen for medical reasons. In their review, Lopez and colleagues <sup>120</sup> reported that there is no  
458 strong evidence of changes in weight and body composition with this OC type.

459

460 Interestingly, in 2020, Caldwell et al. <sup>38</sup> questioned for the first time the influence of combined  
461 hormonal contraceptive use on weight loss success in women with overweight or obesity. In a  
462 sample of 110 women enrolled in a behavioral weight-loss program they showed that combined  
463 hormonal contraceptive use (i.e., combined OC (n=15) and vaginal rings (n=3)) influenced  
464 weight loss. Weight was reduced from baseline to 6-month (i.e., weight-loss phase) in both  
465 contraceptive users and non-users however contraceptive users regained weight between  
466 months 6 and 18 (i.e., weight-loss maintenance phase) whereas non-users remained weight  
467 stable.

468 Contrary to common belief, there is no strong evidence showing a significant effect of OC use  
469 and weight gain. Yet, the new work of Caldwell and al. <sup>38</sup> highlight the potential importance of  
470 exogenous hormone therapies in the context of weight control strategies for women with

471 overweight and obesity. In this context, it appears essential to better understand the influence  
472 of OC use on both components of energy balance, namely the “Big two” (i.e., EI and EE).

### 473 **7-Conclusions**

474 The necessity of utilization and development of contraceptive strategies for birth regulation is  
475 undeniable and contraceptive pills appear as a quite easy approach for women. Moreover, OC  
476 represent also a strategy for premenstrual symptoms, acne or bulimia nervosa management. In  
477 a context where half of American and European individuals have overweight or obesity, the  
478 need to develop weight regulation management is a public health emergency. To date no study  
479 have clearly shown that OC use or women under prolonged OC use are more prone to weight  
480 gain<sup>6</sup>. However recently, it has been shown that weight loss maintenance was reduced in women  
481 taking hormonal contraceptives which were mainly OC prescriptions<sup>38</sup>. Understanding how OC  
482 can affect energy balance and mechanisms involved in EI and EE is of major importance to  
483 better individualize weight regulation management. As highlighted in the present review, more  
484 data on the effect of OC use (both short and long term) on EI and EE in women are required  
485 using rigorously conducted randomized controlled trials. The objective to keep in mind for  
486 future studies should be to better individualize prescription of weight loss program to ensure its  
487 effectiveness.

### 488 **8-Future perspectives**

489 To date, no study has investigated the independent and combined (i.e. antagonist, potentiater)  
490 effect of ethinyl estradiol and progestin on the underlying mechanisms mediating EE and EI.  
491 Importantly, due to their differences (i.e. nature, dose, bioactivity and potency), further animal  
492 and in vitro studies are thus needed to determine whether synthetic hormones contained in OC  
493 mimic or not the cellular actions and adaptations of natural ovarian hormones regarding EE and  
494 EI.

495 Few observational and clinical studies are currently available regarding the effect of OC use on  
496 EI and EE and the lack of randomized controlled trials prevents conclusive evidence for an  
497 effect of OC use on EI and EE. Due to the high proportion of women of childbearing age using  
498 OC, it appears essential to decipher the role of OC on both components of energy balance in  
499 function of the characteristic of the populations (e.g. age, weight status) and nature of OC (e.g.  
500 monophasic, triphasic, combined OC, progestin-only pill). This information would result on a  
501 better contraception counselling and, overall, management of women's health.

502 Finally, the results of Caldwell et al.'s study bring new insight into weight loss management in  
503 women with overweight or obesity. Additional studies are also needed to question the role of  
504 OC in weight loss success and metabolic adaptations during a multidisciplinary weight loss  
505 program. Exercise is a key factor of weight loss success due to its action on both EE and EI.  
506 Future research should investigate which exercise modalities (e.g. nature, duration, intensity,  
507 frequency) would be more efficient to favour weight loss and weight maintenance in function  
508 of women's specificities. A physiological approach using in vivo assessment is also needed to  
509 understand which tissues and systems are implicated in the modification of whole-body changes  
510 in EI and EE.

## 511 **Tables and Figure Legends**

512 **Figure 1:** Schematic representation of mechanisms of E2 and P4 and potential mechanisms of  
513 OC action on energy intake. Cellular data strongly suggest that E2 mainly exerts its effects on  
514 brain through its receptor ER $\alpha$ . E2 seems to induce its anorexigenic action by increasing GLP-  
515 1<sup>25</sup> and decreasing Ghrelin<sup>24</sup> brain signaling. Dotted square: potential cellular mechanisms  
516 from rodent studies by which E2 and P4 can exert orexigenic and anorexigenic effects <sup>26,29,30</sup>.  
517 Oral contraceptives action on orexigenic and anorexigenic peptides are still unknown.  
518 However, OC use has been shown to decrease CCK level <sup>39</sup>. E2: 17 $\beta$ - estradiol; P4:  
519 Progesterone, OC: Oral contraceptives; FSH: follicle-stimulation hormone; LH: Luteinizing



520 hormone; CCK: cholecystokinin, ER $\alpha$ : estrogen receptor alpha; ; GLP-1: glucagon-like peptide  
521 1; PR: Progesterone receptor POMC: Proopiomelanocortin; CART: cocaine amphetamine  
522 regulator transcription, Foxo1: Forkhead box protein O1, NPY: neuropeptide Y; Agrp: agouti  
523 related peptide; AMPK: AMP activated protein kinase; mTOR: mammalian target of  
524 rapamycin; VMH: ventro medial hypothalamus; ARC: arcuate nucleus of hypothalamus; 3V:  
525 third ventricle. Green line: stimulation; red line: inhibition; dotted gray line: potential  
526 mechanisms for OC.

527 **Figure 2:** Schematic representation of mechanisms of E2 and P4 and potential mechanisms of  
528 OC action on energy expenditure. Most data are based on animal studies which suggest that  
529 E2 increase EE by action on brain (dotted square)<sup>28,58</sup>, adipose tissue<sup>55,59</sup>, skeletal muscle<sup>43</sup>  
530 and liver. Few clinical studies have suggested that OC use can promote oxidative stress in  
531 liver<sup>51,52</sup> and skeletal muscle<sup>45-47</sup>. E2: 17 $\beta$ -estradiol; P4: Progesterone, OC: Oral contraceptives;  
532 FSH: follicle-stimulation hormone; LH: Luteinizing hormone; UCP1: uncoupling protein 1;  
533 FGF 21 Fibroblast growth Factor 21; ROS reactive oxygen species, ER $\alpha$ : estrogen receptor  
534 alpha, AMPK: AMP activated protein kinase; ER: endoplasmic reticulum, VMH: ventro medial  
535 hypothalamus; ARC: arcuate nucleus of hypothalamus; 3V: third ventricle, SNS: sympathetic  
536 nervous system Green line: stimulation; red line: inhibition; dotted gray line: potential  
537 mechanisms for OC.

