Review

Ovulation Disorders and Lifestyle Factors as Co-Dependent Underlying Causes of Ovulatory Infertility—A Literature Review with a Proposed Classification of Etiological Factors of Ovulatory Infertility

Magdalena Skowrońska , Michał Pawłowski , Robert Milewski *

Posted Date: 12 September 2023

doi: 10.20944/preprints202309.0746.v1

Keywords: ovulatory infertility; ovulation disorders; lifestyle; diet; physical exercise; insulin resistance; PCOS

Review

Ovulation Disorders and Lifestyle Factors as Co-Dependent Underlying Causes of Ovulatory Infertility—A Literature Review with a Proposed Classification of Etiological Factors of Ovulatory Infertility

Magdalena Skowrońska [1], Michał Pawłowski [2] and Robert Milewski [2,*]

[1] Doctoral Studies, Medical University of Bialystok, Poland, 15-089 Białystok; magdalena.skowronska@sd.umb.edu.pl
[2] Department of Biostatistics and Medical Informatics, Medical University of Bialystok, Poland, 15-089 Białystok; robert.milewski@umb.edu.pl (R.M.) michal.pawlowski@umb.edu.pl (M.P.)
* Correspondence: Correspondence: robert.milewski@umb.edu.pl

Abstract: Ovulatory infertility is a serious clinical problem whose direct causes are still largely unknown. In addition to pathologies that make it impossible for a couple to establish a pregnancy, there are a number of other factors that have a bearing on fertility, including lifestyle factors, particularly diet. Although numerous studies have been performed linking such factors with ovulatory infertility, most of them lack the necessary clinical significance, focusing instead on observational data and establishing associative relationships. This paper includes a literature review focusing on connections between lifestyle factors such as diet, physical exercise, oxidative stress, sleep, and supplementation, and ovulatory infertility. Special emphasis was given to issues such as obesity and insulin resistance and their mutual relationship with other factors linked to ovulatory infertility. In addition, making use of the conclusions of literature review, the authors propose a classification of relationships between ovulation disorders and lifestyle factors in ovulatory infertility based on the WHO classification of ovulation disorders, and indicate areas that merit further research. The data presented in the paper shows that the issues of proper diet and physical exercise are those that would merit from robust clinical studies focused specifically on ovulation infertility, while studies concerning the relationship between oxidative stress, sleep, and supplementation and ovulatory infertility do not seem to be promising directions as far as clinical significance is concerned.

Keywords: ovulatory infertility; ovulation disorders; lifestyle; diet; physical exercise; insulin resistance; PCOS

1. Introduction

Infertility and fertility disorders are prevalent in a large proportion of the population. Globally, the incidence of infertility is approx. 50-70 million of couples [1]. Infertility is defined as failure to establish a clinical pregnancy after 12 months of regular unprotected sexual intercourse [2]. In the majority of cases, infertility may be attributed to the male, female, or combined factor, with numerous causes or risk factors identified as connected with infertility. Female infertility may result from ovarian insufficiency, diminished ovarian reserve (DOR), fallopian tube obstruction, or abnormal anatomy of the female reproductive system.

Ovulation disorders, manifesting as menstrual irregularities, are the cause of infertility in around 25% of couples who have difficulty conceiving. The World Health Organization (WHO) categorizes ovulation disorders into the following three groups:

1. Group I, i.e. disorders caused by hypothalamic-pituitary insufficiency;
2. Group II, i.e. disorders caused by secondary ovarian failure;
3. Group III, i.e. disorders caused by primary ovarian failure [3].

 doi:10.20944/preprints202309.0746.v1

Diagnostics of ovulatory infertility should cover the following aspects: patient interview with special focus on regularity of menstrual bleeding and ovulation, and physical examination with gynecological examination; in addition, ultrasound assessment of the menstrual cycle is used. The following hormonal tests are also recommended: follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, thyroid-stimulating hormone (TSH), testosterone, progesterone, and prolactin. In clinically justified situations, in order to rule out diminished ovarian reserve, anti-Müllerian hormone (AMH) concentration tests should be performed [4].

Other very important aspects must be considered in the context of infertility and these include lifestyle and environmental factors such as diet, physical activity, stress, and environmental pollution, among many others. They may have a negative or positive impact on female fertility, including the course of ovulation [5]. Research into the relationship between lifestyle/environmental factors and ovulatory infertility should focus on establishing which factors can be linked to particular ovulation disorders recognized as causes of infertility.

The analysis of possible causes of ovulatory infertility presented in this paper is based on the literature review performed by the authors and adopts the aforementioned WHO classification of ovulation disorders as the framework for conclusions. The authors made the logical assumption that the WHO classification is exhaustive and thus the disorders included in it constitute all the currently known pathologies that may possibly constitute causes of ovulatory infertility. Thus, the authors stipulated that a causal link between a particular factor (i.e. a pathology or a lifestyle factors) and ovulatory infertility must be established through its relationship with one or several of the ovulation disorders included in the WHO classification. In other words, the following rationale was followed: ovulation disorders are primary causes of ovulatory infertility, while the analyzed factors play various secondary roles ranging from causative to coincidental. This rationale is reflected in the methodology of the study.

The aim of this review was: 1) to perform and present a review of literature data in the area of possible, probable, and suspected causes of ovulatory infertility; 2) to identify the role of lifestyle factors in the etiology of ovulatory infertility; 3) to propose a classification of relationships between ovulation disorders (as categorized by WHO) and lifestyle factors as causes of ovulatory infertility; and 4) to identify areas for further research.

2. Materials and methods

The study was carried out as a review of literature published from 1988 to 2023 in the following databases: PubMed/Medline, EMBASE (Elsevier), Scopus, Web of Science, and Google Scholar. The review focused on the current scientific consensus concerning the relationship between ovulation disorders, lifestyle factors, and ovulatory infertility.

The study also involved a comparison between the conclusions drawn from the literature review and the WHO classification of ovulation disorders with the view of compiling a novel classification of relationships between ovulation disorders and lifestyle factors as probable causes of ovulatory infertility. The WHO classification itself was chosen based on several factors. First of all, it provided a clear framework of ovulation disorders, which the authors considered as the key elements in the complex inter-relationships between the studied factors involved in ovulatory infertility. In addition, the classification is clinically relevant and thus made it possible to analyze the degree of relationships between lifestyle factors and ovulatory infertility beyond the broad and often vague conclusions encountered in literature. Moreover, based on data thus collected and their analysis, recommendations and areas for further research were proposed.

3. Results and discussion

WHO Group I ovulation disorders and their influence on ovulatory infertility

WHO Group I ovulation disorders, i.e. hypogonadotropic hypogonadism, are caused by failure of the pituitary hypothalamus. Women suffering from these conditions usually experience amenorrhea (primary or secondary) – often called hypothalamic amenorrhea – characterized by low

 doi:10.20944/preprints202309.0746.v1

levels of gonadotropins and estrogen deficiency. Approximately 10% of women with ovulation disorders suffer from a group I ovulation disorder [3].

The cause of hypogonadotropic hypogonadism is usually not known. However, it can be congenital, such as when it is associated with the anosmia known as Kallmann syndrome. Moreover, hypogonadotropic amenorrhea often develops as a result of low body weight or excessive exercise. Other disorders belonging to this group are: septo-opto dysplasia, panhypopituitarism, craniopharyngioma, and Langerhans histiocytosis X. Treatment of WHO Group I ovulation disorders may consist in hormone supplementation or through lifestyle interventions, i.e. weight normalization and exercise [3].

Few papers link ovulatory dysfunction to ovulatory infertility in the case of WHO Group I ovulation disorders. On the contrary, a recent paper by Naseem et al. reports that lack of ovulation and markers of diminished ovarian reserve before treatment may not reflect poor reproductive potential [6]. Unfortunately, literature lacks research papers directly linking WHO Group I disorders to ovulatory infertility. Hence, although it can be surmised – by analogy with the other groups – that ovulatory infertility may indeed occur in cases of ovulation disorders included in group I, research is needed in this area to prove whether this is indeed the case.

WHO Group II ovulation disorders and their influence on ovulatory infertility

Group II ovulation disorders are defined as dysfunctions of the hypothalamic-pituitary-ovarian axis. They affect approx. 85% of all women with ovulation disorders. Common conditions such as polycystic ovary syndrome (PCOS), hyperprolactinemia, thyroid dysfunction, and endometriosis fall into this category. Treatment options for disorders from this group consist of weight reduction, various types of medical treatment, including laparoscopic ovarian diathermy (LOD), ovulation induction with injectable gonadotropins, and assisted conception [3].

a. Polycystic Ovarian Syndrome (PCOS)

PCOS is the most common endocrine disorder and the leading cause of ovulatory infertility in women. It occurs in 5-10% of the population of women of reproductive age [7]. The Rotterdam Criteria is the most widely used classification of PCOS, now endorsed by most scientific societies and health authorities [8–11]. The Rotterdam definition suggests that polycystic ovary syndrome can be diagnosed in any woman with at least two of the following three features: clinical and/or biochemical hyperandrogenism (HA), ovulation abnormalities, and an ultrasound image of polycystic ovaries [12].

Polycystic ovary syndrome is a highly inherited complex polygenic, multifactorial disorder. Pathophysiological abnormalities in gonadotropin secretion or action, ovarian folliculogenesis, steroidogenesis, insulin secretion or action, and adipose tissue function, among others, have been described in PCOS. Furthermore, women with PCOS are at increased risk of developing the following disorders: glucose intolerance and type 2 diabetes mellitus; hepatic steatosis and metabolic syndrome; hypertension, dyslipidemia, vascular thrombosis, cerebrovascular accidents, and possibly cardiovascular events; obstetric complications; endometrial atypia or carcinoma and possibly ovarian malignancy; as well as mood and psychosexual disorders.

