

Review

Not peer-reviewed version

The Role of the Mediterranean Diet in Assisted Reproduction: A Literature Review

 $\underline{\text{Dimitris Baroutis}}^*, \underline{\text{Theodoros Kalampokas}} \text{, Eleni Katsianou}, \underline{\text{Alexandros Psarris}} \text{, } \underline{\text{George Daskalakis}} \text{, } Konstantinos Panoulis}, \underline{\text{Makarios Eleftheriades}}$

Posted Date: 28 June 2024

doi: 10.20944/preprints202406.1924.v1

Keywords: Mediterranean Diet; Infertility; Fertility; Assisted Reproductive Techniques; Assisted Reproduction; ART; IVF



Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Review

The Role of the Mediterranean Diet in Assisted Reproduction: A Literature Review

Dimitris Baroutis 1,2,*, Theodoros Kalampokas 1, Eleni Katsianou 1, Alexandros Psarris 2, George Daskalakis 2, Konstantinos Panoulis 1 and Makarios Eleftheriades 1

- ¹ Aretaieio Hospital, National and Kapodistrian University, Athens, Greece; dbaroutis@gmail.com (D.B.); kalamp@yahoo.com (T.K.); elenifwkou@gmail.com (E.K.); panouliskonstantinos@gmail.com (K.P.); makarios@hotmail.co.uk (M.E.)
- ² Alexandra Hospital, National and Kapodistrian University, Athens, Greece; dbaroutis@gmail.com (D.B.); psarris.alexandros@gmail.com (A.P.); gdaskalakis@yahoo.com (G.D.)
- * Correspondence: dbaroutis@gmail.com

Abstract: The Mediterranean Diet, characterized by high intake of plant foods and unsaturated fats, has been suggested to improve assisted reproductive technology (ART) outcomes. This literature review aimed to summarize the evidence from observational studies on the associations between preconception Mediterranean Diet and ART outcomes. PubMed/MEDLINE, Embase, ScienceDirect, and Google Scholar databases were searched to identify relevant studies. Seven observational studies (n=2,321 women on ART) were included. Adherence to the Mediterranean Diet was assessed by food frequency questionnaires with 6-195 items. Three studies found that higher Mediterranean Diet scores improved Clinical Pregnancy or Live Birth rates, while two studies showed a positive effect on ART eggs and embryos. However, two studies reported no significant associations with ultimate ART success, and four studies found no effects on oocyte and embryo number or quality. Evidence for the effects of greater adherence to the Mediterranean Diet on ART outcomes is limited but promising. Additional rigorous research is needed to clarify and weigh the degree of association between the Mediterranean Diet and ART success.

Keywords: mediterranean diet; infertility; fertility; assisted reproductive techniques; assisted reproduction; ART; IVF

1. Introduction

The Mediterranean Diet, developed in countries around the Mediterranean, emphasizes a high consumption of plant foods such as fruits, vegetables, whole grains, legumes, nuts, and olive oil, combined with moderate amounts of fish, poultry, eggs, and dairy products [1–3]. The Mediterranean Diet's value in supporting and improving human health is indisputable, as it exhibits a significant protective effect against cardiovascular diseases [1,4], Diabetes Mellitus, Metabolic Syndrome [5], and certain types of cancer [1,6]. Recent research highlights the Mediterranean Diet as a useful tool for promoting Fertility and improving Assisted Reproduction results, even supporting the position that the Mediterranean Diet should be recommended to infertile couples who resort to Assisted Reproduction methods (ART) for having a child [7].

Infertility, defined by the World Health Organization as a disease, plagues up to 15% of reproductive-age couples, with its incidence and prevalence increasing [8–11]. Assisted Reproduction, a branch of Reproductive Medicine science, includes procedures such as IVF and ICSI and serves infertile couples to conceive and create a complete family [8,9]. Although Assisted Reproduction Techniques (ART) have greatly contributed to Infertility treatment, they remain expensive and invasive methods, with possible complications and live and viable birth rates per ART/IVF cycle of only 30% [12]. Therefore, it becomes obvious the need to improve these techniques per se and the adjunctive treatment of infertility in couples seeking treatment through ART with

complementary, easily applicable measures, such as dietary intervention, to further improve both the final and intermediate results of Assisted Reproduction.

The majority of studies have examined and highlighted the benefit of specific components and foods of the Mediterranean Diet in improving several parameters of Human Fertilization, such as semen quality [13–22], egg quality and development [13,23–31], embryo quality, and optimization of conditions for their subsequent implantation in the endometrium [13]. The Mediterranean Diet is rich in antioxidants, polyunsaturated fatty acids (such as $\omega 3$ & $\omega 6$ fatty acids), monounsaturated fatty acids (PUFAs & MUFAs), fiber, and vitamins C, E, and the vitamin B complex [32–36], which contribute to Reproductive Health [37] through mechanisms that include reducing inflammation [36], increasing insulin sensitivity [13], and protecting against oxidative stress and its damage [23–28,38,39].

Despite the Mediterranean Diet being defined as an entity since the 1960s [40], the investigation of its relationship with the improvement of Human Fertility and especially with Assisted Reproduction has only recently gained more interest. The fact that the majority of the existing literature investigates the individual nutritional elements and substances individually should be emphasized, overlooking their possible synergistic action in a wider context by considering them as a whole that constitutes a Diet - Nutritional Pattern/Model. Therefore, the holistic examination of the Mediterranean Diet and the highlighting of the beneficial role of the individual components and foods that make it up through the overall combination and interaction is of particular research interest with possible further clinical applications and bridging an important knowledge gap.

