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Association of MTFHR polymorphism and male infertility – A review on meta-analysis

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Abstract

Infertility, a medical condition which is defined as the inability of an individual to conceive even after one year of regular unprotected active sexual intercourse as per the World Health Organization.

Methylenetetrahydrofolate reductase (MTHFR), is an enzyme which reduces 5–10-methylenetetrahydrofolate to 5-methyltetrahydrofolate and conversion of homocysteine into methionine is by methyl group which is obtained by 5-methyltetrahydrofolate, a biologically active form. Many polymorphisms of MTHFR gene have been stated in many studies, among all, only two polymorphisms - C677T and A1298C are important clinically and studied most. The systematic search of the articles and literature published in MEDLINE-PubMed database updated till October, 2021 using the terms "(Methylenetetrahydrofolate reductase /MTHFR) and (male infertility)" was conducted. The articles in English language were only included in the study. Information about first author name, year of publication, country, genotyping method, sample size in case and control groups, significance and inference are collected and entered in a table in MS Excel for further analysis. Even with high advancement in the present period, the prevalence of infertility is high and the success ratio for the treatment of infertility either with medications or using Assisted Reproductive Techniques (ARTs) is significantly less. This situation signifies that the research and further elaborative and explorative studies regarding different medications, treatments, procedures and techniques have to be increased with high advancement in the science and technology in the

medical field. Further the technology has to used to detect the chances of genetic abnormalities such as chromosome deletion, Single Nucleotide Polymorphism (SNP) for proper management of the infertility. It can be concluded that MTHFR polymorphism is associated with male infertility.

Keywords: Methylenetetrahydrofolate reductase, MTHFR, male infertility.

Introduction

Infertility, a medical condition which is defined as the inability of an individual to conceive even after one year of regular unprotected active sexual intercourse as per the World Health Organization. Presently, Infertility has been a major condition which is multifactorial in nature and is supposed to have been affected approximately about 15% to 20% of the couples who are desperate for pregnancy [1–3]. Among the total incidence of infertility, male factors are responsible for about 40% to 50%, especially defect in sperms or semen quality or both [4–5]. The causative factors for male infertility may be multifactorial with a very complex pathogenesis, involving lifestyle, organic diseases, genetic factors, environmental risk factors, and their interactions [6–8].

DNA synthesis, methylation and amino acid metabolism involves a group of inter-convertible coenzymes called Folates. DNA methylation and gene expression can be altered by deficiency of folate and polymorphisms of folate pathway genes resulting in male infertility [9]. Methylenetetrahydrofolate reductase (MTHFR), is an enzyme which reduces 5–10-methylenetetrahydrofolate to 5-methyltetrahydrofolate and conversion of homocysteine into methionine is by methyl group which is obtained by 5-methyltetrahydrofolate, a biologically active form [10]. Many polymorphisms of MTHFR gene have been stated in many studies [11], among all, only two polymorphisms - C677T and A1298C are important clinically and studied most [12]. C677T polymorphism occurrence differs greatly through the world [13, 14]. Polymorphism of C667T is associated with DNA hypo methylation [11] and hyperhomocysteinemia [15]. It has been stated in many case control studies that MTHFR gene variants and decreased sperm count is associated leading to male infertility [16–21]. The aim of the present meta-analysis was to find the prevalence of association between MTHFR C677T polymorphism and male infertility.

Materials and Methods

The systematic search of the articles and literature published in MEDLINE-PubMed database updated till October, 2021 using the terms "(Methylenetetrahydrofolate reductase/MTHFR) and (male infertility)" was conducted. The articles in English language were only included in the study. The references cited in the articles were also considered for appropriate information if any. Studies with full text articles published in English about association of male infertility and MTFHR c677T are included. Articles such as Letters to the Editor, Prefaces, Brief Communication, Corrections/Erratum, Reviews, Monographs and Editorials were excluded from the study. Institutional Ethical Clearance was not required as this is a review of literature of the articles published as per the inclusion criteria.

Information about first author name, year of publication, country, genotyping method, sample size in case and control groups, significance and inference are collected and entered in a table in MS Excel for further analysis.

