The effect of the ketogenic diet in increasing and/or restoring fertility in polycystic ovarian syndrome (PCOS) patients

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Abstract

The effect of the ketogenic diet will be assessed using three factors: the efficacy of the diet as inferred from clinical trials, the advantage of the treatment when compared with other therapies and and the caloric and metabolic sustainability of the diet over a period long enough to restore fertility to childbearing patients.

The hypothesised mechanism of action of PCOS and the ketogenic diet will be discussed and evaluated with the aid of existing scientific literature and articles. Currently, there exists ambiguity surrounding the cause of PCOS. This makes it difficult to determine the true effect of various interventions on infertility within the disorder.

Overall, the efficacy of the ketogenic diet in short intervals demonstrates promising elevation in fertility amongst overweight PCOS patients. However, there is a lack of experimental evidence exploring the effect of the ketogenic diet on lean PCOS patients who make up a significant portion of the target population. Moreover, the nutritional sustainability of the diet makes it unlikely for patients to maintain success due to the difficulty in maintaining ketosis.

Instead, this report suggests that a less restrictive version of the ketogenic diet could be implemented for these patients, but further research and trials would be required to affirm this. As an alternative, this report also suggests that a personalised dietary plan for patients may prove to be quite beneficial as it would be more likely in ensuring long-term success.

Key Words: Polycystic Ovarian Syndrome, Ketogenic Diet, Insulin Sensitivity, Follicle Stimulating Hormone, Lutenising Hormone, Ovaries, Fertility, Low-Carbohydrate, Insulin Resistance, Hyperinsulinemia, Hyperandrogenism, Ovarian Function, Reproductive Health, Nutrition, Menstrual Cycle

Introduction

Over the years, the ketogenic diet has surged in popularity immensely in the last decade; primarily for its short-term effect on weight loss (Batch, 2020). With high amounts of fat, moderate amounts of protein and a low amount of carbohydrates (Masood, 2023), it has been endorsed by several celebrities in the media and was the most searched diet on Google in the USA in 2020 (McGaugh, 2022).

PCOS (Polycystic Ovarian Syndrome) has also been receiving its fair share of attention - perceived as an increasingly common health problem, the disorder affects 4-20 per cent of women of reproductive age worldwide (Deswal, 2020). Characterised by three factors, (high androgen levels, anovulation and cystic ovarian growths) the common symptoms faced by women are hirsutism, menstrual irregularity and mainly infertility (Lujan, 2008). Infertility is often claimed to be the most demoralising symptom (Willmott, 2002) amongst women, almost posing as a threatening insult to their womanhood and therefore, this report will be focusing on the improvement of the symptom caused by PCOS.

This report aims to argue the question, “Is the ketogenic diet successful in elevating fertility in PCOS patients?”. Currently, ambiguity exists surrounding the cause of PCOS. Therefore, medical professionals approach intervention by managing the symptoms of the disorder. This makes it difficult to determine the true effect of various interventions on infertility within the disorder. Moreover, the more conventional approach to controlling infertility with this disorder is weight loss and insulin resistance management, which is often suggested by following a low-carbohydrate diet (Moran, 2013). The ketogenic diet has been trialled on a considerable amount of women with PCOS and although there is a lot of promising research in support of the efficacy of the ketogenic diet, long-term adherence to it proves to be a major obstacle (Batch, 2021). Its rigorous dietary restrictions make it unlikely for patients to stick to it over longer periods. Hence, the objective of this report is to decide whether it would be 'holistically' successful amongst these women. The 'holistic'

success of the KD will be determined by three factors; efficacy, impact and nutritional sustainability. This will be covered in greater detail in the third section of the report.

The next section of this report will be focussing on the biological mechanism of the ketogenic diet on the female body and how it is seen to regulate insulin levels in patients.

Biological Mechanisms Of PCOD And The KD

PCOS is a complex ovarian disorder, and its aetiology remains unknown to this day (Dunaif, 1997). However, it is widely believed that a combination of genetic, hormonal, and environmental factors contribute to its development. Key features of PCOS include hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (Goodarzi, 2011). Evidence suggests that insulin resistance plays a central role in the pathogenesis of PCOS, with up to 70% of women with PCOS exhibiting insulin resistance regardless of body weight (Lizneya, 2016). Additionally, familial clustering and twin studies have implicated a strong genetic component, although no single gene has been definitively linked to the condition (Rotterdam, 2004). These complexities are significant because many of the current models assessing the effects of different interventions—such as lifestyle changes, insulin-sensitizing agents, and hormonal treatments—are based on evolving hypotheses rather than fully elucidated mechanisms. Therefore, conclusions regarding PCOS-related infertility, though supported by clinical trials and empirical evidence, may be subject to change as ongoing research continues to refine our understanding of the disorder (Teede, 2018).

Hyperandrogenism

Scientists hypothesise that the disorder consists of a continuous cycle of hyperandrogenaemia from theca cells in the ovaries and the androgen excess is regarded as the driving force in the development of the symptoms (Morreale, 2018). Theca cells (responsible for androgen secretion) secrete an amplified amount of androgens. This leads to a disruption in the neuroendocrine system, causing an overproduction of gonadotropins by the hypothalamus (Ashraf, 2019). The increased hypothalamic GnRH favours the production of LH (induces the production of androgens) over FSH (converts androgens into estrogen; responsible for follicular development). This causes follicular arrest in its early stages due to the reduction of FSH and overproduction of LH (Shabaan, 2019) This

leads to anovulation and the increased number of follicles and overexpression of enzymes involved in androgens produces an excessive amount of these hormones. With the absence of the egg in the fallopian tube, fertilisation cannot occur, leading to infertility.

