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The effects of hormonal contraceptives on glycemic regulation

Manuel E. Cortés[1,2] and Andrea A. Alfaro[3,4]

[1]*Departamento de Ciencias Químicas y Biológicas, Universidad Bernardo O'Higgins, Santiago, Chile*
[2]*Reproductive Health Research Institute, Santiago, Chile*
[3]*Liceo Experimental Manuel de Salas, Universidad de Chile, Ñuñoa, Chile*
[4]*Programa de Magíster en Educación en Salud y Bienestar Humano, Universidad Metropolitana de Ciencias de la Educación, Santiago, Ñuñoa, Chile*

A number of side effects have been linked to the use of hormonal contraceptives, among others, alterations in glucose levels. Hence, the objective of this mini-review is to show the main effects of hormonal contraceptive intake on glycemic regulation. First, the most relevant studies on this topic are described, then the mechanisms that might be accountable for this glycemic regulation impairment as exerted by hormonal contraceptives are discussed. Finally, we briefly discuss the ethical responsibility of health professionals to inform about the potential risks on glycemic homeostasis regarding hormonal contraceptive intake.

Keywords: Glycemic homeostasis, Hormonal contraception, Insulin resistance, Impaired glucose tolerance

Introduction

Since the early 1950s, when Mexican chemist Luis. E. Miramontes and co-researchers carried out the synthesis of norethisterone (norethindrone), the first oral contraceptive (Miramontes, Rosenkranz and Djerassi 1951; Djerassi et al. 1954), the subsequent mass use of hormonal contraceptive methods has resulted in immense and significant changes to mankind, from artificial birth control, to the social phenomenon which came to be known as "Women's Liberation," or the "Sexual Revolution" and related behaviors previously discussed in this journal (Norris 2013). Contraceptive use has radically affected population pyramids, especially in the more developed countries which, from having broad-based pyramids reflecting a high birthrate, have moved to narrow-based pyramids, evidence of an aging population and the associated burdens on their health, and retirement systems, as well as on their workforce. When the so-called "pill" went on the market in the 1960s, the flourishing pharmaceutical industry offered it as a universal and safe method, free from side effects which they already knew of or "suspected." However, the arrival of synthetic oral contraceptives has not been without risks to health. As

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any other drug, they possess not only therapeutic effects but also side effects (Sitruk-Ware and Nath 2013), which contraindicate their use in some patients. In fact, following the conference on "Metabolic Effects of Gonadal Hormones and Contraceptive Steroids" held in Boston in 1968, it was stated that, according to available data, no organ was free from the effects of the pill (Salhanick, Kipnis, and Vande Wiele 1969).

Glycemia constitutes a fundamental homeostatic variable, and hence its alteration can lead to a number of pathophysiological conditions affecting the internal milieu of the human being. Since the early 1960s, the intake of oral contraceptives has been associated with an increased risk of developing disorders of glucose metabolism (Waine et al. 1963). For that reason, the objective of this article is to review the main effects of the use of hormonal contraceptives on glycemic regulation.

Search for Bibliographic Information

Articles were searched for in the following bibliographic databases: PubMed, ISI Web of Knowledge, SCOPUS Database, SciELO, ScienceDirect, Google Scholar, and Google Books. Search languages used were English and Spanish; among the words used when searching were "oral contraceptives" and "glycemia," "oral contraceptives" and "insulin resistance," "oral contraceptives" and "diabetes," "anticonceptivos orales" and "glicemia," "anticonceptivos orales" and "resistencia insulínica," and "anticonceptivos orales" and "diabetes." Finally, twenty-four references on these topics were reviewed depending on their availability. In addition, sixteen other references were added to be used in the rationale and concluding remarks.