Consequently, this review focuses on summarizing the existing knowledge and literature on one of the most popular diets, arguably the Mediterranean Diet, regarding its role and impact on the outcome of Assisted Reproduction.

2. Materials and Methods

2.1. Process of Studies Retrieval

A thorough research was performed using databases and online platforms such as PubMed/MEDLINE, Embase, Google Scholar, ScienceDirect, Scopus, Web of Science (Clarivate), and UpToDate. The 'snowball literature searching method' of finding additional bibliographic sources was also followed from the References Lists to expand the pool of available bibliographic sources used, extracting information on the Mediterranean Diet, Infertility, Assisted Reproduction Techniques, and especially on the correlation and interaction between them.

2.2. Algorithm Search

(ICSI OR "Intracytoplasmic sperm injection" OR IVF OR fertility OR infertility OR ART OR "assisted conception" OR "assisted reproductive technology" OR "assisted reproductive" OR "assisted reproduction") AND ("mediterranean diet")

2.3. Screening - Eligibility Criteria

The selection of the included studies was carried out based on their relevance to the subject in terms of their title and abstract and after the examination of the full manuscript. Studies that examine the Mediterranean Diet and Mediterranean Diet patterns in infertile couples seeking to have children through ART, as a whole and not with an emphasis on specific ingredients, vitamins, trace elements, foods, etc., included in it, were selected. Only studies dealing with ART for the purpose of IVF/ICSI were included. Studies focusing only on cryopreservation and storage of embryos, donation, or surrogacy were included. Studies focusing only on specific pathological conditions associated with infertility, such as endometriosis or polycystic ovary syndrome, were excluded. Only published original research studies were included, while other literature and systematic reviews and case report studies were excluded. Furthermore, studies that did not include methods for evaluating adherence to the Mediterranean Diet were excluded. There was no time limit, and the search language was English. Given the large heterogeneity of the studies, quantitative meta-analysis was not feasible. The

finding process, the examination, and inclusion of the selected studies from the aforementioned databases took place from October 2022 to July 2023.

3. Results

3.1. Study Features & Demographics

After a thorough search of the above-mentioned databases, seven studies were found that met the inclusion criteria in the present literature review [41–47], of which six were cohort studies, while one was a cross-sectional study (Noli et al.) [47], which in total included 2,321 women with Infertility under ART therapy [8,9]. Individual sample sizes ranged from 161 to 590 women. Our review studies included both women with initial treatment with IVF cycles and women in later cycles, evaluating the association of adherence to the Mediterranean Diet before ART therapy, with intermediate outcomes (number and quality of eggs at retrieval, number and quality of embryos, embryo transfer, implantation) and the final results of Assisted Reproduction. The main characteristics of the studies in the present literature review are summarized in Table 1.

Table 1. The included studies of the review and their key characteristics.

First Author (year)	Country	Study Desigr	Sample size and characteristics	ART protocol	Method of Evaluation of the Mediterranean Diet - 195-questions about	Duration of the Study and Follow – up period	l Results	Mediterranean Diet and ART	Confounders
Vujkovic et al. (2010) [41]	Netherlands	Prospective Cohort	IVF/ICSI treatment at a university IVF clinic, median age of women ≈35 years, median BMI ≈23 kg/m 2	Not clarified	foods in a FFQ analyzed in terms of main components to identify dietary patterns - The evaluation of following the Mediterranean Dietary Pattern was done with a score of 0-8	- Conducted from September 2004 to January 2007 - Preconception diet of the previous 4 weeks - Follow-up after ART not clarified	ofhCG 15 days after ovulation)	pregnancy by 1.4 times although not statistically significant (OR 1.4, 95% CI 1.0-	- BMI, smoking, alcohol, IVF / ICSI therapy, ovarian - stimulation protocol
Twigt et al. (2012) [4:	2]Netherlands	Prospective Cohort	199 women undergoing 1st IVF/ICSI cycle at a university IVF clinic	Not clarified	- 6 questions about the frequency of intake of fruits, vegetables, meat fish, whole grain products and fatty foods. –Preconception	- Conducted from October 2007 to October 2010 – Pre- Conception Diet - Follow-up after ART not		- 1 unit increase in PDR score increased the odds of pregnancy progression by 1.65 (aOR 1.65, 95% CI 1.08–2.52)	- Woman's Age, Smoking, Partner's PDR Score, Couple's BMI, ART Treatment Indication

Karayiannis et al. (2018) [43]	Greece	Prospective Cohort	244 non-obese women aged 22-41 years with BMI<30kg/m2undergoing at IVF cycle (ICSI) in a private IVF clinic. Mainly rinfertile couples of male etiology	and/or hMG at a max	- 76-point Mediterranean Diet score from 0-55 that assessed intake of foods from 10 food groups	-Held from 2013 to 2016 - Pre-conception diet - Follow-up after ART not s clarified	- Oocytes retrieved, mature oocytes, fertilisation rate, embryo quality at day 3, clinical pregnancy, live births (8,9)	- Clinical Pregnancy: 50% in the upper tertile (MedDietScore ≥36, n =86) vs. 29% in the lower tertile (MedDietScore ≤30, n =79), p =0.01 - Live births: 49% in upper tertile vs. 27% in lower tertile, p =0.01 - Differences in clinical pregnancy and live births were found only in women <35 year of age - No significant differences were found in the other results	Supplement Use
Gaskins et al. (2019) [44]	USA	Prospective Cohort	357 women aged 31-39 years and BMI: 21-28 who- underwent a total of 608 cycles of ART treatment	- Multiple Protocols		- Evaluation of data from 2007 to 2017 - Pre-conception diet - Women were followed for 1 (55%), 2 (26%), 3 (13%9, or 4-6 cycles of ART (5%)	- Live births or - Clinical Pregnancy	- The Mediterranean Diet was found to improve live birth rates above the first quartile of adherence (0.44, 95% CI: 0.39-0.49, p <0.05) while in the first quartile: (0.31, 95% CI: 0.25–0.39, p < 0.05) - However, there was no further improvement in live birth rates above the second quartile	- Age, BMI, Caloric Intake,

