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

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Abstract

The ketogenic diet is reported to increase and/or restore fertility in polycystic ovarian syndrome patients, although clinical evidence is limited and largely anecdotal and ambiguous. It was found that the efficacy of the ketogenic diet for short intervals demonstrated promising elevation in fertility amongst overweight – but not lean - PCOS patients. However, the nutritional sustainability of the diet made it unlikely for patients to maintain success due to the difficulty in maintaining ketosis. This study quantified the diet's effectiveness in PCOS patients 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 in childbearing patients. The diet's hypothesized mechanism of action was presented and discussed. This report found that a less restrictive version of the ketogenic diet could be implemented for these patients with a similar probability of fertility restoration, but further research and trials would be required to confirm this effect. As an alternative, this report also suggests that a personalised dietary plan for patients may prove to be beneficial as it would be more likely to elicit compliance.

Keywords

Polycystic ovarian syndrome, Ketogenic diet, Ovarian function, Reproductive health, Fertility, Menstrual cycle, Hyperandrogenism, Insulin resistance, Follicle stimulating hormone, Lutenising hormone

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Introduction

The ketogenic diet has surged in popularity in the last decade; primarily for its short-term effect on weight loss (1). With high amounts of fat, moderate amounts of protein and a low amount of carbohydrates (2), it has been endorsed by several celebrities in the media and was the most searched diet on Google in the USA in 2020 (3).

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% of women of reproductive age worldwide (4). Characterised by three markers, (high androgen levels, anovulation and cystic ovarian growths) the common symptoms faced by women are hirsutism, menstrual irregularity and infertility (5). Infertility is often claimed to be the most demoralising symptom (6) amongst women, almost posing as a threatening insult to their womanhood and therefore, this report will focus on the improvement of this particular symptom caused by PCOS.

This report quantitates evidence that may attribute the ketogenic diet (KD) to an increase/ restoration in/of fertility in PCOS patients. There is as yet no definitive cure for PCOS hence medical professionals approach intervention by managing the symptoms of the disorder. Conventional approaches to restoring fertility in patients with this disorder are weight loss and insulin resistance management, which is often suggested by following a low-carbohydrate diet (7). The ketogenic diet has been tested in women with PCOS. Although results from research in support of the efficacy of the ketogenic diet appear promising, long-term adherence to it proves to be a major obstacle (8). Its rigorous dietary restrictions make it unlikely for patients to adhere to it over longer periods. Hence, the objective of this report was to find whether the diet – or its variations - would be 'holistically' successful amongst these women. The 'holistic' success of the KD was determined by three factors; efficacy, comparative advantage and nutritional sustainability.

Biological mechanisms of PCOS and the KD

PCOS is a complex ovarian disorder, and its aetiology remains unknown (9). This is significant because it could be argued that since the models of the effect of different interventions on the disorder are mostly hypothesised, the conclusions for the cause of infertility could be subject to future changes that depend on ongoing research.

Hyperandrogenism

Scientists hypothesise that the disorder consists of a continuous cycle of hyperandrogenaemia from theca cells in the ovaries and the resulting androgen excess is regarded as the driving force in the development of the symptoms (10). This leads to a disruption in the neuroendocrine system, causing an overproduction of gonadotropins by the hypothalamus (11). 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 (12). This in turn, leads to anovulation and the increased number of follicles. The 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 may be linked to the action of insulin. Androgen excess favours the growth of abdominal visceral adipose tissue deposits (13). 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 is associated with the secretion of excess amounts of a protein known as (retinol-binding protein 4) RBP4, in turn, associated with increased insulin resistance (14). This induces a heightened response of the pancreas and liver, causing an increased secretion of insulin (hyperinsulinemia), and this further stimulates ovarian androgen production (15) 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. These clinical signs are similar between both phenotypes, but insulin resistance has been proven difficult to quantify (16) which creates further ambiguity in recording the extent to which insulin resistance affects lean women when compared with 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 may 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 may not be effective and suggests that a combination of remedies may be required.

Ketogenic diet

Similar to 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. When compensatory glycogen stores deplete to a level much lower where the production of glucose is insufficient 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 (17) (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 a normalization of insulin release due to the loss of adipose tissue (18), which increases insulin sensitivity. The resultant improvement in androgen levels in PCOS patients may restore or increase 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 (19). Present results also imply an essential role of BMI in both diseases. Since T2D is often targeted by moderate to low carbohydrate diets, the low-carbohydrate characteristic of the KD would be beneficial for alleviating the symptoms of PCOS.