Hyperinsulinemia

The hyperandrogenic state in PCOS also seems to be linked to the action of insulin. Androgen excess favours the growth of abdominal visceral adipose tissue deposits (Welt, 2005). These tissues play an active component in total body fat; their unique biochemical characteristics cause them to release hormones of their own. Increased visceral fat deposition has been seen to secrete excess amounts of a protein known as (retinol-binding protein 4) RBP4, shown to increase insulin resistance (Cunha, 2021). This induces a heightened response of the pancreas and liver, causing an increased secretion of insulin (hyperinsulinemia), and this further stimulates ovarian androgen production (Graham, 2006) This causes women to gain weight; insulin resistance and infertility occurs in both obese and lean PCOS phenotypes but is much more prevalent in those who are overweight. According to Gutch, these clinical signs are similar between both phenotypes, but insulin resistance has been proven difficult to quantify (Gutch, 2015) which creates further ambiguity in recording the extent of which insulin resistance affects lean women compared to overweight women.

This cyclical pathogenetic interaction between insulin resistance, hyperinsulinemia and hyperandrogenism leads to further ovarian dysfunction that can result in anovulation and infertility. Therefore, an improvement in insulin resistance in women with PCOS decreases the level of hyperandrogenism which would increase the chances of ovulation for pregnancy. However, the complexity and multi-factorial nature of the mechanism causing infertility may indicate that one specific type of intervention could be unlikely to combat the symptom and suggests that a combination of remedies may be required.

Now that we have understood how infertility occurs in PCOS patients, we will move on to focus on the potential impact of the ketogenic diet on this symptom of the disorder.

Ketogenic Diet Action

Like PCOS, the precise mechanism of action of the ketogenic diet is not known, although many possible explanations have been proposed. This

also leaves this mechanism vulnerable to change as it is largely hypothesised.

The diet consists of high fat (55-60%), moderate protein (30-35%) and very low carbohydrate intake (5-10%). When the body undergoes carbohydrate deprivation, insulin secretion is significantly reduced, and the body experiences some metabolic changes. When glycogen stores deplete to a level much lower where the production of glucose isn't sufficient to meet the needs of the body, ketogenesis begins.

Due to low glucose availability, the stimulus for insulin secretion is also decreased, which reduces the stimulus for fat and glucose storage. Fats are broken down into fatty acids, which are further metabolised to acetoacetate (Masood, 2022) (later converted to beta-hydroxybutyrate and acetone). These are basic ketone bodies and are synthesised instead of glucose to be easily used for energy production for the vital organs.

It is suggested that this low carbohydrate approach leads to more regular levels of insulin released through the loss of adipose tissue (Kinzig, 2010), which increases insulin sensitivity which would inherently improve androgen levels in PCOS patients, elevating fertility. Reportedly, there is a polygenic overlap exhibited between Type-2 diabetes and PCOS, extending the current understanding of the common genetic variants influencing the two diseases (Li, 2022). Present results also imply an essential role of BMI in both diseases. Since T2D is often targeted through moderate to low carbohydrate diets, this may further demonstrate that the low-carb characteristic of the KD would be beneficial for the alleviating symptoms of PCOS.

However, it is currently unknown whether the effects of KD on glucose homeostasis are the result of only weight loss or result of reduced dietary carbohydrate intake too. This is because patients often lose weight with the ketogenic diet due to ketone bodies providing greater ATP production than glucose (Paoli, 2013), so it is easier to maintain a calorie deficit. This decrease in overall weight favours fertility (Silvestris, 2018), leading to an increase in pregnancy chances. Furthermore, obese patients are deemed to be affected by both extrinsic IR (caused by excess body mass) and intrinsic IR (Stepto, 2013) (caused by PCOS) which creates ambiguity in how IR is targeted when ketosis is achieved. This argument will be pursued in the main body of this report.

The next section of the report will dive into the main argument; discussing the success of the KD by evaluating trials conducted on patients and comparing each factor and its contribution to the diet's overall success.

Discussion

National Health Interview Survey Dataset

The ‘holistic’ success of the KD will be assessed based on three factors:

1. Efficacy: Do trials show that the diet can elevate fertility amongst PCOS patients?
2. Comparative advantage: Does the diet compare favorably with other treatments possible/available for PCOS patients ?
3. Sustainability: If the effects of the diet are positive, can they be sustained for longer periods until childbirth? This factor will specifically investigate the nutritional quality of the diet and whether this can be maintained over longer periods. It must be mentioned here that ‘sustainability’ is only as long as it takes to sustain and increase fertility until childbirth.

A larger emphasis will be placed on 'efficacy' as it's the most important factor in the argument, forming the fundamental core of this research question. The elevation in fertility will be discussed using improvements in the LH/FSH ratios, menstrual cycle regulations and successful pregnancies (if available) from each of the trials.

