DOI: https://doi.org/10.53350/pjmhs22168801

ORIGINAL ARTICLE

Both The Folate Therapy and the Folate Treatment Combined with Zinc Had an Effect on the Endocrine Markers and Sperm Characteristics of Sub-Fertile Males

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ABSTRACT
Aim: The purpose of this study was to see how folate and folate + zinc treatment affected endocrine markers and sperm properties in sub fertile males.
Methods: The methodical research in addition meta-analysis was carried out. From 1969 to May 2020, databases were searched by Medline, Scopus, Google scholar, and Persian databases have been examined that used the set of pertinent keywords comprising "folate or folic acid AND (infertility, infertile, sterile)". Any standardized clinical studies that took oral folic acid or folate plus zinc on a selection of sub fertile males for semen analysis are included in the. Endocrine characteristics and sperm parameters were among the information gathered. Comprehensive Meta-analysis Version 2 was used for data methods.
Results: Eight researches remained comprised in the total. Seven researches have enough information for a meta-analysis. "Sperm concentration was significantly greater in males treated using folate than in men not supplied using folate (P.002)." Furthermore, folate supplementation unaided did not appear to remain additional beneficial than the placebo in terms of sperm morphology (P =.057) or motility (P =.653). In comparison to the placebo, folate with dietary supplementation had no measurable difference in blood testosterone (P =.87), inhibin B (P =.85), FSH (P =.056), or sperm motility (P =.168). However, as given a placebo, folate with zinc had a substantially bigger influence on semen parameters (P.002), morphology (P.002), and blood folate level (P.002).
Conclusion: Folate and zinc supplementation improves sperm qualities in infertile men. Nonetheless, because of the significant heterogeneity of the papers used in this meta-analysis, those findings must be regarded with care. More research is necessary to corroborate the existing results.
Keywords: Effect of Folate, Folate Plus Zinc Supplementation, sperm properties, sub fertile males.

INTRODUCTION
Subfertility is characterized by an inability to consider afterwards one year of steady, defenseless intercourse. Around 16% of couples are infertile, with half of the instances involving a male component. One in every twenty men in the general population is thought to be infertile [1]. Coping through persistent childlessness due to reduced fertility may be extremely challenging for couples, prompting them to turn to artificial reproductive procedures. However, these procedures do not address the underlying reason for infertility [2]. A huge variety of andrological illnesses go undiagnosed, including spontaneous male infertility, which is mostly caused by changes in lifestyle, and environmental factors, including dietary habits. Many researchers noticed an improvement in sperm parameters when antioxidants were used, indicating that these compounds reduce the damaging effects of free radicals on spermatozoa [3]. One of these antioxidant agents is folate, a B vitamin that is involved in a variety of metabolic activities, especially DNA replication. DNA mixture remains essential for formation of spermatozoa. Numerous enzymes complicated in DNA mixture require zinc or vitamin B. Folate has a role in the oxidative process. Defects in the oxidative route contribute to the development of reduced fertility. Folic acid, a generic version of folate, was shown to successfully scavenge oxidizing free radicals and, at the same, may be considered an antioxidant. Although water-soluble, folic acid suppresses lipid peroxidation [4]. Folic acid could thus protect bio-constituents like cellular membranes or DNA against free radical harm. Zinc is an essential micronutrient that functions as the component for over 85 metalloenzymes elaborate in DNA transcription also protein mixture. Additionally, zinc finger proteins remain involved in hereditary production of steroid hormone receptors and have antioxidants in addition anti-inflammatory effects. Additionally, research has indicated that zinc remains vital in testicular maturation, spermatogenesis, in addition sperm motility. Interestingly, several studies found that supplementing vitamin b12 plus zinc sulfate resulted in a 76% rise in standard sperm count in addition the 5% rise in aberrant morphology in subfertile males. There is little data given on belongings of folic acid also zinc on subfertility. According to research literature, there's also an increasing interest in folic acid and zinc among subfertile males. Several investigations have shown that the impacts of folic acid in addition zinc on spermatogenesis remain significant [5].