Results

Vandana Rai et al in their study risk was estimated as pooled odds ratios (ORs) with confidence intervals (CIs)

for assessment[22]. Seventeen case–control studies involving 4392 breast infertile males and 3667 fertile males were found suitable for the inclusion in the present meta-analysis. Their study results showed that the C677T polymorphism was significantly associated with male infertility in Asian population using all the five genetic models (ORT vs. C (allele contrast model) = 1.86, 95% CI 1.7–2.0; ORTT vs. CC (homozygote model) = 1.96, 95% CI 1.67–2.30; ORCT vs. CC (co-dominant model) = 1.40, 95% CI 1.18–1.62; ORTT?CT vs. CC (dominant model) = 1.53, 95% CI 1.30–1.77; ORTT vs. CT?CC (recessive model) = 1.67, 95% CI 1.44–1.92). They have concluded that the results of their meta-analysis strongly supported an association between C677T polymorphism and male infertility in Asians.

Fereshteh Aliakbari et al found Crude odds ratio (OR) with a confidence interval of 95% (CI) was used to assess the relationship between MTHFR polymorphism and male infertility risk [23]. In their study, MTHFR polymorphisms had significant associations with male infertility risk (CT + TT vs. CC: OR = 1.37, 95% CI: 1.21–1.55, P = 0.00, I2 = 41.9%); (CC vs. CA + AA: OR = 0.82, 95% CI: 0.52–1.30, P = 0.04, I2 = 50.1%). Further, when stratified by ethnicity, the significant association results were observed in Asians and Caucasians for 677C/T and just Asians for 1298A/C. They concluded that some of MTHFR polymorphisms like MTHFR 677C > T are associated with an elevated male infertility risk. Further they specified that to provide more accurate and complete gene-environment communication with male infertility risk, more analytical studies are needed.

Tian-Lu Shi et al have analysed overall, 22 case–control studies with 5049 cases and 4157 controls in their meta-analysis, which contained 20 studies of MTHFR C677T polymorphism, 12 studies of MTHFR A1298C polymorphism and 4 studies of MTRR A66G polymorphism [24]. Their results indicated that MTHFR C677T, A1298C, and MTRR A66G polymorphisms were significantly associated with male infertility in Asian populations (Dominant model: MTHFR CC+CT vs TT: OR=0.60, 95% CI (0.53, 0.67), P<.00001; MTHFR AA+AC vs CC: OR=0.62, 95% CI (0.49, 0.79), P=.0001; MTRR AA+AG vs GG: OR=0.60, 95% CI (0.45, 0.81), P=.001. Recessive model: MTHFR CC vs CT+TT: OR=0.67, 95% CI (0.61, 0.74), P<.00001; MTHFR AA vs AC+CC: OR=0.79, 95% CI (0.70, 0.88), P<.0001; MTRR AA vs AG+GG: OR=0.70, 95% CI (0.56, 0.88), P=.002. Heterozygote model: MTHFR CC vs CT: OR=0.74, 95% CI (0.67, 0.82), P<.00001; MTHFR AA vs AC: OR=0.83, 95% CI (0.73, 0.93), P=.002; MTRR AA vs AG: OR=0.76, 95% CI (0.60, 0.92), P=.02. Homozygote model: MTHFR CC vs TT: OR=0.48, 95% CI (0.41, 0.56), P<.00001; MTHFR AA vs CC: OR=0.61, 95% CI (0.39, 0.93), P=.02; MTRR AA vs GG: OR=0.51, 95% CI (0.36, 0.72), P=.0001. Allele model: MTHFR C vs T: OR=0.70, 95% CI (0.66, 0.75), P<.00001; MTHFR A vsC: OR=0.82, 95% CI (0.71, 0.95), P=.01; MTRR A vs G: OR=0.76, 95% CI (0.66, 0.88), P=.00003). They have finally concluded that their meta-analysis indicates MTHFR C677T, A1298C, and MTRR A66G polymorphisms are the risk factors with susceptibility to male infertility in Asians.

Li-Juan Han et al in their analysis study have used crude odds ratios and their 95% confidence intervals to assess the association between MTHFR C677T and A1298C polymorphisms and male infertility risk [25]. They have used the Bayesian false discovery probability (BFDP) to assess the credibility of statistically significant associations. In further sensitivity analysis and BFDP

test, the positive results were only considered as "noteworthy" in the overall population (TT vs CC: BFDP =0.294, CT + TT vs CC:BFDP =0.300, T vs C: BFDP =0.336), East Asians (TT vs CC: BFDP =0.089, TT vs CT + CC: BFDP =0.020, T vs C: BFDP<0.001), West Asians (TT vs CC: BFDP =0.584), hospital-based studies (TT vs CC: BFDP =0.726, TT vs CT + CC: BFDP =0.126), and OAT (TT vs CT + CC: BFDP =0.494) for MTHFR C677T. In addition, a significantly increased male infertility risk was found in East Asians and population-based studies for MTHFR A1298C. Finally thay have concluded that the study indicates the association of MTHFR C677T with increased male infertility risk in East Asians, West Asians, and OAT. No significant association was observed on the MTHFR A1298C with male infertility risk.

