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Folic Acid Supplementation on Fetal Growth at Different Gestational Ages

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Folate, Vitamin B9, is found naturally in our day to day foods. It is vital for synthesis of DNA and normal cell division in humans. Studies have revealed constantly that maternal folic acid[FA] intake prior to and in early conception decreases neural tube defects. The aim of the current study is to evaluate the relationship between FA intake by the mother during conception and fetal growth at different gestational ages and also if, periconceptional and preconceptional FA intake has a positive effect on fetal growth, hence reducing the risk of low birth weight babies or small for gestational age (SGA) babies. 180 pregnant women were classified based on their period of FA intake as preconception, periconception FA intake and nil FA intake. Standard fetal biometric parameters were measured using ultrasonogram during the 1st , 2nd and 3rd trimester of their pregnancy. Preconception FA intake had a positive effect on fetal growth as compared to those who abstained from FA supplementation. Intake during preconception and peri-conception i.e. immediately after confirmation of pregnancy was found to have a reduced risk of low fetal weight as against those who did not consume FA. Fetal biometry showed significant difference between preconception and periconception groups. In conclusion, preconceptional and periconceptional FA supplementation of 0.4-0.5 mg/ day was positively affecting fetal growth and caused an optimal birth weight by decreasing the incidence of low birth weight.

Keywords: FA; Pregnancy; Supplementation; Weight for Gestational Age.

Pregnancy usually necessitates a higher consumption of all nutrients. Insufficient nutritional intake peri- conceptionally can result in fetal weight discrepancies and other congenital anomalies[1,2]. Fetal growth depends on many factors, which can be classified into maternal, placental, and fetal factors. In this connection, maternal nutritional status has been shown to play a vital role [3,4,5].

Folic acid [FA] is vitamin B9, rich in whole grains, kale, leafy vegetables, and orange. During fetal growth, cells proliferate enormously and require a high quantity of folate to synthesize DNA and RNA[6]. Therefore, FA demand is increased during pregnancy because of placental and fetal growth[7]. Insufficient folate ingestion results in reduced serum and RBC's

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folate concentrations, elevated homocysteine (Hcy) level, and megaloblastic alterations in the hemopoitic cells and also other fast cleaving cells[8]. Thus folate deficiency elevates the risk for several developmental anomalies, like defects in the neural tube and congenital birth defects[5,7]. Administration of 400 µg daily before conception and also during pregnancy can decrease the possibility of the fetus having neural tube defects. Earlier studies have established that periconceptional FA intake can avoid 60 to 70% of defects of neural tube, including anencephaly, rachichisis and spina bifida.

According to recommendations of updated guidelines of American College of Obstetrics and Gynecology [AAFP] periconceptional FA administration (0.4 mg) as a multi-vitamin for all the female planning for conception. For an individual who plans to conceive and who has no family history of a child with any spinal or neural anomalies, the AAFP intensely advised to take FA around 0.4 to 0.8 mg/d; it also suggests 0.4 mg of folate administration to all female in their reproductive age even though they are not prepared to conceive. AAFP and various other institutions recommends 4 mg/day FA intake by a female having a previous record of a child with neural tube developmental anomalies[9].

Various investigations have revealed a positive correlation between FA consumption and fetus development[10, 11]. Most studies paid attention to the association between fetal growth and FA supplementation during mid and/or late pregnancy. Very little data is available with regard to the effect of FA administration during early fetal development[12]. The early weeks of conception are the crucial period for forming the placenta, development of the embryo, and programming of the fetus. There is little knowledge regarding the importance of FA intake at earlier development of the fetus[5,13] and is still in hypothetical phase[14]. Therefore the present study investigates whether periconceptional maternal FA intake aids in the growth of a fetus.

MATERIALS AND METHODS

Study Design

This study was carried out at Chettinad hospital and research institute, Chennai, between 2016-2018 after obtaining approval from the institutional human ethical committee (Ref: IHEC/04/18Dec2015/Desp.No.155/18.01.2016). Informed consent was acquired from all conceived women who participated in the study. Self-reported FA intake was collected from the information given in the questionnaire, and the subjects (between 21 to 45 years old) were classified into three groups: Group 1- Preconceptional group (n-60): defined as women taking FA supplementation any time prior to conception; Group 2- periconceptional or post-conception group (n-60): defined as mothers started taking FA from the day conception was confirmed or after that but prior to the eighth week of pregnancy; Group 3 - No FA intake (n-60): regarded as no intake of FA supplementation ever. The female who begins to take FA following the eighth week of conception and diseases like diabetes mellitus and hypertension were excluded from the study. The range of FA consumed by the subjects was in the range of 0·4–0·5 mg/d, usually in the form of multivitamins.