		474 women aged 23-40 years, with BMI: 18.3-		- Mediterranean Diet Score from 0-9 that assessed intake of 9	- Held from September 2014 to December 2016	- Retrieved Eggs, Quality and Number o	- No significant correlation was noted with clinical pregnancy rates - No significant association of the Mediterranean Diet Score with oocyte count, embryo quality, clinical pregnancy or live births emerged f - Minimally lower risk of	- Age, Physical Activity, BMI,
Ricci et al. (2019) [45] Italy	Prospective Cohort	years, with BMI: 18.3- Not 26.3, treated with an IVF clarified cycle in an Italian IVF clinic	larified	food groups, via 78-	- Pre-conception diet - Follow-up after ART not	Embryos on Day 2/3, Embryo Transfer, Clinical Pregnancy, Live Births	failure to achieve clinical pregnancy for intermediate Mediterranean Diet Score in women >35 years (aRR 0.84, 95% CI 0.71–1.00, p < 0.05) with no associated increase in live birth rates	Smoking, Daily Caloric Intake, Previous ART Cycles
Sun et al. (2019) [46] China	Prospective Cohort	590 infertile women aged G 28-35.5 years undergoing ag IVF treatment an	gonist or ntagonist rotocol	- Mediterranean Diet Score from 0-8 that assessed the intake of 8 food groups (alcohol removed), via a 69- question food frequency non- validated FFQ	- Held from September 2016 to December 2017 - Pre-conception diet - Follow-up only for Embryo Transfer	- Retrieved Eggs, Number of Embryos, Quality of Embryos on Day 3, Clinical Pregnancy, Implantation	- Higher Mediterranean Diet Score led to an increase in the number of available embryos (8.4 ±5.26 vs. 7.4 ±4.71, p =0.028) - No significant differences emerged in the other results under examination	
Noli et al. (2023) [47] Italy	Cross - Sectional	296 infertile women aged - 19-39 years, with normal ac BMI and ovarian reserve, G	cting	- Mediterranean Diet Score from 0-9 that assessed intake of 9	- Held from September 2014 to February 2019 - Pre-conception diet	- Unexpected poor ovarian response after	- Low Mediterranean Diet Score led to an increased risk of Unexpected poor response,	- Age, BMI, fSmoking, Endometriosis,

undergoing IVF	agonist or food groups, via 78-	- No follow-up was stimulation (≤3 mate	re statistically significant	Caloric intake,
treatment	antagonist questions of food	performed after ART, as a eggs in ovulation)	association especially for the	Alcohol, Caffeine
	protocol frequency in a certified	d cross-sectional study that is	middle tertile of the	
	- Initial FFQ	a snapshot of data in a	Mediterranean Diet Score	
	dose of	specific time period	versus the lower tertile: aOR	
	gonadotro		0.29 (95% CI 0.11-0.76)	
	pins 150-		- For middle and upper tertile	•
	225 IU		women combined vs. lower:	
	/day		aOR 0.34 (95% CI 0.14-0.82)	

ART: Assisted Reproduction Techniques, ICSI: Intra-cytoplasmic sperm inclusion, IVF: In-vitro Fertilization, FFQ: Food Frequency Questionnaire, OR: Odds Ratio, aOR: advance Odds Ratio, RR: Relative Risk, CI: Confidence Interval.

3.2. Evaluation of Adherence/Following of the Mediterranean Diet

The assessment of adherence/following of the Mediterranean Diet in the included studies was carried out through food frequency questionnaires (FFQ – Food Frequency Questionnaire) which include a calibration - score for the degree of adherence to the Mediterranean Diet. Higher FFQ scores were associated with more faithful adherence to the Mediterranean Diet before ART treatment. Twigt et al. [42] used a 6-food group questionnaire in the form of "YES or NO" in response to their consumption, which was based on the National Dutch Dietary Guidelines [48], but this modified questionnaire had not been previously validated and evaluated. The studies of Karayiannis et al. [43] and Gaskins et al. [44] used the MedDietScore [48] with a scale of 0-55, while the studies of Ricci et al. [45] and Sun et al. [46] used a variant of the MDS with a scale of 0-9 [1]. Vujkovic et al. [41] used a FFQ with analysis based on main dietary characteristics to infer adherence to certain dietary patterns, including the Mediterranean Diet, with a score of 0-8. Finally, Noli et al. [47] used a validated and recognised 78-food groups and items FFQ [49]. The individual FFQs showed great heterogeneity among themselves, which makes their comparison very difficult and challenging. Indicatively, the agreement rate of MedDietScore [48] and of MDS [1] is about 65% [50].

3.3. ART Protocols

The ART protocols followed varied among the studies in this review, including GnRH agonists and antagonists, as well as other hormonal adjuvant regimens, based on the experience and region of each IVF center.

