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Original Article

A study on periconceptional folic acid supplement intake and serum folic acid levels in pregnant mothers

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ABSTRACT

Background: Survey-based studies have examined the timing of receiving periconceptional folic acid supplementation. To assess the impact of the periconceptional folic acid supplementation, a postulate that multigravida mothers are more likely to have received the supplementation and the level of serum folic acid in them assayed during the first trimester is likely to be higher than primigravida mothers was put forth. Serum folic acid levels were measured in primigravida and multigravida mothers during the first trimester.

Methods: One hundred twenty primigravida and multigravida mothers registered at antenatal clinic of a tertiary care referral centre were included. Serum folic acid assay from samples collected during the first trimester was carried out by chemiluminescence immuneassay. The mothers were followed up during subsequent OPD visits, during admission for delivery and through mobile phones for assessing the delivery outcomes. World Health Organization cutoff values for serum folic acid were used to analyse the results.

Results: None of the mothers received folic acid supplement before conception. Mean interval from last menstrual period to receiving the first dose of folic acid supplementation was 71.2 days in primigravida and 67.6 days in multigravida mothers. Overall, 21/120 (17.5%) of primigravida mothers and 34/120 (28.3%) of multigravida mothers had serum folic acid values less than 6 ng/ml (deficiency and possible deficiency).

Conclusion: None of the mothers received folic acid supplements before conception. Significant proportion of mothers, particularly the multigravida having less than normal levels serum folic acid indicates correctable lacunae amenable for preventive intervention.

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Introduction

Globally, each year, 3–4 lakh infants are born with neural tube defects (NTDs) like spina bifida, anencephaly, myelomeningocele, craniorachischisis, spinal dysraphism and encephalocele.[1] The prevalence is approximately 1–5 per 1000 live births at global level.[2] Many studies have demonstrated that mothers who reported taking adequate intake of dietary folic acid and/or multivitamins containing folic acid supplementation before becoming pregnant had a reduction in the risk of having a child with a neural tube defect.[3–5] The recent Cochrane review on the effects and safety of periconceptional oral folic acid supplementation for preventing birth defects concluded that folic acid, alone or in combination with vitamins and minerals, prevents NTDs.[6]

As early as in 1992, the US Public Health Service Commission made recommendations that all women of child-bearing age in the US who are capable of becoming pregnant take 0.4 mg daily supplement of folic acid to prevent neural tube defects.[7] The World health Organization in its latest recommendation also advocates that all women, from the moment they begin trying to conceive until 12 weeks of gestation, should take folic acid supplement (400 μg folic acid daily).[8]

Survey-based studies have examined the timing of receiving folic acid supplementation. It is reasonable to assume that primigravida mothers come in contact with healthcare professionals for the first time and hence, are unlikely to have been exposed to the knowledge and practice of periconceptional folic acid supplementation. However, multigravida mothers, by virtue of having come in contact with obstetricians or other professionals, are likely to have been exposed earlier to the practice of periconceptional folic acid supplementation and hence are more likely to have taken such supplementation. This should translate into higher levels of serum folic acid in multipara mothers during the first trimester as compared to primigravida mothers.

Materials and methods

This was a cross-sectional observational study. Pregnant women were recruited from the antenatal outpatient department (OPD) of the obstetric setup of a tertiary care centre of Maharashtra. The study was carried out between December 2015 and October 2017. One hundred twenty primigravida and the same number of multigravida mothers (all of who had undergone a previous hospital-based delivery) registered at antenatal clinic were included in the study. The sample size was calculated based on the hypothesis that multigravida mothers are less likely to have serum folic acid levels below the cutoff for sufficiency as compared with primigravida (15% vs 30%). With a significance (1-α) level of 5% and power (1-β) of 80 percent to detect this difference, the minimum required sample size of 240 mothers (120 in each group) were studied. Periconceptional period was defined as starting from a month before the planned pregnancy or last menstrual period to the end of first trimester.

The study was cleared by the Institutional Ethics Committee. Consent was taken from each mother for collection of demographic data and to draw 2 ml blood for the assay of serum folic acid. A detailed study proforma incorporating all the demographic details, pregnancy order and folic acid/multivitamin supplementation status was filled for each mother. Details regarding abortions and previous anomaly, if any, were also recorded. The time gap in days was also computed for each mother from the last menstrual period (LMP) to receiving the first dose of folic acid tablet during the current pregnancy. All included mothers underwent at least one ultrasound scan before delivery. The assay of serum folic acid level was outsourced to a NABL accredited laboratory (Dr Lal Pathlabs, CAP-7171001, ISO-FS 60411, NABL-M-0061). The serum sample with unique identification bar code and patient name was transported to the laboratory at New Delhi with maintenance of cold chain during transit. Serum folic acid assay was carried out by chemiluminescence immunoassay.