Of all women with PCOS, about two-third ovulate irregularly, with the chance of ovulatory infertility increasing as a result [13,14]. This indicates that PCOS is a leading factor of ovulatory infertility.

b. Hyperprolactinemia

Hyperprolactinemia is the most common dysfunction of the hypothalamic-pituitary axis and is more common in women. The incidence of hyperprolactinemia ranges from 0.4% in the general adult population to as much as 9-17% in women with reproductive disorders [15]. Hyperprolactinemia causes hypogonadism, menstrual irregularities or amenorrhea in women, low serum testosterone levels in men, and infertility and sexual dysfunction in both men and women [16]. In women,

 doi:10.20944/preprints202309.0746.v1

pathological hyperprolactinemia usually manifests itself as an ovulation disorder and is often associated with secondary amenorrhea and ovulatory infertility. However, cases of very high prolactin levels are not uncommon, sometimes occurring in women with normal ovulation and not requiring any treatment. The disorder can also be asymptomatic [17,18]. Hyperprolactinemia is often accompanied by insulin resistance (IR), an important clinical problem nowadays [15]. As hyperprolactinemia is often associated with ovulatory infertility, conducting further research into whether it might be a direct cause of ovulatory infertility would be worthwhile.

c. Thyroid Dysfunction

Thyroid disorders are the second most common endocrine conditions in women of reproductive age. By influencing the actions of the folliculotropic and luteinizing hormones, thyroid hormones are involved in regulating the menstrual cycle and achieving fertility. Thus, they affect all aspects of reproduction [19]. Severe thyroid dysfunction can lead to menstrual and ovulation disorders and ovulatory infertility through direct and indirect interactions with the hypothalamic-pituitary-ovarian axis and reproductive organs. However, the exact incidence of infertility in women with thyroid disorders remains unknown [20]. Hence, it seems reasonable to conduct studies in this direction to establish or disprove a direct relationship between thyroid disorders and ovulatory infertility.

d. Endometriosis

Endometriosis is an inflammatory estrogen-dependent condition associated with pelvic pain and infertility [21]. It appears to be one of the most common benign gynecological proliferations in premenopausal women since it is estimated that 10-15% women of reproductive age suffer from pelvic endometriosis [22]. The disorder affects gametes and embryos, fallopian tubes and embryo transport, and the eutopic endometrium – all of these abnormalities likely affecting fertility. For this reason, an association between endometriosis and infertility is well supported with evidence throughout literature, yet a definite causal relationship is still controversial [23]. Current treatment options for endometriosis-associated infertility focus either on stimulating follicle development and ovulation or inhibiting the growth and development of endometrial lesions [24].

As mentioned above, it has not been unequivocally proven that endometriosis is a disease that causes ovulatory infertility, as there are other co-occurring factors that can affect infertility in endometriosis. A relationship certainly exists, but current studies have not ascertained causality between the two conditions.

WHO Group III ovulation disorders and their influence on ovulatory infertility

Group III ovulation disorders are caused by primary ovarian failure. Around 5% of women with ovulation disorders are affected by a group III ovulation disorder [3].

Primary ovarian insufficiency is a subclass of ovarian dysfunctions in which the cause is within the ovary. In most cases, an unknown mechanism leads to premature exhaustion of the resting pool of primordial follicles. Primary ovarian insufficiency might also result from genetic defects such as Fragile X Syndrome (FXS) and Turner's syndrome as well as chemotherapy, radiotherapy, drugs, surgery, environmental factors, or autoimmune diseases. It is not related to lifestyle or the use of a proper diet [25]. The main symptom is the absence of regular menstrual cycles and the diagnosis is confirmed when elevated follicle-stimulating hormone levels and reduced estradiol concentrations are detected in the serum. The disorder usually leads to sterility and has a pronounced effect on reproductive health when it manifests at a young age [3].

Among women with ovulation disorders categorized in group III, extremely low ovarian reserve parameters are not always associated with the absence of follicles in the ovary [26]. Spontaneous pregnancy is rare in women with WHO Group III ovulation disorders with reports of spontaneous conception ranging from 2.2% to 14.2% [27].

The percentage of pregnancies achieved in group III ovulation disorders is very low and the mechanisms by which ovarian activation strategies induce spontaneous conception are unknown.

 doi:10.20944/preprints202309.0746.v1

Therefore, it can be assumed that the vast majority of women with group III ovulation disorders experience ovulatory infertility.

Relationship between lifestyle factors and ovulatory infertility

a. Diet vs. ovulatory infertility

Nutrients play a number of functions in the human body, i.e. providing energy, serving as building materials, and controlling body processes. They are inseparable from diet as food is a significant and essential source of nutrients. For this reason, diet – understood as consumption of particular food ingredients and individual model of nutrition in the holistic sense – may have an impact on the ovulatory cycle and female infertility [28].

A study performed by Grieger et al. connected Western diet with infertility and a slightly increased time-to-pregnancy [29]. Research performed by Chavarro et al. focused on the influence of macronutrients on fertility showed that the overall intake of carbohydrates and the glycemic load of diet were positively correlated with the risk of ovulatory infertility. Among those same women, increased protein consumption was connected with increased risk of ovulatory infertility, with increased risk of ovulatory dysfunction mainly caused by consumption of proteins of animal origin, which was directly connected with ovulatory infertility. Women characterized by increased consumption of proteins of animal origin also consumed more saturated fatty acids compared with those who consumed less proteins of animal origin. For this reason, a potential influence of both high-carbohydrate diets with a high glycemic load and high consumption of saturated fatty acids need to be emphasized as they may intensify the relationship between animal fat consumption and ovulatory dysfunction. On the other hand, no relationship between consumption of various fibers and the risk of ovulatory infertility has been discovered. As far as vegetable proteins are concerned, a beneficial influence on ovulation has been shown: when 5% of energy was sourced from vegetable instead of animal protein, the risk of non-ovulatory infertility was more than halved [30].

A literature review showed that high consumption of saturated fatty acids (SFA) and trans fatty acids (TFA) is connected with increased risk of ovulatory infertility. The review suggested that high consumption of TFAs (over 1% of energy) is a risk factor of both female and male infertility [31]. There are other studies, however, that did not show a correlation between SFA consumption and increased risk of ovulatory dysfunction [32]. On the other hand, Chavarro et al. showed that any increase in the consumption of energy from unsaturated trans fatty acids by 2% compared to carbohydrates was connected with a 73% greater risk of ovulatory infertility and that sourcing 2% of energy from trans fats instead of polyunsaturated n-6 fats was connected with a similar increase of the risk of ovulatory infertility [33].

Moreover, appropriate quality and quantity of consumed fatty acids seems to be of crucial importance in terms of ovulatory infertility. Insufficient contents of fats in diet may contribute to abnormal menstrual cycles [33]. In addition, results obtained by Mumford et al. showed that high-fat diet induced increased testosterone synthesis in women, which has a negative impact on ovulation [32]. However, as far as ovulatory dysfunctions are concerned, the quality of fats in diet seems more important than their quantity. Polyunsaturated fatty acids (PUFA) ratios, particularly the omega-6 (n-6) to omega-3 (n-3) ratio may be among the most important factors.

It is becoming increasingly common in literature to compare the "Mediterranean-type dietary pattern" with the "Western-type dietary pattern" (WDP). In a study performed by Toledo et al., MedDP was characterized by high consumption of vegetables, fruit, olive oil, wholegrain products, low fat dairy and poultry, and oily fish and nuts at low consumption of red meat and simple sugars. WDP, on the other hand, was characterized by high consumption of processed meats, red meat, fast-food products, eggs, full-fat dairy, highly processed products, sauces, and refined grain products, at low consumption of fish, nuts, or olive oil. The results of the study showed a positive relationship between adherence to MeDP and higher probability of establishing a pregnancy [34]. Similarly, Karayiannis et al. showed that better adherence to the Mediterranean-type diet in a six-month period

 doi:10.20944/preprints202309.0746.v1

before in vitro fertilization (IVF) was connected with a higher chance of achieving a clinical pregnancy and live birth among women younger than 35 years of age [35].

Moreover, the current data concerning diet and female infertility suggest that certain dietary modifications may be beneficial in the prevention of low-grade chronic inflammation present in PCOS and might lead to improvements in reproductive outcomes in these patients by regulating the menstruation cycles and lowering the probability of ovulatory infertility. Nevertheless, it is not currently clear whether particular dietary and lifestyle modifications have a beneficial impact on patients' reproductive outcomes of patients. Further studies combined with effective collection of nutritional data from patients seeking infertility treatment would provide crucial insight into the potential role of dietary modifications in improving reproductive outcomes in women with PCOS.

Dietary modifications may have a direct influence on body mass reduction and are one of the treatment options of group II diseases, which account for 85% of causes of ovulatory dysfunction. Due to the considerable importance of diet in the treatment of ovulatory dysfunction, it is necessary to fully determine what nutritional modifications are the most advisable in the treatment of ovulation disorders.

b. Insulin resistance (IR) vs. ovulatory infertility

Carbohydrate metabolism disorders are a serious and overly common problem nowadays, most often affecting people with excessive body weight or hormonal imbalances. IR is one condition of this type that affects both female and male fertility [36]. Literature discusses associations between IR and PCOS [37–44], hyperprolactinemia [15,45], endometriosis [46], and thyroid disorders [47,48]. However, the best studied disorder affecting ovulatory function in the context of IR is PCOS, which is in turn a factor contributing to ovulatory infertility.

IR is a metabolic disorder defined as the inability of a known quantity of insulin (exogenous or endogenous) to increase glucose uptake and use the glucose in the patient's body to the degree typical for the healthy population [49]. Certain lifestyle factors such as sedentary lifestyle, or improper dietary patterns leading to overweight or obesity have a negative impact of the sensitivity of human cells to insulin [50]. Insulin resistance is an independent predictor of impaired glucose tolerance, type 2 diabetes [51], and cardiovascular diseases in the general population [52]. Furthermore, insulin resistance is strongly connected with obesity [53]. It is known that lifestyle modifications through combined diet and exercise have a positive impact on tissue sensitivity to insulin and glucose homeostasis in overweight persons [54–57]. In addition, such modifications also result in reduced levels of pro-inflammatory markers in the body, whose elevated concentrations are also found in the course of insulin resistance [58] as well as PCOS [59]. Thus, considering the fact that PCOS constitutes one of the causes of ovulation disorders, it seems that insulin resistance and obesity need to be analyzed as possible indirect factors contributing to ovulatory infertility associated with lifestyle choices.

i. IR – PCOS vs. ovulatory infertility

A meta-analysis of data from 619 women in 14 studies, performed by Xing et al., showed that using insulin-sensitizing drugs had a positive influence on the frequency of menstruation, the profile of sex hormones, and metabolic parameters in overweight women and those with PCOS [43]. The results of a study performed by Lee et al. showed that Homa-IR (an indicator used to assess insulin resistance calculated on the basis of fasting insulin and glucose concentrations in serum) [60] correlated negatively with SHBG concentration ($R = -0.304$, $p < 0.0001$). However, no correlation with ovary volume or the number of follicles was found [44]. The results of these studies suggest that reduced insulin resistance may have a beneficial impact on ovulatory function, thus reducing the risk of ovulatory infertility.

A study performed by Gower et al., which included 30 women with PCOS, showed that a diet with reduced carbohydrate contents was connected with a 27% reduction in fasting insulin ($p < 0.001$) and a 23% reduction of the level of testosterone in serum ($p < 0.05$) [61]. This indicates that adhering to a diet with a reduced carbohydrate content was connected with reduced insulin resistance and an improved hormonal profile in women with PCOS. This may lead to improved ovulatory function

 doi:10.20944/preprints202309.0746.v1

and reduced ovulatory infertility. However, the quoted study was performed on a small number of women, therefore it can be expected that the conclusions formulated by the authors are preliminary, which is why performing more research in this area would be recommended.

ii. IR – overweight and obesity vs. ovulatory infertility

Overweight and obesity are also strongly directly connected with PCOS [62,63]. Approx. 50% of women with PCOS are overweight or obese, with most of them characterized by the abdominal phenotype, which means that the excess adipose tissue collects mainly around the abdomen [64]. Interestingly, even though obesity is not among the diagnostic criteria of PCOS, both overweight and non-overweight patients with PCOS have more visceral adipose tissue (VAT) than women without PCOS, while VAT is correlated positively with the total androgen level, which suggests that overweight plays an important role in PCOS [65]. Moreover, excess central adipose tissue is closely connected with low-grade chronic inflammation and IR, which may contribute to increased risk of PCOS [66,67]. Furthermore, due to their relationship with PCOS, overweight and obesity seem to play a role in the etiology of ovulatory infertility, but in order to establish its precise nature, i.e. correlative, causative, or coincidental, more clinical research is needed.