538 **Table 1:** Studies investigating the effect of OC on energy expenditure at rest

539 **Table 2:** Studies investigating the effect of OC on energy expenditure during metabolic  
540 challenge

541 **Table 3:** Studies investigating the effect of OC on energy expenditure during acute exercise

542

544 **8-References**

- 545 1. Ford ES, Mokdad AH, Ajani UA. Trends in risk factors for cardiovascular disease among  
546 children and adolescents in the United States. *Pediatrics*. Dec 2004;114(6):1534-44.  
547 doi:10.1542/peds.2004-0674
- 548 2. Kautzky-Willer A, Harreiter J, Pacini G. Sex and Gender Differences in Risk, Pathophysiology  
549 and Complications of Type 2 Diabetes Mellitus. *Endocr Rev*. 06 2016;37(3):278-316.  
550 doi:10.1210/er.2015-1137
- 551 3. Williams RL, Wood LG, Collins CE, Callister R. Effectiveness of weight loss interventions--is  
552 there a difference between men and women: a systematic review. *Obes Rev*. Feb 2015;16(2):171-86.  
553 doi:10.1111/obr.12241
- 554 4. de Melo NR, Aldrighi JM, Faggion D, et al. A prospective open-label study to evaluate the  
555 effects of the oral contraceptive Harmonet (gestodene75/EE20) on body fat. *Contraception*. Jul  
556 2004;70(1):65-71. doi:10.1016/j.contraception.2003.10.016
- 557 5. Hall KS, Trussell J. Types of combined oral contraceptives used by US women. *Contraception*.  
558 Dec 2012;86(6):659-65. doi:10.1016/j.contraception.2012.05.017
- 559 6. Gallo MF, Lopez LM, Grimes DA, Carayon F, Schulz KF, Helmerhorst FM. Combination  
560 contraceptives: effects on weight. *Cochrane Database Syst Rev*. Jan 2014;(1):CD003987.  
561 doi:10.1002/14651858.CD003987.pub5
- 562 7. Lopez LM, Edelman A, Chen-Mok M, Trussell J, Helmerhorst FM. Progestin-only  
563 contraceptives: effects on weight. *Cochrane Database Syst Rev*. Apr 2011;(4):CD008815.  
564 doi:10.1002/14651858.CD008815.pub2
- 565 8. Ravussin E, Bogardus C. Energy balance and weight regulation: genetics versus environment.  
566 *Br J Nutr*. Mar 2000;83 Suppl 1:S17-20. doi:10.1017/s0007114500000908
- 567 9. Hall KD, Heymsfield SB, Kemnitz JW, Klein S, Schoeller DA, Speakman JR. Energy balance and  
568 its components: implications for body weight regulation. *Am J Clin Nutr*. Apr 2012;95(4):989-94.  
569 doi:10.3945/ajcn.112.036350
- 570 10. Miles-Chan JL, Dulloo AG. Posture Allocation Revisited: Breaking the Sedentary Threshold of  
571 Energy Expenditure for Obesity Management. *Front Physiol*. 2017;8:420.  
572 doi:10.3389/fphys.2017.00420
- 573 11. Blundell JE, Gibbons C, Caudwell P, Finlayson G, Hopkins M. Appetite control and energy  
574 balance: impact of exercise. *Obes Rev*. Feb 2015;16 Suppl 1:67-76. doi:10.1111/obr.12257
- 575 12. Beaulieu K, Oustric P, Finlayson G. The Impact of Physical Activity on Food Reward: Review  
576 and Conceptual Synthesis of Evidence from Observational, Acute, and Chronic Exercise Training  
577 Studies. *Curr Obes Rep*. Jun 2020;9(2):63-80. doi:10.1007/s13679-020-00372-3
- 578 13. Blundell JE, Caudwell P, Gibbons C, et al. Body composition and appetite: fat-free mass (but  
579 not fat mass or BMI) is positively associated with self-determined meal size and daily energy intake in  
580 humans. *Br J Nutr*. Feb 2012;107(3):445-9. doi:10.1017/S0007114511003138
- 581 14. Casanova N, Beaulieu K, Finlayson G, Hopkins M. Metabolic adaptations during negative  
582 energy balance and their potential impact on appetite and food intake. *Proc Nutr Soc*. 08  
583 2019;78(3):279-289. doi:10.1017/S0029665118002811
- 584 15. Institute EP. World Modern Contraceptive Prevalence by Methods, Latest Year (Data from  
585 U.N Population Division). 2017.
- 586 16. United Nations, affairs Doeas. World Contraceptive Patterns. United Nations 20132013.
- 587 17. Vazquez MJ, Velasco I, Tena-Sempere M. Novel mechanisms for the metabolic control of  
588 puberty: implications for pubertal alterations in early-onset obesity and malnutrition. *J Endocrinol*. 08  
589 2019;242(2):R51-R65. doi:10.1530/JOE-19-0223

- 590 18. Broberger C. Brain regulation of food intake and appetite: molecules and networks. *J Intern*  
591 *Med.* Oct 2005;258(4):301-27. doi:10.1111/j.1365-2796.2005.01553.x
- 592 19. López M, Tena-Sempere M. Estrogens and the control of energy homeostasis: a brain  
593 perspective. *Trends Endocrinol Metab.* Aug 2015;26(8):411-21. doi:10.1016/j.tem.2015.06.003
- 594 20. Frank A, Brown LM, Clegg DJ. The role of hypothalamic estrogen receptors in metabolic  
595 regulation. *Front Neuroendocrinol.* Oct 2014;35(4):550-7. doi:10.1016/j.yfrne.2014.05.002
- 596 21. Brown LM, Clegg DJ. Central effects of estradiol in the regulation of food intake, body weight,  
597 and adiposity. *J Steroid Biochem Mol Biol.* Oct 2010;122(1-3):65-73. doi:10.1016/j.jsbmb.2009.12.005
- 598 22. Asarian L, Geary N. Modulation of appetite by gonadal steroid hormones. *Philos Trans R Soc*  
599 *Lond B Biol Sci.* Jul 29 2006;361(1471):1251-63. doi:10.1098/rstb.2006.1860
- 600 23. Clegg DJ, Brown LM, Woods SC, Benoit SC. Gonadal hormones determine sensitivity to  
601 central leptin and insulin. *Diabetes.* Apr 2006;55(4):978-87. doi:10.2337/diabetes.55.04.06.db05-  
602 1339
- 603 24. Clegg DJ, Brown LM, Zigman JM, et al. Estradiol-dependent decrease in the orexigenic  
604 potency of ghrelin in female rats. *Diabetes.* Apr 2007;56(4):1051-8. doi:10.2337/db06-0015
- 605 25. Maske CB, Jackson CM, Terrill SJ, Eckel LA, Williams DL. Estradiol modulates the anorexic  
606 response to central glucagon-like peptide 1. *Horm Behav.* 07 2017;93:109-117.  
607 doi:10.1016/j.yhbeh.2017.05.012
- 608 26. de Souza FS, Nasif S, López-Leal R, Levi DH, Low MJ, Rubinsten M. The estrogen receptor  $\alpha$   
609 colocalizes with proopiomelanocortin in hypothalamic neurons and binds to a conserved motif  
610 present in the neuron-specific enhancer nPE2. *Eur J Pharmacol.* Jun 11 2011;660(1):181-7.  
611 doi:10.1016/j.ejphar.2010.10.114
- 612 27. Tsai YC, Lee YM, Lam KK, Wu YC, Yen MH, Cheng PY. The role of hypothalamic AMP-activated  
613 protein kinase in ovariectomy-induced obesity in rats. *Menopause.* 2010 Nov-Dec 2010;17(6):1194-  
614 200. doi:10.1097/gme.0b013e3181dfca27
- 615 28. Martínez de Morentin PB, González-García I, Martins L, et al. Estradiol regulates brown  
616 adipose tissue thermogenesis via hypothalamic AMPK. *Cell Metab.* Jul 01 2014;20(1):41-53.  
617 doi:10.1016/j.cmet.2014.03.031
- 618 29. Cota D, Proulx K, Smith KA, et al. Hypothalamic mTOR signaling regulates food intake.  
619 *Science.* May 12 2006;312(5775):927-30. doi:10.1126/science.1124147
- 620 30. González-García I, Martínez de Morentin PB, Estévez-Salguero Á, et al. mTOR signaling in the  
621 arcuate nucleus of the hypothalamus mediates the anorectic action of estradiol. *J Endocrinol.* 09  
622 2018;238(3):177-186. doi:10.1530/JOE-18-0190
- 623 31. Ibrahim BA, Briski KP. Deferred feeding and body weight responses to short-term  
624 interruption of fuel acquisition: impact of estradiol. *Horm Metab Res.* Jul 2015;47(8):611-21.  
625 doi:10.1055/s-0034-1387792
- 626 32. Ibrahim BA, Alenazi FSH, Briski KP. Energy status determines hindbrain signal transduction  
627 pathway transcriptional reactivity to AMPK in the estradiol-treated ovariectomized female rat.  
628 *Neuroscience.* Jan 22 2015;284:888-899. doi:10.1016/j.neuroscience.2014.10.068
- 629 33. Brinton RD, Thompson RF, Foy MR, et al. Progesterone receptors: form and function in brain.  
630 *Front Neuroendocrinol.* May 2008;29(2):313-39. doi:10.1016/j.yfrne.2008.02.001
- 631 34. Acharya KD, Nettles SA, Sellers KJ, et al. The Progesterone Receptor Interactome in the Female  
632 Mouse Hypothalamus: Interactions with Synaptic Proteins Are Isoform Specific and Ligand  
633 Dependent. *eNeuro.* 2017 Sep-Oct 2017;4(5)doi:10.1523/ENEURO.0272-17.2017
- 634 35. Kitamura T, Feng Y, Kitamura YI, et al. Forkhead protein FoxO1 mediates Agrp-dependent  
635 effects of leptin on food intake. *Nat Med.* May 2006;12(5):534-40. doi:10.1038/nm1392
- 636 36. Stelmańska E, Sucajtys-Szulc E. Enhanced food intake by progesterone-treated female rats is  
637 related to changes in neuropeptide genes expression in hypothalamus. *Endokrynol Pol.*  
638 2014;65(1):46-56. doi:10.5603/EP.2014.0007
- 639 37. Gray JM, Wade GN. Food intake, body weight, and adiposity in female rats: actions and  
640 interactions of progestins and antiestrogens. *Am J Physiol.* May 1981;240(5):E474-81.  
641 doi:10.1152/ajpendo.1981.240.5.E474