METHODOLOGY
Google scholar examined 480 results. Furthermore, the source sections of relevant trials, observational studies, and meta-analyses were manually examined to discover additional trials that were overlooked by the computerized search. The authors were approached for any further missing information. Cone plots and Egger's test were used to investigating selection bias. Figure 1 depicts the selection process of RCTs for inclusion in the review of the literature.

The meta-analysis includes trials that matched the basic guidelines:

1 Semen or endocrine investigations were performed on a sample of subfebrile men.
2 A controlled trial research was planned.
3 Comparing oral folic acid supplementation as mono-preparations or in conjunction using zinc sulfate in the experimental group, independent of the kind of treatment group.

Researchers retrieved the collected details for every research using a pre-defined checklist: first author, study design, survey period, and trial quality. This was evaluated by two authors by using Oxford Center for Evidence-Based Medicine's therapeutic study criteria. Statistical analyses were performed separately by two writers, and discrepancies were addressed by a discussion with a third researcher. The publication bias was classified as low, uncertain, or high for each area. Disagreements are generally settled by conversation, and if required, further material was obtained from the source author. Figure 2 summarizes the risk of bias for all publications. Figure 3 depicts the risk of bias in each research. Two experiments found that random sequence generation and allocation concealment were acceptable. A study looked at the problem of treatment allocation utilizing computer-generated different numbers. In another study, researchers reported achieving acceptable consists of materials by employing blinded drugs stored in the hospital pharmacy. The hospital pharmacy categorized tablets according to the randomized list and gave them to the research assistant who would prescribe them to the patients.

RESULTS

Seven RCTs were selected from 565 relevant publishing trials. Six RCTs reported sperm quantity parameters, four RCTs reported sperm motility and morphology, and two RCTs reported serum folate, FSH, inhibin B, and testosterone levels. Seven trials had enough data for meta-analysis, with three RCTs reporting sperm concentration, mobility, and morphology and three RCTs reporting blood folate, FSH, inhibin B, and testosterone (Figure 1). Table 1 summarizes the features of each of those studies. The forest plots from the meta-analysis of folic acid supplementation trials are shown in Figure 4. The impact of folate on concentrations proved significantly greater than the placebo (3.08; [96 percent CI: 0.938 to 4.23]). One hundred and fourteen viable and 77 subfertile guys took part in the study. The treatments comprised of the daily dosage of folic acid (7 mg) or a placebo for 28 weeks.

Before in addition after the intervention, each subject provided one standardized semen example for sperm concentration in accordance with WHO recommendations. The study's findings revealed no statistically significant increase in semen parameters in males who received folate supplementation alone vs the placebo. Furthermore, folate fortification did not appear to remain additional actual than placebo in terms of morphology (-0.287; [96 percent CI: -0.576 to 0.007], P =.057; heterogeneity I3 = 1 percent: P =.45) and sperm motility (-0.087; [96 percent CI: -0.474 to 0.0.297], P =.653; heterogeneity I2 = 42 percent: P =.162). Folate plus Zinc supplementation had no measurable effect on serum testosterone (0.153; [96 percent CI: -1.7 to 1.8], P =.87; heterogeneity I2 = 94 percent; P =.002), inhibin B (0.116; [95 percent CI: -1.0 to 0.34], P =.84; heterogeneity I2 = 86 percent ; P =.008), FSH (-0.434;).

Table 1:

Variable	Sum of RCT	SMD 96%	Q-value	P-value	I-sq	P-value
Motility	6	0.595(-0.253 to 1.442)	83.075	0.004	11.818	0.168
Sperm	5	1.829 (0.969 to 2.690)	82.892	0.001	17.535	0.000
FSH	3	0.430(-0.867 to0.007)	1.123	0.291	10.868	0.056
Morphology	4	1.095(0.737 to 1.452)	0.262	0.879	0.001	0.001
Morphology	5	-0.286(-0.579 to0.008)	2.695	0.442	0.057	0.001
serum folate level	3	3.693(2.964 to 4.421)	0.000	0.376	0.785	0.001
Motility	1	4 -0.089(-0.473 to 0.296)	5.149	0.162	47.722	0.653