A study performed by Dietz de Loos et al. in 183 women showed that changes in the proportion of body mass had a statistically significant impact on the probability of occurrences of ovulatory dysfunction (estimation 0.157 SE 0.030, $p < 0.001$) and hyperandrogenism (estimation 0.097 SE 0.027, $p < 0.001$), with the frequency of occurrence of ovulatory dysfunction decreasing as a result of decreasing body mass and increasing as a result of increasing body mass. This means that a reduction in body mass alone led to improvements in both diagnostic features and PCOS phenotype [68]. These data allow to conclude that body mass normalization alone may result in an improvement of ovulatory function and reduction of ovulatory infertility.

Similarly, a study was performed by Dokras et al. in which the impact of body mass reduction on the health of women with PCOS was assessed. Three groups were compared, using hormonal contraception or intensive lifestyle changes, or both these interventions combined, in order to achieve a 10% reduction in body mass. All three groups showed marked improvement in general health condition. The group that used hormonal contraception with simultaneous implementation of lifestyle changes achieved the most pronounced improvement of results in the area of body hair, total testosterone concentration in serum, and general physical well-being compared to a single intervention [69]. While this finding cannot be interpreted as a direct associative relationship with ovulatory infertility, the fact that reduced body mass has a positive impact on the health of women with PCOS suggests that this same phenomenon may translate into a positive impact on ovulatory infertility; however, more research is needed in this area.

Research shows that hormonal imbalance is closely connected not only with insulin resistance but also obesity in patients with PCOS, which suggests that these co-dependent factors may have an impact on the more complex issue of ovulatory infertility.

iii. IR – hyperprolactinemia vs. ovulatory infertility

Numerous scientific studies have shown a link between IR and hyperprolactinemia [15,70–74]. Elevated levels of prolactin (PRL) are often associated with increased tissue resistance to insulin. Many scientific theories are proposed that explain the likely mechanisms behind this phenomenon. The issue of the reciprocal relationship between hyperprolactinemia and IR is important and certainly requires further research and observation.

In a 2009 study that included 16 hyperprolactinemic and 12 healthy subjects, HOMA-IR values were calculated for both groups. The baseline insulin level in patients with hyperprolactinemia was higher than that of the control group (6.85 +/- 4.68; 3.66 +/- 0.88 microU/ml respectively; $p < 0.05$). The mean HOMA-IR and HOMA-B values were higher in patients compared to the control group (1.49 +/- 1.30; 0.78 +/- 0.27 respectively; $p = 0.02$ and 136.28 +/- 72.53; 64.77 +/- 23.31, respectively, $p < 0.001$). This suggests that patients with hyperprolactinemia were more resistant to insulin than the controls [74].

Another study performed by dos Santos Silva et al. evaluated the prevalence of obesity, overweight, and IR in patients with prolactinoma resulting in hyperprolactinemia, before and after

 doi:10.20944/preprints202309.0746.v1

treatment resulting in normalization of prolactin (PRL). Twenty-two patients with prolactinoma completed six months of treatment. Their PRL levels normalized but no significant difference in BMI was observed. However, there was a significant decrease in insulin resistance index (HOMA-IR) and glucose levels as assessed by the homeostasis model [71].

The above studies suggest that an association exists between the occurrence of hyperprolactinemia and insulin resistance, which is in turn often associated with ovulation disorders. For this reason, it is worthwhile to conduct more research concerning the relationship between ovulatory infertility and hyperprolactinemia.

iv. IR – thyroid diseases vs. ovulatory infertility

A number of papers have shown that carbohydrate metabolism may be impaired in thyroid diseases with hyper- or hypothyroidism [75]. Moreover, several studies have shown that insulin resistance occurs in the course of hyperthyroidism, which has been associated with increased HOMA-IR, decreased Matsuda (i.e. insulin sensitivity index designed to indicate the values that are comparable to Rd (the rate of disappearance of plasma glucose) as measured by an insulin clamp (insulin infusion of 1mU/kg per minute, corrected at an insulin concentration of 100 microU/mL) with a glucose marker [76]) and Belfior (i.e. insulin resistance index (IRI), originally described by Belfior et al., based on the assessment of glucose and insulin levels during a 75 g glucose tolerance test [77]) indices, which clearly suggest the onset of insulin resistance [78–80]. Other studies have shown reduced tissue sensitivity to insulin in hypothyroidism [81,82]. Some other studies, however, do not support the above observations [83].

A number of studies suggest that severe thyroid dysfunction can lead to menstrual disorders and infertility through direct and indirect interactions with the hypothalamic-pituitary-ovarian axis and reproductive organs [20]. Insulin resistance may occur in both hypothyroidism and hyperthyroidism, which may be indirectly associated with ovulation disorders in women. Although papers on insulin resistance are conflicting in their conclusions, it would be worthwhile to perform more research in this area.

c. Oxidative stress vs. ovulatory infertility

Oxidative stress (OS) is a phenomenon that occurs when the systems of oxidation and anti-oxidation in the human body are imbalanced, which is connected with the presence and development of various diseases. Cigarette smoking, alcohol consumption, consumption of processed foods, certain medications, and pesticides contained in foods are among those factors that lead to excess production of pro-oxidative substances. In addition, factors that increase the risk of oxidative stress include air pollution, UV radiation, prolonged stress, as well as excess physical effort. Age is another important factor as the mechanisms that protect the body from free radicals weaken with age [84–86]. OS is one of the numerous factors that play an important role in ovulatory infertility [87–89], mainly through its involvement in the etiology of PCOS.

A systematic review and meta-analysis from 2013 performed for 68 studies in which 4933 patients with PCOS and 3671 control patients participated showed that concentrations of several byproducts of oxidative stress were significantly elevated in patients with PCOS compared to the control group. Moreover, the meta-analysis showed that certain antioxidant markers were lowered in PCOS. Concentrations of glutathione, which plays the main protective role against oxidative stress, were reduced in patients with PCOS, compared to the control group [89]. However, the authors of the meta-analysis did not show whether the factor that causes increased OS might be obesity, common in PCOS, or whether OS might be independent from overweight/obesity. The above findings suggest that, irrespective of whether or not association between co-morbid obesity and OS exists, it can be concluded that OS may be regarded as a factor contributing to ovulatory infertility through its etiological role in PCOS.

A literature review performed by Wenqian et al. discusses interactions between OS and hyperandrogenism, insulin resistance, and overweight/obesity in ovulatory dysfunction in PCOS [88]. PCOS, HA, and IR may be induced or aggravated in cases of OS imbalance. In the case of PCOS, high carbohydrate diet may induce OS increase, which results in the body entering low-grade chronic

 doi:10.20944/preprints202309.0746.v1

inflammation, at the same time increasing the production of androgens; it may also have an impact on disturbed action of insulin and aggravation of IR. High levels of insulin also further worsens HA. IR may also increase the level of free fatty acids (FFA) in serum, which in connection with high carbonate diet may increase OS. Moreover, oxidative stress interacts with HA and IR, creating a vicious circle in the emergence and progression of PCOS [88]. In addition, overweight and obesity, which often occur in PCOS, also contribute to the development of OS and low-grade chronic inflammation [90]. It can thus be concluded that hyperandrogenism, IR, and obesity all constitute indirect factors that contribute to ovulatory infertility through their complex associations with PCOS.

Apart from the role of OS in PCOS-related ovulatory infertility, it is also linked with another WHO type II disorder, i.e. endometriosis. A systematic literature review discussing the effects of oxidative stress on endometriosis confirms that oxidative stress negatively affects fertility in women with endometriosis. OS can affect various physiological functions, such as oocyte maturation, ovarian steroidogenesis, ovulation, and embryo implantation. An imbalance between pro- and antioxidant mechanisms leads to oxidative stress in the peritoneal milieu, follicular fluid, and ovarian environment, which may partially explain endometriosis-associated infertility [91].

Furthermore, oxidative stress is increasingly often linked with thyroid disorders [92–95]. It has also been shown that thyroid dysfunction may co-exist with ovulation disorders [20]. However, many of the mechanisms involved in the development of thyroid pathology are still unknown. Yet, a noticeable association exists between increased pro-oxidant production and oxidative damage, and the development of thyroid disease. In addition, thyroid disorders might also initiate or increase the release of reactive oxygen species (ROS) and thus oxidative stress, leading to increasing oxidative damage [96]. Since thyroid diseases are associated with oxidative stress, it can be inferred that in the case of concomitant thyroid diseases, fertility disorders may result from impaired ovulatory function and ovulatory infertility caused by exposure to oxidative stress. However, the literature review performed as part of this study did not produce publications directly linking oxidative stress to ovulatory infertility.

Similarly, no studies could be found linking exposure to oxidative stress with increased risk of hyperprolactinemia and a concomitant increased risk of ovulatory infertility. A single study could be produced, however, which shows that chronic estradiol exposure induces oxidative stress in the hypothalamus, reducing hypothalamic dopamine levels and causing hyperprolactinemia [97]. This leads to a provisory conclusion that OS-related factors may contribute to the development of hyperprolactinemia, which is associated with insulin resistance, ovulatory dysfunction, and ovulatory infertility, but more research is doubtlessly needed in this area.

On the basis of the studies discussed above, it can be inferred that a mutual interaction between the ovulatory function and OS exists in WHO group II disorders. This has an impact on ovulatory infertility. Correcting oxidative stress by reducing adipose tissue, medications, exercise, and/or lifestyle modifications may have a beneficial impact on these disorders. At this stage, however, due to the insufficient number of conclusive studies, controversies concerning the influence of oxidative stress on ovulatory infertility still exist.

d. Sleep vs. ovulatory infertility

Sleep is an important component of normal physiology with sleep disturbances a common occurrence in today's society. Abnormal sleep patterns are connected with health condition and co-morbidities such as obesity, hypertension, diabetes, depression, and low quality of life [98]. Moreover, disruption of circadian rhythms may be linked with menstrual disorders [99], which may in turn lead to ovulatory dysfunction and ovulatory infertility.