- 642 38. Caldwell AE, Zaman A, Ostendorf DM, et al. Impact of Combined Hormonal Contraceptive Use  
643 on Weight Loss: A Secondary Analysis of a Behavioral Weight-Loss Trial. *Obesity (Silver Spring)*. 06  
644 2020;28(6):1040-1049. doi:10.1002/oby.22787
- 645 39. Karlsson R, Lindén A, von Schoultz B. Suppression of 24-hour cholecystokinin secretion by  
646 oral contraceptives. *Am J Obstet Gynecol*. Jul 1992;167(1):58-9. doi:10.1016/s0002-9378(11)91626-3
- 647 40. Hirschberg AL, Byström B, Carlström K, von Schoultz B. Reduced serum cholecystokinin and  
648 increase in body fat during oral contraception. *Contraception*. Feb 1996;53(2):109-13.  
649 doi:10.1016/0010-7824(95)00265-0
- 650 41. Bal NC, Maurya SK, Sopariwala DH, et al. Sarcolipin is a newly identified regulator of muscle-  
651 based thermogenesis in mammals. *Nat Med*. Oct 2012;18(10):1575-9. doi:10.1038/nm.2897
- 652 42. Torres MJ, Kew KA, Ryan TE, et al. 17 $\beta$ -Estradiol Directly Lowers Mitochondrial Membrane  
653 Microviscosity and Improves Bioenergetic Function in Skeletal Muscle. *Cell Metab*. 01  
654 2018;27(1):167-179.e7. doi:10.1016/j.cmet.2017.10.003
- 655 43. Ribas V, Drew BG, Zhou Z, et al. Skeletal muscle action of estrogen receptor  $\alpha$  is critical for  
656 the maintenance of mitochondrial function and metabolic homeostasis in females. *Sci Transl Med*.  
657 Apr 2016;8(334):334ra54. doi:10.1126/scitranslmed.aad3815
- 658 44. Boudina S, Sena S, Sloan C, et al. Early mitochondrial adaptations in skeletal muscle to diet-  
659 induced obesity are strain dependent and determine oxidative stress and energy expenditure but not  
660 insulin sensitivity. *Endocrinology*. Jun 2012;153(6):2677-88. doi:10.1210/en.2011-2147
- 661 45. Kane DA, Lin CT, Anderson EJ, et al. Progesterone increases skeletal muscle mitochondrial  
662 H<sub>2</sub>O<sub>2</sub> emission in nonmenopausal women. *Am J Physiol Endocrinol Metab*. Mar 2011;300(3):E528-35.  
663 doi:10.1152/ajpendo.00389.2010
- 664 46. Cauci S, Buligan C, Marangone M, Francescato MP. Oxidative Stress in Female Athletes Using  
665 Combined Oral Contraceptives. *Sports Med Open*. Dec 2016;2(1):40. doi:10.1186/s40798-016-0064-x
- 666 47. Chen JT, Kotani K. Different Effects of Oral Contraceptive and Dydrogesterone Treatment on  
667 Oxidative Stress Levels in Premenopausal Women. *J Clin Med Res*. Feb 2018;10(2):146-153.  
668 doi:10.14740/jocmr3307w
- 669 48. Zhu L, Brown WC, Cai Q, et al. Estrogen treatment after ovariectomy protects against fatty  
670 liver and may improve pathway-selective insulin resistance. *Diabetes*. Feb 2013;62(2):424-34.  
671 doi:10.2337/db11-1718
- 672 49. Meda C, Barone M, Mitro N, et al. Hepatic ER $\alpha$  accounts for sex differences in the ability to  
673 cope with an excess of dietary lipids. *Mol Metab*. 02 2020;32:97-108.  
674 doi:10.1016/j.molmet.2019.12.009
- 675 50. Allard C, Bonnet F, Xu B, et al. Activation of hepatic estrogen receptor- $\alpha$  increases energy  
676 expenditure by stimulating the production of fibroblast growth factor 21 in female mice. *Mol Metab*.  
677 04 2019;22:62-70. doi:10.1016/j.molmet.2019.02.002
- 678 51. Chen J, Li Y, Lavigne JA, Trush MA, Yager JD. Increased mitochondrial superoxide production  
679 in rat liver mitochondria, rat hepatocytes, and HepG2 cells following ethinyl estradiol treatment.  
680 *Toxicol Sci*. Oct 1999;51(2):224-35. doi:10.1093/toxsci/51.2.224
- 681 52. Wan L, O'Brien P. Molecular mechanism of 17 $\alpha$ -ethinylestradiol cytotoxicity in isolated rat  
682 hepatocytes. *Can J Physiol Pharmacol*. Jan 2014;92(1):21-6. doi:10.1139/cjpp-2013-0267
- 683 53. Xu Y, López M. Central regulation of energy metabolism by estrogens. *Mol Metab*. 09  
684 2018;15:104-115. doi:10.1016/j.molmet.2018.05.012
- 685 54. Gavin KM, Sullivan TM, Kohrt WM, Majka SM, Klemm DJ. Ovarian Hormones Regulate the  
686 Production of Adipocytes From Bone Marrow-Derived Cells. *Front Endocrinol (Lausanne)*. 2018;9:276.  
687 doi:10.3389/fendo.2018.00276
- 688 55. Santos RS, Frank AP, Fátima LA, Palmer BF, Öz OK, Clegg DJ. Activation of estrogen receptor  
689 alpha induces beiging of adipocytes. *Mol Metab*. 12 2018;18:51-59.  
690 doi:10.1016/j.molmet.2018.09.002
- 691 56. Musatov S, Chen W, Pfaff DW, et al. Silencing of estrogen receptor alpha in the ventromedial  
692 nucleus of hypothalamus leads to metabolic syndrome. *Proc Natl Acad Sci U S A*. Feb  
693 2007;104(7):2501-6. doi:10.1073/pnas.0610787104

