Factors Associated with Compliance of Folic Acid Consumption among Pregnant Women

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ABSTRACT: **Background**: The prevalence of major malformations in the general population is estimated at 5% of all live births. Prenatal diagnosis is an important scientific tool that allows reliable consultation and improves pregnancy outcome. In 2008, congenital malformations were the leading cause of death in Muslim infants and the second cause of death in Jewish infants in Israel. It is known that folic acid consumption prior to pregnancy decreases the rate of several fetal malformations.

Objectives: To assess the folic acid consumption rate and to characterize variables associated with its use among pregnant women attending a rural medical center.

Methods: A cross-sectional observational study was conducted at our institution. Pregnant women in the second or third trimester of pregnancy or within 3 days postpartum were interviewed. The main variable measured was the use of folic acid. Demographic variables and the rate of prenatal testing were assessed. A secondary analysis of the population that reported no consumption of folic acid was carried out.

Results: Out of 382 women who participated in the study, 270 (71%) reported consumption of folic acid. Using a multivariate analysis model, we found that maternal education, planning of pregnancy, and low parity were independent predictors of folic acid consumption. Women who were not consuming folic acid tended to perform fewer prenatal tests during pregnancy.

Conclusions: High maternal educational level, planning of pregnancy, and low parity are related to high consumption rates of folic acid. Women who were not taking folic acid performed fewer prenatal tests during pregnancy.

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KEY WORDS: prenatal diagnosis, fetal malformation, folic acid, neural tube defects (NTD)

It is estimated that at least 5% of babies are born with congenital anomalies. Of these, 2 to 3 will have anomalies that can be recognized prenatally by non-invasive screening tests or by invasive tests at birth. In such cases, prenatal diagnosis is an important scientific tool for achieving improved pregnancy outcome [1].

PRENATAL TOOLS TO DIAGNOSE CONGENITAL ANOMALIES

Trisomy 21, 18, 13, monosomy X, and other sex chromosome aneuploidies are responsible for up to 95% of live-born chromosomal abnormalities [2]. Combination of ultrasound and maternal serum screening tests can identify some of these aneuploidies [2,3]. Some genetic diseases can be detected prenatally as prenatal genetic tests are offered in Israel to the entire population and for individual cases with family history of specific genetic diseases [4]. Non Invasive Prenatal Testing (NIPT), Chorionic Villi Sampling (CVS), and amniocentesis are additional helpful prenatal diagnosis tools [5,6].

In 2008, 75.5% of Israel's population was defined as Jewish, 20.2% as Muslim, and 4.3% as "other" [7]. Congenital anomalies were the leading cause of death in Muslim babies and the second death cause in Jewish babies [8,9] with the most common congenital malformations being heart defects and NTD [10]. As known, folic acid consumption prior and during pregnancy contributes to the reduction in the risk of congenital malformations rate [11].

Neural tube defects (NTDs) are a group of anomalies that occur due to lack of neural tube closure. It is usually characterized by high level of α feto protein (αFP) in the maternal serum and amniotic fluid [12]. Folic acid consumption prior to conception and during the early stages of pregnancy plays a role in preventing NTDs and other congenital anomalies [11].

An increase in folic acid consumption was noted in Israel following guidelines by the Ministry of Health for folic acid consumption pre-conceptionally and during pregnancy in 2000 [13]. Relevant studies indeed found that the rate of compliance increased over the years from 30% in 2002 [14] to 34% in 2005 [15] and 50% in 2009 [16]. Accordingly, a decrease of about 38% in the incidence of open NTDs was noted [17].

The objective of this study was to assess the folic acid consumption rate and to characterize variables associated with its use among pregnant women attending our rural hospital.

PATIENTS AND METHODS

A cross-sectional observational study, conducted at a rural medical center.

Our hospital is a secondary regional medical center that includes 495 beds and serves a population of approximately

380,000. Our population is diverse and represents the human landscape of the Israeli population.