However, it is currently unknown whether weight loss or reduced dietary carbohydrate intake independently and by themselves contribute to the effect of KD on glucose homeostasis. This is because patients often lose weight with the ketogenic diet due to ketone bodies providing greater ATP production than glucose (20), hence it is easier to maintain a calorie deficit. This decrease in overall weight favors fertility (21), leading to an increase in the probability of becoming pregnant. Furthermore, obese patients are deemed to be affected by both extrinsic IR (caused by excess body mass) and intrinsic IR (22) (caused by PCOS) which creates ambiguity in how IR is targeted when ketosis is achieved.

Discussion

The 'holistic' success of the KD will be assessed based on three factors. To quantify efficacy, data from clinical trials will be evaluated and scored in a pugh matrix. To quantify comparative advantage, a pugh matrix will compare the efficacy, side effects/cost and sustainability to other treatments. To quantify sustainability, a resulting pugh matrix will score the nutritional quality of the diet and whether this can be maintained over longer periods. It must be mentioned that 'sustainabiliy' is only as long as it takes to sustain and increase fertility until childbirth. A greater emphasis will be placed on 'efficacy' as it is 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).

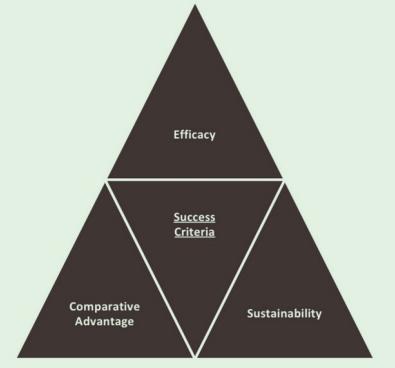

Figure 1. Assessing the success of the Ketogenic diet

Efficacy

The efficacy of the KD on PCOS patients has been highly debated but trials seem to display promising results. A trial in an overweight women cohort who were required to consume a LCKD (low-calorie ketogenic diet) over 24 weeks with a little under 20 grams of carbohydrates a day found that there was a 12.1% reduction in body weight and an improvement in the fasting serum insulin level in the blood, which suggested that the patients had gained increased insulin sensitivity through the diet (23). The FSH/LH ratio demonstrated improvement as well and two women became pregnant during the study despite previous infertility problems. The study suggested that LCKD led to a reversal of the effect of hyperinsulinemia on the secretion of androgens from the ovaries. However, the trial did not measure hormone levels at specified points during the menstrual cycle. Since none of the women were amenorrheic, the FSH/LH ratios may have been normal indicators of the stages of their menstrual cycle. The study did demonstrate reversion to insulin sensitivity throughout the cohort and achievement of fertility in some patients.

Another trial reported achieving similar results with statistically significant decreases in 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 (24). Improvements in menstrual regularity, FSH/LH ratios and successful conceptions suggested an increase in fertility, associated with the KD. The authors concluded that further studies were required to clarify the molecular mechanism of the beneficial effect of the ketogenic diet to conclusively establish the diet as an appropriate clinical intervention for the disorder. The use of the single-arm design in the study rendered it unable to distinguish between the effect of the KD, placebo and the effect of natural history (25).

In addition, the KD was beneficial when implemented in conjunction with assisted reproductive technology (26). 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. More evidence may be required to support the effectiveness of the KD with IVF and other assistive reproductive technologies. (E.g: laparoscopic drilling) Nonetheless, this study suggested that PCOS patients undergoing IVF may increase pregnancy chances by a KD.

As mentioned earlier, whether the weight loss and carbohydrate restriction could act independently to alleviate PCOS symptoms need more investigation. This is important because if the increased insulin sensitivity was to result solely from weight loss, then any diet with a general caloric deficit would yield similar improvements in fertility. Even though this would not take away the overall success of the KD, it would diminish its significance as a dietary intervention amongst others. For example, consuming a Mediterranean diet (higher carbohydrate content) confers a beneficial effect on some reproductive and metabolic parameters, such as menstrual regulatiry and glucose homeostasis, in PCOS afflicted women (27). However, it could be

argued that the Mediterranean diet targets a different aspect of the disorder; it is known to decrease the inflammatory response (28) whereas the KD places a larger emphasis on reducing insulin resistance. It could be that in each case, the focus on inflammation and insulin resistance respectively leads to an overall relief in all symptoms, inclusive of fertility decrease.

