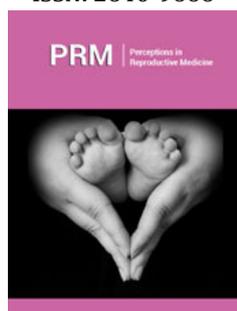


Importance of Paternal Folate Supplementation in Prevention of Neural Tube Defects and its Role in Embryonic Growth-A Newer Developing Concept-A Short Communication

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Abbreviations: ART: Artificial Reproductive Technology; NTD's: Neural Tube Defects; MTHFR: Methylene Tetra Hydro Folate Reductase; ICSI: Intracytoplasmic Sperm Injection; RBC: Red Blood Cell; GCP: Glutamate Carboxy Peptidase; CRL: Crown Rump Length

Short Communication

Folic acid (FA) food fortification has substantially resulted in marked decreases in the birth prevalence rate of neural tube deficits [1]. Further better maternal folate status also significantly lowered the risks of neonates and incidence of small for gestational age children [2]. Similarly, the group of Hoek et al. showed that in both low and high periconceptional maternal folate levels as determined by red blood cell (RBC) folate are associated with reduced growth trajectories of human embryo and embryonic cerebellum [3,4]. Previously studies in humans mainly focused on the effect of paternal folate status on semen parameters. Boomnyarangkul et al. [5] in a randomized trial showed that 3 months of 5mg of FA/d resulted in increased percentage of motile sperms, that increased from 11.4% to 20.4%. Although maternal diet with the long-term health of her offspring has been well studied, understanding of how paternal diet might affect fetal health remains limited. It has been seen that male overnutrition/obesity is associated with worse semen parameters and decreased reproductive potential. Obese men have a contribution in higher rates of miscarriage and couples with an obese male partner using artificial reproductive technology (ART) have significantly lower live birth rates compared with normal weight men [6]. Paternal undernutrition can also have an adverse effect on offspring. Mcpherson et al. [7] showed that undernourished male rodents contributed to reduced postnatal growth and a paradoxical increase in obesity in offspring. This study further showed that paternal diet restriction led to impaired sperm function, sperm DNA methylation, pregnancy rates and embryo development [8]. These deleterious effects can get reversed by supplementing diet restricted male mice with micronutrients like folate before conception. Another mouse model showed that paternal folate deficiency has an effect on sperm epigenome by changing the level of DNA methylation in spermatogenesis leading to higher DNA damage in spermatocytes [8]. This was the 1st study to show that paternal folate status might play an important role in determining pregnancy outcomes and the health of the offspring.

Recently Hoek et al. [9] examined the association between periconceptional paternal folate status and embryonic growth trajectories using a prospective cohort study design. Of the cohort of 511 singleton pregnancies, 303 were spontaneously conceived, while 208 used in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) for the same. Paternal red blood cell (RBC) folate levels were measured and the cohort was divided into quartiles. Embryonic growth was found by measuring, crown rump length (CRL) and embryo volume at 7, 9 and 11-weeks' gestation with the use of 3D-Ultrasound and virtual reality software. For spontaneous pregnancies this quartile (Q3) of paternal RBC folate levels quartile (had the highest embryonic growth, while lower and higher folate levels in Q2 and Q4 were associated with reduced growth. The 1st quartile had decreased embryonic growth trajectories compared to Q3, but surprisingly, the difference was not statistically significant. If there is an

optimum range for paternal folate status, then one would expect levels above and below that range to show reduced embryonic growth, although the relationship was not linear. It is possible that there is a confounding value which was not accounted for in the regression analysis.

This relationship between paternal folate status and embryonic growth was not seen in the IVF/ICSI pregnancies, which Hoek et al. explain might be due to IVF/ICSI overriding the influence of paternal folate status on epigenetic programming of the embryo. A possible explanation is that IVF/ICSI pregnancies lack the influence of seminal fluid an effect that might counteract the influence of paternal folate status. Contact of seminal fluid with the cervix and endometrium leads to adaptive immune response in the female, which might aid with embryo implantation and placental development, while decreasing the likelihood of gestation disorders, like fetal growth and restriction and preeclampsia [10]. Being the 1st investigators who have attempted to examine this association between paternal folate status (both low and high long-term folate status) and embryonic growth trajectories, Hoek et al. [9] emphasize on the importance of paternal folate status but still stop short at recommending folate supplementation for fathers. Though minimal studies have been done in this subject in humans, Naushad & Das[11] showed that maternal methylene tetra hydro folate reductase (MTHFR) C677T and paternal glutamate carboxypeptidase (GCP) IIC15IT polymorphisms are associated with increased risk of neural tube defects (NTD) in South India, although they did not study that extensively as Hoek et al. [9]. Pauwels et al. [12] found no statistically significant correlation between paternal food folate intake, birthweight and DNA methylation in offspring. However, Ratan et al. [13] found lower folate levels in fathers of children born with NTD's when compared with control group.

Since no current guidelines for paternal folate supplementation exist, it was not surprising that only 8.1% of the men in the study used these supplements, with an increasing number of men using them over the 4 quartiles. As seen by the reduced embryonic growth trajectory in Q4 group, a possibility exists that there might be detrimental effects of excessive paternal folate. A need for making any recommendations for paternal folate supplementation for fathers exists and investigating this further is required to understand the paternal folate contribution for conception, gestation and birth and to find out the optimal folate levels in men. Still this study stimulates more investigative questions, i.e. could paternal folate deficiency be responsible as one of the factors which could explain the incomplete success of maternal folate supplementation in preventing neural tube defects (NTD's)? How does paternal folate status affect growth later in pregnancy or in the post-natal period? The study by Hoek et al. [9] was done in Holland, where widespread folate food fortification is not done. But in countries like USA, where

folate food fortification is done, it will be important to understand how paternal RBC folate levels compare and if they are associated with the risks or benefits observed in the Hoek et al. [9]. It is clear that the father's nutritional status with regard to the micronutrient play a larger role in couple fertility than was thought to begin with, but a more complete understanding of the micronutrients which are essential to normal reproduction and live birth is required.

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