The study population included pregnant women who were in their second or third trimester of pregnancy and postpartum women prior to discharge. They were examined from January to July 2014 by our team.

Women who agreed to participate in the study were interviewed either in Hebrew or Arabic by a medical student (Y.Y.) or a resident (S.A.). Our questionnaire was self-developed. The main variable measured was consumption of folic acid. Additional demographic variables and prenatal tests that were performed during pregnancy were recorded and are listed in Table 1, Table 2, and Table 3.

Our population was divided into two groups according to maternal reporting of non-consumption of folic acid (study group) and consumption of folic acid (control group). Next, secondary analysis for the two groups was performed for demographic data and performance of prenatal tests.

Among other factors for socioeconomic status assessment, reference average monthly family income in our study was 3818 USD which is the average income per household in Israel [18].

Descriptive statistics were calculated and reported as averages, medians, standard deviations, and percentiles as appropriate. The *t*-test was used for comparison of continuous variables between the two groups and either Fisher's exact test or Pearson's chi-square were performed for comparison between categorical variables as appropriate.

Multivariate logistic regression model was carried out to assess independent predictors for folic acid consumption. In this model we included variables that were found significant in the first stage. These factors were examined to assess whether they independently affect folic acid consumption. Differences between variables were considered significant when $P < 0.05$.

Our power analysis was based on a survey from 2002 [14] in which women reported preconception folic acid consumption. Based on this difference between Jewish (35% consumption rate) and non-Jewish (21% consumption rate) women and using Raosoft software (Raosoft Inc. Seattle, WA, USA) at an acceptable level of 95% confidence interval, our sample size was calculated at 320 women.

RESULTS

The inclusion criteria were met by 428 women, of which 46 refused to participate in the study (10.7%) leaving 382 women. Fifty percent of the women who participate in the study were recruited from the post-partum maternity unit and another 50% from other units including: Emergency room (17%), High-risk pregnancy unit (19%), and Ultrasound unit (15%).

Demographic characteristics of our population are shown in Table 1.

Table 1. Demographic characteristics of study population (N=382)

Parameter	Result
Age Average ± SD	30.3 ± 5.1
Religion n (%)	Jewish 218 (57%)
	Muslim 159 (42%)
	Christian 2 (1%)
	Other 3 (1%)
Place of residence n (%)	Urban 170 (45%)
	Suburban 207 (55%)
Level of education, average ± SD	13.6 ± 3.4
Average family income n (%)	Above 4015 USD: 224 (68%)
	Under 4015 USD: 106 (32%)
Consanguinity n (%)	27 (11%)
Gravidity, average ± SD (Median)	2.7 ± 1.8 (2)
Parity, average ± SD (Median)	1.9 ± 1.5 (2)
Planned Pregnancy n (%)	271 (74%)
Method of pregnancy n (%)	Spontaneous 292 (89%)
	ART 37 (11%)

ART = assisted reproductive technique, SD = standard deviation

Table 2. Prenatal tests performed by the total study population (N=382)

Parameter	Result n (%)
Nuchal translucency	264 (71%)
Early 2nd trimester ultrasound	304 (80%)
Mid trimester anatomy scan	330 (87%)
Amniocentesis	61 (16%)
Glucose challenge test	326 (86%)
Prenatal visits	Monthly 284 (79%)
	Every 2 month 47 (13%)
	Every 3 month 30 (8%)

Folic acid was consumed by 270 women (71%), and 111 women (29%) reported non-consumption of folic acid. Of those who reported consumption of folic acid, 38% were consuming prior to pregnancy and 62% after becoming pregnant.

Results of prenatal tests are shown in Table 2. Demographic characteristics of the study and control group are presented in Table 3. Performance of prenatal tests in the two groups is presented in Table 4. Performance of NT, early and late second trimester anatomy scan and glucose challenge test were all significantly lower in the study group as well as frequency of antenatal visits ($P < 0.05$).