3.4. Results - Associations of the Mediterranean Diet and ART Outcomes

The association and role of the Mediterranean Diet with Assisted Reproduction for each of the 7 studies is summarized below and aggregated in Table 2:

- 1) The study of Vujkovic et al. (2010) [41] found that higher adherence to a Mediterranean Diet among couples undergoing IVF/ICSI was associated with increased odds of clinical pregnancy (OR 1.4, 95% CI 1.0–1.9). However, adherence to the Mediterranean Diet was not associated with embryo quality.
- 2) The study of Twigt et al. (2012) [42] reported that each one-unit increase in the mother's preconception nutritional risk score assessing adherence to the Dutch Dietary Guidelines [50] was associated with a 65% increase in the likelihood of ongoing pregnancy pregnancy progression (Ultrasound detection heart rate at 10 weeks of gestation) after a 1st ART cycle.
- 3) The study of Karayiannis et al. (2018) [43] observed that higher Mediterranean Diet scores were associated with increased clinical pregnancy rates (RR 1.98, 95% CI 1.05-3.78) and live birth rates (RR 2.64, 95% CI 1.37-5.07) among women under 35 years of age undergoing their 1st cycle of in vitro fertilization. No associations were observed between the Mediterranean Diet and the number of eggs or the quality of the embryos.
- 4) The study of Gaskins et al. (2019) [44] found that the Mediterranean Diet was associated with improvement in live birth rates above the first quartile of adherence (0.44, 95% CI: 0.39-0.49, p < 0.05), versus the first quartile: (0.31, 95% CI: 0.25-0.39, p <0.05). However, there was no further improvement in live birth rates above the second quartile. No significant correlation was noted with clinical pregnancy rates.
- 5) The study of Ricci et al. (2019) [45] reported no significant associations between Mediterranean Diet adherence score and oocyte number, embryo quality, clinical pregnancy, or live birth rates among women undergoing IVF. A marginally lower risk of failure to achieve clinical pregnancy for the intermediate Mediterranean Diet Score in women >35 years was noted (aRR 0.84, 95% CI 0.71–1.00, p < 0.05) with no associated increase in live birth rates.
- 6) The study of Sun et al. (2019) [46] found that higher Mediterranean Diet scores were associated with increased number of fetuses (p=0.028). However, no associations were observed for oocyte number, embryo quality, clinical pregnancy or live birth rates.

7) Finally, Noli et al. (2023) [47] found that lower scores in adherence to the Mediterranean Diet were associated with an increased risk of unexpected poor ovarian response (aOR 0.29, 95% CI 0.11–0.76).

Table 2. The Clinical Correlation of the Mediterranean Diet with Assisted Reproduction.

Study	Number/Qualit Oocytes	y ofNumber/Quality of Embryos	Clinical Pregnancy Live Births
Vujkovic et a (2010) [41]	ll. No correlation	No correlation	OR 1.4, 95% CI 1.0– 1.9 Not evaluated
Twigt et al. (2012 [42]		Not evaluated	65% increase in ongoing pregnancy with 1Not evaluated unit increase in nutrition score
Karayiannis et a (2018) [43]	ll. No correlation	No correlation	RR 1.98, 95% CIRR 2.64, 95% CI 1.05-3.78 1.37-5.07
(2017) [11]	ıl. Not evaluated	Not evaluated	Improvement in live births above the first quartile Not evaluated following the Mediterranean Diet
Ricci et al. (2019) [45]	9) No correlation	No correlation	No correlation No correlation
Sun et al. (2019 [46]	9) No correlation	Increased numbe with highe nutrition scor (p=0.028)	er No correlation Not evaluated
Noli et al. (2023 [47]	Increased response with nutrition score	poor lowerNot evaluated	Not evaluated Not evaluated

In all studies, the results were statistically processed for potential confounders, which are referred for each study in Table 1.

4. Discussion

This literature review aimed to investigate the role of compliance with the Mediterranean Diet in Assisted Reproduction. More specifically, the contribution of adherence to the Mediterranean Diet to the period before treatment with ART cycles, to the intermediate components of Assisted Reproduction Techniques, as well as to the final outcome, i.e., pregnancy (biochemical or clinical) and live births [8,9]. This review is one of the few that approaches the Mediterranean Diet as an indivisible food pattern and does not focus on individual foods and elements included in it, but on their synergistic action and interaction to improve the results of Assisted Reproduction.

Thus, the 7 included studies [41–47], which are probably the only original research studies that have investigated the association of pre-treatment adherence to the Mediterranean Diet with treatment with ART cycles, lead to ambiguous conclusions, with an overall positive sign. In total, the findings of the studies indicated a modest improvement in clinical pregnancy rates and live births [41,43,44] when there was a higher score in adherence to the Mediterranean Diet, but this association was not linear nor proportional [44,47]. This practically indicates the existence of a threshold (cut-off point) of compliance – score above which no additional benefits are observed in the results of Assisted Reproduction, with a more faithful adherence to the Mediterranean Diet. In contrast, in the interim results of ART, only the study by Sun et al. (2019) [46] found that higher Mediterranean Diet scores

were associated with increased number of fetuses (p=0.028). Noli et al. [47] pointed out in their cross-sectional study that reduced adherence to the Mediterranean Diet led to a poor response to ovarian stimulation and a reduced number of eggs per ovulation (\leq 3 mature eggs per ovulation). Taking into consideration the above, leads to the conclusion that the action of the Mediterranean Diet lies in optimizing the receptivity of the endometrium [41], implantation, in smooth placentation and later in the support and development of pregnancy due to its high nutritional value [51–53]. Possible components in the mechanism of these beneficial effects are the anti-inflammatory [36] and antioxidant properties [32–36] of plant foods, plant fibers and unsaturated fatty acids ω 3 and ω 6 of the Mediterranean Diet [1–3,13,32–36,54–56] which favor the development of an appropriate endometrial microenvironment.