A modification of the ketogenic diet; a eucaloric Mediterranean ketogenic diet (still carbohydrate-restrictive) with a larger emphasis on green leafy vegetables that slightly less lipid reliant compared to the traditional ketogenic diet was investigated to improve PCOS symptoms. The trial presented similar success with improvements in FSH/LH ratios amongst the overweight PCOS women (29), and although the specific symptom of infertility was not investigated, it may be reasonably assumed 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 to measure weight loss in the trial, this suggests that carbohydrate restriction plays an integral role in the elevation of fertility, regardless of weight loss. Nonetheless, conclusive evidence is lacking to show that the carbohydrate-restrictive nature of the ketogenic diet causes the elevation in fertility. However, there is sufficient evidence to suggest that the KD causes symptomatic improvement in PCOS patients.

Interestingly, several approaches have emerged that target the insulin-resistant presentation in PCOS patients with insulin-independent mechanisms. SGLT2 inhibitors have demonstrated promising results in improving insulin sensitivity in PCOS patients (30). 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-2 inhibitors such as lower blood pressure, improved glucose metabolism, reduced oxidative stress and inflammation (31). 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% (32). Although the use of SGLT-2is is not widespread and is 'off-label' as an intervention for PCOS, these promising results suggest an alternative approach without directly targeting insulin resistance. This could mean that the carbohydrate-restricting nature of the ketogenic diet involving insulin may not be the only effective approach.

In addition, the trial of acarbose (an alpha glucosidase inhibitor) in PCOS patients with hyperinsulinemia demonstrated a positive clinical effect (33). These category of drugs 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-2 inhibitors, are both fairly easy to administer as patients consume them orally, often in tablet form. Nonetheless, despite promising research, further long-term, double-blind studies are necessary to establish whether

acarbose can be used as an adjunct or unique therapy in such patients.

Another insulin-independent option targeting PCOS symptoms would be through bariatric surgery. This procedure restores the functionality of the hypothalamic pituitary axis, thereby reducing cardiovascular risk and improving fertility (34). However, even though most women of reproductive age fitting the profile of PCOS have been included in several studies, very few studies have specifically targeted PCOS patients. A study with a limited number of PCOS patients (35) were followed for up to 26 months after bariatric surgery, and most women presented with better menstrual function as well as spontaneous ovulation as opposed to before the surgery (36). Furthermore, after 2 years, all women had resumed regular menstrual cycles, half had resolution of hirsutism as well as hypertension, dyslipidaemia and diabetes being almost completely resolved. In another clinical trial, 5 women became pregnant within a short time frame after the surgery (37). Nonetheless, this treatment tends to be used in more severe cases or as a final line of treatment because it is an expensive, invasive, surgical procedure with a lengthy recovery period.

These approaches are important because they encompass a range of interventions that approach the disorder through a mechanism that does not (solely) target insulin resistance. Thus, targeting the other aspects of the disorder may also be beneficial and increase pregnancies. Insulin resistance treatment is not recommended for all patients with PCOS (38). 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 the members of 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.

Table 1. Pugh Matrix Assessing the efficacy of the KD in PCOS Patients

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) (39)	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 minumum possible score is -7, the maximum possible score is +7

Overall, based on this Pugh matrix in Table 1, it would be reasonable to conclude that the ketogenic diet displays promising effects in elevating fertility in PCOS patients despite requiring further research. 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

The ketogenic diet appears to be effective in obese/overweight PCOS patients. However, there is no conclusive evidence that the KD is effective in lean PCOS patients struggling with infertility (40). Overweight/obese phenotypes experience more severe symptoms of menstrual dysfunction which leads to more severe cases of infertility (41). 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 design trials with sufficient statistical power. 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 (42) which could be classed as rather generic advice.

Although obese women with PCOS are more likely to experience anovulatory infertility compared to leaner women, this should not undermine the significance of the number 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. Regarding obese/overweight women (BMI of over 24 kg/m^3), results from multiple trials obtained favourable results of the KD as an intervention, with a greater emphasis on the LCKD (43). KD was statistically signficant in a select small number of studies, in increasing fertility prospects, often resulting in regulation of FSH/LH, the regularization 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 restore fertility is still inconclusive.

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)

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 **minimize 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 minumum 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.