Fetal ultrasound was performed on all subjects recruited for the study during the 1st, 2nd, and 3rd trimester of gestation. Fetal biometric measurement is crown-rump length (CRL), Nuchal translucency (NT), head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC), femur length (FL), and estimated fetal weight (EFW) were measured Trans abdominally during each ultrasound examination.

All the data were computed as mean ± standard error. The data analysis was done by employing one way ANOVA. To determine the difference between the individual groups, an independent t test was performed using SPSS software (IBM, USA, ver. 21) and significance was taken when P value was less than 0.05

RESULTS

During the period between 2016 and 2018, 180 pregnant women took part in this study. Table 1 lists the features of women enrolled in the study. Among group 1 31.66 % (19) were Nulliparous, and 68.33 % (41) were multiparous. In group 2, 35% (21) were Nulliparous, and 65% (39) were multiparous. Among group 3, 56.66% (34) were Nulliparous and 43.33% (26) were multiparous.

The association between FA use and fetal development features in the first, second and third

trimester of conception are represented in Tables 2,3 and 4, respectively. As observed during the 1st trimester and 2nd trimester, there was a significant variation between the groups (Table 2 & 3). In the third trimester . Group 1 showed higher BPD (F-51.10667, P < 0.05), HC (F-687.97895, P- < 0.05), AC (F-55.82911, P- < 0.05),FL (F-222.27436, P- < 0.05), and EFW (F-138.05683, P- < 0.05s) (Table 4). The fetal biometry of group 3 was significantly less compared to group 1 and 2. The third-trimester results indicate that women of group 1 EFW were optimal even though in group 2, EFW higher than group 3 (Table 4).

DISCUSSION

Folate is a type of vitamin-B, that is usually found in most of the day to day foods consumed by us[15] and plays an important role in the synthesis of DNA and in division of cell[16]. Folate plays a vital role in homocysteine metabolism and helps retain adequate levels in the body[17]. The unavailability of FA is implicated in the causation of many diseases, namely anemia (megaloblastic variety)[18], neurological problems[19], and elevated homocysteine levels [20]. Folate as FA is utilized in dietary supplementations and fortified foodstuffs.

Table 1. Characteristics of participants in the study stratified by category of folic acid use

	Group 1	Group 2	Group 3
Mean age (years) Mean ± SD	26.66 ± 5.37	26.62 ± 5.01	26.9 ± 4.13
Height (cm) Mean ± SD	155.4 ± 4.81	156.35 ± 6.01	155.6 ± 5.87
Weight (kg) Mean ± SD	62.69 ± 3.77	62.67 ± 3.93	62.4 ± 5.87
Nulliparous [n (%)]	19 (31.66)	21 (35)	34 (56.66)
Multiparous [n (%)]	41 (68.33)	39 (65)	26 (43.33)

Table 2. First trimester fetal biometry

Parameters	First trimester** Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	f-ratio value	P-value
Crown-rump length (mm)	70.45 ± 1.0	67.64 ± 0.68	65.01 ± 0.54	69.00654	<0 .00001
Biparietal diameter (mm)	21.38 ± 0.74	19.95 ± 0.55	18.86 ± 0.38	28.5897	< 0.00001
Nuchal translucency (mm)	1.68 ± 0.05	1.74 ± 0.01	1.93 ± 0.03	62.9278	< 0.00001

**Associated fetal growth measurements by ultrasound in first trimester among women of preconception folic acid use, periconception folic acid use and no use of folic acid. Values represented as mean ± SD, significance: p-value < 0.05

Table 3. Second trimester fetal biometry

Parameters	Second trimester ** Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	f-ratio value	P-value
Head circumference (mm)	179.38 ± 0.69	180.16 ± 0.35	181.8 ± 0.52	30.94421	< .00001
Abdominal circumference (mm)	169.26 ± 3.39	159.26 ± 2.81	154.88 ± 2.40	38.74229	< .00001
Femur length (mm)	35.26 ± 1.38	34.43 ± 0.97	33.38 ± 0.52	5.10725	0.020338
Biparietal Diameter (mm)	50.85 ± 1.66	49.71 ± 1.09	47.91 ± 1.22	7.20532	0.006411.