Studies Relating the Use of Oral Hormonal Contraceptives and the Impairment of Glycemic Regulation

In an interesting article, Shawe and Lawrenson (2003) have discussed the recommendation for the best practice when prescribing hormonal contraceptives in women, especially those suffering from glycemic disorders such as diabetes mellitus. They argue that there is little evidence that any changes in glycemic control caused by combined oral contraceptives are of clinical relevance. However, there are several studies that show the opposite. In the late 1960s a classic article written by Spellacy (1969) suggested that an abnormal carbohydrate metabolism in oral contraceptive users was characterized by impaired glucose tolerance. In this regard, Wynn et al. (1979) argued that even though there is evidence that estrogen and progestin[1] oral contraceptives modify carbohydrate metabolism, the results of related studies are non-conclusive due to the scarce consideration given to subject selection and estrogen doses, and to doses and type of progestin used. In an investigation involving 2,205 women (1,628 of whom used combined estrogen/progestin contraceptives, and 577 did not), these researchers performed glucose tolerance tests on both user and non-user subjects (women using oral contraceptives were separated in six groups based on contraceptive composition), finding altered glucose tolerance in all groups of subjects using estrone progestin (nortestosterone derived) and gonane D-norgestrel (levonorgestrel) oral contraceptives. No changes were observed regarding glucose tolerance among subjects using pregnane progestin (progesterone derived). This research team

also reported that women using the oral contraceptive with the highest estrogen level (75 μg or higher) presented the greatest glucose tolerance alteration. They also noted increased insulin release in all the groups except among users of contraceptives containing pregnane progestin, which showed no change (Wynn et al. 1979). Later, Skouby et al. (1985) studied the metabolic effects of a low-dose triphasic oral contraceptive (ethinyl estradiol and levonorgestrel) on glucose tolerance and plasma insulin response among other metabolic variables, in sixteen women with previous gestational diabetes and in nineteen healthy women. Investigations were performed prior to the hormonal intake and after intake for 2 and 6 months, using the oral glucose tolerance test. Before treatment, the women with previous gestational diabetes had significantly elevated fasting glucose and impaired glucose tolerance when compared to those of the healthy control women. Following the intake period, the glucose and insulin responses to oral glucose remained unchanged. Using the euglycemic clamp, the same research group compared this variable between six non-diabetic and six women suffering from previous gestational diabetes pre- and post-intake of a low-dose triphasic oral contraceptive (ethinyl estradiol and levonorgestrel) over a 6-month period. As a result, an increased insulin resistance was observed which was not sufficient to impair glucose tolerance either in the previous gestational diabetic women nor in the non-diabetic women; however, given its reduced sample, this study is not conclusive enough (Skouby et al. 1987). Pérez et al. (1987) studied glucose tolerance in 200 women taking oral hormonal contraceptives (ethinyl estradiol and norgestrel), grouped in cohorts of patients with and without cardiovascular risk. Even though no differences were found between the two groups, both evidenced significant differences when comparing, following an oral glucose overload, their basal glycemia before taking the contraceptive, after 6 months of use, and after a year of intake. In a cross-sectional study, Simon et al. (1990) studied 1,290 consecutive, healthy, non-pregnant women of child-bearing age. Compared with non-users taking no progestagens, oral contraceptive users had higher 2-h plasma glucose and higher fasting plasma insulin. These authors argued that oral contraceptive intake appears to induce an increase of insulin-resistance markers. Godsland et al. (1990) studied 1,060 women taking oral contraceptives (different progestin formulations: levonorgestrel, norethindrone, and desogestrel). These women were subjected to an oral glucose overload and, when comparing their metabolic variables with a four hundred and eighteen woman control group, it was observed that depending on the dose and type of progestin, combination drugs were associated with glycemias 43–61 percent higher than in controls, insulin responses 12–40 percent higher, and C-peptide responses 18–45 percent higher. Conversely, progestin-only formulations had only minor metabolic effects. Watanabe et al. (1994) studied one hundred and eighty-six women, fifty six of whom constituted the control group (they had never used oral contraceptives or at least had not used them during the last 2 years), sixty eight used them in low doses (contraceptive 1, 30 μg ethinyl estradiol and 300 μg norgestrel; and contraceptive 2, 30 μg ethinyl estradiol and 150 μg levonogestrel) and sixty two used a contraceptive in high doses (high-dose contraceptive, 50 μg ethinyl estradiol and 500 μg desogestrel); the last two groups had been using contraceptives for at least 6 months. Oral glucose tolerance tests were performed on all participants, and the results confirmed the development of