However, the positive effect of the Mediterranean Diet on the final outcome of Assisted Reproduction was not shown by all the studies and in fact some found the absence of a statistically significant correlation [45,46]. These differences can be attributed to the heterogeneity in the size of the studies, to the individual characteristics of the examined infertile women, to the ability to limit errors from confounders and in particular to the great heterogeneity in the methods of evaluating the adherence to the Mediterranean Diet, as their final calibration, indicatively, it was based on 6 to 195 different food items and groups.

4.1. Potential Applications

Although the results so far are conflicting and do not demonstrate a clear and catalytic effect of the Mediterranean Diet on Assisted Reproductive Techniques [8,9] and its outcome, it is a fact that the Mediterranean Diet is the most popular beneficial dietary pattern for human health and fertility promotion [5,13,38,55,56]. It is therefore considered appropriate to properly inform infertile couples who resort to assisted reproduction methods about the possible beneficial actions of the Mediterranean Diet and to encourage them to comply with it, but also to participate in relevant research programs with the aim of improving the existing knowledge arsenal against Infertility and the progress of IVF science. Clinicians of Assisted Reproduction can integrate pre-treatment nutritional counseling to prospective infertile couples and recommend the Mediterranean Diet as the preferable one, after the patients' dietary habits have been previously examined and evaluated with valid and certified questionnaires (FFQs). Optimizing candidates' adherence to the Mediterranean Diet and its outcomes in ART cycles can be supported by the provision of individualized dietary plans (adapted to the Mediterranean Diet standards) by appropriate nutritionists, based on personal preferences, cultural background, as well as possible appropriate dietary restrictions (diabetic patients for instance). Decision-making on the part of patient-candidates needs to be based on full information about the possible benefits of the Mediterranean Diet on their reproductive potential but also about the limitations that are set, so that the goals remain at realistic levels.

4.2. Limitations and Areas for Future Research

It is particularly important to mention the limitations of the present literature review, so that its findings can be interpreted in an appropriate context and at the same time to highlight possible gaps in the scientific knowledge and the opportunities for further research. In particular, out of the total of 7 studies, 6 were cohort studies, while 1 was a cross-sectional study (Noli et al.) [47], which indicates from their nature the impossibility of drawing safe conclusions about the real causal relationship of the Mediterranean Diet and its possible extensions to intermediate and final results of Assisted Reproduction Techniques. All existing studies examine the Mediterranean Diet before ART treatment and not during pregnancy, although its value during pregnancy has been previously demonstrated by multiple studies. Furthermore, the studies also showed heterogeneity in the ART protocol followed, based on the experience of each IVF center and its location. The review did not focus on the effect of the Mediterranean Diet on the sperm parameters of infertile men, which is now well known to have multiple benefits [13–22,38,57–61]. This poses a further important limitation as male infertility is considered to contribute equally to the infertility of reproductive age couples [62], a fact that must be taken into consideration in the interpretation of the results. This literature review

focuses only on infertile couples seeking childbearing through ART and therefore any beneficial effects of the Mediterranean Diet shown by the studies mentioned should not be generalized to other couples and women of reproductive age seeking pregnancy through natural conception, although other studies support their existence [18–20,23–28,63–68]. An important limitation is posed by the fact that the FFQs were based on the personal recall from memory of the examined women, which involves a high risk of recall bias.

In this light, it seems appropriate and particularly beneficial for the Science of Reproductive Medicine and especially for the field of Assisted Reproduction, to organize research groups to further investigate the role of the proven beneficial in multiple aspects of Human Health, Mediterranean Diet in Assisted Reproduction Techniques. In order to draw safer conclusions in this regard, it becomes necessary to conduct randomized clinical trials (RCTs), ideally multicenter, with a larger number of participating couples, both women and men with infertility. It is suggested that they should be followed for a defined short but inferentially short period of time, e.g., 6 months as in the PREPARE study [69], which increases the potential for follow-up and compliance. It is highly important to develop objective and standardized ways of assessing adherence to the Mediterranean diet with possible monitoring by research teams and specialized nutritionists at regular intervals, in a hybrid manner, by phone and face-to-face meetings. This will significantly reduce multiple confounding factors that arise both due to the heterogeneity of existing FFQs and errors arising from recall from memory [70].

5. Conclusions

In conclusion, it appears that the Mediterranean Diet is an excellent dietary pattern that promotes Health and Fertility and possibly higher adherence to it may result in improved parameters of Assisted Reproduction, especially Clinical Pregnancy and Live and Viable Child Births. However, further rigorous research by organizing Randomized Clinical Trials is deemed imperative to concretize and weigh its contribution to Assisted Reproduction and to formulate appropriate Public Health Policies and guidelines for the concerned couples whose goal of creating a family with children is challenged by the Infertility they face.

Supplementary Materials: Not applicable.