Due to the lack of experimental evidence, the effect of the KD can only be predicted on the lean PCOS phenotype. Lean patients have intrinsic IR whereas obese patients have intrinsic IR (caused by PCOS) and extrinsic IR (44) (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. Since the KD improves insulin sensitivity, it can be assumed that

carbohydrate deprivation would have a beneficial effect on the insulin resistance present in these patients; in turn increasing fertility. KD is hence an effective strategy in controlling the endocrine and metabolic disorders connected to PCOS by acting on weight loss, insulin regulation and fertility outcomes. Results from other clinical trials also suggest targeting the low-grade inflammation seen in the disorder to induce overall symptomatic relief in these patients (45) (which would benefit fertility prospects). The Mediterranean diet is suited to target inflammation as it contains larger amounts of antioxidant-rich foods than the KD. Antioxidant rich MD triggers an anti-inflammatory response in the body (46). The MD may hence prove to be another stand-alone dietary intervention in increasing fertility in lean PCOS women. Nevertheless, the specific macro and micro-nutrient combination needed for an effective nutritional plan to restore fertility has not been determined.

Overall, using the Pugh matrix in Table 2, the impact of the KD on the improvement of fertility remains ambiguous, especially involving lean PCOS patients as there scant 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) (47) it is still insufficient in appropriately determining the effect of its role as a prescription for infertility.

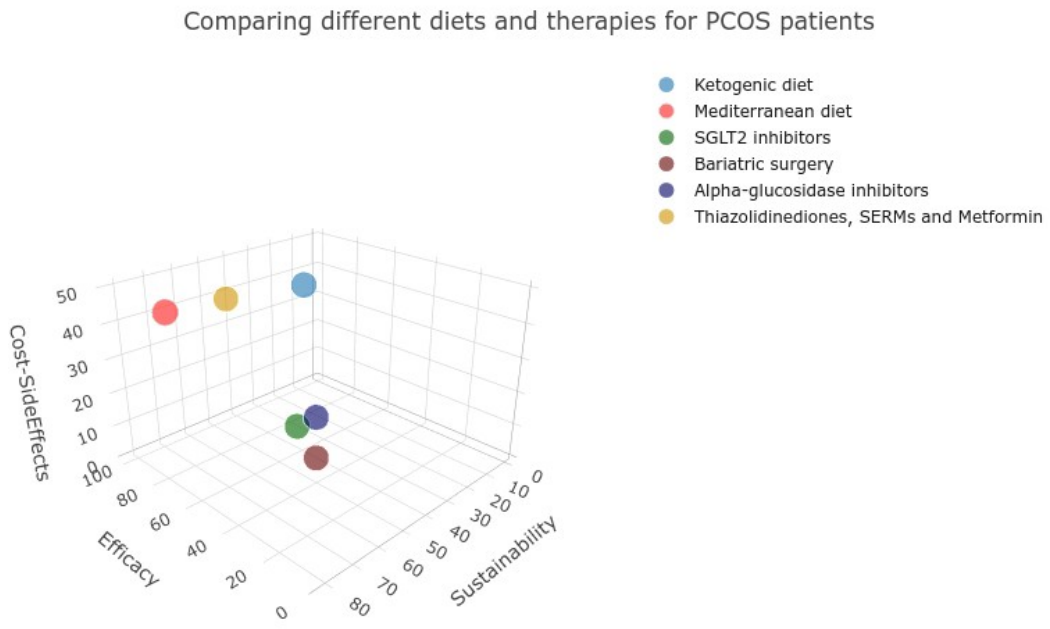

Figure 2. Comparing different diets and therapies for PCOS patients.

The 3-D plot (Figure 2) 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.

Sustainability

The promotion of long-term fertility is important amongst women because infertility is often associated with anovulation and menstrual irregularities which impact bone density (48) 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 is not only beneficial for successful pregnancies, but also for overall bodily function.

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. 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 risk (49). 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 can elevate risk for coronary heart disease. From this, it would be reasonable to state that an increased risk of CHD may accompany the adoption of KD in PCOS patients. Contrastingly, it has been suggested that the LDL particle concentration is of no concern if the increase is mainly in larger LDL particles. This may not be true, however, because according to the Women's Health Study, the evaluation of LDL particle size found 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 nonetheless promote the formation of fatty deposits. Given that the risk factors for cardiovascular diseases are more common in PCOS afflicted women than those without, the potential risk of the elevation of cholesterol levels accompanied by the KD needs consideration (51). More studies are needed to assess the long-term term use of the KD in metabolic diseases and to evaluate the cardiovascular risk associated with this diet.