impaired glucose tolerance in both pill groups, allowing for an estimation of insulin sensitivity and glucose effectiveness, as well as for beta-cell function. Low-dose users had lower insulin sensitivity and glucose effectiveness compared to controls and inappropriately low beta-cell function in relation to the insulin. High-dose contraceptive users, on the other hand, had metabolic variables that did not differ from controls. These researchers concluded that low-dose contraceptive use results in insulin and glucose resistance, which is not compensated by increased beta-cell function. The reduced glucose tolerance would be primarily due to the defect in glucose effectiveness, and these oral contraceptive users may be at risk of contracting diabetes or cardiovascular disease. In 1995, Shamma et al. (1995) used the hyperglycemic–hyperinsulinemic clamp in seven healthy, normally cycling, non-obese, non-diabetic women before and after using an implant contraceptive (36 mg of levonorgestrel) over an 8-week treatment, observing decreased insulin sensitivity and increased pancreatic insulin release as compensatory response, which might constitute a problem for diabetic patients; this study, nonetheless, cannot be considered conclusive based on its reduced sample size. Mastorakos et al. (2006) compared the effects of combined oral contraceptives containing cyproterone acetate or desogestrel on insulin sensitivity in adolescent girls with polycystic ovary syndrome. For that purpose, they compared a group of eighteen patients who received 0.15 mg of desogestrel plus 0.030 mg of ethinyl estradiol daily, and a group of eighteen patients who received 2 mg of cyproterone acetate plus 0.035 mg of ethinyl estradiol daily, for 21 days followed by a 7-day rest, for 1 year. All patients performed an oral glucose tolerance test before and after the 12-month treatment. These researchers found that, following a 1-year treatment, the homeostasis model assessment index of insulin resistance had increased significantly in both groups, concluding that treatment of adolescent girls with polycystic ovary syndrome with the two combined oral contraceptives administered, resulted in unfavorable changes of insulin sensitivity. In addition, these investigators found that cyproterone acetate is associated with increased insulin secretion and hyperinsulinemia. In an interesting work, Friedrich et al. (2012) studied the effect of combined oral contraceptives on the responsiveness of growth hormone. The contraceptive contained ethynil estradiol as estrogen, and levonorgestrel, desogestrel, norgestigmate, dienogest, or chlomardinon acetate as the progestin. These researchers found an enhanced responsiveness of the growth hormone to hyper- and hypoglycemia in women using the oral contraceptives ($n = 15$) as compared with the control subjects (without contraceptive, $n = 10$). According to the results, these authors recognize the effect of an increase in glucose levels attributed to oral contraceptives and even propose them as candidates to revert deep hypoglycemic episodes and hypoglycemia unawareness in women with diabetes in the future. A recent study lead by Piltonen et al. (2012) studied forty-two women (thirteen used oral contraceptives, fifteen used transdermal contraceptive patches, and fourteen used contraceptive vaginal rings). After continuous use over 9 weeks, fasting serum levels of glucose remained unchanged but the area under the curve values of glucose in oral glucose tolerance test rose significantly in all three study groups. Fasting serum levels of insulin increased significantly from baseline during the use of oral and vaginal contraceptives, and a similar trend was seen in the transdermal patch group. The area under the curve of insulin rose

significantly during the use of oral and transdermal contraceptives, and there was a tendency to increase in the vaginal ring group. In conclusion, the results obtained by these authors demonstrate that commonly used contraceptives have some unfavorable effects on glucose metabolism.

Mechanisms that Could Explain Impaired Glycemic Regulation due to the Use of Hormonal Contraceptives