Author Contributions: Conceptualization, D.B., T.K., E.K., A.P., G.D., K.P., and M.E.; methodology, D.B., T.K. and A.P.; validation, D.B., T.K., E.K., A.P., G.D., K.P., and M.E.; formal analysis, D.B., T.K., E.K., and A.P.; investigation, D.B., T.K., E.K., and A.P.; resources, D.B., T.K., E.K., A.P., G.D., K.P., and M.E.; data curation, D.B., T.K., E.K., and A.P.; writing—original draft preparation, D.B. and E.K.; writing—review and editing, G.D., K.P., and M.E.; visualization, D.B., T.K., E.K., and A.P.; supervision, T.K., G.D., K.P., and M.E.; project administration, G.D., K.P., and M.E. 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: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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

References

- 1. Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, et al. Mediterranean diet pyramid: A cultural model for Healthy Eating. Am J Clin Nutr. 1995;61(6):1402S-1406S.
- 2. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003;348(26):2599–608.

- 4. Widmer RJ, Flammer AJ, Lerman LO, Lerman A. The Mediterranean diet, its components, and cardiovascular disease. Am J Med. 2015;128(3):229–38.
- 5. Guasch-Ferré M, Willett WC. The Mediterranean diet and Health: A Comprehensive Overview. J Intern Med. 2021;290(3):549–66.
- 6. Mentella, Scaldaferri, Ricci, Gasbarrini, Miggiano. Cancer and mediterranean diet: A Review. Nutrients. 2019;11(9):2059.
- 7. Fontana R, Torre S. The deep correlation between energy metabolism and reproduction: A view on the effects of nutrition for women fertility. Nutrients. 2016;8(2):87.
- 8. Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, et al. The International Glossary on infertility and Fertility Care, 2017. Fertil Steril. 2017;108(3):393–406.
- 9. Zegers-Hochschild F. The ICMART glossary on art terminology. Hum Reprod. 2006;21(8):1968–70.
- 10. World Health Organization. Infertility [Internet]. [cited 2022 Nov 21]. Available from: https://www.who.int/health-topics/infertility#tab=tab_1
- 11. American Society for Reproductive Medicine. ASRM [Internet]. [cited 2022 Dec 11]. Available from: https://www.asrm.org/
- 12. Smith AD, Tilling K, Nelson SM, Lawlor DA. Live-birth rate associated with repeat in vitro fertilization treatment cycles. JAMA. 2015;314(24):2654.
- 13. Łakoma K, Kukharuk O, Śliż D. The influence of metabolic factors and diet on fertility. Nutrients. 2023;15(5):1180.
- 14. Krausz C. Male infertility: Pathogenesis and clinical diagnosis. Best Pract Res Clin Endocrinol Metab. 2011;25(2):271–85.
- 15. Torres-Arce E, Vizmanos B, Babio N, Márquez-Sandoval F, Salas-Huetos A. Dietary antioxidants in the treatment of male infertility: Counteracting oxidative stress. Biology. 2021;10(3):241.
- 16. Salas-Huetos A, Bulló M, Salas-Salvadó J. Dietary patterns, foods and nutrients in male fertility parameters and fecundability: A systematic review of Observational Studies. Hum Reprod Update. 2017;23(4):371–89.
- 17. Salas-Huetos A, Babio N, Carrell DT, Bulló M, Salas-Salvadó J. Adherence to the Mediterranean diet is positively associated with sperm motility: A cross-sectional analysis. Sci Rep. 2019;9(1):3389.
- 18. Kljajic M, Hammadeh M, Wagenpfeil G, Baus S, Sklavounos P, Solomayer E-F, et al. Impact of the vegan diet on sperm quality and sperm oxidative stress values: A preliminary study. J Hum Reprod Sci. 2021;14(4):365–71.
- 19. Bhattacharya SM, Ghosh M, Nandi N. Diabetes mellitus and abnormalities in semen analysis. J Obstet Gynaecol Res. 2013;40(1):167–71.
- 20. Keskes-Ammar L, Feki-Chakroun N, Rebai T, Sahnoun Z, Ghozzi H, Hammami S, et al. Sperm oxidative stress and the effect of an oral vitamin E and selenium supplement on semen quality in infertile men. Arch Androl. 2003;49(2):83–94.
- 21. Attaman JA, Toth TL, Furtado J, Campos H, Hauser R, Chavarro JE. Dietary fat and semen quality among men attending a fertility clinic. Hum Reprod. 2012;27(5):1466–74.
- 22. Falsig A-ML, Gleerup CS, Knudsen UB. The influence of omega-3 fatty acids on semen quality markers: A systematic PRISMA review. Andrology. 2019;7(6):794–803.
- 23. Silvestris E, Lovero D, Palmirotta R. Nutrition and female fertility: An interdependent correlation. Front Endocrinol (Lausanne). 2019;10:346.
- 24. Noli SA, Ricci E, Cipriani S, Ferrari S, Castiglioni M, La Vecchia I, et al. Dietary carbohydrate intake, dietary glycemic load and outcomes of in vitro fertilization: Findings from an observational Italian cohort study. Nutrients. 2020;12(6):1568.
- 25. Koloverou E, Esposito K, Giugliano D, Panagiotakos D. The effect of Mediterranean diet on the development of type 2 diabetes mellitus: A meta-analysis of 10 prospective studies and 136,846 participants. Metabolism. 2014;63(7):903–11.
- 26. Abiemo EE, Alonso A, Nettleton JA, Steffen LM, Bertoni AG, Jain A, et al. Relationships of the Mediterranean dietary pattern with insulin resistance and diabetes incidence in the multi-ethnic study of atherosclerosis (MESA). Br J Nutr. 2012;109(8):1490–7.
- 27. Huo R, Du T, Xu Y, Xu W, Chen X, Sun K, et al. Effects of mediterranean-style diet on glycemic control, weight loss and cardiovascular risk factors among type 2 diabetes individuals: A meta-analysis. Eur J Clin Nutr. 2014;69(11):1200–8.
- 28. Sleiman D, Al-Badri MR, Azar ST. Effect of mediterranean diet in diabetes control and cardiovascular risk modification: A systematic review. Front Public Health. 2015;3:69.
- 29. Nehra D, Le HD, Fallon EM, Carlson SJ, Woods D, White YA, et al. Prolonging the female reproductive lifespan and improving egg quality with dietary omega-3 fatty acids. Aging Cell. 2012;11(6):1046–54.
- 30. Wathes DC, Abayasekara DR, Aitken RJ. Polyunsaturated fatty acids in male and female reproduction. Biol Reprod. 2007;77(2):190–201.