694 57. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance.  
695 *Physiol Rev.* Jan 2004;84(1):277-359. doi:10.1152/physrev.00015.2003

696 58. González-García I, Contreras C, Estévez-Salguero Á, et al. Estradiol Regulates Energy Balance  
697 by Ameliorating Hypothalamic Ceramide-Induced ER Stress. *Cell Rep.* 10 09 2018;25(2):413-423.e5.  
698 doi:10.1016/j.celrep.2018.09.038

699 59. Liu P, Ji Y, Yuen T, et al. Blocking FSH induces thermogenic adipose tissue and reduces body  
700 fat. *Nature.* 06 2017;546(7656):107-112. doi:10.1038/nature22342

701 60. Refn H, Kjaer A, Lebech AM, Borggaard B, Schierup L, Bremmelgaard A. Metabolic changes  
702 during treatment with two different progestogens. *Am J Obstet Gynecol.* Jul 1990;163(1 Pt 2):374-7.  
703 doi:10.1016/0002-9378(90)90585-u

704 61. Winkler UH, Sudik R. The effects of two monophasic oral contraceptives containing 30 mcg of  
705 ethinyl estradiol and either 2 mg of chlormadinone acetate or 0.15 mg of desogestrel on lipid,  
706 hormone and metabolic parameters. *Contraception.* Jan 2009;79(1):15-23.  
707 doi:10.1016/j.contraception.2008.08.011

708 62. Rodriguez AM, Monjo M, Roca P, Palou A. Opposite actions of testosterone and progesterone  
709 on UCP1 mRNA expression in cultured brown adipocytes. *Cell Mol Life Sci.* Oct 2002;59(10):1714-23.  
710 doi:10.1007/pl00012499

711 63. Rodríguez-Cuenca S, Monjo M, Gianotti M, Proenza AM, Roca P. Expression of mitochondrial  
712 biogenesis-signaling factors in brown adipocytes is influenced specifically by 17beta-estradiol,  
713 testosterone, and progesterone. *Am J Physiol Endocrinol Metab.* Jan 2007;292(1):E340-6.  
714 doi:10.1152/ajpendo.00175.2006

715 64. McIlvrde S, Mushtaq A, Papacleovoulou G, et al. A progesterone-brown fat axis is involved in  
716 regulating fetal growth. *Sci Rep.* 09 2017;7(1):10671. doi:10.1038/s41598-017-10979-7

717 65. Leeners B, Geary N, Tobler PN, Asarian L. Ovarian hormones and obesity. *Hum Reprod*  
718 *Update.* 05 01 2017;23(3):300-321. doi:10.1093/humupd/dmw045

719 66. Witte MM, Resuehr D, Chandler AR, Mehle AK, Overton JM. Female mice and rats exhibit  
720 species-specific metabolic and behavioral responses to ovariectomy. *Gen Comp Endocrinol.* May 01  
721 2010;166(3):520-8. doi:10.1016/j.ygcn.2010.01.006

722 67. Davidsen L, Vistisen B, Astrup A. Impact of the menstrual cycle on determinants of energy  
723 balance: a putative role in weight loss attempts. *Int J Obes (Lond).* Dec 2007;31(12):1777-85.  
724 doi:10.1038/sj.ijo.0803699

725 68. Dye L, Blundell JE. Menstrual cycle and appetite control: implications for weight regulation.  
726 *Hum Reprod.* Jun 1997;12(6):1142-51. doi:10.1093/humrep/12.6.1142

727 69. Czaja JA. Ovarian influences on primate food intake: assessment of progesterone actions.  
728 *Physiol Behav.* Dec 1978;21(6):923-8. doi:10.1016/0031-9384(78)90167-1

729 70. Eck LH, Bennett AG, Egan BM, et al. Differences in macronutrient selections in users and  
730 nonusers of an oral contraceptive. *Am J Clin Nutr.* Feb 1997;65(2):419-24. doi:10.1093/ajcn/65.2.419

731 71. Clegg DJ, Riedy CA, Smith KA, Benoit SC, Woods SC. Differential sensitivity to central leptin  
732 and insulin in male and female rats. *Diabetes.* Mar 2003;52(3):682-7. doi:10.2337/diabetes.52.3.682

733 72. Huang KP, Ronveaux CC, de Lartigue G, Geary N, Asarian L, Raybould HE. Deletion of leptin  
734 receptors in vagal afferent neurons disrupts estrogen signaling, body weight, food intake and  
735 hormonal controls of feeding in female mice. *Am J Physiol Endocrinol Metab.* 04 01  
736 2019;316(4):E568-E577. doi:10.1152/ajpendo.00296.2018

737 73. Budak E, Fernández Sánchez M, Bellver J, Cerveró A, Simón C, Pellicer A. Interactions of the  
738 hormones leptin, ghrelin, adiponectin, resistin, and PYY3-36 with the reproductive system. *Fertil*  
739 *Steril.* Jun 2006;85(6):1563-81. doi:10.1016/j.fertnstert.2005.09.065

740 74. Krishnan S, Tryon RR, Horn WF, Welch L, Keim NL. Estradiol, SHBG and leptin interplay with  
741 food craving and intake across the menstrual cycle. *Physiol Behav.* 10 15 2016;165:304-12.  
742 doi:10.1016/j.physbeh.2016.08.010

743 75. Rogers NH, Perfield JW, Strissel KJ, Obin MS, Greenberg AS. Reduced energy expenditure and  
744 increased inflammation are early events in the development of ovariectomy-induced obesity.  
745 *Endocrinology.* May 2009;150(5):2161-8. doi:10.1210/en.2008-1405

746 76. Xu Y, Nedungadi TP, Zhu L, et al. Distinct hypothalamic neurons mediate estrogenic effects on  
747 energy homeostasis and reproduction. *Cell Metab.* Oct 05 2011;14(4):453-65.  
748 doi:10.1016/j.cmet.2011.08.009

749 77. Gorzek JF, Hendrickson KC, Forstner JP, Rixen JL, Moran AL, Lowe DA. Estradiol and tamoxifen  
750 reverse ovariectomy-induced physical inactivity in mice. *Med Sci Sports Exerc.* Feb 2007;39(2):248-56.  
751 doi:10.1249/01.mss.0000241649.15006.b8

752 78. Richard D. Effects of ovarian hormones on energy balance and brown adipose tissue  
753 thermogenesis. *Am J Physiol.* Feb 1986;250(2 Pt 2):R245-9. doi:10.1152/ajpregu.1986.250.2.R245

754 79. Henry CJ, Lightowler HJ, Marchini J. Intra-individual variation in resting metabolic rate during  
755 the menstrual cycle. *Br J Nutr.* Jun 2003;89(6):811-7. doi:10.1079/BJN2003839

756 80. Bisdee JT, James WP, Shaw MA. Changes in energy expenditure during the menstrual cycle.  
757 *Br J Nutr.* Mar 1989;61(2):187-99. doi:10.1079/bjn19890108

758 81. Howe J, Rumpler W, Seale J. Energy expenditure by indirect calorimetry in premenopausal  
759 women: variation within one menstrual cycle. *J Nutr Biochem;* 1993. p. 268-273.