Table 2:

Variables	Mean + SD	N (%)	Mean + SD	N (%)	P-value
Age	31.28+5.68		31.48+7.10		0.773
Pre-treatment info					
1 2 3		6 16 12		2 15 16	0.172
Count	36.93+24.15		31.78+23.15		0.070
Morphology	47.46+17.03		45.18+17.90		0.057
Sperm Motility	40.35+19.98		41.70+18.44		0.341
Therapy data					
Count	42.27+25.53		36.84+24.22		0.032
Morphology	51.30+16.15		47.41+17.52		0.02
Sperm Motility	44.25+13.57		42.60+13.56		0.316

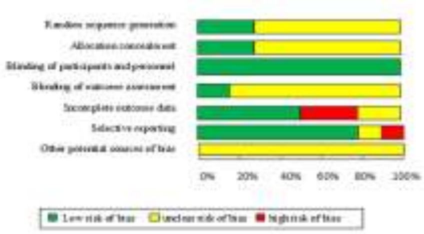

Figure 1:

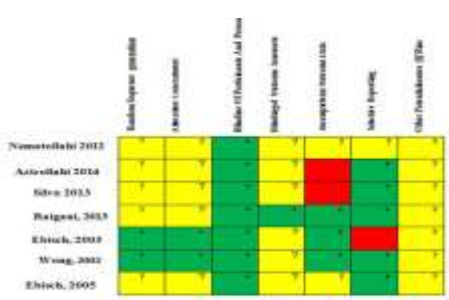

Figure 2:

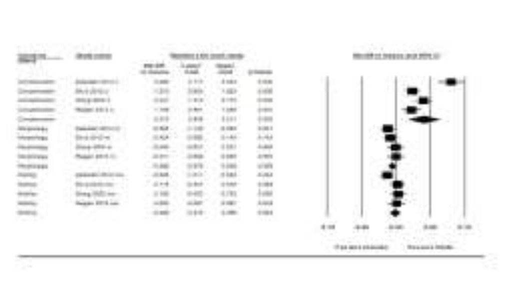

Figure 3:

DISCUSSION

Folate increased sperm concentration in guys who were infertile. The concept further revealed that folate with zinc supplementation improved sperm counts, shape, and overall blood folate levels in infertile men. Folate is required for DNA, transferring RNA, and amino acids cysteine also homocysteine production [6]. It has been found that folate efficiently cleans oxidizing free radicals, making this a scavenger. Folic acid may thereby preserve bio-constituents similar cellular membranes or DNA from free radical injury [7]. Folic acid must be transformed into the physiologically active form 5-methyltetrahydrofolate before it can be used. MTHFR, an essential protein in proteins involved, does this reaction. According to an animal in vivo and in vitro research, zinc deficiency lowers dietary folate ingestion as well as metabolism due to its activity as a cofactor for the intestinal absorption enzyme. Although zinc remains not the component of MTHFR enzyme, this remains necessary for methionine synthesis and betaine homocysteine methyltransferase. Although folic acid also zinc both have protective characteristics, it remains yet another route for which those micronutrients might disturb apoptosis, as oxidative stress appears to affect apoptosis [8]. The estimated quality of virtually all featured papers in our comprehensive study was similarly inadequate, lowering the dependability of our findings. To improve reliability, future trials must be designed in accordance with the CONSORT guidelines. Folate plus zinc treatment improved sperm concentration, morphology, and blood folate levels but had no measurable effect on sperm motility in medium to low males [9]. Nevertheless, our findings revealed that folic acid and zinc sulfate had no influence on endocrine markers. The current original study conclusions, unfortunately, are difficult to evaluate due to the considerable heterogeneity of most of the research. More research is needed to corroborate the existing conclusions [10].

CONCLUSION

Folate and zinc supplementation improved sperm qualities in infertile men. Nevertheless, because of the substantial variability across included research, the present report's conclusions are difficult to evaluate. More research is necessary to corroborate the existing results.

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