Efficacy

This section will be investigating the success of the several trials of the KD conducted on PCOS patients and we will evaluate the effect of this intervention on the patients.

The efficacy of the KD on PCOS patients has been highly debated but trials conducted on patients seem to display promising results. A scientific trial conducted by John Mavropoulos was conducted on a group of overweight women who were required to consume a LCKD (low-calorie ketogenic diet) over 24 weeks with a little under 20 grams of carbohydrates a day. In the study, there was a 12.1% reduction in body weight and an improvement in the fasting serum insulin level in the blood, which proved that the patients had gained increased insulin sensitivity through the diet (Mavropoulos, 2005). Furthermore, results showed that the FSH/LH ratio had improved too and two women became pregnant during the study despite previous infertility problems. The study further suggests that the LCKD may lead to a reversal of the effect of hyperinsulinemia on the secretion of androgens from the ovaries which seems to be a promising intervention for the patients. However, a

limitation of the trial is that the hormonal measures were not taken during specified points during the menstrual cycle. This proves to be an issue because none of the women were amenorrheic, so the tests of the FSH/LH ratios could have just been subject to the changes in the stages of their menstrual cycle. This is significant as it decreases the validity of the improvement in the FSH/LH ratios previously discussed in the argument. Overall, this study does prove to display some positive results in the insulin levels and to a certain extent, in the LH/FSH ratios which places some credibility in favour of the ketogenic diet on PCOS patient fertility.

Another trial conducted by Raffaele Cincione reported achieving similar results with positive outcomes in the decrease of LH and testosterone at the end of the 45-day trial with 5 successful pregnancies achieved despite previous unsuccessful attempts. In addition, 5 women experienced a natural reappearance of a regular menstrual cycle after years of amenorrhea (Cincione, 2021). Improvements in menstrual regularity, FSH/LH ratios and successful conceptions all indicated an increase in fertility, displaying the beneficial effect of the KD. Furthermore, the statistical test conducted on the trial obtained a p-value of less than 0.05, increasing the likelihood that the results collected were not due to chance. However, this trial once again concludes that further studies are required to clarify the molecular mechanism of the beneficial effect of the ketogenic diet to appropriately establish the diet as an appropriate clinical intervention for the disorder. Moreover, the use of the single-arm design in the study does pose the inability to distinguish between the effect of the KD, a placebo effect and the effect of natural history (Evans, 2010). Although the possibility of this occurring in the study is unlikely because several dramatic metabolic changes were recorded such as significant decreases in LH levels, testosterone levels and insulin serum levels, it may still pose a small risk to the validity of the results in the study.

In addition, the KD proves to be beneficial when implemented with forms of assisted reproductive technology (Palafox-Gómez, 2023). The addition of the KD as a dietary intervention in patients undergoing IVF improved the embryo implantation rate to the uterine wall despite previous failures. Even though the quality of the embryo itself remained unaffected, the clinical pregnancy rate and the thickness of the endometrium demonstrated significant improvements. This is critical in favour of the KD as it displays the versatility of the intervention, it seems to improve fertility outcomes involving IVF but is beneficial as it stands without any technological aid. However, this is only one trial and further experimental evidence is required to support the effectiveness of the KD with IVF and

other assistive reproductive technologies. (E.g: laparoscopic drilling) Nonetheless, this sparks interest and promise in the field of reproductive technologies concerning PCOS patients which is beneficial for further research surrounding the efficacy of the KD.

Regarding all these trials, further research is required to determine whether the benefits were only from the weight loss or supported by the carbohydrate restriction too. This is important because if the increased insulin sensitivity proves to be solely from weight loss, then any diet with a caloric deficit for each woman would yield similar improvements in fertility. Even though this would not take away the overall success of the KD as it stands, it would diminish its significance as a dietary intervention amongst others. For example, certain studies trialling the Mediterranean diet (higher carbohydrate content) on PCOS patients have shown to display results depicting a beneficial impact on some reproductive and metabolic parameters in these women regarding menstrual regularity and glucose homeostasis (Stathos, 2023). However, it could be argued that the Mediterranean diet targets a different aspect of the disorder; it is known to soothe the inflammatory response (Koelman, 2022) caused by the symptoms whereas the KD places a larger emphasis on reducing insulin resistance exacerbated by the disorder. It could be that in each case, the focus on inflammation and insulin resistance respectively leads to an overall relief in all symptoms, elevating fertility with it. Moreover, a different trial conducted by Antonio Paoli used a modification of the ketogenic diet; a eucaloric Mediterranean ketogenic diet (still carbohydrate-restrictive) with a larger emphasis on green leafy vegetables and was slightly less lipid reliant compared to the traditional ketogenic diet. The trial presented similar success with improvements in FSH/LH ratios amongst the overweight PCOS women (Paoli, 2020), and although the specific symptom of infertility was not investigated, we can assume that the improvement in these metabolic markers suggests an overall boost in menstrual health which contributes to the elevation of fertility. Consequently, since there was no intention of weight loss in the trial, this suggests that carbohydrate restriction plays an integral role in the elevation of fertility, regardless of weight loss. Nonetheless, we still cannot say with full certainty that the carbohydrate-restricting nature of the ketogenic diet causes the elevation in fertility but there is sufficient evidence that it favours the improvement of the symptom.