760 82. Benton MJ, Hutchins AM, Dawes JJ. Effect of menstrual cycle on resting metabolism: A  
761 systematic review and meta-analysis. *PLoS One.* 2020;15(7):e0236025.  
762 doi:10.1371/journal.pone.0236025

763 83. Lazowitz A, Dindinger E, Harrison M, Aquilante CL, Sheeder J, Teal S. An exploratory analysis  
764 on the influence of genetic variants on weight gain among etonogestrel contraceptive implant users.  
765 *Contraception.* 09 2020;102(3):180-185. doi:10.1016/j.contraception.2020.05.002

766 84. Day DS, Gozansky WS, Van Pelt RE, Schwartz RS, Kohrt WM. Sex hormone suppression  
767 reduces resting energy expenditure and {beta}-adrenergic support of resting energy expenditure. *J*  
768 *Clin Endocrinol Metab.* Jun 2005;90(6):3312-7. doi:10.1210/jc.2004-1344

769 85. Melanson EL, Gavin KM, Shea KL, et al. Regulation of energy expenditure by estradiol in  
770 premenopausal women. *J Appl Physiol (1985).* Nov 01 2015;119(9):975-81.  
771 doi:10.1152/jappphysiol.00473.2015

772 86. Gavin KM, Melanson EL, Hildreth KL, Gibbons E, Bessesen DH, Kohrt WM. A Randomized  
773 Controlled Trial of Ovarian Suppression in Premenopausal Women: No Change in Free-Living Energy  
774 Expenditure. *Obesity (Silver Spring).* 11 2020;28(11):2125-2133. doi:10.1002/oby.22978

775 87. Wallace RB, Heiss G, Burrows B, Graves K. Contrasting diet and body mass among users and  
776 nonusers of oral contraceptives and exogenous estrogens: the Lipid Research Clinics Program  
777 Prevalence Study. *Am J Epidemiol.* May 1987;125(5):854-9. doi:10.1093/oxfordjournals.aje.a114601

778 88. Procter-Gray E, Cobb KL, Crawford SL, et al. Effect of oral contraceptives on weight and body  
779 composition in young female runners. *Med Sci Sports Exerc.* Jul 2008;40(7):1205-12.  
780 doi:10.1249/MSS.0b013e31816a0df6

781 89. Tucci SA, Murphy LE, Boyland EJ, Dye L, Halford JC. Oral contraceptive effects on food choice  
782 during the follicular and luteal phases of the menstrual cycle. A laboratory based study. *Appetite.* Dec  
783 2010;55(3):388-92. doi:10.1016/j.appet.2010.06.005

784 90. Ihalainen JK, Löfberg I, Kotkajuuri A, Kyröläinen H, Hackney AC, Taipale-Mikkonen RS.  
785 Influence of Menstrual Cycle or Hormonal Contraceptive Phase on Energy Intake and Metabolic  
786 Hormones-A Pilot Study. *Endocrines.* Jun 2021;2(2):79-90. doi:10.3390/endocrines2020008

787 91. Arnoni-Bauer Y, Bick A, Raz N, et al. Is It Me or My Hormones? Neuroendocrine Activation  
788 Profiles to Visual Food Stimuli Across the Menstrual Cycle. *J Clin Endocrinol Metab.* 09  
789 2017;102(9):3406-3414. doi:10.1210/jc.2016-3921

790 92. McNeil G, Bruce AC, Ross E, James WP. Energy balance in women using oral contraceptives.  
791 *Proceedings of the Nutrition Society;* 1988. p. 58A.

792 93. Diffey B, Piers LS, Soares MJ, O'Dea K. The effect of oral contraceptive agents on the basal  
793 metabolic rate of young women. *Br J Nutr.* Jun 1997;77(6):853-62. doi:10.1079/bjn19970084

794 94. Napolitano A, Zanin R, Palma F, et al. Body composition and resting metabolic rate of  
795 perimenopausal women using continuous progestogen contraception. *Eur J Contracept Reprod*  
796 *Health Care.* 2016;21(2):168-75. doi:10.3109/13625187.2015.1079610

- 797 95. Duhita MR, Schutz Y, Montani JP, Dulloo AG, Miles-Chan JL. Oral Contraceptive Pill Alters  
798 Acute Dietary Protein-Induced Thermogenesis in Young Women. *Obesity (Silver Spring)*. 09  
799 2017;25(9):1482-1485. doi:10.1002/oby.21919
- 800 96. Jensen MD, Levine J. Effects of oral contraceptives on free fatty acid metabolism in women.  
801 *Metabolism*. Mar 1998;47(3):280-4. doi:10.1016/s0026-0495(98)90257-8
- 802 97. Kimm SY, Glynn NW, Aston CE, Poehlman ET, Daniels SR. Effects of race, cigarette smoking,  
803 and use of contraceptive medications on resting energy expenditure in young women. *Am J*  
804 *Epidemiol*. Oct 2001;154(8):718-24. doi:10.1093/aje/154.8.718
- 805 98. Duhita MR, Schutz Y, Montani JP, Dulloo AG, Miles-Chan JL. Assessment of the Dose-  
806 Response Relationship between Meal Protein Content and Postprandial Thermogenesis: Effect of Sex  
807 and the Oral Contraceptive Pill. *Nutrients*. Jul 2019;11(7)doi:10.3390/nu11071599
- 808 99. Elliott-Sale KJ, McNulty KL, Ansdell P, et al. The Effects of Oral Contraceptives on Exercise  
809 Performance in Women: A Systematic Review and Meta-analysis. *Sports Med*. Oct 2020;50(10):1785-  
810 1812. doi:10.1007/s40279-020-01317-5
- 811 100. Joyce S, Sabapathy S, Bulmer A, Minahan C. Effect of long-term oral contraceptive use on  
812 determinants of endurance performance. *J Strength Cond Res*. Jul 2013;27(7):1891-6.  
813 doi:10.1519/JSC.0b013e3182736935
- 814 101. Suh SH, Casazza GA, Horning MA, Miller BF, Brooks GA. Effects of oral contraceptives on  
815 glucose flux and substrate oxidation rates during rest and exercise. *J Appl Physiol (1985)*. Jan  
816 2003;94(1):285-94. doi:10.1152/jappphysiol.00693.2002
- 817 102. Bonen A, Haynes FW, Graham TE. Substrate and hormonal responses to exercise in women  
818 using oral contraceptives. *J Appl Physiol (1985)*. May 1991;70(5):1917-27.  
819 doi:10.1152/jappl.1991.70.5.1917
- 820 103. Bemben DA, Boileau RA, Bahr JM, Nelson RA, Misner JE. Effects of oral contraceptives on  
821 hormonal and metabolic responses during exercise. *Med Sci Sports Exerc*. Apr 1992;24(4):434-41.
- 822 104. Rebelo AC, Zuttin RS, Verlengia R, Cesar MeC, de Sá MF, da Silva E. Effect of low-dose  
823 combined oral contraceptive on aerobic capacity and anaerobic threshold level in active and  
824 sedentary young women. *Contraception*. Apr 2010;81(4):309-15.  
825 doi:10.1016/j.contraception.2009.11.005
- 826 105. Tremblay J, Peronnet F, Massicotte D, Lavoie C. Carbohydrate supplementation and sex  
827 differences in fuel selection during exercise. *Med Sci Sports Exerc*. Jul 2010;42(7):1314-23.  
828 doi:10.1249/MSS.0b013e3181cbba0b
- 829 106. Isacco L, Thivel D, Pereira B, Duclos M, Boisseau N. Maximal fat oxidation, but not aerobic  
830 capacity, is affected by oral contraceptive use in young healthy women. *Eur J Appl Physiol*. May  
831 2015;115(5):937-45. doi:10.1007/s00421-014-3075-7
- 832 107. Vaiksaar S, Jürimäe J, Mäestu J, et al. No effect of menstrual cycle phase on fuel oxidation  
833 during exercise in rowers. *Eur J Appl Physiol*. Jun 2011;111(6):1027-34. doi:10.1007/s00421-010-  
834 1730-1
- 835 108. Isacco L, Duché P, Boisseau N. Influence of hormonal status on substrate utilization at rest  
836 and during exercise in the female population. *Sports Med*. Apr 2012;42(4):327-42.  
837 doi:10.2165/11598900-000000000-00000
- 838 109. Wysocki S. Improving patient success with oral contraceptives: the importance of counseling.  
839 *Nurse Pract*. Apr 1998;23(4):51-2, 55-6, 59-62.
- 840 110. Carpenter S, Neinstein LS. Weight gain in adolescent and young adult oral contraceptive  
841 users. *J Adolesc Health Care*. Sep 1986;7(5):342-4. doi:10.1016/s0197-0070(86)80163-2
- 842 111. Franchini M, Caruso C, Nigrelli S, Poggiali C. Evaluation of body composition during low-dose  
843 estrogen oral contraceptives treatment. *Acta Eur Fertil*. 1995 Mar-Apr 1995;26(2):69-73.
- 844 112. Reubinoff BE, Grubstein A, Meiorow D, Berry E, Schenker JG, Brzezinski A. Effects of low-dose  
845 estrogen oral contraceptives on weight, body composition, and fat distribution in young women.  
846 *Fertil Steril*. Mar 1995;63(3):516-21. doi:10.1016/s0015-0282(16)57419-6
- 847 113. Bannemerschult R, Hanker JP, Wünsch C, Fox P, Albring M, Brill K. A multicenter,  
848 uncontrolled clinical investigation of the contraceptive efficacy, cycle control, and safety of a new low