** Associated fetal growth measurements by ultrasound in second trimester among women of Preconception folic acid use, periconception folic acid use and no use of folic acid
Values represented mean ± SD, significance: p-value <0.05

Table 4. Third trimester fetal biometry

Parameters	Third Trimester** Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	f-ratio value	P-value
Biparietal Diameter (mm)	84.03 ± 0.90	82.5 ± 0.86	78.53 ± 1.12	51.10667	< .00001
Head circumference (mm)	300.51 ± 1.53	294.10 ± 1.31	269.56 ± 1.70	687.97895	< .00001
Abdominal circumference (mm)	296.76 ± 6.98	286.25 ± 4.58	264.16 ± 4.41	55.82911	< .00001
Femur length (mm)	62.21 ± 0.54	60.2 ± 0.25	55.31 ± 0.80	222.27436	< .00001
EFW (grms)	2409.18 ± 82.37	2007.26 ± 49.76	1776.71 ± 63.99	138.05683	< .00001

**Associated fetal growth measurements by ultrasound in third trimester among women of preconception folic acid use, periconception folic acid use and no use of folic acid. Values represented mean ± SD, significance: p-value < 0.05

In this study, we reveal that preconceptional and periconceptional FA intake in the recommended dose of 0.4-0.5 mg/d is related to increased fetus growth (Tables 2, 3, 4)compared to women who did not use FA equivalence considerably changes the impact. Preconceptional and periconceptional FA intake are also correlated with decreased incidence of having infants with lower body weight at birth or being small for gestational age at birth.

Folate is vitamin B9; takes important role in cell division, programmed cell death, intracellular signaling, and programming. All these processes are essential to have a complete and wholesome fetal development[7]. Therefore, supplementation of FA during gestation influences fetal growth along with placental growth as well[21,22, 23, 24, 25].

Our study support earlier findings that demonstrated an optimistic association between elevated FA administration, with an increase in birth weight of the babies[23, 26, 27, 28, 29]. The fetal growth and development are maximum in 2nd half of gestation. This contradicts many studies, where only the periconceptional and pre-conceptional periods are taken into account. An adequate FA intake throughout this crucial period might directly influence synthesis and division processes in the fetus. Few researches have estimated the association between folate supplementation versus an earlier period of conception and fetal growth[12]. Many studies report a raise in incidence of infants with higher birth weight in those women who begun to consume FA even before pregnancy.

Fascinatingly, decreased occurrence of SGA was also reported in infants of women who preconceptionally began intake. Though, similar to many other studies that compared FA and growth of the fetus, a higher dose of FA, i.e.up to 2·5 mg) was administered[30-34]. This study stresses the importance of the periconceptional and preconceptional normal range of FA intake to be enough to ensure the increase in fetus growth.

The value of nuchal translucency thickness increased from group 1 to group 3 steadily in the first-trimester fetal biometry (Table 2). Group 1 and 2 had values nearer to the normal value of 1.30 ± 0.54[35]. The same study also cites that the NT values in the 95th percentile falling between 1.8 and 2.35 were associated with chromosomal anomalies in the fetus. Though nuchal translucency has been associated with fetal anomalies, the intake of FA and its relationship has been significantly proven in this study. The usual range of NT[36,37,38] has been found only in the first two groups (Table 2), and hence the preconceptional and periconceptional intake of FA has a direct relation with NT and has to be studied in further detail.

FA serves an essential role in the synthesis of homocysteine. An increase in homocysteine is correlated with a decrease in folate level, and increased homocysteine has been correlated to a reduction in placental vasculopathy and fetal growth[39-42]. In the majority of the conditions of hyperhomocysteinemia, the treatment protocol consists of supplementing a low dose of FA[42]. Moreover, the endothelial function can be

much improved by folate, irrespective of the homocysteine status.

Earlier studies demonstrated that FA intake of 5mg in the 2nd or 3rd trimester could significantly increase the size of the placenta [23,26,28]. As the neural tube defects in India is as high as 4.5 per 1000 total births[43,44], the importance of folic acid consumption (0.4mg/d, as recommended by WHO) can't be stressed more. In this study, mothers who began consuming FA supplements preconceptionally have significantly higher fetal biometry than the female who started taking FA during the 1st to 8th week of gestation.

CONCLUSION

Preconceptional and periconceptional FA intake favors the growth of the fetus, decreases the risk of low birth weight babies. Intake of FA prior to conception is more beneficial to the growth of the fetus than periconceptional use.

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