Interestingly, several approaches have emerged involving insulin-independent mechanisms to tackle the insulin-resistant presentation in PCOS patients which opposes the approach of the KD. For

example, a new drug has displayed an alternative way of tackling insulin resistance through an insulin-independent mechanism. SGLT2 inhibitors in PCOS have demonstrated promising results in improving insulin sensitivity in PCOS patients (Rakic, 2023). They function through stimulating the excretion of glucose through the urine by inhibiting the reabsorption of glucose in the kidney tubules. A range of studies have showcased the benefits of SGLT-2is: lower blood pressure, improved glucose metabolism, reduced oxidative stress and inflammation (Pruett, 2023). With a therapeutic dose, 60-100 g of glucose is excreted through urine, and in a 12-month period, SGLT-2 inhibitors reduce body weight by approximately 2 kg, lower systolic and diastolic blood pressure as well as levels of glycosylated haemoglobin by 0.5-0.9% (Hussein, 2020). Although the use of SGLT-2is is not widespread as an intervention for PCOS, these promising results suggest an alternative approach without targeting insulin. This could mean that the carbohydrate-restricting nature of the ketogenic diet involving insulin may not be the most effective approach to the disorder.

In addition, the trial of acarbose (alpha glucosidase inhibitors) in PCOS patients with hyperinsulinemia has demonstrated a positive clinical effect on the patients (Ciotta, 2001). The inhibitors act by slowing down the absorption of carbohydrates from the intestines, which minimises the sudden rise of blood-glucose concentration. The absence of significant clinical, metabolic and haematochemical side-effects makes it a drug suitable to combat the impaired glucose tolerance in these patients. Furthermore, these inhibitors, as well as the SGLT-2is, are both fairly easy to administer as patients consume them orally, often through a tablet. Nonetheless, despite promising research, further long-term, double-blind studies are warranted to establish whether acarbose can be used as an adjunct or unique therapy in such patients.

Another insulin-independent option targeting PCOS relief would be through bariatric surgery that has shown to lead to a restoration of the hypothalamic pituitary axis, reducing cardiovascular risk and improving fertility (Malik, 2015). However, even though most reproductive age women fitting the profile of PCOS have been included in several studies cited in the review, very few studies have specifically targeted PCOS patients. A study with a limited number of PCOS patients (Eid, 2005) were followed for up to 26 months after bariatric surgery, and most women had received better menstrual function as well as spontaneous ovulation as opposed to before the surgery (Brancatisano, 2008). Furthermore, after 2 years, all women had resumed regular menstrual

cycles, half had resolution of hirsutism as well has hypertension, dyslipidaemia and diabetes being almost completely resolved. In another clinical trial, 5 women quickly became pregnant within a short time frame after the surgery (Baharuddin, 2021). Nonetheless, this treatment tends to be used in more severe cases or as a final line of treatment due to it is a costly, invasive, surgical procedure with a lengthy recovery period.

These approaches are important because they establish a range of interventions that approach the disorder through a mechanism that does not (solely) target the insulin resistance aspect. Thus, this may suggest that combating the other aspects of the disorder may be more beneficial to achieving PCOS resolution, leading to an improvement in pregnancy outcomes. Moreover, discussions have shown that insulin resistance treatment is not recommended for all patients with PCOS (Marshall, 2012). Firstly, although insulin resistance is very common amongst these patients, it is not a universal feature of PCOS. Secondly, diagnoses of some form of insulin resistance in these patients have been done through methods such as measuring fasting insulin and glucose levels, which are not sensitive enough. This is not favourable for the KD as an intervention, and it decreases the likelihood of its efficacy amongst members of the target population. Nonetheless, studies comparing the KD and other insulin-independent approaches would have to be compared with these mechanisms to determine which one would target PCOS better.

Criteria	Weighting	Ketogenic Diet
Efficacy in increasing fertility in obese/overweight patients with PCOS	2	+1
Efficacy in increasing fertility in lean patients with PCOS	2	0
Fertility increased (while of childbearing age) regardless of number of previous years infertile	2	+2
Time elapsed between starting KD and increase in fertility (Time to efficacy)	1	0
**Efficacy in PCOS patients undergoing IVF (implantation, pregnancy and live birth rate)	1	+1
Efficacy is PCOS cause diagnosis agnostic; i.e. it is effective regardless of whether PCOS is caused by insulin resistance, obesity, hormonal imbalances or a combination of these factors	1	+1
Total		+5

A score of zero indicates insufficient information, the score for a particular category cannot be greater than ± the weighting for that category.
The minimum possible score is -7, the maximum possible score is +7 (39)
TABLE 1. Pugh Matrix Assessing the efficacy of the KD in PCOS Patients.

Overall, based on this Pugh matrix, it would be reasonable to conclude that the ketogenic diet displays promising effects in elevating fertility in PCOS patients despite requiring further research to investigate

further. However, other approaches may be considered more beneficial compared to the KD, (acarbose inhibitors and SGLT-2 inhibitors) given the restrictive nature of the diet may be difficult to adhere to (discussed further under the section "Sustainability"). Nonetheless, although these preliminary treatment options have a more positive weighted score (except for bariatric surgery, since it is expensive and only used in very severe cases of PCOS infertility), they do not have enough evidence from trials supporting their implementation compared to the number of controlled studies conducted with the KD on PCOS patients. Studies comparing the KD with these approaches would be advantageous in clarifying this. The next section of the main argument will focus on the next aspect of the success criteria; the advantage of the KD on PCOS patients compared to other interventions and diets.