What causes hormonal contraceptives to have an effect on glycemic homeostasis? This could result from estrogens, progestins, or the molar concentration ratio of the administered estrogen–progestin. According to Alonso, Llaneza, and González (2008) several clinical and experimental data show that the physiological action of sex steroids and insulin interacts in the target tissues for these hormones. For example, the existence of high concentrations of sex steroids in women seems to contribute to the development of insulin resistance (Sutter-Dub 2002; Alonso, Llaneza and González 2008). Likewise, low plasma levels of the mentioned steroids, or high testosterone appear to increase the risk of developing type 2 diabetes. Although the close link between insulin resistance and plasma steroid levels seems clear, the nature of this relationship has not yet been sufficiently elucidated, especially in humans (Sutter-Dub 2002; Alonso, Llaneza, and González 2008). Sitruk-Ware and Nath (2013) argue that the estrogenic component of contraceptives exerts a relevant role in the alteration of insulin sensitivity. In this regard, studies in rats carried out by Nadal, Díaz and Valverde (2001) show that, at the level of beta cells in pancreatic islets, estrogens can modulate insulin secretion. Particularly, these researchers have reported that in the presence of glucose, estradiol enhances insulin secretion (i.e., an insulinotropic effect of estradiol) (Nadal et al. 1998). The latter confirms that, somehow, the estrogens contained in hormonal contraceptives can alter the dynamics of insulin secretion of the users. Along this line, González et al. (2002) investigated the influence of estradiol on the insulin receptor of ovariectomized rats treated with different hormonal doses. Their results showed that high doses of estradiol cause the carbohydrate mechanism to deteriorate and decrease insulin sensitivity, evidencing the relevance of estrogen dose and concentration for the glycosidic metabolism of women using oral hormonal contraceptives or undergoing hormone replacement. On this topic, Patiño, Díaz-Toledo, and del Barrio (2008) suggest that, in general, the changes detected on carbohydrate metabolism are dependent on ethinyl estradiol doses and on the androgenic effect of progestins (those prepared with 50 μg ethinyl estradiol have been described to lead to decreased glucose tolerance, which is compensated with higher insulin levels following an oral glucose overload (Skouby Petersen and Jespersen 1996)), and therefore there would be no hyperglycemia in healthy women (2008), though this leads to controversy. As regards progestagens, it has been reported that progesterone accelerates the progression of diabetes in female *db*/*db* mice (Picard et al. 2002). Moreover, female, but not male, mice in which the progesterone receptors (PR) have been knocked out (PR–/–), showed lower fasting glycemia than PR + /+ (intact receptors) mice and had higher insulinemia following a glucose injection. It was also found that pancreatic islets from female PR–/– mice were larger and secreted more insulin, due to increased beta-cell mass due to stimulated pancreatic beta cells. This shows the importance of progesterone in the signaling triggering insulin secretion, and also leads one to think that its progestin derivatives

would also alter insulin release from the pancreas, even though the specific mechanisms are not clear as yet. On this matter, it has been suggested (Godsland et al. 1992; Sitruk-Ware and Nath 2013) that most progestins could bind and transactivate the PR, modifying the half-life of insulin and increasing insulin response to increased glucose, a fact dependent both on dosage, progestin molecular structure, and on its combination with estrogen. In the late 1970s, Wynn et al. (1979) proved that progestins decreased insulin sensitivity, thus causing insulin resistance, with the content of levonorgestrel (D-norgestrel) in combined contraceptives the strongest progestin to stimulate insulin secretion. Patiño, Díaz-Toledo and del Barrio (2008) suggested that the action mechanism of progestins on glycemic regulation could be due to the direct action on the pancreatic beta cell, maybe by modifying the insulin release rate (Howell, Tyhurst, and Green 1977), to a decrease in the number of insulin receptors at peripheral level, or to an alteration in the post-receptor response mechanisms, a fact leading to compensatory hyperinsulinemia. In this way, progestins would be acting through an "anti-insulin" effect, increasing peripheral resistance to insulin, causing reduced glucose utilization in the muscle and adipose tissue, but producing increased glycogen storage in the liver. The latter is in agreement with early studies by Spellacy, Buhi, and Birk (1975) showing that the progestin norethindrone (norethisterone) could affect the peripheral action of insulin. A study by Cagnacci et al. (2009) has shown that, in comparison with oral contraceptives, the vaginal ring presents no negative effect on insulin sensitivity and that, seemingly, progestins do not show the same effect on insulin response when non-orally administered. According to Patiño, Díaz-Toledo and del Barrio (2008), progestin androgenic activity exerts an important role on the diabetogenic effect of hormonal contraceptives, hence the importance of determining the selectivity index (i.e., the ratio between the wanted progestational response and the unwanted androgenic response at a given dose) associated with each compound. Even though the hormone formulations currently used in contraceptives contain lower estrogen doses (e.g., ethinyl estradiol) and third-generation progestins (e.g., desogestrel, gestodene, and norgestimate) possess a very low androgenic profile (there is no imbalance towards progestins), and hence their effect on glucose and insulin levels would be minimal (Patiño, Díaz-Toledo, and del Barrio 2008), the available information is still insufficient to rule out possible long-term effects of hormonal contraceptives on glycemia.