A study performed by Eisengerb et al. showed that sleep duration <6 hours (6.1% vs. 2.7%; $p < 0.001$), habitual snoring (37.8% vs. 19.0%; $p < 0.001$), and clinical sleepiness were more common in women with PCOS (12.0% vs. 8.6%; $p < 0.026$) compared to women with unexplained infertility [98]. This may indicate a positive relationship between sleep disturbances and ovulatory infertility, as opposed to idiopathic infertility. A meta-analysis performed in 2017 identified and included 8 studies with adult participants and 5 studies involving adolescents that linked PCOS with the risk of

 doi:10.20944/preprints202309.0746.v1

obstructive sleep apnea (OSA). The meta-analysis showed that the incidence of OSA was higher in adults (0.32; 95% CI: 0.13-0.55) compared to adolescents (0.08; 95% CI: 0.00-0.30) and that the risk of OSA was significantly higher in adult patients with PCOS (odds ratio (OR) 9.74, 95% CI: 2.76-34.41) [100]. Another meta-analysis, performed in 2022, showed that PCOS is positively correlated with the risk of sleep disturbances. The incidence of sleep disturbances was higher (OR = 11.24, 95% CI: 2.00-63.10, Z = 2.75, p = 0.006) in the group in which PCOS was present. Moreover, it was shown that sleepiness as assessed on the Epworth Sleepiness Scale (ESS) was also higher in the group of women with PCOS compared to healthy women (MD = 2.49, 95% CI: 0.80-4.18, Z = 2.88, p = 0.004) [101].

The above results indicate a strong relationship between PCOS and OSA, as well as other sleep disturbances in adult patients. Considering the increased risk of menstrual disorders in women with disturbed circadian rhythm, it can be expected that women suffering from sleep disorders may be more prone to ovulatory dysfunction and ovulatory infertility. Literature data, however, does not allow to connect sleep disturbances with ovulatory infertility in an unequivocal manner. Moreover, the nature of the relationship that exists between sleep disturbances and PCOS – and thus possibly also ovulatory infertility – is unclear, with studies leaning towards co-existence. This means that their results do not make it possible to indicate a possible causal relationship, or even a weaker type of relation. The uncertain nature of the relationships described above is further corroborated by other studies, which do not make a connection between sleep and PCOS. For instance, a study performed by de Sousa et al. did not show an increased incidence of obstructive sleep apnea in adolescents with PCOS, compared to healthy subjects from the control group [102].

In conclusion, sleep disturbances seem common in PCOS; however, most current research is limited due to small sample sizes. What is more, no studies can be found that link sleep disturbances with ovulatory infertility directly, which is why it would seem necessary to perform more research in the area.

e. Physical activity vs. ovulatory infertility

Physical activity is an important component of lifestyle modifications. Most papers are in agreement, e.g. indicating a positive influence of physical activity on the regularity of ovulation [103–107].

A systematic review from 2017 showed that exercise contributed to a reduction in insulin levels and free androgens in overweight and obese women, resulting in restoring regulated ovulation. Moreover, intensive exercise lasting 30-60 min./d were connected with reduced risk of non-ovulatory infertility. In addition, a negative impact of physical activity on ovulation was shown, i.e. increased risk of lack of ovulation in persons performing extremely intensive exercises (>60 min./d) [108]. The study indicates that persons who exercise intensively at increased risk of lack of ovulation are more prone to ovulatory infertility.

In a study performed by Mario et al., women with PCOS were studied in terms of leisure time physical activity (PA), which covers routine activities such as walking as a means of transport, shopping, or moderate movement, regardless of intensity. Active women (>= 7,500 steps/d) with PCOS had a better anthropometric and metabolic profile compared to women with PCOS of the same age preferring sedentary lifestyle (<7,500 steps/d) z PCOS. It was shown that the level of androgens was lower in the group of active women with PCOS compared to those with a sedentary lifestyle. Moreover, PA increased by 2,000 steps/d (regardless of the type of PA) was independently linked with a reduced free androgen index (FAI) in those women [109]. On the basis of this study, it can be concluded that increased leisure time physical activity improves the hormonal profile of women with PCOS, which may translate into improved ovulatory function and reduced risk of ovulatory infertility.

Similarly, a systematic review from 2011 showed that moderately intensive physical activity improves ovulation, reduces IR and body mass. In addition, the improvements did not depend on the type of exercise, their frequency, or the length of a single session [103]. Thus, the quoted study is yet another one which indicates that moderately intensive physical activity may have a beneficial influence on the ovulatory function and reduce ovulatory infertility.

 doi:10.20944/preprints202309.0746.v1

Considering the above, by treating the effects of metabolic disturbances or preventing them – through the introduction of regular physical activity – better reproductive and cardiometabolic outcomes can be achieved in the female population.

f. Supplementation vs. ovulatory infertility

As a balanced diet is an essential component of a healthy lifestyle, a steady supply of vitamins and minerals is important at every stage of life. However, proper supplementation is crucial for some groups of people, e.g. women of childbearing age, primarily due to the possibility of pregnancy. Vitamin and mineral deficiencies are being observed increasingly often in young women, with deficiencies of any of such components possibly having dangerous consequences for both the mother and the child [110]. For this reason, increasingly large numbers of women are choosing to reduce these deficiencies with vitamin supplementation.

As far as consumption of micronutrients is concerned, no definitive evidence has been produced as to the role most of them play in infertility. Apart from the proven negative correlation between periconceptional supplementation with folic acid and neural tube defects [111], there are only studies confirming that supplementation with 1,000mg/d of n-3 acids [112–115], 400 IU/d of vitamin E (in both studied groups vitamin E was administered together with omega-3 fatty acid) [113,115], 200 µg/d of selenium [116,117], 4,000-50,000 IU of vitamin D (higher doses of vitamin D, such as 50,000 IU, were given at 2-week intervals) – in one of the studies vitamin D was administered together with a probiotic; in another, with n-3 fatty acid, in the other two, without additional supplementation [118–121], or 100-200mg/d of coenzyme Q10 [122–124], had a beneficial effect of the health of women with PCOS. These results do not indicate, however, an impact on ovulatory infertility.

Inositol is a carboxylic sugar belonging to the vitamin B family. The two stereoisomers of inositol that are present in the human body are mio-inositol (MI) and D-chiro-inositol (DCI). They both play an important biological role as mediators in various actions of insulin. Inositol can be found in fruit, nuts, and beans and may be used as a dietary supplement. Around 1 g/d of inositol is consumed as part of a normal diet, but absorption of free inositol may be inhibited by glucose. Many previous meta-analyses indicated that MI has an impact on various endocrine parameters. A meta-analysis performed by Unfer et al. showed that patients with PCOS treated with MI had lowered testosterone and SHBG levels [125]. Another meta-analysis noted an influence of MI on the levels of SHBG, androstenedione, prolactin, and total testosterone in patients with PCOS [126]. In addition, a meta-analysis performed by Jethaliy et al. showed a significant influence of MI on the levels of androstenedione and prolactin only [127]. Meta-analyses performed by Zeng and Facchinetti et al., on the other hand, did not show a significant improvement in endocrine parameters such as testosterone level [128,129]. However, considering the prevalence of studies which indicate that the hormonal profile can be improved through the use of MI, it is worth studying whether its supplementation may positively affect the ovulatory function and reduce the risk of ovulatory infertility.

A meta-analysis from 2023, which identified twenty-six randomized controlled trials that included data from 1691 patients (806 inositol, 311 placebo, 509 metformin) showed that the risk of regular menstrual cycle was 1.79 times higher in patients treated with inositol compared to placebo (CI: 1.13; 2.85). What is more, inositols showed equivalence compared to metformin. As far as BMI (MD = -0.45; CI: -0.89; -0.02), free testosterone (MD = -0.41, CI: -0.69; -0.13), total testosterone (MD = -20.39, CI: - 40.12; -0.66), androstenedione (MD = -0.69, CI: -1.16; -0.22), glucose (MD = -3.14; CI: -5.75; -0.54), and AUC (area under the curve) of insulin (MD = -2081.05, CI: -2745.32; -1416.78) are concerned, treatment with inositol resulted in a greater BMI reduction compared to placebo. Inositol also significantly increased the level of globulin, which binds sex hormones, compared to placebo (MD = 32.06, CI: 1.27; 62.85). This meta-analysis suggests that inositol is a safe and effective method of treatment of PCOS. Moreover, inositols showed equivalency in terms of most of the results compared to the golden standard of treatment, i.e. metformin. However, due to the considerable discrepancies in the results of meta-analyses, it would be advisable to perform additional studies in the area [130].

 doi:10.20944/preprints202309.0746.v1

Moreover, several meta-analyses showed improvements in glycemic parameters such as fasting glucose concentration, fasting insulin concentration, glucose/insulin ratio, and HOMA after treatment with MI in patients with PCOS [125,126,128,129,131–133]. However, two other meta-analyses did not indicate an improvement in any of the aforementioned glycemic parameters in women with PCOS [4,127]. What is more, although inositol has been proposed for PCOS treatment, studies concerning the substance are in fact inconclusive as several meta-analyses did show a significant improvement in either BMI or WHR in patients with PCOS after treatment with MI [127–129]. However, the meta-analysis performed by Unfer et al. showed a reduction in BMI, but not WHR, in patients with PCOS after treatment with MI [131]. In conclusion, despite certain promising indications that there may be a negative relationship between inositol supplementation and ovulatory infertility, literature data is too conflicting at this point to conclude that its role is appreciatively more beneficial than placebo.

Limitations of the study

This study has several limitations, most of which are the result of its subject matter. First of all, the topics of lifestyle and diet are seldom studied in a rigorous clinical setting, with observational studies being more common. This results in a considerable uncertainty of results and a preliminary character of many of the studies. Moreover, infertility is a complex issue in itself, in terms of biology, biochemistry, as well as methodology. For this reason, most studies do not offer conclusions that would make it possible to establish clear associative links between the aspects discussed in this paper. Another issue is the complex inter-relationship between lifestyle factors, diet, and ovulatory infertility, especially in terms of insulin resistance, obesity, and PCOS, which makes separating the individual factors and establishing relationships between them exceptionally difficult. In addition, subject literature concerning ovulation disorders is very much biased towards PCOS, which is why data concerning other possible medical causes of ovulatory infertility is scarce. Last but not least, as the study attempts to point directions in an area of research that is characterized by a certain amount of vagueness, in particular as far as diet and lifestyle are concerned, it is burdened with those same issues that other pioneering studies deal with, i.e. a large degree of uncertainty as to the stated conclusions and the need for further research – in particular robust studies performed in clinical settings – in many of the analyzed areas.

4. Conclusions

Since various lifestyle factors seem to have a significant impact on ovulation and the occurrence of ovulatory infertility, it is important to find relationships between them and establish their degrees, which could lead to a reduction in the rate of ovulation disorders. Therefore, the classification and the areas for further research presented below are intended as starting points for studies – especially robust studies performed in clinical settings – that would establish links between ovulatory infertility and the factors that coincide or form a relationship with it. Identifying such links would prove clinically significant and possibly help to improve the comfort of women who want to become pregnant and increase the rate of spontaneous pregnancies.