In multivariate analysis, the following three independent variables increased the likelihood of consuming folic acid: maternal education ($P = 0.014$), planning of pregnancy, 95% confidence interval (CI) 1.12–4.62, and low gravidity ($P = 0.02$).

Table 3. Demographic characteristics for women who did not consume folic acid (study group) vs. women who consumed folic acid (control group)

Parameter	Did not consume folic acid (n=111)	Consumed folic acid (n=270)	*P* value
Age, average ± SD	30.5 ± 5.5	30.2 ± 5	$P = 0.7$
Religion: Jewish, n (%)	45 (41%)	173 (65%)	$P < 0.0001$
Religious	53 (52%)	95 (36%)	$P = 0.009$
Non-religious	25 (25%)	95 (36%)	$P = 0.035$
Orthodox	24 (23%)	72 (28%)	$P = 0.51$
Place of residence, n (%)			
Urban	41 (38%)	128 (48%)	$P = 0.08$
Suburban	67 (62%)	140 (52%)	$P = 0.08$
Level of education, mean ± SD	12.1 ± 4.04	14.2 ± 3	$P < 0.0001$
Average family income, n (%)			
Above average	20 (21%)	86 (37%)	$P = 0.004$
Under average	77 (79%)	147 (63%)	$P = 0.004$
Consanguinity	9 (8.5%)	17 (6%)	$P = 0.50$
Gravidity, mean ± SD, (median)	3.4 ± 1.9 (3)	2.6 ± 1.8 (2)	$P < 0.0001$
Parity, mean ± SD, (median)	2.5 ± 1.7 (2)	1.7 ± 1.4 (1)	$P < 0.0001$
Planned pregnancy	60 (58%)	210 (81%)	$P < 0.0001$
Method of conception, n (%)			
Spontaneous	85 (94%)	206 (87%)	$P = 0.05$
ART	5 (6%)	32 (13%)	$P = 0.05$
Primiparous	37 (34%)	87 (32.5%)	$P = 0.80$
Fetal malformation in the past	7 (6.8%)	17 (6.5%)	$P = 1.00$
Genetic diseases in the family	6 (5.4%)	21 (7.8%)	$P = 0.51$

ART = assisted reproductive technique, SD = standard deviation

Table 4. Rate of prenatal tests in the study group and control group

Parameter	Did not consume folic acid (n=111) n (%)	Consumed folic acid (n=270) n (%)	*P* value
Nuchal translucency	54 (50.5%)	210 (79.8%)	$P < 0.0001$
First trimester screen	40 (36.4%)	154 (58.3%)	$P < 0.0001$
second trimester screen	52 (48.6%)	186 (71.8%)	$P < 0.0001$
Early 2nd trimester ultrasound	71 (64.0%)	233 (86.6%)	$P < 0.0001$
Amniocentesis	13 (11.8%)	48 (17.8%)	$P = 0.17$
Mid trimester anatomy scan	84 (77.1%)	245 (91.4%)	$P < 0.0001$
Glucose challenge test	86 (78.2%)	239 (89.2%)	$P = 0.008$
Prenatal visits			
Monthly	70 (68.6%)	214 (82.9%)	$P = 0.001$
Every 2 month	15 (14.7%)	31 (12.0%)	
Every 3 month	17 (16.7%)	13 (5%)	
Routine blood Tests			
Yes	9 (8.2%)	6 (2.2%)	$P = 0.001$
No	86 (78.2%)	249 (92.2%)	
Sometimes	15 (13.3%)	15 (5.6%)	
Emergency room visits	72 (68.6%)	188 (70.7%)	$P = 0.71$

In the Jewish population, the rate of reported folic acid consumption was not significantly different, whether the pregnancy was planned or unplanned ($P = 0.136$). In contrast, the rate of reported folic acid consumption among Muslim women was significantly higher when the pregnancy was planned ($P = 0.004$). In addition, Jewish women were 1.8 times more likely to consume folic acid when compared with Muslim/other religious women, but this figure did not reach statistical significance (95%CI 0.91–3.62, $P = 0.089$).