- 31. Hammiche F, Vujkovic M, Wijburg W, de Vries JHM, Macklon NS, Laven JSE, et al. Increased preconception omega-3 polyunsaturated fatty acid intake improves embryo morphology. Fertil Steril. 2011;95(5):1820–3.
- 32. Di Tucci C, Galati G, Mattei G, Bonanni V, Capri O, D'Amelio R, et al. The role of alpha lipoic acid in female and male infertility: A systematic review. Gynecol Endocrinol. 2020;37(6):497–505.
- 33. Efrat M, Stein A, Pinkas H, Unger R, Birk R. Dietary patterns are positively associated with semen quality. Fertil Steril. 2018;109(5):809–16.
- 34. Ghafarizadeh A, Malmir M, Naderi Noreini S, Faraji T. Antioxidant effects of n-acetylcysteine on the male reproductive system: A systematic review. Andrologia. 2020;53(1):e13870.
- 35. Lerchbaum E, Obermayer-Pietsch B. Mechanisms in endocrinology: Vitamin D and fertility: A systematic review. Eur J Endocrinol. 2012;166(5):765–78.
- 36. Salas-Huetos A, Rosique-Esteban N, Becerra-Tomás N, Vizmanos B, Bulló M, Salas-Salvadó J. The effect of nutrients and dietary supplements on sperm quality parameters: A systematic review and meta-analysis of randomized clinical trials. Adv Nutr. 2018;9(6):833–48.
- 37. Guasch-Ferré M, Willett WC. The Mediterranean diet and Health: A Comprehensive Overview. J Intern Med. 2021;290(3):549–66.
- 38. Ferramosca A, Zara V. Diet and male fertility: The impact of nutrients and antioxidants on sperm energetic metabolism. Int J Mol Sci. 2022;23(5):2542.
- 39. Takalani NB, Monaneng EM, Mohlala K, Monsees TK, Henkel R, Opuwari CS. Role of oxidative stress in male infertility. Reprod Fertil. 2023;4(3):RAF-23-0024.
- 40. Mediterranean Diet Unesco. The Mediterranean diet: From Ancel Keys to the present, part II [Internet]. 2021 [cited 2023 Jul 28]. Available from: https://mediterraneandietunesco.org/el/the-mediterranean-diet-from-ancel-keys-to-the-present-part-ii/
- 41. Vujkovic M, de Vries JH, Lindemans J, Macklon NS, van der Spek PJ, Steegers EAP, et al. The preconception Mediterranean dietary pattern in couples undergoing in vitro fertilization/intracytoplasmic sperm injection treatment increases the chance of pregnancy. Fertil Steril. 2010;94(6):2096–101.
- 42. Twigt JM, Bolhuis ME, Steegers EA, Hammiche F, van Inzen WG, Laven JS, et al. The preconception diet is associated with the chance of ongoing pregnancy in women undergoing IVF/ICSI treatment. Hum Reprod. 2012;27(8):2526–31.
- 43. Karayiannis D, Kontogianni MD, 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(3):494–502.
- 44. Gaskins AJ, Nassan FL, Chiu Y-H, Arvizu M, Williams PL, Keller MG, et al. Dietary patterns and outcomes of assisted reproduction. Am J Obstet Gynecol. 2019;220(6):567.e1-567.e18.
- 45. Ricci E, Bravi F, Noli S, Somigliana E, Cipriani S, Castiglioni M, et al. Mediterranean diet and outcomes of Assisted Reproduction: An Italian cohort study. Am J Obstet Gynecol. 2019;221(6):627.e1-627.e14.
- 46. Sun H, Lin Y, Lin D, Zou C, Zou X, Fu L, et al. Mediterranean diet improves embryo yield in IVF: A prospective cohort study. Reprod Biol Endocrinol. 2019;17(1):73.
- 47. Noli SA, Ferrari S, Ricci E, Reschini M, Cipriani S, Dallagiovanna C, et al. Adherence to the Mediterranean diet and the risk of unexpected poor response to ovarian stimulation in IVF cycles. Reprod Biomed Online. 2023;47(1):77–83.
- 48. Voedingscentrum. The Netherlands Nutrition Centre [Internet]. [cited 2023 Aug 30]. Available from: https://www.voedingscentrum.nl/nl/service/english.aspx
- 49. Panagiotakos DB, Pitsavos C, Arvaniti F, Stefanadis C. Adherence to the Mediterranean food pattern predicts the prevalence of hypertension, hypercholesterolemia, diabetes and obesity, among healthy adults; the accuracy of the meddietscore. Prev Med. 2007;44(4):335–40.
- 50. Decarli A, Franceschi S, Ferraroni M, Gnagnarella P, Parpinel MT, Vecchia CL, et al. Validation of a food-frequency questionnaire to assess dietary intakes in cancer studies in Italy results for specific nutrients. Ann Epidemiol. 1996;6(2):110–8.
- 51. Assaf-Balut C, García de la Torre N, Fuentes M, Durán A, Bordiú E, del Valle L, et al. A high adherence to six food targets of the Mediterranean diet in the late first trimester is associated with a reduction in the risk of materno-foetal outcomes: The St. Carlos Gestational Diabetes Mellitus Prevention study. Nutrients. 2018;11(1):66.
- 52. Assaf-Balut C, García de la Torre N, Durán A, Fuentes M, Bordiú E, del Valle L, et al. A Mediterranean diet with additional extra virgin olive oil and pistachios reduces the incidence of gestational diabetes mellitus (GDM): A randomized controlled trial: The St. Carlos GDM Prevention Study. PLoS One. 2017;12(10):e0185873.
- 53. Martínez-Galiano J, Olmedo-Requena R, Barrios-Rodríguez R, Amezcua-Prieto C, Bueno-Cavanillas A, Salcedo-Bellido I, et al. Effect of adherence to a Mediterranean diet and olive oil intake during pregnancy on risk of small for gestational age infants. Nutrients. 2018;10(9):1234.