Classification of relationships between ovulation disorders and lifestyle factors as probable causes of ovulatory infertility

Based on the performed literature review and taking into account the existing knowledge gaps, uncertainties, and possible research directions, the authors propose a classification of links between lifestyle factors and ovulatory infertility [Table 1]. The table below couples each of the lifestyle factors discussed in the previous section with a WHO Group II disorder (or several disorders), in accordance with the analyzed literature data. Moreover, the degree of relationship between a particular factor and ovulatory infertility is established in each case. The authors excluded WHO Group I and III from the classification, since the influence of lifestyle factors on ovulatory infertility in these cases seems negligible.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 September 2023 doi:10.20944/preprints202309.0746.v1

Table 1. Classification of relationships between ovulation disorders and lifestyle factors in ovulatory infertility.

Lifestyle factor	Possibly related WHO Classification Group II disorder	Degree of relationship with ovulatory infertility
Diet	PCOS	Possible positive/negative relationship Co-dependence with obesity and insulin resistance
Insulin Resistance	PCOS, hyperprolactinemia, thyroid dysfunction	Possible positive relationship Co-dependence with diet and obesity
Oxidative stress	PCOS, hyperprolactinemia, thyroid dysfunction, endometriosis	Probable positive relationship (degree of relationship varies depending on the disorder) Co-dependence with insulin resistance
Sleep	PCOS	Unknown, possible association
Physical activity	PCOS	Possible negative relationship Possible weak positive relationship Co-dependence with obesity
Supplementation	PCOS	Negligible

Areas for further research

When analyzing the results of the literature review and the proposed classification presented above, the authors paid special attention to applying a highly critical approach to identifying possible areas for further research. First of all, the aspect of clinical significance was regarded as a priority. In other words, those interventions that may feasibly lead to improvements in clinical practice and patient outcomes concerning ovulatory infertility were identified as benefitting further studies. Thus, in order to avoid the common mistake of indicating any area where data is inconclusive as worthy of further research, the authors used their varied expertise in fertility medicine, nutrition, and critical thinking as applied to research. Hence, care was taken to single out those areas in which performing further studies may in fact constitute a waste of resources due to the extremely low probability that results of such studies would have a noticeable impact on the clinical significance of such areas. Consequently, the authors feel that greater attention should be paid to those issues that indeed show promise as far as clinical practice is concerned.

Both hyperprolactinemia [16,17] and thyroid disorders [19] can undeniably result in irregular menstruation and ovulation disorders. They have also been connected to some degree with ovulatory infertility [17,18,21]. However, they have not been proven to be direct causes of ovulatory infertility due to the considerable proportion of spontaneous pregnancies that occur in the course of these disorders [17,18,20]. Moreover, both hyperprolactinemia [15] and thyroid disorders [134] are accompanied by insulin resistance to a greater degree in women experiencing infertility issues than in healthy individuals. It is also known that insulin resistance can be a major problem in the case of ovulatory infertility [135–137]. Given the close relationship between symptoms associated with both hyperprolactinemia and thyroid disorders and ovulatory infertility, it would be advisable to study the relationships in terms of possible causal relationships.

As far as endometriosis is concerned, the condition affects the fallopian tubes, causing abnormalities in their function which can definitely affect ovulatory infertility. Although associations between endometriosis and infertility are well supported in literature, any specific causal relationship is still controversial [23]. In addition, studies are unlikely to link endometriosis with insulin resistance, despite the fact that it often occurs in the course of ovulation disorders. For this reason, this direction of research does not seem promising. Nevertheless, given the high prevalence of endometriosis in women of childbearing age and the morbidity associated with it, it would be worthwhile to conduct more studies concerning the direct cause of ovulatory infertility in the context of endometriosis.

In terms of insulin resistance, it cannot be conclusively stated that it constitutes a direct cause of ovulatory infertility. Above all, insulin resistance itself is a secondary condition, with causes ranging from improper diet to insufficient physical activity. What makes insulin resistance a matter worth investigating in the context of ovulation fertility is its relationship not only with the aforementioned

 doi:10.20944/preprints202309.0746.v1

lifestyle factors but also with PCOS [36]. The relationship appears to be a particularly complex one and the authors feel that studies concerning its exact nature may produce valuable insights into the issues of both the causes and effects of ovulatory infertility – as well as insulin resistance and PCOS. At this stage, what appears to be fairly certain as far as research directions are concerned is that the aspect of causality is particularly worth exploring.

An inadequate diet significantly increases the risk of obesity, which is associated with a number of adverse effects on the mother and the fetus during the prenatal period. Moreover, it has a negative impact on female fertility, i.e. obese women are more prone to ovulation disorders due to dysregulation of the hypothalamic-pituitary-ovarian axis [138]. It has also been shown that following the obesity-promoting Western diet, rich in saturated fats, animal protein, and simple sugars, is associated with a higher risk of ovulatory infertility [29–31,33]. Furthermore, it has been well established that obesity plays a key role in the onset of insulin resistance [139], which often co-occurs with ovulation disorders. Thus, weight reduction is one option of treatment of ovulation disorders; there are no studies, however, that would establish a direct link between inadequate diet and the development of ovulatory infertility. Given the high incidence of obesity-related problems, it would be worthwhile to conduct more studies examining the direct link between obesity/improper diet and ovulatory infertility.

Physical activity may have a bidirectional effect on ovulation disorders. Studies have shown that intense exercise of 30-60 min./d are associated with a reduced risk of non-ovulatory infertility. In contrast, increased risk of non-ovulation has been reported in women who exercise very intensively (>60 min./d), who are often co-morbidly underweight, with impaired HPA function [108]. Therefore, it can be assumed that excessive physical activity may lead to ovulation disorders and, consequently, ovulatory infertility. However, more research on the role of long-term/intensive training and chronic energy deficit in the context of ovulatory infertility is needed.

Although sleep quality appears to be a factor associated with ovulatory infertility, literature data does not provide a definite link between sleep disorders and ovulatory infertility. Moreover, the degree of the relationship between sleep disorders and ovulatory infertility is unclear. Its uncertain nature, discussed earlier in this paper, is further confirmed by other studies that show no association between sleep and PCOS [102]. Therefore, sleep quality is probably a factor that does not merit further investigation in relation to ovulatory infertility, or should at least be prioritized lower than more clinically relevant areas of research.

Similarly, despite the fact that oxidative stress seems to have a significant impact on ovulatory disorders, there is much inconclusive research on the topic while the phenomenon of oxidative stress itself is a very broad research area [89]. This is why would be worthwhile to conduct studies focused on specific oxidative stress triggers, which could narrow down the topic and lead to results that would be clinically applicable.

Inositol supplementation might be a promising method of treatment of ovulatory infertility [130]. However, since literature data is too conflicting at this point to conclude that its role is more beneficial than placebo, more high-quality studies on the topic would need to be conducted to confirm these preliminarily suggested relationships.

It is worth emphasizing that based on the viability of the areas for research indicated in the previous chapter, clinical and observational studies aimed at establishing the precise nature and degree of relationship between lifestyle factors and ovulatory infertility could be designed and performed. Obviously, the nature of infertility as a research problem makes it difficult to collect robust conclusive data; however, when taking into consideration the results of published studies, certain promising directions of research can be established, as well as those that do not appear to be worth pursuing.

Author Contributions: Conceptualization R.M., M.S.; methodology R.M., M.S., M.P.; formal analysis M.S.; resources R.M.; writing—original draft preparation M.S.; writing—review and editing M.P., M.S.; supervision R.M.; funding acquisition R.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: No subjects were involved in the study.

Data Availability Statement: Not applicable.

Acknowledgments: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Boivin, J.; Bunting, L.; Collins, J.A.; Nygren, K.G. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Hum. Reprod.* **2007**, 22, 1506-1512.
2. Vander Borght, M.; Wyns, C. Fertility and infertility: Definition and epidemiology. *Clin. Biochem*. **2018**, 6, 2-10.
3. National Collaborating Centre for Women's and Children's Health (UK). Fertility: Assessment and Treatment for People with Fertility Problems. London: Royal College of Obstetricians & Gynaecologists, February **2013**.
4. The Practice Committee of the American Society for Reproductive Medicine. Use of insulin-sensitizing agents in the treatment of polycystic ovary syndrome. *Fertil. Steril.* **2008**, 90, S69-S73.
5. Carson, S.A.; Kallen, A.N. Diagnosis and Management of Infertility: A Review. *JAMA* **2021**, 326, 65-76.
6. Naseem, H.; Lokman, M.; Fitzgerald C. Management of congenital hypogonadotropic hypogonadism in females. *Human Fertility* **2021**, 1-10.
7. Polson, D.W.; Adams, J.; Wadsworth, J.; Franks, S. Polycystic ovaries–a common finding in normal women. *Lancet* **1988**, 1, 870-2,
8. Legro, R. S.; Arslanian, S.A.; Ehrmann, D.A.; Hoeger, K.M.; Murad, M.H.; Pasquali, R.; Welt, C.K. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society Clinical Practice Guideline. *J. Clin. Endocrinol. Metab.* **2013**, 98, 4565-4592.
9. National Institutes of Health. Evidence-based Methodology Workshop on Polycystic Ovary Syndrome (Final Report). **2012**; URL: https://prevention.nih.gov/sites/default/files/2018-06/FinalReport.pdf.
10. Monash University. Available online: https://www.monash.edu/__data/assets/pdf_file/0004/1412644/PCOS_Evidence-Based-Guidelines_20181009.pdf (accessed on 04.09.2023).
11. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Human reproduction* **2004**, 19, 41-47.
12. Escobar-Morreale, H. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. *Nat Rev Endocrinol* **2018**, 14, 270-284.
13. Hart, R. PCOS and infertility. *Panminerva Med.* **2008**, 50, 305-314.
14. Zehravi, M.; Maqbool, M.; Ara, I. Polycystic ovary syndrome and infertility: an update. *Int J Adolesc Med Health.* **2021**, 34, 1-9.
15. Gierach, M.; Bruska-Sikorska, M.; Rojek, M.; Junik, R. Hyperprolactinemia and insulin resistance. *Endokrynol Pol.* **2022**, 73, 959-967.
16. Glezer, A.; Bronstein, M.D; Prolactinoma. *Arq Bras Endocrinol Metabol.* **2014**, 58, 118-123.
17. Capozzi, A.; Scambia, G.; Pontecorvi, A.; Lello S. Hyperprolactinemia: pathophysiology and therapeutic approach. *Gynecol Endocrinol.* **2015**, 31, 506-510.
18. Majumdar, A.; Mangal, N.S. Hyperprolactinemia. *J Hum Reprod Sci.* **2013**, 6, 168-175.
19. Medenica, S.; Nedeljkovic, O.; Radojevic, N.; Stojkovic, M.; Trbojevic, B.; Pajovic, B. Thyroid dysfunction and thyroid autoimmunity in euthyroid women in achieving fertility. *Eur Rev Med Pharmacol Sci.* **2015**, 19, 977-987.
20. Poppe, K. Management of Endocrine Diseases: Thyroid and female infertility: more questions than answers! *Eur J Endocrinol.* **2021**, 184, R123-R135.
21. Burney, R.O.; Giudice, L.C. Pathogenesis and pathophysiology of endometriosis. *Fertil Steril.* **2012**, 98, 511-519.
22. Mehedintu, C.; Plotogea, M.N.; Ionescu, S.; Antonovici, M. Endometriosis still a challenge. *J Med Life.* **2014**, 7, 349-357.
23. Macer, M.L.; Taylor, H.S. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. *Obstet Gynecol Clin North Am.* **2012**, 39, 535-549.
24. Filip, L.; Duică, F.; Prădatu, A.; Crețoiu, D.; Suciu, N.; Crețoiu, S.M.; Predescu, D.V.; Varlas, V.N.; Voinea, S.C. Endometriosis Associated Infertility: A Critical Review and Analysis on Etiopathogenesis and Therapeutic Approaches. *Medicina* **2020**, 56, 460.
25. De Vos, M.; Devroey, P.; Fauser, B.C. Primary ovarian insufficiency. *Lancet* **2010**, 376, 911-921.