Assessing the effect of gravidity on prenatal tests, we found that as gravidity increased, the rate of performance of NT ($P < 0.001$), early anatomy scans ($P < 0.05$), late second trimester ultrasound ($P < 0.05$), and glucose challenge test ($P < 0.0001$) all decreased.

DISCUSSION

In this cross sectional observational study, we found that the percentage of women who consume folic acid was 71%.

On the basis of the known evidence that preconceptional folic acid consumption reduces NTDs by 50-70% [16], and considering the guidelines of the Ministry of Health in Israel aiming to increase awareness toward importance of folic acid consumption during preconception and early pregnancy [16], it seems that this rate of folic acid consumption might not be enough.

Studies in the general population in Israel have shown an improvement in folic acid consumption following the Ministry of Health recommendations; in 2002 only 30.5% of the population consumed folic acid preconceptionally [14]. Continued research showed an increase to 34% [15] and in 2009, 50% consumed folic acid preconceptionally [16].

Studies that examined folic acid consumption specifically during pregnancy, and not including the preconception period, found that the rate of folic acid consumption might be actually higher. A survey conducted in 2005 found that 77.4% of women consume folic acid during pregnancy (74.9% of Muslims and 79% of Jews) [15]. A study conducted in 2010 in 29 hospitals in Israel found that 83.6% of Jewish women and 84% of Muslim women consumed folic acid at some point during pregnancy [19]. In our study, the rate of folic acid consumption referred to folic acid consumption at any stage during pregnancy (preconceptionally and during pregnancy), therefore it is possible that the rate of women who consumed folic acid before or at the beginning of the pregnancy was lower than 71% and therefore low compared to the general population.

Our multivariate analysis suggests that significant and independent factors for folic acid consumption are high level of maternal education, planned pregnancy, and low gravidity. In our study, we found that a low level of maternal education decreased the chance of consuming folic acid, while each additional year of maternal education increased those chances by 13.5%. Studies conducted on different ethnic population groups as well as other studies on the Israeli population [20] also found similar findings [21,22].

In this study we found that planned pregnancies increased the likelihood of consuming folic acid in the general population and especially in the Muslim population. Studies have shown that lack of pregnancy planning is the most important parameter for folic acid consumption among different ethnic groups [21]. Our study showed that when the pregnancy was achieved following fertility treatments, the rate of folic acid consumption was significantly higher. This parameter reinforces the effect of planned pregnancy on folic acid consumption. In our study 74% of the pregnancies were planned. This is in discordant with data collected in the United States between 2001 and 2008 that showed a rate of 51% [23].

We found that high gravidity significantly decreased the chance to consume folic acid. This is a new and interesting finding. It can be assumed that the reason for this behavior is the natural tendency of women in following pregnancies (that are not the first) to perform less prenatal tests (and to consume less folic acid). Similarly our results show that when gravidity increases, the rate of NT, first and second trimester ultrasound scans, and glucose challenge test decreased significantly.

A study published in 2008 found a higher rate of folic acid consumption during pregnancy among Jewish women ($P = 0.048$), compared to Muslim women [20]. In our study we found that Jewish women were more likely than Muslim women to consume folic acid. This finding was significant in univariate analysis, but in multivariate analysis the difference was only near significant. Despite this finding, it is evident that from the study group (non-consumption of folic acid), 41% were Jewish and did not consume folic acid. This is a high and very disturbing low rate of folic acid consumption that crosses religions.

Compared to other studies, we found that our population performed more NT (71%) and early anatomy scans (80%) than in a study from 2010, citing 54% for NT and 57% for anatomy scans [19]. Still the rate of screening tests (NT, glucose challenge test), ultrasound scans, and regular prenatal visits is considerably low. These data support the hypothesis that the population that does not consume folic acid is characterized by performing fewer prenatal tests.