Comparative Advantage of the KD

Even though the ketogenic diet proves to be effective on the selected PCOS patients in trials, there is a limited number of studies supporting the fact that the diet has been successful on all patients within the target population. For example, nearly all trials of the KD have been conducted on obese/overweight PCOS patients but lean PCOS patients struggling with infertility issues currently have very limited experimental evidence, making it difficult to conclude with regards to the KD's efficacy (Gomez, 2023). The lack of evidence available mainly could be because overweight/obese phenotypes experience more severe symptoms of menstrual dysfunction which leads to more severe cases of infertility (Toosy, 2018). Moreover, infertility and PCOS symptoms are much more prevalent in obese/overweight women and tend to remain dormant in leaner women. The small population of women affected makes it difficult to gather results and sample sizes in trials were often too small to report significant results amongst these women. Instead, clinical research currently suggests that lean PCOS women should aim to maintain their weight and dietary intervention should consist of the consumption of ample amounts of vegetables, fruit, vitamin D and calcium (Goyal, 2017) which could be classed as rather generic advice and universally understood knowledge.

Although obese women with PCOS are more likely to experience anovulatory infertility compared to leaner women, this should not undermine the significance of lean PCOS women affected by infertility. Currently, no intervention is considered appropriate for this category of patients even though studies have been conducted with different familiar,

established drug options such as metformin and myoinositol, let alone the KD. Regarding obese/overweight women (BMI of over 24 kg/m3), plenty of results from multiple trials (previously discussed) conducted display favourable results of the KD as an intervention, with a greater emphasis on the LCKD (Iolanda, 2020). Moreover, the quality of evidence of the KD elevating fertility prospects in each study is greater, often resulting in regulation of FSH/LH, the arrival of the menstrual cycle after a history of amenorrhea and successful pregnancies after unsuccessful attempts. Despite the greater number of trials conducted on overweight/obese women with PCOS, the role of KD as an intervention to elevate infertility is still inconclusive and requires clarification in the treatment of the disorder.

Due to the lack of experimental evidence, we can only predict the effect of the KD on the lean PCOS phenotype. A study conducted by Yildirim et al. concluded that lean patients have intrinsic IR whereas obese patients have intrinsic IR (caused by PCOS) and extrinsic IR (Yildirim, 2003) (caused by weight gain). Therefore, insulin resistance caused by the disorder seems to be inherent in patients regardless of body weight and medical professionals suggest it should be managed accordingly at the start of clinical intervention. The KD proves to improve insulin sensitivity which would allow us to assume that the lack of carbohydrates would have a beneficial effect on the insulin resistance present in these patients which should lead to an overall increase in fertility according to the cyclical interaction of the symptoms. Evidence by Barbarisi confirms this by stating that the KD seems to be an effective strategy in controlling the endocrine and metabolic disorders connected to PCOS by acting on weight loss, insulin regulation and fertility outcomes. However, results from clinical trials conducted by Abdoeldalyl et al. suggest targeting the low-grade inflammatory aspect of the disorder to induce overall symptomatic relief in these patients (Abdoeldalyl, 2021) (which would benefit fertility prospects). This would be established through the Mediterranean diet as it contains larger amounts of antioxidant-rich foods than the KD which would trigger an anti-inflammatory response in the body (Barrea, 2021). Perhaps this may suggest that the MD may prove to be a better dietary intervention in elevating fertility in lean PCOS women than the KD. Nevertheless, the specific macro and micro-nutrient combination needed for an effective nutritional plan to improve infertility has not been determined and although these speculations may be true, they cannot be confirmed with little to no scientific evidence.

Criteria	Weight	Keto -genic Diet	Medi - terranean diet (MD)	SGLT-2 Inhibitors	Bariatric Surgery	Acarbose (Alpha Glucosidase Inhibitors)	Thiazolidine diones, SERMs, Metformin
Overall relative efficacy in increasing fertility in PCOS patients (positive LH/FSH ratio/positive pregnancy testing)	2	+1	0	0	+1	0	+2
Relative Ease of implementation for all types of patients within the target population (e.g: allergies, food/drug intolerance, metabolic disease, diabetes)	2	-1	1	0	-1	0	+2
Treats multiple causes of the disease such as obesity, hormonal imbalance and insulin resistance.	1	+1	0	0	0	0	+1
***Long-term caloric or therapy sustenance (~ 6 months or long enough become fertile)	2	0	2	0	0	0	0
***Results of the diet/therapy permanent ? Body permanently adapts to altered metabolism even after reversion to a normal diet, or does diet need to be continued throughout the lifetime ?	1	0	0	0	0	0	0
Quality of Life affected due to abstenance from agreeable tastes and food and/or forced changes in lifestyle	1	-1	0	-1	-1	-1	-1
Regulatory approval specifically for PCOS use? Or used as off-label.	1	-1	-1	-1	-1	-1	+1
*Self-dose-titration (magnitude of diet) and self-medication (diet) possible.	1	+1	+1	-1	-1	-1	-1
Relative Cost	1	+1	+1	-1	-1	-1	-1
**Adverse or side effects of treatment or therapy	1	0	0	0	-1	0	0
Total		+1	+5	-4	-5	-4	+7