- 54. Trichopoulou A, Martínez-González MA, Tong TYN, Forouhi NG, Khandelwal S, Prabhakaran D, et al. Definitions and potential health benefits of the Mediterranean diet: Views from experts around the world. BMC Med. 2014;12:112.
- 55. Kakoly NS, Earnest A, Teede HJ, Moran LJ, Joham AE. The impact of obesity on the incidence of type 2 diabetes among women with polycystic ovary syndrome. Diabetes Care. 2019;42(4):560–7.
- 56. Kazemi M, Hadi A, Pierson RA, Lujan ME, Zello GA, Chilibeck PD. Effects of dietary glycemic index and glycemic load on cardiometabolic and reproductive profiles in women with polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials. Adv Nutr. 2021;12(1):161–78.
- 57. Makarem N, Chau K, Miller EC, Gyamfi-Bannerman C, Tous I, Booker W, et al. Association of a Mediterranean diet pattern with adverse pregnancy outcomes among US women. JAMA Netw Open. 2022;5(12):e2248165.
- 58. Mijatovic-Vukas J, Capling L, Cheng S, Stamatakis E, Louie J, Cheung N, et al. Associations of diet and physical activity with risk for gestational diabetes mellitus: A systematic review and meta-analysis. Nutrients. 2018;10(6):698.
- 59. Raghavan R, Dreibelbis C, Kingshipp BL, Wong YP, Abrams B, Gernand AD, et al. Dietary patterns before and during pregnancy and maternal outcomes: A systematic review. Am J Clin Nutr. 2019;109(Suppl_7):705S-728S.
- 60. Amati F, Hassounah S, Swaka A. The impact of Mediterranean dietary patterns during pregnancy on maternal and offspring health. Nutrients. 2019;11(5):1098.
- 61. Rodríguez-Rejón AI, Castro-Quezada I, Ruano-Rodríguez C, Ruiz-López MD, Sánchez-Villegas A, Toledo E, et al. Effect of a Mediterranean diet intervention on dietary glycemic load and dietary glycemic index: The predimed study. J Nutr Metab. 2014;2014:985373.
- 62. Agarwal A, Mulgund A, Hamada A, Chyatte MR. A unique view on male infertility around the Globe. Reprod Biol Endocrinol. 2015;13:37.
- 63. Saez Lancellotti TE, Boarelli PV, Monclus MA, Cabrillana ME, Clementi MA, Espínola LS, et al. Hypercholesterolemia impaired sperm functionality in rabbits. PLoS One. 2010;5(10):e13457.
- 64. Minguez-Alarcon L, Mendiola J, Lopez-Espin JJ, Sarabia-Cos L, Vivero-Salmeron G, Vioque J, et al. Dietary intake of antioxidant nutrients is associated with semen quality in Young University students. Hum Reprod. 2012;27(9):2807–14.
- 65. Braga DP, Halpern G, Figueira R de, Setti AS, Iaconelli A, Borges E. Food intake and social habits in male patients and its relationship to intracytoplasmic sperm injection outcomes. Fertil Steril. 2012;97(1):53–9.
- 66. Eslamian G, Amirjannati N, Rashidkhani B, Sadeghi M-R, Hekmatdoost A. Intake of food groups and idiopathic asthenozoospermia: A case-control study. Hum Reprod. 2012;27(11):3328–36.
- 67. Karayiannis D, Kontogianni MD, Mendorou C, Douka L, Mastrominas M, Yiannakouris N. Association between adherence to the Mediterranean diet and semen quality parameters in male partners of couples attempting fertility. Hum Reprod. 2016;32(1):215–22.
- 68. Ricci E, Bravi F, Noli S, Ferrari S, De Cosmi V, La Vecchia I, et al. Mediterranean diet and the risk of poor semen quality: Cross-sectional analysis of men referring to an Italian fertility clinic. Andrology. 2019;7(2):156–62.
- 69. Kermack AJ, Calder PC, Houghton FD, Godfrey KM, Macklon NS. A randomised controlled trial of a preconceptional dietary intervention in women undergoing IVF treatment (prepare trial). BMC Womens Health. 2014;14:130.
- 70. Vetter TR, Mascha EJ. Bias, confounding, and interaction: Lions and tigers, and bears, oh my! Anesth Analg. 2017;125(3):1042–8.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.