26. Kawamura, K.; Cheng, Y.; Suzuki, N.; Deguchi, M.; Sato, Y.; Takae, S.; Ho, C.H.; Kawamura, N.; Tamura, M.; Hashimoto, S.; Sugishita, Y.; Morimoto, Y.; et al. Hippo signaling disruption and act stimulation of ovarian follicles for infertility treatment. *Proc Natl Acad Sci U S A.* **2013**, 110, 17474-79.
27. Fraison, E.; Crawford, G.; Casper, G.; Harris, V.; Ledger, W. Pregnancy following diagnosis of premature ovarian insufficiency: a systematic review. *Reprod Biomed Online.* **2019**, 39, 467-76.
28. Skoracka, K.; Ratajczak, A.E.; Rychter, A.M.; Dobrowolska, A.; Krela-Kaźmierczak, I. Female Fertility and the Nutritional Approach: The Most Essential Aspects. *Adv. Nutr.* **2021**, 12, 2372-2386.
29. Grieger, J.A.; Grzeskowiak, L.E.; Bianco-Miotto, T.; Jankovic-Karasoulos, T.; Moran, L.J.; Wilson, R.L.; Leemaqz, S.Y.; Poston, L.; McCowan, L.; Kenny, L.C.; et al. Pre-pregnancy fast food and fruit intake is associated with time to pregnancy. *Hum Reprod*. **2018**, 33, 1063-70.
30. Chavarro, J.E.; Rich-Edwards, J.W.; Rosner, B.A.; Willett, W.C. Protein intake and ovulatory infertility. *Am. J. Obstet. Gynecol*. **2008**, 198, 210.e1-7
31. Çekici, H.; Akdevelioğlu, Y. The association between trans fatty acids, infertility and fetal life: a review. *Hum. Fertil*. **2019**, 22, 154-163.
32. Mumford, S.L.; Chavarro, J.E.; Zhang, C.; Perkins, N.J.; Sjaarda, L.A.; Pollack, A.Z.; Schliep, K.C.; Michels, K.A.; Zarek, S.M.; Plowden, T.C; et al. Dietary fat intake and reproductive hormone concentrations and ovulation in regularly menstruating women. *Am. J. Clin. Nutr.* **2016**, 103, 868-877.
33. Chavarro, J.E.; Rich-Edwards, J.W.; Rosner, B.A.; Willett, W.C. Dietary fatty acid intakes and the risk of ovulatory infertility. *Am. J. Obstet. Gynecol*. **2007**, 85, 231-237.
34. Toledo, E.; Lopez-del Burgo, C.; Ruiz-Zambrana, A.; Donazar, M.; Navarro-Blasco, I.; Martínez-González, M. A.; de Irala, J. Dietary patterns and difficulty conceiving: a nested case-control study. *Fertil. Steril*. **2011**, 96, 1149-1153.
35. Karayiannis, D.; Kontogianni, M.D.; Mendorou, C.; Mastrominas, M.; Yiannakouris, N. Adherence to the Mediterranean diet and IVF success rate among non-obese women attempting fertility. *Hum. Reprod*. **2018**, 33, 494-502.
36. Zańko, A.; Siewko, K.; Krętowski, A.J.; Milewski, R. Lifestyle, Insulin Resistance and Semen Quality as Co-Dependent Factors of Male Infertility. *Int. J. Environ. Res. Public Health* **2023**, 20, 732.
37. Zeng, X.; Xie, Y.J.; Liu, Y.T.; Long, S.L.; Mo, Z.C. Polycystic ovarian syndrome: Correlation between hyperandrogenism, insulin resistance and obesity. *Clin. Chim. Acta.* **2020**, 502, 214-221.
38. Androulakis, I.I.; Kandaraki, E.; Christakou, C.; Karachalios, A.; Marinakis, E.; Paterakis, T.; Diamanti-Kandarakis, E. Visceral adiposity index (VAI) is related to the severity of anovulation and other clinical features in women with polycystic ovary syndrome. *Clin. Endocrinol*. **2014**, 81, 426-431.
39. Landay, M.; Huang, A.; Azziz, R. Degree of hyperinsulinemia, independent of androgen levels, is an important determinant of the severity of hirsutism in PCOS. *Fertil. Steril*. **2009**, 92, 643-647.
40. Stepto, N.K.; Cassar, S.; Joham, A.E.; Hutchison S.K; Harrison C.L.; Goldstein R.F.; Teede H.J. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic-hyperinsulaemic clamp. *Hum. Reprod*. **2013**, 28, 777-784.
41. Moran, L.J.; Noakes, M.; Clifton, P.M.; Tomlinson, L.; Galletly, C.; Norman, R.J. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab*. **2003**, 88, 812-819.
42. Morley, L.C.; Tang, T.; Yasmin, E.; Norman, R.J.; Balen, A.H. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database Syst. Rev*. **2017**, 11, CD003053.
43. Xing, C.; Li, C.; He, B. Insulin Sensitizers for Improving the Endocrine and Metabolic Profile in Overweight Women With PCOS. *J. Clin. Endocrinol. Metab*. **2020**, 105, 2950-2963.
44. Lee, D.E.; Park, S.Y.; Park, S.Y.; Lee, S.R.; Chung, H.W.; Jeong, K. Clinical and Biochemical Profiles according to Homeostasis Model Assessment-insulin Resistance (HOMA-IR) in Korean Women with Polycystic Ovary Syndrome. *J. Menopausal. Med.* **2014**, 20, 104-110.
45. Atmaca, A.; Bilgici, B.; Ecemis, G.C.; Tuncel, O.K. Evaluation of body weight, insulin resistance, leptin and adiponectin levels in premenopausal women with hyperprolactinemia. *Endocrine* **2013**, 44, 756-761.
46. Yang, B.; Xie, L.; Zhang, H.; Zhu, Q.; Du, Y.; Luo, X.; Chen, X. Insulin resistance and overweight prolonged fertility-sparing treatment duration in endometrial atypical hyperplasia patients. *Journal of gynecologic oncology* **2018**, 29, e35.
47. Kapadia, K.B.; Bhatt, P.A.; Shah, J.S. Association between altered thyroid state and insulin resistance. *J Pharmacol Pharmacother*. 2**012**, 3, 156-160.
48. Gursoy, A. Rising thyroid cancer incidence in the world might be related to insulin resistance. *Med Hypotheses.* **2010**, 74, 35-36.
49. Lebovitz, H.E. Insulin resistance: definition and consequences. *Exp. Clin. Endocrinol. Diabetes* **2001**, 109, 135-148.
50. Reaven, G.M. The insulin resistance syndrome: definition and dietary approaches to treatment. *Annu. Rev. Nutr*. **2005**, 25, 391406.