Concluding Remarks

The evidence discussed in this mini-review is sufficient to state that hormonal contraceptives exert some degree of influence on the mechanisms modulating glycemia. Currently, all physicians, and especially endocrinologists, are recommended to provide counseling for their patients who may have contraceptive prescriptions (Christin-Maitre 2013); however, from our perspective, little is being done to warn patients of the potential health risks involved. Thus, we consider it the duty and ethical responsibility of these health professionals, in the light of the risks linked to the use of hormonal contraceptives, to offer advice and guidance to users, and to warn them of the secondary effects these drugs involve. In this regard, we think that one of the fundamental principles of health professionals and educators should always be the promotion of health maintenance and the prevention of risky behaviors. It should always be kept in mind that to care for a patient as an individual, physicians, and

other health professionals must recognize the patient as a person. Every professional is morally obliged to properly inform the patient; in fact, patients are legally entitled to be informed (Parra 2013). Health professionals should maintain an open dialogue with the patient and family regarding the potential risks that certain treatment and drugs (such as hormonal contraceptives) pose to their health. Health professionals must put the well-being of patients above their own, i.e., should prioritize the well-being of the patient. This primacy of patient well-being should be the guiding principle of health professionals. The altruism of these professionals, to generate confidence in patients, should be immune to any political and economic pressures they and their patients may be facing (Goldman and Dennis 2004). Peck and Norris (2012) argue that prescribing hormonal contraceptives without proper warning of its risks to the user violates the Hippocratic Oath to "do no harm." In addition, these authors argue that while physicians ethically feel they cannot "impose" their own Catholic morality they should rightly insist that their patients be given opportune, adequate, and complete informed consent about all the risks of oral contraceptives. A real alternative, free from side effects, is the use of natural family planning based on fertility awareness, which includes the acceptance of one's fertility, and the shared responsibility of man and woman to live their own fertility in mutual confidence and cooperation (Fehring, Klaus, and Williams 2012), accepting it as a gift. In addition, fertility awareness can be very useful in the assessment of a woman's health (Vigil, Blackwell, and Cortés 2012).

In the future, research in this area ought to be focused on studying the long-term effect of hormonal contraceptives on glycemic homeostasis, on the basis of large, sufficiently representative sample sizes, and on performing reliable clinical tests suitable to determine alterations in insulin sensitivity among women using the contraceptives. We recommend the use of the euglycemic–hyperinsulinemic clamp, considered the gold standard in the assessment of insulin sensitivity (Greenfield et al. 1981), or alternatively the insulin suppression test (Pei et al. 1994), which is highly correlated ($r = 0.93$) with the euglycemic–hyperinsulinemic clamp (Greenfield et al. 1981), and has proved useful even in the identification of women subpopulations regarding insulin sensitivity (Vigil et al. 2007). In case of determining a deleterious effect on glycemic homeostasis, research should aim at identifying the underlying specific mechanisms altered at molecular, cellular, and physiological level.

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Endnote

1. The term "progestin" will be used hereafter to refer specifically to synthetic progestagens, to avoid the more vague "progestagen" (and "gestagen") which also involve naturally occurring compounds, among others, progesterone and its derivatives.

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Biographical Note

Dr. Cortés is professor of physiology and pathophysiology at the Departamento de

Ciencias Químicoas y Biológicas, Universidad Bernardo O'Higgins, Santiago, Chile; and a postdoctoral researcher in the Reproductive Health Research Institute, Santiago, Chile. Miss Alfaro is a biology and natural science teacher at the Liceo Experimental Manuel de Salas, Universidad de Chile; and is currently studying for a Master's degree in Education, majoring in Health and Human Wellness at the Universidad Metropolitana de Ciencias de la Educación, Santiago, Chile. The authors may be contacted through Professor Manuel E. Cortés Departamento de Ciencias Químicas y Biológicas, Universidad Bernardo O'Higgins, General Gana 1702, Santiago, Chile. His email address is manuel.cortes@ubo.cl