849 dose oral contraceptive containing 20 micrograms ethinyl estradiol and 100 micrograms  
850 levonorgestrel over six treatment cycles. *Contraception*. Nov 1997;56(5):285-90. doi:10.1016/s0010-  
851 7824(97)00157-1

852 114. Boerrigter PJ, Ellman H, Dolker M. International clinical experience with a new low-dose,  
853 monophasic oral contraceptive containing levonorgestrel 100 microg and ethinyl estradiol 20 microg.  
854 *Clin Ther*. Jan 1999;21(1):118-27. doi:10.1016/s0149-2918(00)88272-7

855 115. Moore LL, Valuck R, McDougall C, Fink W. A comparative study of one-year weight gain  
856 among users of medroxyprogesterone acetate, levonorgestrel implants, and oral contraceptives.  
857 *Contraception*. Oct 1995;52(4):215-9. doi:10.1016/0010-7824(95)00189-h

858 116. Uras R, Orrù M, Etzi R, et al. Evidence that in healthy young women, a six-cycle treatment  
859 with oral contraceptive containing 30 mcg of ethinylestradiol plus 2 mg of chlormadinone acetate  
860 reduces fat mass. *Contraception*. Feb 2009;79(2):117-21. doi:10.1016/j.contraception.2008.08.007

861 117. Redmond G, Godwin AJ, Olson W, Lippman JS. Use of placebo controls in an oral  
862 contraceptive trial: methodological issues and adverse event incidence. *Contraception*. Aug  
863 1999;60(2):81-5. doi:10.1016/s0010-7824(99)00069-4

864 118. Wongwananuruk T, Panichyawat N, Panchalee T, et al. Comparison of change in body weight  
865 between contraception containing 30-µg ethinylestradiol/2-mg chlormadinone acetate or 30-µg  
866 ethinylestradiol/3-mg drospirenone: a randomised controlled trial. *Eur J Contracept Reprod Health  
867 Care*. Feb 2020;25(1):43-48. doi:10.1080/13625187.2019.1688290

868 119. Berenson AB, Rahman M. Changes in weight, total fat, percent body fat, and central-to-  
869 peripheral fat ratio associated with injectable and oral contraceptive use. *Am J Obstet Gynecol*. Mar  
870 2009;200(3):329.e1-8. doi:10.1016/j.ajog.2008.12.052

871 120. Lopez LM, Ramesh S, Chen M, et al. Progestin-only contraceptives: effects on weight.  
872 *Cochrane Database Syst Rev*. Aug 2016;(8):CD008815. doi:10.1002/14651858.CD008815.pub4

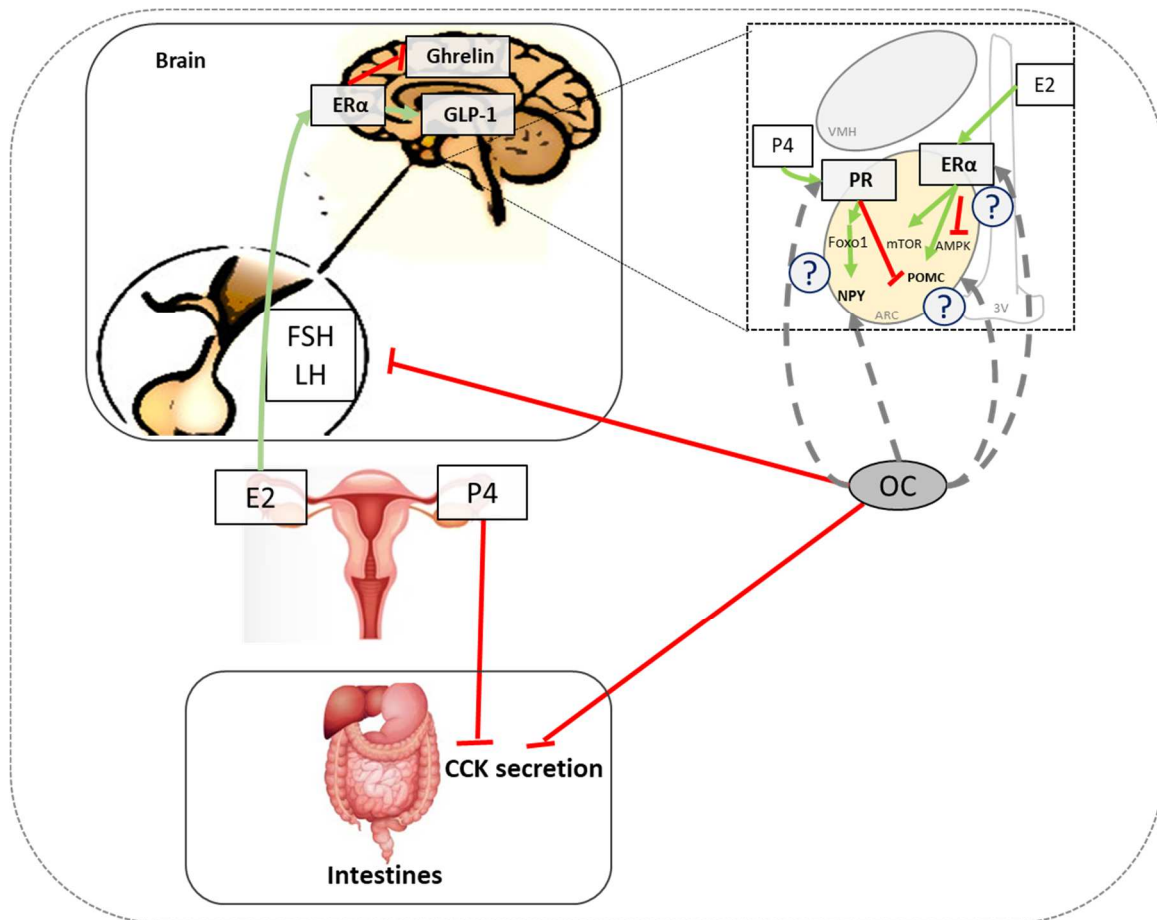
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875 Figures :

876 Figure 1



877

878 **Figure 1:** Schematic representation of mechanisms of E2 and P4 and potential mechanisms of OC action on energy intake.