A score of zero indicates insufficient information, the score for a particular category cannot be greater than ± the weighting for that category.
*For diets, the ratio of carbohydrates, proteins and fats can be temporally continuously adjusted by the patient so as to **minimise adverse effects, while still affecting a metabolic switch from carbohydrates to fats for KD and to non-carbohydrates for MD.
***The reason these criteria do not have lesser values for KD than they do is because once the objective of becoming fertile is achieved, there is presumably no further need to continue on the ketogenic diet.
The Total minimum possible score is -19, the maximum possible score is +19, For subcategories of Efficacy, Sustainability and Cost/Side Effects, the minimum and maximum possible scores are ± 9, ± 6 , and ±4 respectively.

TABLE 2. Pugh Matrix to estimate the comparative advantage of the KD with other diets or treatments in PCOS Patients (with respect to Efficacy, Sustainability and Cost/Side Effects).

Overall, using the Pugh matrix above, the impact of the KD on the improvement of fertility remains ambiguous, especially involving lean PCOS patients as there is little to no evidence available to evaluate its effect on this category of patients. Even though a much greater bank of experimental evidence available favours the effect of the KD on overweight and obese PCOS women, (who form around 80% of the target

population) (Barber, 2019) it is still insufficient in appropriately determining the effect of its role as a prescription for infertility.

The 3-D plot (Figure 1) represents category normalised information with respect to the diets and therapies from the Pugh matrix in Table 2. The greater the score for the category, the better the diet or therapy. It can be seen that the approved drugs, the mediterranean diet and the Ketogenic diet score significantly greater than the alpha-glucosidase inhibitors, the SGLT-2 inhibitors and the Bariatric surgery therapies. The Ketogenic diet is comparable to the Mediterranean diet in the efficacy and cost-side effect attributes but lags in the sustainability attribute.

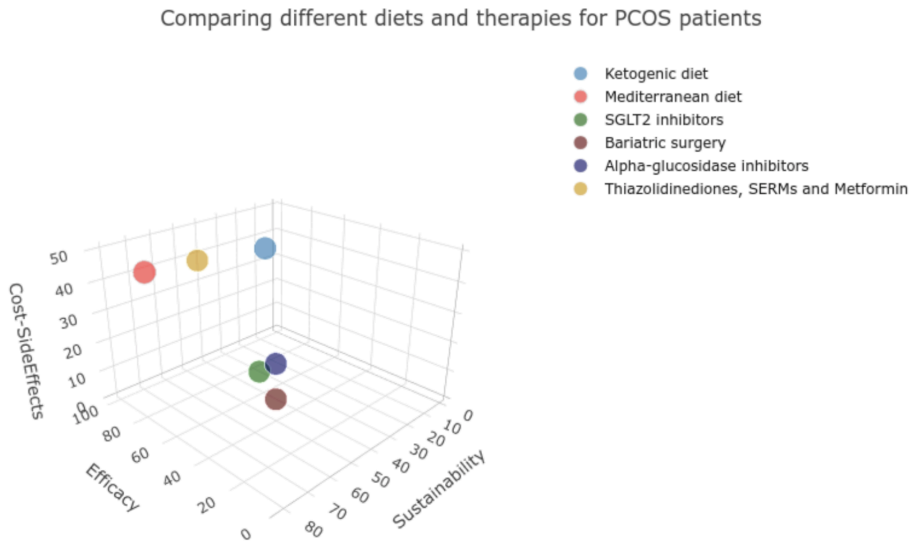

FIGURE 1. Comparing different diets and therapies for PCOS patients.

The next section of the report will focus on the third aspect of our success criteria, sustainability. This will involve evaluating the diet as a whole and will investigate the issues surrounding long-term adherence to the KD and whether this would improve or threaten infertility in PCOS.

Sustainability

The KD yields rapidly successful results involving short-term weight loss, but does it demonstrate long-term benefits? This requires further understanding and research.

The promotion of long-term fertility is important amongst women because infertility is often associated with anovulation and menstrual

irregularities which impact bone density (Melton, 2001) and negatively affect women. The long-term effect of anovulatory infertility can lead to an increased risk of bone fractures and although this correlation requires further research, it indicates the importance of sustaining fertility for as long as possible. The elevation of fertility does not only prove to be beneficial for successful pregnancies, but for overall bodily function.

From what we understand, although the short-term results of the KD have shown significant success, further research is warranted to evaluate the long-term implications of the KD (Batch, 2022). Despite the diet's favourable effect on weight loss and IR, the concomitant increases in LDL-C and very low-density lipoproteins (high-fat content) may lead to increased cardiovascular risks (Ding, 2018). In a 2018 pilot study of young, fit adults undergoing the ketogenic diet found that although the weight loss results were significant, LDL-C increased by 35%. Increases in LDL can contribute to plaque build-up in blood vessels which would severely elevate risks for coronary heart disease. From this, it would be reasonable to state that an increased risk of CHD would pose a significant threat to fertility in PCOS patients. Contrastingly, some have suggested that the LDL particle concentration is of no concern if the increase is mainly in larger LDL particles. This is not entirely correct, however, because according to the Women's Health Study, the evaluation of LDL particle size revealed that the risk for cardiovascular disease associated with large LDL particles was 1.44 compared to 1.63 in smaller LDL particles (50). Both were highly statistically significant, which means that although larger LDL particles are less atherogenic than smaller ones, they promote the formation of fatty deposits, nonetheless. Given that the risk factors for cardiovascular diseases are more common in PCOS women than those without, the potential risk of the elevation of cholesterol levels accompanied by the KD does not seem promising for PCOS patients in general (Crosby, 2021). More studies are warranted to assess the long-term term use of the KD in metabolic diseases and to evaluate the cardiovascular risk factors but also to better define which dietary macronutrient composition is ideal.