The study mothers were followed up during subsequent OPD visits and during admission for delivery for assessing the delivery outcomes. Details of babies' birth weight, length, head circumference, immediate neonatal course and presence/absence of anomalies was recorded. Additional investigations on the babies were carried out only if mandated after clinical assessment by the treating neonatologist.

World Health Organisation cutoff values for serum folic acid were used to analyse the results.[8] Proportions of mothers in the primigravida and multigravida group were compared with four categories of serum folic acid value viz. <3 ng/ml (deficiency), 3 to<6 ng/ml (possible deficiency), 6–20 ng/ml (folic acid sufficiency) and >20 ng/ml (above normal). Mean values were compared between the groups of primigravida and multigravida mothers and comparison of proportions was done for subgroup analysis. Medical software version 9.3.0.0 was used for all the statistical analysis.

Results

The study flow chart is given in Fig. 1. None of the mothers received folic acid supplement before conception. Mean interval from LMP to receiving the first dose of folic acid supplementation was 71.2 days (range 38–125 days) in primigravida and 67.6 (range 3–116) days in multigravida mothers.

Details of age and serum folic acid values of the mothers are summarized in Table 1. Multigravida mothers had lower mean serum folic acid values (12.87 ng/ml) compared to primigravida mothers (15.47 ng/ml). This difference is statistically significant ($p = 0.01$).

Serum folic acid data was further analysed in four subgroups of mothers using the WHO criteria.[8] Results are summarized in Table 2. Eight mothers each (8/120, 6.6%) in both primigravida and multigravida group had serum folic acid values below 3 ng/ml (deficiency). Proportion of mothers having serum folic acid in the range of 3–6 ng/ml(possible deficiency) was significantly higher in the multigravida group (26/120 vs 13/120 mothers, comparison of proportions, $p = 0.03$). Overall, 21/120 (17.5%) of primigravida mothers and 34/120 (28.3%) of multigravida mothers studied had serum folic acid values less than 6 ng/ml (deficiency and possible deficiency).

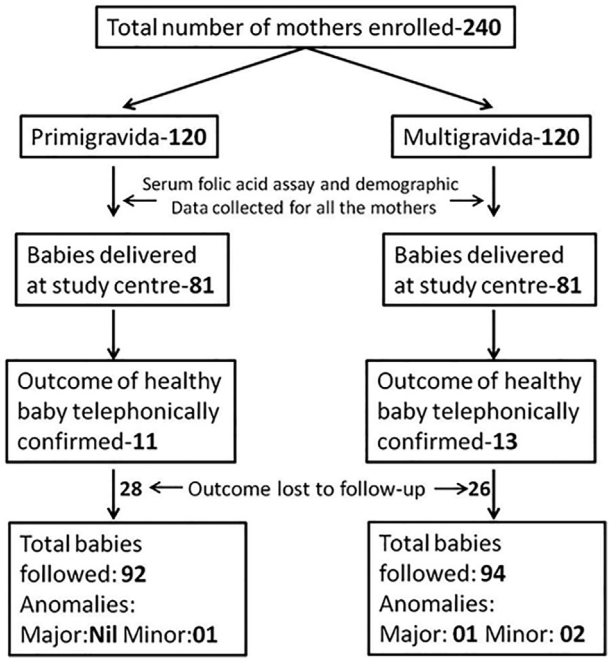

Fig. 1 – Study flowchart.

Anthropometric data of the neonates included in the follow-up was analysed. Mean birth weight, length, and head circumference did not differ significantly between the babies born to primigravida and multigravida mothers. Also, there was no significant correlation between the maternal serum folic acid levels and the anthropometric values of the neonates studied (details provided in the table under Supplementary data).

One baby in the multigravida group (1/94 babies followed up, 1.06%) had neural tube defect in the form of lumbo sacral meningomyelocele with hydrocephalus. The serum folic acid level in this mother was 1.86 ng/ml. No major anomaly was seen or reported among the babies born to the primigravida mothers.

Discussion

This study was carried out to assess the time of receiving the first dose of folic acid supplementation during the pregnancy. The study revealed that none of the mothers, both multigravida and primigravida, started periconceptional folic acid supplementation at the recommended time. It was postulated in this study that multigravida mothers were more likely to have received periconceptional folic acid supplementation before conception and that levels of serum folic acid in them assayed during the first trimester was likely to be higher than primigravida mothers. However, the results revealed that the mean serum folic acid in multigravida mother group was actually significantly lower than that in the primigravida group. Also, a significantly higher proportion of mothers in the multigravida group had serum folic acid values in the deficiency/possible deficiency range (less than 6 ng/ml). These observations are noteworthy in view of the definite role of folate sufficiency status in pregnant mothers in preventing neural tube defects and possibly other congenital anomalies in babies.