879 Cellular data strongly suggest that E2 mainly exerts its effects on brain through its receptor ER $\alpha$ . E2 seems to induce its

880 anorexigenic action by increasing GLP-1<sup>25</sup> and decreasing Ghrelin<sup>24</sup> brain signaling. Dotted square: potential cellular

881 mechanisms from rodent studies by which E2 and P4 can exert orexigenic and anorexigenic effects <sup>26,29,30</sup>. Oral contraceptives

882 action on orexigenic and anorexigenic peptides are still unknown. However, OC use has been shown to decrease CCK level <sup>39</sup>.

883 E2: 17 $\beta$ - estradiol; P4: Progesterone, OC: Oral contraceptives; FSH: follicle-stimulation hormone; LH: Luteinizing hormone;

884 CCK: cholecystokinin, ER $\alpha$ : estrogen receptor alpha; ; GLP-1: glucagon-like peptide 1; PR: Progesterone receptor POMC:

885 Proopiomelanocortin; CART: cocaine amphetamine regulator transcription, Foxo1: Forkhead box protein O1, NPY:

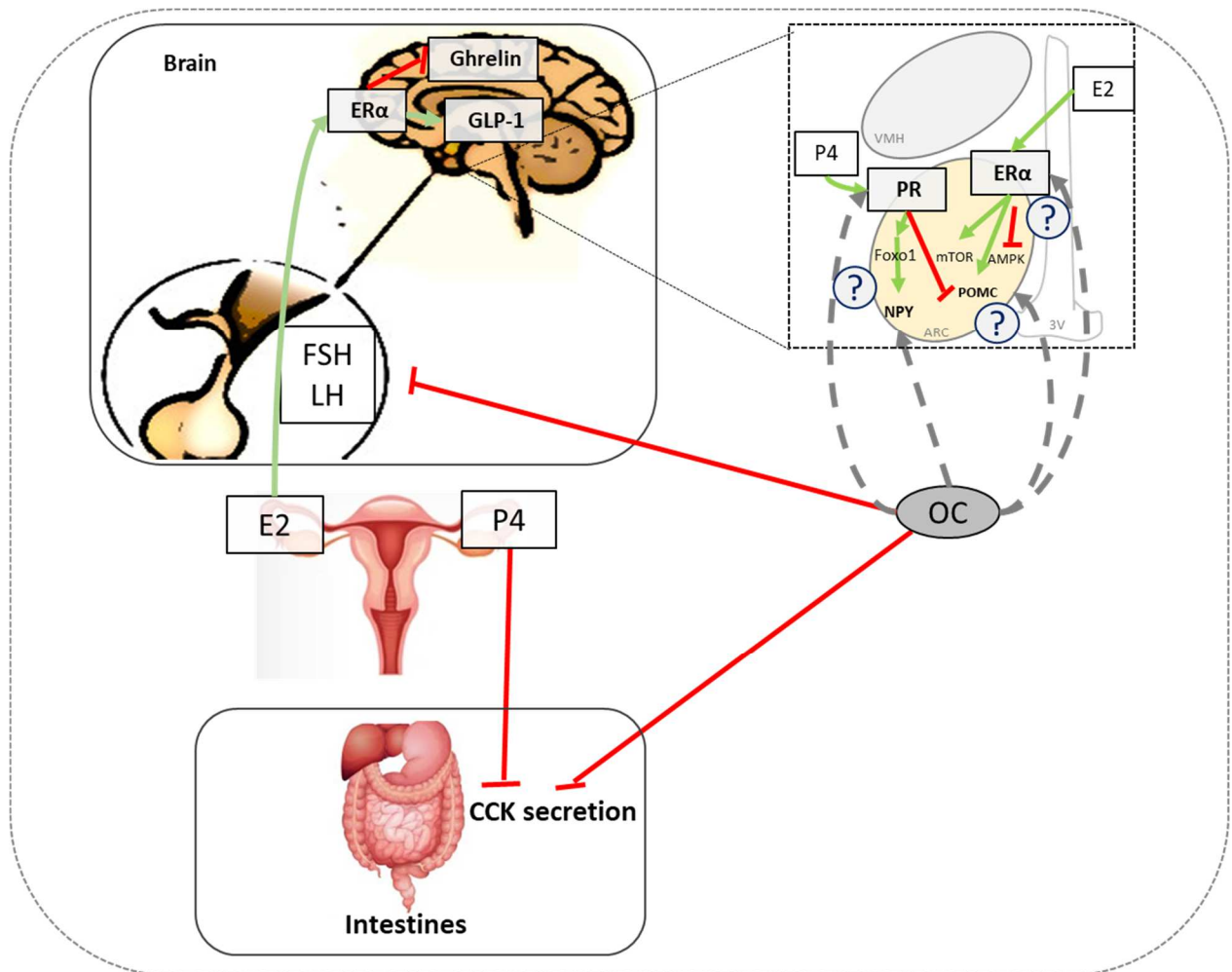
886 neuropeptide Y; Agrp: agouti related peptide; AMPK: AMP activated protein kinase; mTOR: mammalian target of rapamycin;

887 VMH: ventro medial hypothalamus; ARC: arcuate nucleus of hypothalamus; 3V: third ventricle. Green line: stimulation; red

888 line: inhibition; dotted gray line: potential mechanisms for OC.

889

890 Figure 2



891

892 **Figure 2:** Schematic representation of mechanisms of E2 and P4 and potential mechanisms of OC action on energy expenditure.

893 Most data are based on animal studies which suggest that E2 increase EE by action on brain (dotted square)<sup>28,58</sup>, adipose

894 tissue<sup>55,59</sup>, skeletal muscle<sup>43</sup> and liver. Few clinical studies have suggested that OC use can promote oxidative stress in liver<sup>51,52</sup>

895 and skeletal muscle<sup>45-47</sup>. E2: 17β-estradiol; P4: Progesterone, OC: Oral contraceptives; FSH: follicle-stimulation hormone;

896 LH: Luteinizing hormone; UCP1: uncoupling protein 1; FGF 21 Fibroblast growth Factor 21; ROS reactive oxygen species,

897 ERα: estrogen receptor alpha, AMPK: AMP activated protein kinase; ER: endoplasmic reticulum, VMH: ventro medial

898 hypothalamus; ARC: arcuate nucleus of hypothalamus; 3V: third ventricle, SNS: sympathetic nervous system Green line:

899 stimulation; red line: inhibition; dotted gray line: potential mechanisms for OC.