In addition, extreme carbohydrate restriction in the KD can profoundly affect diet quality as it results in the curtailing or sometimes elimination of very important foods such as fruit, vegetables, whole grains and legumes and leads to the increased consumption of animal products (high fat, moderate protein consumption). As a result of this reduction in vegetables and fruits, nutritional deficiencies are likely to occur in PCOS patients undergoing the KD. Even when consuming only consuming

nutrient-dense foods, the typical KD is reported to have multiple micronutrient shortfalls, often deficient in vitamin K, linolenic acid, and water-soluble vitamins (Ashworth. 2009) (vitamin C and B complexes). Particularly in women, several studies have stated that abnormal nutrition may permanently affect the maturation of oocytes (Pilz, 2018) (immature egg cells) which would be detrimental to ovulation prospects leading to a significant decrease in fertility amongst these patients. Additionally, fat-soluble vitamin D deficiencies have been found in patients on a KD and medical imaging has shown that this can lead to bone demoralisation in this population. Even though this decrease in bone density was seen in children, it is plausible to confirm that this could be prevalent in PCOS women too. Observational studies show that a vitamin D deficiency is a risk factor for reduced fertility and various adverse pregnancy outcomes (Williams, 2021). This would negatively affect the elevation of fertility amongst this cohort of PCOS patients and with the inconclusive data and studies supporting the KD, the chances of the diet not inducing some sort of nutritional shortfall remain relatively slim.

In long-term periods, the ketogenic diet has been successful in supporting obese patients with weight loss (24 weeks) which also resulted in the decrease of triglycerides, total cholesterol, and HDL levels (Kong, 2020). However, multiple limitations stand in the way of the evidence of this study. Firstly, the patients did not have PCOS so we cannot be sure that the same results would occur within the target population, let alone elevate fertility amongst these patients. Secondly, the primary aim of the study was to induce weight loss within this group of patients which is not the core of this report; this report wishes to answer if the ketogenic diet can successfully elevate fertility whether that be through weight loss or the reduction in IR. Moreover, it could be argued that 24 weeks is not long enough to be considered "long-term" in the context of this report, because fertility in women would most likely be favourable to last more than 6 months.

Criteria	**Weighting**	**Ketogenic Diet**
*Long-term caloric sustenance (~ 6 months or long enough become fertile)	2	0
*Results of the diet permanent ? Body permanently adapts to altered metabolism even after reversion to a normal diet, or does diet need to be continued throughout the lifetime ?	1	0
Presence of side effects	1	-1
Quality of Life affected due to abstinence from agreeable tastes and food and forced changes in lifestyle	1	-1
Total		-2

A score of zero indicates insufficient information, the score for a particular category cannot be greater than ± the weighting for that category

*The reason these criteria do not have lesser values than they do is because once the objective of becoming fertile is achieved, there is presumably no further need to continue on the ketogenic diet.
The minimum possible score is -7, the maximum possible score is +7

TABLE 3. Pugh Matrix Assessing the Sustainability of the KD on PCOS Patients.

The overarching problem revolving around the unsustainable nature of the diet originates from its core principle - maintaining ketosis. The maintenance of ketosis for long-term dietary intervention is rarely successful mainly due to receiving 60-70% of your caloric intake from fats instead of carbohydrates. A single meal with too high a proportion of carbohydrates will cause the body to fall out of ketosis and quickly return to using carbohydrates as its main energy source. Furthermore, because of the limited number of robust studies and the lack of strong evidence evaluating the diet's potential risks, recommendations supporting the KD for PCOS patients with infertility issues should be made with lots of medical guidance and frequent medical testing. In conclusion, even though the KD has proven to be effective in short periods, the large number of potential side effects it could cause as well as the limited trials supporting it prove it to be unfavourable as a sustainable treatment for PCOS patients with infertility.

The next section of the report will conclude all the discussions that have been argued throughout the report and will conduct an overall evaluation of the KD's 'holistic success' on PCOS patients.

Discussion & Analysis

	Carbohydrate Restriction (KD) (average grams of carbohydrates)	Glucose Metabolism (mg/dl average blood glucose level)	Insulin Sensitivity (μIU/ml, average insulin levels in blood)	Weight Loss (average kg loss)	Nutritional Deficiency (percentage of subjects developing nutritional deficiency – e.g: ketonuria - due to KD)
Carbohydrate Restriction (KD) (average grams of carbohydrates)	1	-0.97	0.24	0.74	0.78
Glucose Metabolism (mg/dl average glucose in blood)	-0.97	1	0.75	-0.79	-0.43
Insulin Sensitivity (μIU/ml, average insulin levels in blood)	0.24	0.75	1	-0.16	-0.37
Weight Loss (average kg loss)	0.74	-0.79	-0.16	1	0.56
Nutritional Deficiency (percentage of subjects developing nutritional deficiencies – e.g: ketonuria – due to KD)	0.78	-0.43	-0.37	0.56	1

TABLE 4. Correlation Matrix with Factors Known to Contribute to PCOS Resolution.