51. Lee, S.H.; Park, S.Y.; Choi, C.S. Insulin Resistance: From Mechanisms to Therapeutic Strategies. *Diabetes. Metab. J.* **2022**; 46, 15-37.
52. Hill, M.A.; Yang, Y.; Zhang, L.; Sun, Z.; Jia, G.; Parrish, A. R.; Sowers, J. R. Insulin resistance, cardiovascular stiffening and cardiovascular disease. *Metabolism* **2021**, 119, 154766.
53. Kahn, B.B.; Flier, J.S. Obesity and insulin resistance. *The Journal of clinical investigation* **2000**, 106, 473-481.
54. Monzillo, L.U.; Hamdy, O.; Horton, E.S.; Ledbury, S.; Mullooly, C.; Jarema, C.; Porter, S.; Ovalle, K.; Moussa, A.; Mantzoros, C. S. Effect of lifestyle modification on adipokine levels in obese subjects with insulin resistance. *Obes. Res*. **2003**, 11, 1048-1054.
55. Risérus, U.; Arnlöv, J.; Berglund, L. Long-term predictors of insulin resistance: role of lifestyle and metabolic factors in middle-aged men. *Diabetes Care* **2007**, 30, 2928-2933.
56. Bird, S.R.; Hawley, J.A. Update on the effects of physical activity on insulin sensitivity in humans. *BMJ Open Sport Exerc. Med*. **2017**, 2, e000143.
57. Wilcox, G. Insulin and insulin resistance. *Clin. Biochem. Rev*. **2005**, 26, 19-39.
58. Matulewicz, N.; Karczewska-Kupczewska, M. Insulin resistance and chronic inflammation. *Postepy Hig. Med. Dosw*. **2016**, 70, 1245-1258.
59. Rudnicka, E.; Suchta, K.; Grymowicz, M.; Calik-Ksepka, A.; Smolarczyk, K.; Duszewska, A.M.; Smolarczyk, R.; Meczekalski, B. Chronic Low Grade Inflammation in Pathogenesis of PCOS. *Int. J. Mol. Sci*. **2021**, 22, 3789.
60. Qu, H.Q.; Li, Q.; Rentfro, A.R.; Fisher-Hoch, S.P.; McCormick, J.B. The definition of insulin resistance using HOMA-IR for Americans of Mexican descent using machine learning. *PloS one* **2011**, 6, e21041.
61. Gower, B.A.; Chandler-Laney, P.C.; Ovalle, F.; Goree, L.L.; Azziz, R.; Desmond, R.A.; Granger, W.M.; Goss, A.M.; Bates, G.W. Favourable metabolic effects of a eucaloric lower-carbohydrate diet in women with PCOS. *Clin. Endocrinol.* **2013**, 79, 550-557.
62. Legro, R.S. The genetics of obesity: lessons for polycystic ovary syndrome. *Ann. N. Y. Acad. Sci.* **2000**, 900, 193-202.
63. Balen, A.H.; Conway, G.S.; Kaltsas, G.; Techatrasak, K.; Manning, P.J.; West, C. Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. *Hum. Reprod*. **1995**, 10, 2107-2111.
64. Gambineri, A.; Pelusi, C.; Vicennati, V.; Pagotto, U.; Pasquali, R. Obesity and the polycystic ovary syndrome. *Int. J. Obes. Relat. Metab. Disord.* **2002**, 26, 883-896.
65. Jena, D.; Choudhury, A.K.; Mangaraj, S.; Singh, M.; Mohanty, B.K.; Baliarsinha, A.K. Study of Visceral and Subcutaneous Abdominal Fat Thickness and Its Correlation with Cardiometabolic Risk Factors and Hormonal Parameters in Polycystic Ovary Syndrome. *Indian J. Endocrinol. Metab.* **2018**,22, 321-327.
66. Song, F.; Jia, W.; Yao, Y.; Hu, Y.; Lei, L.; Lin, J.; Sun, X.; Liu, L. Oxidative stress, antioxidant status and DNA damage in patients with impaired glucose regulation and newly diagnosed Type 2 diabetes. *Clin. Sci.* **2007**, 112, 599-606.
67. Huang, Z.H.; Manickam, B.; Ryvkin, V.; Zhou, X.J.; Fantuzzi, G.; Mazzone, T.; Sam, S. PCOS is associated with increased CD11c expression and crown-like structures in adipose tissue and increased central abdominal fat depots independent of obesity. *J. Clin. Endocrinol. Metab.* **2013**, 98, E17-E24.
68. Dietz de Loos, A.L.P.; Jiskoot, G.; Timman, R.; Beerthuizen, A.; Busschbach, J.J.V.; Laven, J.S.E. Improvements in PCOS characteristics and phenotype severity during a randomized controlled lifestyle intervention. *Reprod. Biomed*. **2021**, 43, 298-309.
69. Dokras, A.; Sarwer, D.B.; Allison, K.C.; Milman, L.; Kris-Etherton, P.M.; Kunselman, A.R.; Stetter, C.M.; Williams, N.I.; Gnatuk, C.L.; Estes, S.J.; Fleming, J.; Coutifaris, C.; Legro, R.S. Weight Loss and Lowering Androgens Predict Improvements in Health-Related Quality of Life in Women With PCOS. *J. Clin. Endocrinol. Metab*. **2016**, 101, 2966-2974.
70. Berinder, K.; Nyström, T.; Höybye, C.; Hall, K.; Hulting, A. L. Insulin sensitivity and lipid profile in prolactinoma patients before and after normalization of prolactin by dopamine agonist therapy. *Pituitary* **2011**, 14, 199–207.
71. dos Santos Silva, C. M.; Barbosa, F. R.; Lima, G. A.; Warszawski, L.; Fontes, R.; Domingues, R. C.; Gadelha, M. R. BMI and metabolic profile in patients with prolactinoma before and after treatment with dopamine agonists. *Obesity* **2011**, 19, 800–805.
72. Tuzcu, A.; Bahceci, M.; Dursun, M.; Turgut, C.; Bahceci, S. Insulin sensitivity and hyperprolactinemia. *J Endocrinol Invest.* **2003**, 26, 341–346.
73. Yavuz, D.; Deyneli, O.; Akpinar, I.; Yildiz, E.; Gözü, H.; Sezgin, O.; Haklar, G.; Akalin, S. Endothelial function, insulin sensitivity and inflammatory markers in hyperprolactinemic pre-menopausal women. *Eur J Endocrinol.* **2003**, 149, 187–193.
74. Tuzcu, A.; Yalaki, S.; Arikan, S.; Gokalp, D.; Bahcec, M.; Tuzcu, S. Evaluation of insulin sensitivity in hyperprolactinemic subjects by euglycemic hyperinsulinemic clamp technique. *Pituitary* **2009**, 12, 330–334.
75. Gierach, M.; Gierach, J.; Junik, R. Insulin resistance and thyroid disorders. Endokrynol Pol. **2014**, 65, 70-76.
76. Matsuda, M.; DeFronzo, R.A. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* **1999**, 22, 1462–1470.

77. Belfiore, F.; Iannello, S.; Volpicelli, G. Insulin sensitivity indices calculated from basal and OGTT-induced insulin, glucose, and FFA levels. *Mol Genet Metab* **1998**, 63, 134-41.
78. Donckier, J.E. Endocrine diseases and diabetes. W: Pickup J.C., Williams G. (red.). Textbook of diabetes. Blackwell Publishing 2003: 27.1–27.15
79. Yavuz, D.G.; Yuksel, M.; Deyneli, O.; Ozen, Y.; Aydin, H.; Akalin, S. Association of serum paraoxonase activity with insulin sensitivity and oxidative stress in hyperthyroid and TSH-suppressed nodular goitre patients. *Clin Endocrinol* **2004**; 61: 515–521.
80. Yavuz, D. G.; Yazici, D.; Toprak, A.; Deyneli, O.; Aydin, H.; Yüksel, M.; Akalin, S. Exogenous subclinical hyperthyroidism impairs endothelial function in nodular goiter patient. *Thyroid* **2008**, 18, 395–400.
81. Rochon, C.; Tauveron, I.; Dejax, C.; Benoit, P.; Capitan, P.; Fabricio, A.; Berry, C.; Champredon, C.; Thieblot, P.; Grizard, J. Response of glucose disposal to hyperinsulinaemia in human hypothyroidism and hyperthyroidism. *Clin Sci* **2003**, 104, 7–15.
82. Stanická, S.; Vondra, K.; Pelikánová, T.; Vlcek, P.; Hill, M.; Zamrazil, V. Insulin sensitivity and counterregulatory hormones in hypothyroidism and during thyroid hormone replacement therapy. *Clin Chem Lab Med* **2005**, 43, 715–720.
83. Owecki, M.; Nikisch, E.; Sowiński, J. Hypothyroidism has no impact on insulin sensitivity assessed with HOMA-IR in totally thyroidectomized patients. *Acta Clin Belg* **2006**, 61, 69–73.
84. Preiser, J.C. Oxidative Stress. *JPEN J Parenter Enteral Nutr* **2012**, 36, 147-154.
85. Aseervatham, G.S.; Sivasudha, T.; Jeyadevi, R.; Arul Ananth, D. Environmental factors and unhealthy lifestyle influence oxidative stress in humans-an overview. *Environ. Sci. Pollut. Res. Int.* **2013**, 20, 4356-4369.
86. Al-Gubory, K.H. Environmental pollutants and lifestyle factors induce oxidative stress and poor prenatal development. *Reprod. Biomed.* **2014**, 29, 17-31.
87. Rudnicka, E.; Duszewska, A.M.; Kucharski, M.; Tyczyński, P.; Smolarczyk, R. Oxidative stress and reproductive function: oxidative stress in polycystic ovary syndrome. *Reproduction* **2022**, 164, F145-F154.
88. Li, W.; Liu, C.; Yang, Q.; Zhou, Y.; Liu, M.; Shan, H. Oxidative stress and antioxidant imbalance in ovulation disorder in patients with polycystic ovary syndrome. *Front Nutr.* **2022**, 9, 1018674.
89. Murri, M.; Luque-Ramírez, M.; Insenser, M.; Ojeda-Ojeda, M.; Escobar-Morreale, H.F. Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): a systematic review and meta-analysis. *Hum. Reprod. Update* **2013**, 19, 268-288.
90. Puschel, G.P.; Klauder, J.; Henkel, J. Macrophages, low-grade inflammation, insulin resistance and hyperinsulinemia: a mutual ambiguous relationship in the development of metabolic diseases. *J. Clin. Med.* **2022**, 11, 4358.
91. Scutiero, G.; Iannone, P.; Bernardi, G.; Bonaccorsi, G.; Spadaro, S.; Volta, C. A.; Greco, P.; Nappi, L. Oxidative Stress and Endometriosis: A Systematic Review of the Literature. *Oxidative medicine and cellular longevity* **2017**, 7265238.
92. Fortunato, R.S.; Ferreira, A.C.; Hecht, F.; Dupuy, C.; Carvalho, D.P. Sexual dimorphism and thyroid dysfunction: a matter of oxidative stress? *J Endocrinol.* **2014**, 221, R31-R40.
93. Mancini, A.; Di Segni, C.; Raimondo, S.; Olivieri, G.; Silvestrini, A.; Meucci, E.; Currò, D. Thyroid Hormones, Oxidative Stress, and Inflammation. *Mediators of inflammation* **2016**, 6757154.
94. Macvanin, M.T.; Gluvic, Z.; Zafirovic, S.; Gao, X.; Essack, M.; Isenovic, E.R. The protective role of nutritional antioxidants against oxidative stress in thyroid disorders. *Front Endocrinol.* **2023**, 13, 1092837.
95. Ameziane, E.l.; Hassani, R.; Buffet, C.; Leboulleux, S., Dupuy, C. Oxidative stress in thyroid carcinomas: biological and clinical significance. *Endocr Relat Cancer.* **2019**, 26, R131-R143.
96. Kochman, J.; Jakubczyk, K.; Bargiel, P.; Janda-Milczarek, K. The Influence of Oxidative Stress on Thyroid Diseases. *Antioxidants* **2021**, 10, 1442.
97. MohanKumar, S.M.; Kasturi, B.S.; Shin, A.C.; Balasubramanian, P.; Gilbreath, E.T.; Subramanian, M.; Mohankumar, P.S. Chronic estradiol exposure induces oxidative stress in the hypothalamus to decrease hypothalamic dopamine and cause hyperprolactinemia. *American journal of physiology. Regulatory, integrative and comparative physiology* **2021**, 300, R693-R699.
98. Eisenberg, E.; Legro, R.S.; Diamond, M.P.; Huang, H.; O'Brien, L.M.; Smith, Y.R.; Coutifaris, C.; Hansen, K.R.; Santoro, N.; Zhang, H. Sleep Habits of Women With Infertility. *J. Clin. Endocrinol. Metab.* **2021**, 106, e4414-e4426.
99. Baker, F.C.; Driver, H.S. Circadian rhythms, sleep, and the menstrual cycle. *Sleep Med.* **2007**, 8, 613-622.
100. Helvaci, N.; Karabulut, E.; Demir, A.U.; Yildiz, B.O. Polycystic ovary syndrome and the risk of obstructive sleep apnea: a meta-analysis and review of the literature. *Endocr. Connect.* **2017**, 6, 437-445.
101. Wang, C.; Huang, T.; Song, W.; Zhu, J.; Liu, Y.; Chen, X.; Sun, X.; Wu, Q.; Chen, H.; Liao, H.; et al. A meta-analysis of the relationship between polycystic ovary syndrome and sleep disturbances risk. *Front. Physiol.* **2022**, 13, 957112.
102. de Sousa, G.; Schlüter, B.; Buschatz, D.; Menke, T.; Trowitzsch, E.; Andler, W.; Reinehr, T. A comparison of polysomnographic variables between obese adolescents with polycystic ovarian syndrome and healthy, normal-weight and obese adolescents. *Sleep Breath* **2010**, 14, 33-38.