We did serum folic acid assay in our study. In a study by D Bruyn et al, a positive correlation between serum and RBC folic acid was demonstrated.[9] Another study found that serum folic acid in non-pregnant women of reproductive age responded to supplementation in the short term.[10] Since the study focused on the short-term supplementation (periconceptional) of folate, assay for serum folic acid levels which is sensitive to short-term intake was carried out.

In a study reported from North India, the mean serum folic acid observed among the pregnant mothers was 10.1 ng/ml.[11]

Table 1 – Summary statistics: age and serum folic acid values of pregnant mothers.

Parameter	Primigravida N = 120	Multigravida N = 120	P Value (comparision of means)
Age in years			
Range	18–35	19–39	
Mean (±2SD)	23 (3.25)	25.6 (3.86)	
Serum folic acid value (ng/ml)			
Range	1.82–24	1.46–24	**p = 0.01**
Mean(±2 SD)	15.47 (7.94)	12.87 (8.07)	

Table 2 – Subgroup analysis for serum folic acid levels using WHO cutoff values.

Serum folic acid (ng/ml)	No of mothers with WHO folic acid cutoff values (comparison of proportions)		
	Primigravida N = 120	Multigravida N = 120	p Value
<3	8 (6.6%)	8 (6.6%)	NS
3–5.99	13 (10.8%)	26 (21.6%)	**0.03**
6–20	51 (42.6%)	51 (42.6%)	NS
>20	48 (40%)	35 (29.1%)	0.10

Using the World Health Organization cutoff levels, Saxena et al found a total of 29.4% of women having folic acid deficiency (≤5.9 ng/ml), and out of them 3 were having folic acid levels below 3 ng/ml.[11] Eight mothers each in the primigravida and multigravida group had folic acid values less than 3 ng/ml in our study. Singh et al found low serum folic acid values in 57% of mothers.[12] Our study revealed that 17.5% of primigravida and 28.3% of multigravida mothers had serum folic acid values less than 6 ng/ml suggesting that efforts needs to be done to educate mothers regarding the correct time to start folic acid supplementation. Ensuring intake of recommended dose of folate supplement during the periconceptional period could decrease the incidence of folate deficient mothers and would ensure folate sufficiency during the critical period of embryogenesis. Such efforts are likely to have impact on prevention of congenital anomalies, mainly, the neural tube defects.

We observed that one baby in the multigravida group was born with lumbosacral meningomyelocele with hydrocephalus. The serum folic acid level in this mother was in deficient range (1.81 ng/ml). She had a previous baby with the similar defects (hospital birth) who died during the neonatal period. Yet she had not started the supplementation at the correct time as she was not aware of this. Though it is a single affected neonate in our study, this catastrophic event was preventable. Such cases highlight the need for emphasis and education on universal use of folate supplement before planning a pregnancy.

Studies have examined the correlation between maternal folic acid status and the impact on anthropometric parameters in their newborn babies. Reduced folic acid has been implicated in many adverse pregnancy outcomes other than NTDs too. In one study of over 2,000 pregnant women, low second trimester serum or red cell folic acid was associated with an almost doubled risk of preterm birth.[13] In another study of 683 mothers and 614 neonates, maternal early pregnancy red cell folic acid was an important determinant of infant birthweight.[14] In a study by Gadgil et al, maternal plasma folic acid was not correlated to neonatal anthropometry.[15] On the contrary, in a study by Ahmed et al, birth weight, length and head circumference of newborns showed a significantly positive correlation with maternal serum folic acid.[16] In our study, there was no correlation of newborn anthropometric parameters with the maternal serum folic acid levels in both the primigravida and multigravida mothers.

The major strength of the study is the sample size of the mothers included. It is one of the largest in the literature comparing the two groups of mothers. A shortcoming in the study that can be addressed in future research is to look for the effect of confounding factors such as dietary intake on serum folate levels.

In conclusion, none of the mothers received folic acid supplementation within the recommended time. A high level of deficiency in mothers, particularly in the multigravida group, points to a lost window of opportunity for intervention by reinforcement of education during the first pregnancy. Many strategies can be adopted at the individual, health care set up and mass level to improve the awareness and enhance the uptake of periconceptional folic acid supplementation by all prospective mothers in our country.

Disclosure of competing interest

The authors have none to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mjafi.2021.05.013.

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