In addition, extreme carbohydrate restriction in the KD can profoundly affect diet quality as it results in the curtailing or sometimes the elimination of very important foods such as fruit, vegetables, whole grains and legumes while increasing the 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 (52) (vitamin C and B complexes). Particularly in women, several studies have stated that abnormal nutrition may permanently affect the maturation of oocytes (53) (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 were found in patients on a KD and medical imaging showed that such deficiency could lead to bone demineralisation in this population. Observational studies showed that a vitamin D deficiency is a risk factor for reduced fertility and various adverse pregnancy outcomes (54). This would negatively affect the increase of fertility among this cohort of PCOS patients.

Over long-term periods, the ketogenic diet was successful in supporting obese patients with weight loss (24 weeks) which also resulted in the decrease of triglycerides, total cholesterol, and HDL levels (55). However, this study presented several limitations. Firstly, the cohort did not comprise of PCOS patients so there was no assurance that the same results would be seen with the target population. Secondly, the primary aim of the study was to induce weight loss within this group of patients; not to measure fertility increases. 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 restoration in women would most likely last more than 6 months.

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

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 minumum possible score is -7, the maximum possible score is +7

The overarching problem revolving around the unsustainable nature of the diet originates from its core principle; that of maintaining ketosis. The maintenance of ketosis for long-term dietary intervention is rarely successful mainly due to receiving 60-70% of the 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 (56). 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 caution and frequent medical monitoring. Even though the KD is effective over short periods, the large number of potential side effects it could cause as well as the limited number of trials that followed patients over the long-term make it unfavourable as a sustainable treatment for PCOS patients with infertility.

Analysis

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

	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	0.78	-0.43	-0.37	0.56	1

The correlation matrix in Table 4 shows 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.

The strongest correlation calculated is between carbohydrate restriction (achieved with 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, in turn, increasing 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. 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 (weak) negative correlation exhibited between weight loss and insulin sensitivity contradicts 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 (57).

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 (achieved by the KD) is favorable 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 trials in order to compile more reliable correlation coefficients and find anomalies.

The table above shows that the KD is efficacious in PCOS patients with impaired fertility and correlates with improvements in FSH/LH ratios as well as improvements in menstrual irregularities; which in turn contribute to the increase 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 there is evidence of success with obese/overweight patients. Lastly, the sustainability of the KD proves to be its biggest weakness; the adverse side effects involving nutritional deficiencies and cholesterol increases may negatively affect fertility. It may be hypothesized that in the long run, the diet is not likely to cause patients to see the same success over longer periods, compared to the success they see over short-term periods.

Conclusion

There is evidence that the KD is successful in increasing fertility in obese/overweight PCOS patients over shorter periods and would be likely to elevate fertility within the period of dietary intervention. KD is also successful in improving fertility rates when implemented in conjunction with IVF. It has a demonstrable mechanism of action linked with pathways that correlate with the hormonal imbalance associated symptoms in PCOS patients. The pugh matrices assigned it a relatively favorable score in terms of efficacy and comparative advantage; but not for sustainability. Over 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 (including those on fertility). The KD has a competitive disadvantage when compared with metformin, as shown in Table 2. This implies that it would most probably work best paired with medication, rather than as a solitary intervention. That being the case, it may be that a less restrictive version of KD, combined with lesser doses of medication, may act in synergy for increasing fertility in PCOS patients, regardless of their BMI. Such a regimen would have the advantages of increased fertility due to carbohydrate restriction paired with partial ketosis from the diet, as well as metformin's antihyperglycemic effects; lesser side effects from both the moderate diet and the lower dose medication as well as leveraging the KD's known and unknown mechanisms to normalize menstruation, ovulation and elevate fertility.

A variation of the KD to a less restrictive – micro and macronutrient preserving, but mild ketosis inducing - version might be a more reasonable approach to elevating fertility

among patients in the target population, independent of BMI, for prolonged success. Alternatively, a personalised plan for patients may ensure that the women with infertility can maintain the lifestyle changes and prevent complications and side effects (58). This less restrictive variation of the KD may be administered in conjunction with (lower doses) of antihyperglycemic medications to provide suitable synergies and to avoid prolonging the interval between starting the diet and the restoration of fertility.

The trials evaluated in this report are mostly pilot trials, requiring future trials and research to confirm the initial conclusions. Trials involving long-term applications (longer than 1 year) of the proposed less restrictive KD in PCOS patients should be conducted to measure 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.

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, SGLT: Sodium-glucose-co-transporter, RBP-4: Retinol binding protein-4, T2D: Type-2 diabetes

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