900

Table1: Studies investigating the effect of OC on energy expenditure at rest

Authors	Reference number	Population and Design	Methods	Contraceptive	Endpoints	Main results
<b>McNeill et al 1988 Abstract</b>	92	Observational study (n=5) 1 cycle with OC vs one cycle without OC	Indirect calorimetry, 7days-activities dairy; 7days weighted intake dairy	Levonorgestrel (30 µg/d)	BMR, EI, body weight, Physical activity index	Decrease in BMR during the OC cycle. No significant differences in EI and PA
<b>Diffey et al 1997</b>	93	Cross-sectional study OC+ (n=24) vs OC- (n=22) 18-31y	Indirect calorimetry (Deltatrac II), skinfolds, BIA	Phasic and monophasic OC EthE (30-50 µg) Levonorgestrel (50-150 µg), Desogestrel (150 µg), Norethisterone (500 µg)	BMR, anthropometry, body composition	No difference in absolute BMR between groups ANCOVA with body weight, FM and FFM showed an increase in BMR of ~5% in OC+
<b>Eck et al 1997</b>	70	Cross-sectional study OC+ (n=17) vs OC- (n=15) 18-35y	Indirect calorimetry (MedGraphics <i>Critical Care Monitor</i> ), daily food record (5days)	Triphasic OC Ortho-Novum 777 EthE (35 µg) Norethindrone (0.05 mg) Norethindrone (0.75 mg) Norethindrone (1 mg)	REE, food intake, anthropometry	No difference in REE or EI between groups. Larger intake from CHO and lower intake from fat in OC- vs OC+ group
<b>Jensen &amp; Levine 1998</b>	96	Cross-sectional study OC+ (n=13) vs OC- (n=13) OC+: 28y and OC-: 30y	Indirect calorimetry, isotope tracer infusion and blood samples	Monophasic OC EthE (30-35 µg) Norethindrone (no information) Levonorgestril (no information) Desogestril (no information)	REE, FFA metabolism, OGTT response	No difference in REE between OC+ and OC-

				Ethinodiol (no information)		
<b>Kimm et al 2001</b>	97	Longitudinal study, different ethnic population (n=147; 76 Black women and 71 White women) Contraceptive+: n = 48 (31 Black women and 17 White women); Contraceptive-: n = 99 (45 Black women and 54 White women) 18-21y	Indirect calorimetry (Deltatrac II), DXA	OC: non information Long-acting agents (Depo-Provera) Norplant System	REE, body composition	Regression model for contraceptive use: REE was 50 kcal/day higher in contraceptive+ than contraceptive- (p = 0.04).
<b>Napolitano et al 2015</b>	94	Longitudinal study 12-month treatment OC- (n=26) vs desogestrel (DSG; n=42) vs levonorgestrel-releasing intrauterine (LNG-IUS; n=34) 49.8y (perimenopausal)	Indirect calorimetry (Deltatrac II), BIA	DSG (75 µg) LNG-IUS (52 mg)	Body weight, body composition, RMR	Increased FM in the LNG-IUS (+1.1%) and the DSG (+2.8%) users after 12month treatment compared with control group. RMR: no difference in control (-3.8 kJ/day) and LNG-IUS (-115.5 kJ/day) groups. Greater, but not significant, decrease in RMR in DSG group (-305.9 kJ/day)
<b>Duhita et al 2017</b>	95	Cross-sectional study Normal (NP) or high (HP) protein meal in women taking (n=8) or not (n=8) OC and 8 men 23y	Indirect calorimetry (Quark), BIA, isocaloric test meal with 11% or 24% of protein	Monophasic OC EthE (20-35 µg)	REE, postprandial EE	Higher baseline EE in men vs women and no difference in REE between OC+ and OC- . No difference in REE

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between luteal and  
follicular phase

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BIA: bioimpedance; BMR: basal metabolic rate; CHO: carbohydrates; DXA: dual-energy X-ray absorptiometry; EthE: ethinylestradiol; EI: energy intake; FFA: free fatty acids; FM: fat mass; FFM: fat-free mass; OC: oral contraceptives; REE: resting energy expenditure; RMR: resting metabolic rate.

Table2: Studies investigating the effect of OC on energy expenditure during metabolic challenge

Authors	Reference number	Population Design	Methods	Contraceptive	Endpoints	Main results
<b>Duhita et al 2017</b>	95	Cross-sectional study Normal (NP) or high (HP) protein meal in women taking (n=8) or not (n=8) OC and 8 men 23y	Indirect calorimetry (Quark), BIA, isocaloric test meal with 11% or 24% of protein	Monophasic OC EthE (20-35 µg)	REE, postprandial EE	Increased postprandial EE following HP compared with NP meal in OC- and men only.
<b>Duhita et al. 2019</b>	98	Cross-sectional study Elevated meal protein content (isocaloric meal with 11, 23, 31% protein) OC+ (n=7), OC- (n=7) and men (n=7) OC+: 22.6y OC-:24.4y Men:23y	Indirect calorimetry (Quark), BIA, isocaloric test meal, VAS	Monophasic OC EthE (20-35 µg)	REE, postprandial EE, VAS	REE: no difference between OC- and OC+ Men: protein meal dose-response in EE OC-: increased postprandial EE from 11% to 23% but no difference between 23 and 31% OC+: no effect of meal protein content

BIA: bioimpedance; CHO: carbohydrates; DXA: dual-energy X-ray absorptiometry; EthE: ethinylestradiol; EE: energy expenditure; EI: energy intake; OC: oral contraceptives; REE: resting energy expenditure; VAS: visual analogue scale.

Table 3: Studies investigating the effect of OC on energy expenditure during acute exercise

Authors	Reference number	Population Design	Methods	Contraceptive	Endpoints	Main results
<b>Bemben et al. 1992</b>	103	Cross-sectional study Influence of OC on metabolic and hormonal responses during submaximal exercise OC+ (n=8) and OC- (n=8) 21-30y	Indirect calorimetry (AMETEK), blood samples, $VO_{2max}$ , prolonged submaximal exercise (treadmill – 90 min at 50% of $VO_{2max}$ )	Monophasic and triphasic OC EthE (35 µg) Progestin ( $\leq 1$ mg (Norethindrone, Ethynodiol diacetate))	EE, substrate metabolism and hormonal responses during exercise	No difference in EE during exercise between OC+ and OC-
<b>Vaiksaar et al. 2000</b>	107	Cross-sectional study OC+ (n =8) Influence of different phases of OC (active vs non active) cycle on endurance capacity in rowers 21y	Indirect calorimetry (MetaMax), blood samples, DXA, 1h endurance test (rowing) at 70% of $VO_{2max}$	Monophasic OC EthE (20 µg) Gestodene (75 µg)	EE and substrate metabolism during exercise	No difference in EE during exercise between active and non-active-pill phases.
<b>Suh et al. 2003 (and related studies by the same group: Jacobs et al. 2005; Casazza et al. 2004)</b>	101	Longitudinal study Influence of OC use on substrate metabolism at rest and during prolonged submaximal exercise Women (n = 8) 4-months of OC use	Open-circuit system (Ametak), skinfolds, isotope tracer infusion and blood samples $VO_{2peak}$ , 60 min cycling at 45 and 65% of $VO_{2peak}$ ,	Triphasic OC EthE (35 µg) Norgestimate (0.18 mg) Norgestimate (0.215 mg) Norgestimate (0.25 mg)	EE, substrate metabolism and hormonal responses at rest and during exercise	No difference in EE at rest and during both exercise between OC- and OC+

<b>Isacco et al. 2012 (and related study by the same group: Isacco et al. 2014)</b>	106,108	Cross-sectional study Influence of OC on metabolic responses during prolonged submaximal exercise OC- (n = 10) OC+= (n = 11)	Indirect calorimetry (Oxycon pro-Delta), DXA, blood samples VO <sub>2max</sub> , 45 min cycling at 65% of VO <sub>2max</sub>	Monophasic OC EthE (20-30 µg) Gestodene (75 µg) Desogestrel (150 µg) Drosipirenone (no information) Levonorgestrel (no information)	EE, substrate metabolism and hormonal responses during exercise	No difference in EE during exercise between OC+ and OC-
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DXA: dual-energy X-ray absorptiometry; EthE: ethinylestradiol; EE: energy expenditure; OC: oral contraceptives; VO<sub>2max</sub>: Maximal oxygen consumption; VO<sub>2peak</sub>: peak reached for oxygen consumption.