This correlation matrix displays the relationship of the ketogenic diet with other factors discussed in the report such as glucose metabolism, insulin sensitivity (resistance), nutritional deficiencies and weight loss. It contains the calculated correlation coefficients derived from the results of the 4 main clinical trials conducted on PCOS patients that have been previously discussed. (Mavropoulos, Cincione, Paoli and Paláfox Gomez) This matrix has been constructed to compile all the results from the main clinical trials previously discussed in the report.

The strongest correlation calculated is between carbohydrate restriction (KD) and glucose metabolism, implying that the greater the restriction of carbohydrates, the lower the rate of glucose conversion to ATP for energy due to the lack of sugar in the diet. This would have a promising effect on insulin resistance, as the carbohydrate restriction favours insulin sensitivity repair in insulin-resistant patients, hence elevating fertility in women with PCOS. In addition, the relationship between glucose metabolism and insulin sensitivity is also strong, indicating a positive link between the two factors (higher metabolism of glucose would lead to greater insulin sensitivity or the opposite could occur). This is illustrated in reports previously discussed; when PCOS patients have impaired glucose metabolism, the opposite effect occurs and their insulin sensitivity decreases. However, the contradictory negative correlation exhibited between weight loss and insulin sensitivity goes against the information provided by the previous discussions. This is because it suggests that increased weight loss would lead to decreased insulin sensitivity (or vice versa) which does not align with studies discussing the effect of weight loss on insulin resistance (Kong, 2020).

It would be reasonable to suggest that the carbohydrate-restricting nature of the KD is favourable for alleviating infertility in PCOS phenotypes, as it targets the insulin-resistance presentation in the disorder. Thus, this matrix derived from the results of the 4 clinical trials further emphasises that the lack of carbohydrates (present in the KD) is favourable for PCOS patients. However, it is important to note that correlation does not equate to causation and although some of these relationships are strong, they do not necessarily mean that the increase of one factor would cause the increase in the other. Furthermore, this matrix quantifies the results from only four clinical trials in this report – it would be beneficial to obtain results from more real-life trials in order to compile more reliable correlation coefficients and spot anomalies.

The table above has shown that the KD is efficacious amongst PCOS patients with fertility issues and has proven to cause improvements in FSH/LH ratios and menstrual irregularities which all contribute to the elevation of fertility. In terms of the impact of the KD, the lack of studies and trials conducted with lean PCOS patients limits the KD's effectiveness in targeting the entirety of the target population, but it has been proven to be successful with obese/overweight patients which is why the overall conclusion can be considered inconclusive. Lastly, the sustainability of the KD proves to be its biggest weakness; the adverse side effects involving nutritional deficiencies and cholesterol increases threaten fertility and in the long run, the diet is not likely to cause patients to see the same success over longer periods, compared to the short-term success they see.

Conclusion

This finally provokes the question; is it successful? In general, this report suggests that the KD has proven to be successful amongst PCOS patients in shorter periods and would be likely to elevate fertility within the period of dietary intervention and it is rated favourably in the Pugh Matrix displayed above. Based on a longer period, however, the KD is unlikely to be efficacious purely based on the difficulty to adhere to the diet because of its unorthodox nutritional restraints and adverse side effects. The sum of the success ratings is +1, which displays that the effect of the KD on PCOS is promising despite the mixture of strengths and weaknesses of the diet. However, the KD does not seem to combat the disorder as well as metformin as displayed above in the Pugh matrix and would most probably work best paired with medication, rather than a solitary intervention. Furthermore, the trials evaluated in this report are mostly pilot trials, requiring future trials and research to be released to affirm these speculations and initial conclusions.

This report does propose that trials involving long-term applications (longer than 1 year) of the KD with PCOS patients should be conducted to measure and gauge the effectiveness over longer periods. Furthermore, further research conducted into understanding the causes of PCOS and its mechanisms would be beneficial in developing more comprehensive and specific interventions to elevate fertility. In addition, the specific nutritional content involved in the KD proves to be its biggest weakness with patients adhering to it. Therefore, this report does suggest that although the KD may be unsustainable; a variation of the KD to a less restrictive version might be a more reasonable approach to elevating

fertility amongst patients in the target population for prolonged success. Alternatively, a personalised plan for patients may provide appropriate relief to ensure that the women with infertility can maintain the lifestyle changes and prevent complications arising and side effects (Cowan, 2023).

Abbreviations

PCOS: Polycystic ovarian syndrome, KD: Ketogenic diet, IR: Insulin resistance, LCKD: Low-calorie ketogenic diet, MD: Mediterranean diet, LH: Lutenising hormone, FSH: Follicle-stimulating hormone, GnRH: Gonadotropin hormone-releasing hormone, ATP: Adenosine triphosphate, IVF: In-vitro fertilisation, LDL: Low-density lipoprotein

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