Vandana Rai et al in their study have calculated the pooled odds ratio (OR) with 95%confidence interval for risk assessment [26]. In the thirty four studies with 3,098 DS case mothers and 4,852 control mothers were included in their metaanalysis. The pooled OR was estimated under five genetic models and significant association was found between maternal MTHFR 677C.T polymorphism and Down syndrome under four genetic models except recessive model (for T vs. C, OR = 1.26, 95% CI = 1.09–1.46, p = 0.001; for TT vs. CC, OR = 1.49, 95% CI = 1.13–1.97, p = 0.008; for CT vs. CC, OR = 1.29, 95% CI = 1.10–1.51, p = 0.001; for TT+CT vs. CC, OR = 1.35, 95% CI = 1.13–1.60, p = 0.0008; for TT vs. CT+CC, OR = 0.76, 95% CI = 0.60–0.94, p = 0.01). They have finally came to conclusion that the results support maternal MTHFR C677T polymorphism is a risk factor for DS- affected pregnancy.

Mancheng Gong et al in their study included only high quality studies that observed the association between MTHFR polymorphism and male infertility risk [27]. Crude odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of association between the MTHFR polymorphism and male infertility risk. Among the twenty-six studies involving 5,575 cases and 5,447 controls they analysed, MTHFR 677C>T polymorphism showed significant associations with male infertility risk in both fixed effects (CT+TT vs. CC: OR = 1.34, 95% CI: 1.23–1.46) and random effects models (CT+TT vs. CC: OR = 1.39, 95% CI: 1.19–1.62). Further, when stratified by ethnicity, sperm concentration and control sources, the similar results were observed in Asians, Caucasians, Azoo or OAT subgroup and both in population-based and hospital-based controls. Overall the results indicated that the MTHFR polymorphism is associated with an increased risk of male infertility.

Zhengju Ren et al in their study used Odds ratios (ORs) and 95% confidence intervals (95%CIs) to assess the strength of associations with a random-effect model or a fixed-effect model based on the heterogeneity analysis results [28]. Sensitivity analysis was used to confirm the reliability and stability of the meta-analysis. In their meta-analysis study, a total of nine studies, including 1,713 cases and 1,104 controls were included. The pooled results indicated that the MTHFR C667T polymorphism was significantly associated with increased risk of male infertility in the Chinese population in the allele model (T vs. C: OR = 1.47, 95%CI = 1.32±1.63), the dominant model (TT + CT vs. CC: OR = 1.51, 95%CI = 1.30±1.77), the additive model (TT vs. CC: OR = 2.08, 95%CI = 1.68±2.58) and the recessive model (TT vs. CT+CC: OR = 1.58, 95%CI =

1.31±1.90), whereas the MTHFR A1298C and MS A2756G polymorphisms were not risk factors. There was no significant heterogeneity in any genotype contrasts among the studies. The sensitivity analysis indicated that the results of their meta-analysis were relatively stable. Their study suggests that the MTHFR C667T polymorphism may contribute to the genetic susceptibility to male infertility in the Chinese population, whereas MTHFR A1298C and MS A2756G polymorphisms may be unrelated to male infertility.

Discussion

Even with high advancement in the present period, the prevalence of infertility is high and the success ratio for the treatment of infertility either with medications or using Assisted Reproductive Techniques (ARTs) is significantly less. This situation signifies that the research and further elaborative and explorative studies regarding different medications, treatments, procedures and techniques have to be increased with high advancement in the science and technology in the medical field. The quality of the human sperm is also declining day by day with increase in advances in the technology resulting increased sedentary life of the individuals. Oligospermia and asthenozoospermia is more commonly seen now a days even in fertile males which signifies the depth of the present situation. Other factors such as stress in professional and personal life, change in food habits, consumption of alcohol, tobacco smoking, increased usage of drugs and exposure to pollution, intake of adulterated food are also having a significant effect on the individual males sexual life.

Conclusion

The advaced imageology & diagnostic technology has to be accurately utilized for perfectly knowing the cause and giving adequate treatment. Once the infertile couples are blessed with a child the research and advancements in the field are said to be fruitful. Further the technology has to use to detect the chances of genetic abnormalities such as chromosome deletion, Single Nucleotide Polymorphism (SNP) for proper management of the infertility. It can be concluded that MTHFR polymorphism is associated with male infertility.

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