Half of the participants in our study were recruited from the maternity post-partum unit, which includes a mixed unbiased population.

We acknowledge several limitations of our study, the main one being that we only interviewed women in either Hebrew or Arabic. The population attending our hospital also includes Russian and Amharic speakers. These women were interviewed using the help of Russian/Ethiopian translators. Accordingly, we should take into account that these gaps in language and even translation, as well as cultural differences may have affected the study results. Noteworthy is that the literature describes bias in interviews that may result from lack of question understanding, inconvenience, and lack of memory [20].

Facing the relatively low rate of folic acid consumption, different programs might be considered to improve this rate. One option is to provide free folic acid supplements [24] or provide them at a low cost (as folic acid is not expensive).This may solve non-consumption due to low income and does not require high level of education. Research that tested the effectiveness of this program showed a sevenfold increase in folic acid consumption [25]. Another option is using a media campaign or brochures. This type of approach can be effective in reaching a sizable population in a short period of time and is less costly [24]. Those programs, however, will probably not improve the consumption rate in cases where the pregnancy is unplanned. To solve the problem of non-consumption of folic acid in unplanned pregnancies, consumption of folic acid is recommended throughout the fertile period [16].

In Israel, religious leaders distribute brochures to couples registering for marriage in addition to other strategies to increase consumption. All have led to a sixfold increase in consumption [14]. Increase in awareness, however, has not been necessarily translated to a significant increase in consumption. Hence, we are obligated to bridge this gap. Our study helps to define the variables that are the source of the lack of folic acid consumption.

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Capsule

Macrophages feel the heart beat

Macrophages, best known for their phagocytic function in the immune system, also have multiple tissue-specific functions, not least in the heart. Hulsmans et al. explored the role of macrophages that are abundant in the atrioventricular node of the mouse. These macrophages express the connexin 43 (CX43) protein that forms gap junctions between cells, which allow electrical coupling of cells. Macrophages forming such connections alter the electrophysiological function of cardiomyocytes. Deletion of the CX43 protein from macrophages delays conduction by the atrioventricular node, and ablation of macrophages blocks conductance of atrial impulses to the ventricles. Macrophages thus influence normal heart contraction, but because of their alternative function as immune effectors, they might also contribute to heart abnormalities associated with inflammatory diseases.

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Capsule

Oncostatin M drives intestinal inflammation and predicts response to tumor necrosis factor, thus neutralizing therapy in patients with inflammatory bowel disease

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are complex chronic inflammatory conditions of the gastrointestinal tract that are driven by perturbed cytokine pathways. Anti-tumor necrosis factor-α (TNF) antibodies are mainstay therapies for IBD. However, up to 40% of patients are nonresponsive to anti-TNF agents, which makes the identification of alternative therapeutic targets a priority. West and colleagues showed that, relative to healthy controls, inflamed intestinal tissues from patients with IBD express high amounts of the cytokine oncostatin M (OSM) and its receptor (OSMR), which correlate closely with histopathological disease severity. The OSMR is expressed in nonhematopoietic, nonepithelial intestinal stromal cells, which respond to OSM by producing various proinflammatory molecules, including interleukin (IL)-6, the leukocyte adhesion factor ICAM1, and chemokines that attract neutrophils, monocytes, and T cells. In an animal model of anti-TNF-resistant intestinal inflammation, genetic deletion or pharmacological blockade of OSM significantly attenuates colitis. Furthermore, according to an analysis of more than 200 patients with IBD, including two cohorts from phase 3 clinical trials of infliximab and golimumab, high pretreatment expression of OSM is strongly associated with failure of anti-TNF therapy. OSM is thus a potential biomarker and therapeutic target for IBD, and has particular relevance for anti-TNF-resistant patients.

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