103. Harrison, C.L.; Lombard, C.B.; Moran, L.J.; Teede, H.J. Exercise therapy in polycystic ovary syndrome: a systematic review. *Hum. Reprod. Update* **2011**, 17, 171–183.
104. Kort, J.D.; Winget, C.; Kim, S.H.; Lathi, R.B. A retrospective cohort study to evaluate the impact of meaningful weight loss on fertility outcomes in an overweight population with infertility. *Fertil. Steril*. **2014**, 101, 1400-1403.
105. Nybacka, Å.; Carlström, K.; Ståhle, A.; Nyrén, S.; Hellström, P. M.; Hirschberg, A.L. Randomized comparison of the influence of dietary management and/or physical exercise on ovarian function and metabolic parameters in overweight women with polycystic ovary syndrome. *Fertil Steril.* **2011**, 96, 1508-1513.
106. Hutchison, S.K.; Stepto, N.K.; Harrison, C.L.; Moran, L.J.; Strauss, B.J.; Teede, H.J. Effects of exercise on insulin resistance and body composition in overweight and obese women with and without polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **2011**, 96, E48-56.
107. Palomba, S.; Giallauria, F.; Falbo, A.; Russo, T.; Oppedisano, R.; Tolino, A.; Colao, A.; Vigorito, C.; Zullo, F.; Orio, F. Structured exercise training programme versus hypocaloric hyperproteic diet in obese polycystic ovary syndrome patients with anovulatory infertility: a 24-week pilot study. *Hum. Reprod. Update* **2008**, 23, 642-650.
108. Hakimi, O.; Cameron, L.C. Effect of Exercise on Ovulation: A Systematic Review. *Sports. Med.* **2017**, 47, 1555-1567.
109. Mario, F.M.; Graff, S.K.; Spritzer, P.M. Habitual physical activity is associated with improved anthropometric and androgenic profile in PCOS: a cross-sectional study. *J. Endocrinol. Invest.* **2017**, 40, 377-384.
110. Rzeźnik, M.; Suliburska, J. Suplementacja witaminowo-mineralna u kobiet w wieku prekoncepcyjnym. *Forum Zaburzeń Metabolicznych* **2016**, 7, 106-110.
111. Cetin, I.; Berti, C.; Calabrese, S. Role of micronutrients in the periconceptional period. *Hum. Reprod.* **2010**, 16, 80-95.
112. Mejia-Montilla, J.; Reyna-Villasmil, E.; Domínguez-Brito, L.; Naranjo-Rodríguez, C.; Noriega-Verdugo, D.; Padilla-Samaniego, M.; Vargas-Olalla, V. Supplementation with omega-3 fatty acids and plasma adiponectin in women with polycystic ovary syndrome. *Endocrinol Diabetes Nutr.* **2018**, 65. 192-199.
113. Jamilian, M.; Shojaei, A.; Samimi, M.; Afshar Ebrahimi, F.; Aghadavod, E.; Karamali, M.; Taghizadeh, M.; Jamilian, H.; Alaeinasab, S.; Jafarnejad, S.; Asemi, Z. The effects of omega-3 and vitamin E co-supplementation on parameters of mental health and gene expression related to insulin and inflammation in subjects with polycystic ovary syndrome. *J. Affect. Disord*. **2018**, 229, 41-47.
114. Mirmasoumi, G.; Fazilati, M.; Foroozanfard, F.; Vahedpoor, Z.; Mahmoodi, S.; Taghizadeh, M.; Esfeh, N.K.; Mohseni, M.; Karbassizadeh, H.; Asemi Z. The effects of flaxseed oil omega-3 fatty acids supplementation on metabolic status of patients with polycystic ovary syndrome: a randomized, double-blind placebo-controlled trial. *Exp. Clin. Endocrinol. Diabetes* **2018**, 126, 222–228.
115. Ebrahimi, F.A.; Samimi, M.; Foroozanfard, F.; Jamilian, M.; Akbari, H.; Rahmani, E.; Ahmadi, S.; Taghizadeh, M.; Memarzadeh, M.R.; Asemi, Z. The effects of omega-3 fatty acids and vitamin E co-supplementation on indices of insulin resistance and hormonal parameters in patients with polycystic ovary syndrome: a randomized, double-blind placebo-controlled trial. *Exp. Clin. Endocrinol. Diabetes* **2017**, 125, 353–359.
116. Mohammad Hosseinzadeh, F.; Hosseinzadeh-Attar, M.J.; Yekaninejad, M.S.; Rashidi, B. Effects of selenium supplementation on glucose homeostasis and free androgen index in women with polycystic ovary syndrome: a randomized, double blinded, placebo controlled clinical trial. *J. Trace Elem. Med. Biol.* **2016**, 34, 56–61.
117. Razavi, M.; Jamilian, M.; Kashan, Z.F.; Heidar, Z.; Mohseni, M.; Ghandi, Y.; Bagherian, T.; Asemi, Z. Selenium supplementation and the effects on reproductive outcomes, biomarkers of inflammation, and oxidative stress in women with polycystic ovary syndrome. *Horm. Metab. Res.* **2016**, 48, 185-190.
118. Jamilian, M.; Foroozanfard, F.; Rahmani, E.; Talebi, M.; Bahmani, F.; Asemi, Z. Effect of Two Different Doses of Vitamin D Supplementation on Metabolic Profiles of Insulin-Resistant Patients with Polycystic Ovary Syndrome. *Nutrients* **2017**, 9, 1280.
119. Ostadmohammadi, V.; Jamilian, M.; Bahmani, F.; Asemi, Z. Vitamin D and probiotic co-supplementation affects mental health, hormonal, inflammatory and oxidative stress parameters in women with polycystic ovary syndrome. *J. Ovarian Res*. **2019**, 12, 5.
120. Jamilian, M.; Samimi, M.; Mirhosseini, N.; Afshar Ebrahimi, F.; Aghadavod, E.; Talaee, R.; Jafarnejad, S.; Hashemi Dizaji, S.; Asemi, Z. The influences of vitamin D and omega-3 co-supplementation on clinical, metabolic and genetic parameters in women with polycystic ovary syndrome. *J. Affect. Disord*. **2018**, 38, 32-38.
121. Menichini, D.; Facchinetti, F. Effects of vitamin D supplementation in women with polycystic ovary syndrome: a review. *Gynecol. Endocrinol*. **2020**, 36, 1-5.

122. Izadi, A.; Ebrahimi, S.; Shirazi, S.; Taghizadeh, S.; Parizad, M.; Farzadi, L.; Gargari, B. P. Hormonal and Metabolic Effects of Coenzyme Q10 and/or Vitamin E in Patients With Polycystic Ovary Syndrome. *J. Clin. Endocrinol. Metab*. **2019**, 104, 319-327.
123. Karamali, M.; Gholizadeh, M. The effects of coenzyme Q10 supplementation on metabolic profiles and parameters of mental health in women with polycystic ovary syndrome. *Gynecol. Endocrinol.* **2022**, 38, 45-49.
124. Zhang, T.; He, Q.; Xiu, H.; Zhang, Z.; Liu, Y.; Chen, Z.; Hu, H. Efficacy and Safety of Coenzyme Q10 Supplementation in the Treatment of Polycystic Ovary Syndrome: a Systematic Review and Meta-analysis. *Reprod. Sci*. **2023**, 30, 1033-1048.
125. Unfer, V.; Facchinetti, F.; Orrù, B.; Giordani, B.; Nestler, J. Myo-inositol effects in women with PCOS : a meta-analysis of randomized controlled trials. *Endocr. Connect*. **2017**, 6, 647-658.
126. Pundir, J.; Psaroudakis, D.; Savnur, P.; Bhide, P.; Sabatini, L.; Teede, H.; Coomarasamy, A.; Thangaratinam, S. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. *An Int. J. Obstet. Gynaecol*. **2018**, 125, 299-308.
127. Jethaliya, H.; Gajjar, N.; Patel, V.; Deshpande, S.; Patel, R. Efficacy of Myo-inositol on Anthropometric, Metabolic, and Endocrine Outcomes in PCOS Patients: a Meta-analysis of Randomized Controlled Trial. *Reprod. Sci*. **2022**, 29, 2282-2298.
128. Zeng, L. Effectiveness of myoinositol for polycystic ovary syndrome : a systematic review and meta-analysis. *Endocrine* **2018**, 59, 30-38.
129. Facchinetti, F.; Orrù, B.; Grandi, G.; Unfer V. Short-term effects of metformin and myo-inositol in women with polycystic ovarian syndrome (PCOS): a meta-analysis of randomized clinical trials. *Gynecol. Endocrinol*. **2019**, 35, 198-206.
130. Greff, D.; Juhász, A. E.; Váncsa, S.; Váradi, A.; Sipos, Z.; Szinte, J.; Park, S.; Hegyi, P.; Nyirády, P.; Ács, N.; Várbíró, S.; Horváth, E. M. Inositol is an effective and safe treatment in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Reprod. Biol. Endocrinol*. **2023**, 21, 10.
131. Unfer, V.; Carlomagno, G.; Dante, G.; Facchinetti, F. Effects of myo-inositol in women with PCOS: a systematic review of randomized controlled trials. *Gynecol. Endocrinol*. **2012**, 28, 509-15.
132. Unfer, V.; Nestler, J.E.; Kamenov, Z.A.; Prapas, N.; Facchinetti, F. Effects of inositol(s) in women with PCOS: a systematic review of randomized controlled trials. *Int. J. Endocrinol.* **2016**, 2016, 1849162.
133. Bhide, P.; Pundir, J.; Gudi, A.; Shah, A.; Homburg, R.; Acharya, G. The effect of myo-inositol/di-chiro-inositol on markers of ovarian reserve in women with PCOS undergoing IVF/ICSI: a systematic review and meta-analysis. *Acta. Obstet. Gynecol. Scand*. **2019**, 98, 1235-1244.
134. Lei, Y.; Yang, J.; Li, H.; Zhong, H.; Wan, Q. Changes in glucose-lipid metabolism, insulin resistance, and inflammatory factors in patients with autoimmune thyroid disease. *J Clin Lab Anal.* **2019**, 33, e22929.
135. Chavarro, J.E.; Rich-Edwards, J.W.; Rosner, B.A.; Willett, W.C. A prospective study of dietary carbohydrate quantity and quality in relation to risk of ovulatory infertility. *Eur. J. Clin. Nutr*. **2009**, 63, 78-86.
136. Moran, L. J.; Norman, R. J. The obese patient with infertility: a practical approach to diagnosis and treatment. *Nutr Clin Care*. **2002**, 5, 290-297.
137. Dickerson, E. H.; Cho, L. W.; Maguiness, S. D.; Killick, S. L.; Robinson, J.; Atkin, S. L. Insulin resistance and free androgen index correlate with the outcome of controlled ovarian hyperstimulation in non-PCOS women undergoing IVF. *Hum reprod.* **2010,** 25, 504-509.
138. Broughton, D. E.; Moley, K. H. Obesity and female infertility: potential mediators of obesity's impact. *Fertil Steril.* **2017**, 107, 840-847.
139. Ahmed, B.; Sultana, R.; Greene, M. W. Adipose tissue and insulin resistance in obese. *Biomed Pharmacother.* **2021**, 137, 111315.